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1 Cannabidiol normalises medial temporal, midbrain and striatal dysfunction in people at clinical high-
2 risk for psychosis

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29 **Word Count:**

30 Abstract: 350 words

31 Text: 3000 words

32 **KEY POINTS:**

33 **Question:** What are the neurocognitive mechanisms that underlie the putative therapeutic effects of
34 cannabidiol in psychosis?

35 **Findings:** We show that a single oral dose of cannabidiol modulated activation in the striatum, medial
36 temporal cortex and midbrain in clinical high-risk (CHR) patients, such that in each of these regions, the level
37 of activation following administration of cannabidiol to CHR patients was intermediate between that in healthy
38 controls and in CHR patients under placebo.

39 **Meaning:** These results suggest that cannabidiol may normalize dysfunction in these brain regions,
40 which are critically implicated in psychosis. This may underlie its therapeutic effects in psychosis.

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61 **ABSTRACT:**

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63 **Importance:** Cannabidiol (CBD) has antipsychotic effects in humans, but how these are mediated in the brain
64 remains unclear.

65 **Objective:** To investigate the neurocognitive mechanisms that underlie the therapeutic effects of CBD in
66 psychosis.

67 **Design:** Parallel-group, double-blind, randomized, placebo-controlled design in people at clinical high risk
68 (CHR) for psychosis. Healthy control (HC) participants were studied under identical conditions without any
69 drug treatment.

70 **Setting:** Academic Health Science Centre, UK

71 **Participants:** Thirty-three medication-naïve CHR and 19 HC participants.

72 **Intervention:** CHRs received a single oral dose of either 600mg of CBD (CHR-CBD) or a placebo (CHR-
73 PLB). HCs were not given any drug. All participants were then studied using functional magnetic resonance
74 imaging (fMRI) whilst performing a verbal learning task.

75 **Main Outcomes and Measures:** Brain activation during verbal encoding and recall, indexed using the blood-
76 oxygen level-dependent haemodynamic response (BOLD) fMRI signal.

77 **Results:** Seventeen CHR-PLB [mean (SD) age= 25.35 (5.24) years; 10 females] and 16 CHR-CBD
78 [mean (SD) age= 22.43 (4.95) years; 6 females] were compared with 19 HC [mean (SD) age= 23.89 (4.14)
79 years; 8 females] participants. Brain activation (indexed using median sum of squares ratio of the BOLD
80 effects model component to residual sum of squares) was analyzed from 16 CHR-PLB, 15 CHR-CBD and 19
81 HC. CHR-PLB had reduced activation relative to HC in the right caudate during encoding (CHR-PLB:
82 median=-0.027, IQR= -0.041, -0.016; HC: median=0.020, IQR= -0.022, 0.056; $p<0.001$), and in the
83 parahippocampal gyrus and midbrain during recall (CHR-PLB: median=0.002, IQR= -0.016, 0.010; HC:
84 median=0.035, IQR= 0.015, 0.039; $p=0.000096$). Within these three regions, activation in the CHR-CBD was
85 greater than in CHR-PLB, but lower than in HCs (parahippocampal gyrus/ midbrain- CHR-PLB: median=-
86 0.007, IQR= -0.019, 0.008; CHR-CBD: median= -0.013, IQR= -0.027, 0.002; HC: median=0.034, IQR= 0.005,
87 0.059; $p<0.005$): the level of activation was thus intermediate to that in the other two groups. There were no
88 significant group differences in task performance.

89 **Conclusions and relevance:** CBD may partially normalize alterations in parahippocampal, striatal and
90 midbrain function associated with the CHR state. As they are critical to the pathophysiology of psychosis, the
91 influence of CBD at these sites could underlie its therapeutic effects on psychotic symptoms.

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118 **Introduction**

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120 Epidemiological and clinical studies have implicated regular cannabis use as a risk factor for the development¹
121 of psychosis, and for poor clinical outcomes after its onset²⁻⁴. Psychosis is also associated with alterations in
122 the endocannabinoid system (reviewed here^{5,6}), independent of exposure to cannabis. The endocannabinoid
123 system thus represents a potential therapeutic target for psychosis^{7,8}. Its main central receptor, the CB1
124 cannabinoid receptor is ubiquitous in brain^{9,10} and modulates the function of neurotransmitters, thought to be
125 critically perturbed in psychosis, including dopamine and glutamate¹¹. The constituent of cannabis responsible
126 for its acute psychotomimetic effects¹²⁻¹⁴ and its association with the development and relapse of psychosis is
127 delta-9-tetrahydrocannabinol (THC)^{1-4,15,16}. In contrast, Cannabidiol (CBD), one of the major non-psychoactive
128 constituents of cannabis, has broadly opposite neural and behavioural effects¹⁷⁻²³. In particular, we have shown
129 that CBD has opposing effects to THC on activation in the striatum^{17,18} during verbal memory and salience
130 processing, on amygdala responses¹⁷ during emotional processing, and on the functional connectivity¹⁹ of these
131 regions. Furthermore, pre-treatment with CBD blocks the experimental induction of psychotic symptoms by
132 THC^{17,20}, and clinical studies indicate that CBD has antipsychotic and anxiolytic properties in patients with
133 mental disorders (^{24,25}also reviewed in^{7,8}). CBD was non-inferior to antipsychotic medication in a 4-week
134 clinical trial in first-episode psychosis²⁶, and improved psychotic symptoms when used as an adjunct to
135 antipsychotic medication in a 6-week trial in patients with chronic psychosis²⁷.

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137 Although there is good evidence that CBD can have beneficial effects on psychotic symptoms, how these
138 effects are mediated in the brain remains unclear. The present study sought to address this issue by examining
139 the effects of CBD in individuals at clinical high-risk for psychosis (CHR). CHR subjects typically experience
140 clinically significant psychotic symptoms that are qualitatively similar to those seen in patients with frank
141 psychosis²⁸, and are associated with high levels of distress²⁹. Contemporary preclinical models propose that
142 psychosis involves a perturbation of activity in the medial temporal lobe (MTL) that drives subcortical
143 dopamine dysfunction through projections to the striatum and midbrain³⁰. Moreover neuroimaging studies in
144 CHR subjects indicate that the later onset of psychosis is linked to alterations in parahippocampal structure³¹
145 and function³²⁻³⁴ and to elevated striatal and midbrain dopamine activity.

146 In the present study, on the basis of previous studies, we expected that CHR subjects would display altered
147 responses in the MTL, midbrain and striatum relative to HC. Our main hypothesis was that CBD would
148 attenuate functional abnormalities in this triad of regions. While the MTL is critical for new learning³⁵, the
149 midbrain³⁶⁻³⁹ and striatum³⁹⁻⁴³ also play a key role in supporting the encoding and updating of contextual
150 information in memory. Therefore, we employed the verbal paired associate learning task (VPA), which
151 engages these processes and brain regions^{13,14}. Furthermore, transient psychotomimetic effects of THC have
152 been related to its modulation of striatal¹³ and midbrain¹⁴ function and CBD¹⁷ has been shown to oppose these
153 striatal effects of THC during this task.

154

155 **METHODS**

156 Detailed methods are included as part of supplementary material (see eMethods and Figure S1A for
157 CONSORT diagram). Thirty-three antipsychotic medication-naïve CHR participants²⁸ were recruited from
158 early intervention services in the UK. Nineteen age-matched (± 3 years) healthy controls (HC) were recruited
159 by local advertisement. All participants provided written informed consent. Individuals with history of
160 previous psychotic or manic episode, neurological disorder or current DSM-IV diagnosis of substance
161 dependence, IQ less than 70 and contraindication to MRI or treatment with CBD were excluded.
162 Psychopathology was measured using Comprehensive Assessment of At-Risk Mental States (CAARMS;
163 positive and negative symptoms)²⁸ and state-trait anxiety inventory- state subscale (STAI-S)⁴⁴ at baseline
164 before drug administration. Two CHR participants were excluded, one from each of the CBD-treatment and
165 placebo-treatment arms, after failing to correctly perform the imaging task, resulting in $n=15$ participants in the
166 CHR-CBD group and $n=16$ in the CHR-PLB group.

167

168 Using a parallel-group, double-blind, placebo-controlled design, CHR participants were
169 randomized to either CBD (CHR-CBD) or placebo (CHR-PLB) treatment and received a single oral dose of
170 600mg of CBD (THC-Pharm), a dose previously effective in established psychosis²⁶, or an identical placebo
171 capsule respectively. Three hours after taking the CBD or placebo capsule, participants underwent functional
172 magnetic resonance imaging (fMRI) whilst performing a VPA task that we have previously used in
173 conjunction with fMRI and pharmacological challenge^{13,14}, including CBD administration¹⁷ (see eMethods for

174 justification of CBD dose and time of fMRI scanning, and Figure S1B for CBD plasma levels). HC
175 participants were investigated under identical conditions, but did not receive any study drug.
176 All participants were asked to have refrained from cannabis for 96 hours, alcohol for a minimum of 24 and
177 nicotine for 6 hours before scanning and any other recreational drugs for two weeks before the study day. A
178 urine sample prior to scanning was used to screen for use of illicit drugs.

179
180 The VPA task (described in detail in eMethods) comprised 3 conditions (encoding, recall, and baseline), with
181 stimuli presented visually in blocks and accuracy of responses recorded online. During encoding, participants
182 were shown word-pairs and asked to say 'yes' or 'no' aloud after each pair to indicate whether they went well
183 together. The same word pairs were presented in the encoding condition 4 times, so that the associations could
184 be learned over repeated blocks. During recall, one of the words from previously presented pairs was shown
185 and participants were asked to say the word that it had previously been associated with. Subjects said "pass" if
186 they could not recall the missing word. During baseline, participants viewed a pair of blank blue rectangles of
187 identical dimensions as in the encoding/ recall condition.

188
189 For each participant, the blood oxygen level-dependent haemodynamic (BOLD) response of the brain during
190 each encoding and recall block, measured using a 3T MRI scanner (gradient echo sequence axially; 39 x 3mm
191 slices, 3.3mm slice gap; 30ms echo time; compressed acquisition with a 2s repetition time and 3s silence), was
192 contrasted with that during the baseline condition.

193
194 **Analysis** | fMRI data were analyzed with software developed at the Institute of Psychiatry, Psychology and
195 Neuroscience (XBAM, version 4.1), using a nonparametric approach to minimize assumptions
196 (<https://www.kcl.ac.uk/ioppn/depts/neuroimaging/research/imaginganalysis/Software/XBAM.aspx>)^{45,46}.

197 Images were corrected for motion⁴⁷, spatially smoothed and the experimental design was convolved with two
198 gamma-variate functions to model the BOLD response. Using the constrained BOLD effects model, a best fit
199 between the weighted sum of these convolutions and the change over time at each voxel was computed⁴⁸.

200 Following least-squares fitting of this model to the time series at each voxel, a sum of squares (SSQ) ratio
201 statistic (ratio of the model component to residual sum of squares) was estimated for the encoding and recall

202 conditions relative to baseline. Significance of the estimated SSQ values at each voxel was determined by
203 permutation testing^{49,50}. SSQ ratio maps for each individual were transformed into standard stereotactic
204 space^{51,45} and group activation maps were computed for each group in each drug condition by determining the
205 median SSQ ratio at each voxel (over all individuals) in the observed and permuted data maps. Group
206 activation maps for each condition were compared against each other (CHR-PLB vs HC and CHR-CBD vs
207 CHR-PLB) using non-parametric repeated-measure analysis of variance (ANOVA)⁴⁵. The voxel-wise
208 statistical threshold was set at $p=0.05$ and the cluster-wise thresholds were adjusted to ensure that the number
209 of false positive clusters per brain would be <1 (regions that survived this critical statistical threshold and the
210 corresponding p values are reported).

211 The BOLD response in each subject was modelled using only trials associated with correct responses in the
212 recall condition. To test the hypothesis that activation in the CHR-CBD group would be intermediate between
213 that of HC and CHR-PLB subjects we examined whether a linear relationship in brain activation (CHR-PLB $>$
214 CHR-CBD $>$ HC or CHR-PLB $<$ CHR-CBD $<$ HC) existed within the whole brain.

215
216 Recall performance was analysed using repeated-measures analysis of variance. Correlational analysis between
217 recall score and brain activation was conducted using Pearson's test (two-tailed).

218

219 **RESULTS**

220 There were no significant group differences between the CHR-PLB and HC and CHR-PLB and CHR-CBD
221 groups in demographic and clinical variables, except that the CHR-PLB group had fewer years of education
222 than the HC group (Table 1).

223

224 **fMRI results**

225 **Main effects of encoding and recall in healthy controls**

226

227 In HC, relative to the baseline condition, the encoding condition was associated with activation in the left
228 anterior cingulate cortex, the right caudate, the left precentral gyrus, and the cuneus (eTable 1). The recall
229 condition relative to the baseline condition was associated with activation in the left parahippocampal and left

230 transverse temporal gyri, and decreased activation in the left middle occipital, the right lingual and inferior
231 frontal gyri (eTable 2).

232

233

234 **Differences in activation associated with the CHR state (CHR-PLB vs HC)**

235

236 **Encoding** | During the encoding condition, CHR-PLB participants showed greater activation than HC in the
237 right middle frontal gyrus and adjacent parts of the inferior frontal gyrus and insula; the left insula/ claustrum
238 and adjacent inferior frontal gyrus and putamen; the right precentral gyrus and adjacent postcentral gyrus and
239 inferior parietal lobule; and the left cerebellum and adjacent lingual gyrus (Table 1, Figure 1A). Relative to
240 CHR-PLB, HC showed greater activation in the right subcallosal gyrus/ caudate head; the left anterior
241 cingulate; the right caudate tail extending to the posterior cingulate cortex; and in the right precuneus and
242 cuneus (Table 2A, Figure 1A).

243

244 **Recall** / During the recall condition, the CHR-PLB participants showed greater activation than HC in clusters
245 encompassing the right inferior frontal, middle frontal and precentral gyri, and insula; the right cuneus,
246 fusiform, lingual gyri and posterior cingulate gyri; and the left cerebellum and middle occipital and fusiform
247 gyri (Table 2B, Figure 1B). HC showed greater activation in four clusters in the left hemisphere: these
248 involved the parahippocampal gyrus, midbrain, cerebellum and thalamus; superior temporal and middle
249 temporal gyri; superior and transverse temporal gyri; and middle frontal gyrus (Table 2B, Figure 1B).

250

251 **Effect of CBD on activation in CHR participants (CHR-PLB vs CHR-CBD)**

252

253 **Encoding** | During the encoding condition, the CHR-PLB group showed greater activation than the CHR-CBD
254 group in a cluster in the left parahippocampal gyrus that extended into the superior temporal gyrus and
255 cerebellum, but less activation in the precentral gyri (Table 3A, Figure 1C).

256 **Recall** / During the recall condition, the CHR-PLB showed less activation than the CHR-CBD group in three
257 clusters, with foci in the left cingulate gyrus and adjacent body of caudate; the right precentral gyrus, extending

258 to the cingulate gyrus; and in the medial frontal gyrus (Table 3A, Figure 1D). There were no clusters of greater
259 activation in the CHR-PLB than the CHR-CBD group.

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263 **Between-group linear analysis**

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265 This analysis identified clusters where there was a linear pattern of activation across the 3 groups, such that
266 activation in the CHR-CBD group was intermediate to that in the CHR-PLB and HC groups.

267

268 **Encoding** | There were 7 clusters where encoding-related engagement was greatest in the CHR-PLB group,
269 lowest in the HC group, and at an intermediate level in the CHR-CBD group. These involved the right inferior
270 frontal and middle frontal gyri and insula; left insula and putamen; 3 clusters in the precentral gyri; right
271 fusiform gyrus and adjacent cerebellum; left cerebellum and fusiform gyrus (Table 3B, Figure 2A-B; Also see
272 supplementary figure S2A displaying all regions). The right inferior frontal gyrus, left insula and precentral
273 clusters overlapped with the regions where the CHR-PLB showed increased activation during encoding
274 relative to the HC group in the earlier paired comparison.

275

276 There were 4 clusters where there was a linear between-group relationship in the opposite direction (CHR-
277 PLB < CHR-CBD < HC). These involved the left caudate head and putamen and anterior cingulate cortex; right
278 subcallosal gyrus and caudate head; tail of the right caudate and adjacent posterior cingulate cortex; and the
279 precuneus and right cuneus. In these clusters, activation during encoding was greatest in the HC group, lowest
280 in the CHR-PLB group, and at an intermediate level in the CHR-CBD group (Table 3B, Figure 2A-B; Also see
281 supplementary figure S1A displaying all regions). All 4 clusters overlapped with clusters where HC had shown
282 greater activation than the CHR-PLB group during encoding in the previous paired comparison.

283

284 **Recall** / In 3 clusters, recall-related engagement was greatest in the CHR-PLB participants, and lowest in HC,
285 and at an intermediate level in the CHR-CBD participants. These clusters comprised the right inferior frontal
286 gyrus extending to ipsilateral middle frontal gyrus and insula; precuneus extending to cuneus, lingual, middle

287 occipital and fusiform gyri and cerebellum on the right side; and cerebellum extending to fusiform, lingual and
288 inferior occipital gyri on the left side (Table 3C, Figure 2C-D; Also see supplementary figure S2B displaying
289 all regions). All 3 clusters overlapped with clusters where the CHR-PLB had shown greater activation than HC
290 during recall in the paired comparison.

291
292 Conversely, there were 4 clusters where activation was greatest in the HC group, lowest in the CHR-PLB
293 group and at an intermediate level in the CHR-CBD participants. These included the left parahippocampal
294 gyrus, midbrain and cerebellum; left thalamus; the left transverse temporal gyrus extending to superior
295 temporal gyrus; and the left precentral and cingulate gyri and caudate body (Table 3C, Figure 2C-D; Also see
296 supplementary figure S2B displaying all regions). The left parahippocampal gyrus and transverse temporal
297 gyrus clusters overlapped with clusters where HC had shown greater activation than CHR-PLB participants
298 during recall in the paired group comparison.

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300 **Relationship between recall performance and brain activation:**

301 Across all participants, total recall score was directly correlated ($r=0.28$, $p=0.046$) with the level of left
302 parahippocampal activation during recall. See eResults for exploratory analyses examining relationship
303 between brain activation and symptoms.

304

305 **DISCUSSION**

306 As expected and in line with data from previous neuroimaging comparisons of CHR subjects and
307 controls⁵²⁻⁵⁴, we found that under placebo conditions, CHR participants showed differential
308 activation relative to controls in several regions. These regions of differential response included the
309 three areas thought to be critical to the pathophysiology of the CHR state, the striatum (during
310 verbal encoding), and the MTL and midbrain (during verbal recall).

311

312 To test our main hypothesis, we identified regions where there was a linear pattern of activation
313 across the three subject groups, such that the level of activation in CHR subjects given CBD was
314 intermediate to that in the CHR-placebo and control groups. We found that this pattern of
315 differential activation was evident in the striatum during encoding, and in the parahippocampal

316 cortex and midbrain during recall. Moreover, these regions of differential activation overlapped with
317 the areas where CHR participants under placebo conditions had shown altered activation in the
318 paired comparison with the controls. These findings suggest that during verbal encoding, the
319 administration of a single dose of CBD attenuated the reduction in the striatal response that evident
320 in CHR participants relative to controls under placebo conditions. Similarly, administration of CBD
321 appeared to attenuate the reduction in the parahippocampal and midbrain responses during verbal
322 recall that was seen in CHR participants under placebo conditions relative to controls. Although this
323 interpretation is cautious because the findings are based on cross-sectional as opposed to within-
324 subject comparisons, these data suggest that in these regions, CBD may partially normalise
325 responses to verbal encoding and recall in CHR subjects. As there were no significant differences in
326 memory performance, this differential activation was not attributable to differential task
327 performance.

328
329 Acute effects of CBD on responses in these areas in CHR participants are consistent with previous
330 data from two studies that used a single dose of CBD in healthy volunteers. These studies indicated
331 that in controls, CBD augmented parahippocampal and striatal activation^{17,18} during the same
332 learning task¹⁷ as used in the present study and had a similar effect on parahippocampal and striatal
333 responses during an attentional salience task¹⁸. In both of these studies, the administration of a single
334 dose of THC induced transient psychotic symptoms, and the effect of THC on parahippocampal and
335 striatal activation was the opposite to that of CBD.

336
337 Preclinical models suggest that overactivity in the MTL region drives subcortical dopamine
338 dysfunction through projections to the striatum and midbrain^{55,56}. Moreover, neuroimaging studies in
339 CHR subjects indicate that the subsequent onset of psychosis is linked to alterations in MTL
340 structure³¹ and function^{32,34}, and to elevated striatal and midbrain dopamine function⁵⁷⁻⁵⁹. Effects of
341 CBD on parahippocampal, striatal and midbrain function in CHR participants are thus of particular
342 interest as these areas may play a critical role in the pathophysiology of psychosis³⁰. A partial
343 normalization of dysfunction in these regions could contribute to the therapeutic effects of CBD that
344 have been reported in patients with psychosis^{26,27} and anxiety disorders²⁵.

345
346 The molecular mechanism of action that may underlie the effects of CBD in CHR patients is
347 unclear. CBD has effects on a number of signaling pathways^{11,60,61}, including on the CB1 receptors
348 ^{62,63} and may modulate glutamatergic neurotransmission particularly in the hippocampus through
349 multiple pathways⁶⁴⁻⁶⁶ and striatal glutamatergic and CB1 receptor expression⁶⁷. In patients with
350 psychosis, the effects of CBD on psychotic symptoms have been related to its influence on levels of
351 the endogenous cannabinoid anandamide²⁶. Future studies therefore need to investigate the
352 neurochemical and receptor level mechanisms that may underlie the antipsychotic effects of CBD.

353
354 Across all participants, the level of activation in the left parahippocampal cortex during verbal recall
355 was directly correlated with total recall score during the task, consistent with the key role of this
356 region in relational memory binding and retrieval^{68,69} and in supporting association-based recall⁷⁰.
357 Attenuated parahippocampal engagement in CHR-PLB is consistent with meta-analytic and
358 independent evidence from studies in patients with established psychotic disorders such as
359 schizophrenia⁷¹⁻⁷³ and in studies in those at clinical^{34,74} and familial/ genetic^{73,75} risk of psychosis.
360 Further discussion of the results is presented as supplementary material (see eDiscussion 1).

361 362 **Limitations**

363 Our results need to be considered in light of certain caveats including related to study design (see
364 eDiscussion 2).

365 366 **Conclusions**

367 This study suggests that a single dose of CBD in an experimental setting may partially normalise
368 dysfunction in the MTL, striatum and midbrain in subjects at CHR for psychosis. It would be useful
369 to now investigate whether similar modulatory effects are evident in patients who have received a
370 course of treatment with CBD in a clinical setting.

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619 SB and PM designed the study; SB supervised the collection (RW, EAK) and analysis (AON) of the data and
620 wrote the first draft of the paper. All authors contributed to the interpretation of the data, revised the
621 manuscript and have approved the final manuscript.

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Tables:

Table 1. Sociodemographic and clinical measures at baseline

	HC (n=19) ^a	CHR-PLB (n=17)	CHR-CBD (n=16)	Statistics
Age (years), mean±SD	23.89±4.14	25.35±5.24	22.43±4.95	HC vs CHR-PLB: <i>p</i> = 0.36 CHR-PLB vs CHR-CBD: <i>p</i> = 0.11
Gender (m: f)	16:8	7:10	10:6	HC vs CHR-PLB: <i>p</i> = 0.50 CHR-PLB vs CHR-CBD: <i>p</i> = 0.30
Education (years), mean±SD	16.94±1.59	12.00±3.69	14.50±3.06	HC vs CHR-PLB: <i>p</i> = 0.01 CHR-PLB vs CHR-CBD: <i>p</i> = 0.15
CAARMS positive symptoms	-	42.94±29.46	40.19±20.79	<i>p</i> = 0.75
CAARMS negative symptoms	-	28.41±20.49	23.25±16.49	<i>p</i> = 0.43
STAI-S	-	38.94±10.17	40.31±9.06	<i>p</i> = 0.68
Number of patients who made a transition to psychosis (n)	-	1	1	<i>p</i> = 1
Urine Drug screen (UDS) results: Clean	- ^b	8	10	CHR-PLB vs CHR-CBD: <i>p</i> =0.45
THC	-	5	2	
Morphine	-	0	1	
Benzodiazepines	-	1	0	
PCP	-	1	0	
Missing	-	2	3	
Cannabis Use: Lifetime use (Current use) (n)	- ^c	17 (7)	15 (7)	Lifetime use: <i>p</i> =0.48; Current use: <i>p</i> =1
Cannabis Use: Frequency- More than once a week	-	12	11	<i>p</i> =0.38
Once/ twice monthly	-	3	1	
Few times a year	-	0	2	
Only once/ twice lifetime	-	2	1	
Alcohol Use: Lifetime use (Current use) (n)	- ^d	13 (10)	12 (11)	Lifetime use: <i>p</i> =1; Current use: <i>p</i> =0.59
Alcohol Use: Frequency- Daily	-	2	1	<i>p</i> =0.59
More than once a week	-	4	4	
Few times a month	-	3	4	
Few times a year	-	2	3	
Only once/ twice lifetime	-	2	0	
Nicotine Use: Lifetime use (Current use) (n)	- ^e	7 (5)	11 (9)	Lifetime use: <i>p</i> =0.16; Current use: <i>p</i> =1
Nicotine Use: Frequency- Daily	-	6	8	<i>p</i> =0.68
More than once a week	-	1	2	
Few times a month	-	0	1	
Total recall score	29.74±2.51	27.62±4.42	28.31±2.91	<i>F</i> _{2,48} =1.84, <i>p</i> =0.17

651 ^a- HC were selected to have minimal drug use and hence not compared with CHR groups on these parameters
 652 ^b- HC tested negative on UDS for all substances tested.
 653 ^c- Cannabis use < 10 times lifetime (no current users).
 654 ^d- Alcohol use: Lifetime users-13; Frequency (More than once a week- 5; Few times a month- 3; Few times a year- 4)
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 656 ^e- Nicotine use: Lifetime users-5 (2 current users); Frequency (Daily-2; Few times a month- 1; Few times a year- 1;
 657 Only once/ twice lifetime- 1)
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Table 2 A: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) participants and healthy controls (HC, n=19) during verbal encoding

CHR-PLB > HC					
Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
Middle frontal gyrus extending to inferior frontal gyrus and insula	36	37	10	165	0.0001
Clastrum/ Insula extending to inferior frontal gyrus and putamen	-25	26	3	96	0.001
Precentral gyrus extending to postcentral gyrus and inferior parietal lobule	40	-7	36	134	0.00051
Left cerebellum extending to lingual gyrus	-40	-67	-16	77	0.0011
CHR-PLB < HC					
Subcallosal gryus / caudate head	14	11	-10	72	0.00093
Anterior cingulate	-4	41	0	18	0.00093
Caudate tail extending to posterior cingulate cortex	18	-33	16	28	0.00021
Precuneus extending to cuneus	4	-63	30	156	0.00021

674 TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

675

676 Table 2B: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) participants and healthy
 677 controls (HC, n=19) during verbal recall

CHR-PLB > HC					
Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
Inferior frontal gyrus extending to middle frontal gyrus, insula and precentral gyrus	47	11	23	146	0.0001
Cuneus extending to fusiform gyrus, lingual gyrus and posterior cingulate cortex	29	-74	7	196	0.0001
Cerebellum extending to middle occipital gyrus and fusiform gyrus	-36	-63	-13	83	0.0015
CHR-PLB < HC					
Parahippocampal gyrus extending to midbrain, cerebellum and thalamus	-18	-26	-13	131	0.000096
Superior temporal gyrus extending to the middle temporal gyrus	-50	-18	0	80	0.00038
Superior temporal gyrus extending to the transverse temporal gyrus	-50	-30	13	33	0.003
Middle frontal gyrus	-25	11	33	57	0.0034

678 TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

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697 Table 3A: Differences in activation between placebo-treated CHR (CHR-PLB, n=16) and CBD-treated CHR
 698 (CHR-CBD, n=15) subjects during verbal encoding and recall

Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
Encoding: CHR-PLB > CHR-CBD					
Parahippocampal gyrus, extending to superior temporal gyrus and cerebellum	-29	-30	-13	75	0.0032
Encoding: PLB-CHR < CBD-CHR					
Precentral gyrus	43	-7	30	40	0.0033
	-40	-11	36	72	0.0005
Recall: PLB-CHR < CBD-CHR					
Cingulate gyrus, extending to body of caudate	-14	15	30	365	0.00010
Precentral gyrus, extending to cingulate gyrus	43	-18	33	362	0.00010
Medial frontal gyrus	-7	0	49	61	0.0021

699 TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.
 700 There were no significant clusters for **PLB-CHR > CBD-CHR** during recall.
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703 Table 3B: Linear relationship in activation across all groups during verbal encoding (CHR-PLB, n=16; CHR-
704 CBD, n=15; HC, n=19)

Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
CHR-PLB > CHR-CBD > HC					
Inferior frontal gyrus, extending to middle frontal gyrus and insula	40	37	10	135	0.0001
Insula, extending to putamen	-36	11	10	112	0.0004
Precentral gyrus	-40	-11	30	39	0.0040
	-51	-4	16	34	0.0031
	40	-11	36	124	0.0002
Fusiform gyrus, extending to cerebellum	43	-44	-13	53	0.0027
Cerebellum, extending to fusiform gyrus	-22	-52	-16	100	0.0004
CHR-PLB < CHR-CBD < HC					
Caudate head, extending to anterior cingulate and putamen	-14	22	0	44	0.0041
Subcallosal gyrus/ caudate head	14	11	-10	87	0.0011
Caudate tail, extending to posterior cingulate cortex	18	-37	13	65	0.0038
Precuneus, extending to Cuneus	4	-63	30	185	0.0001

705 TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.

706 Table 3C: Linear relationship in activation across all groups during verbal recall (CHR-PLB, n=16; CHR-
 707 CBD, n=15; HC, n=19)
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Region	Coordinates of peak (TAL)			Cluster size	p value*
	X	Y	Z		
CHR-PLB > CHR-CBD > HC					
Inferior frontal gyrus, extending to middle frontal gyrus and insula	47	11	23	120	0.0001
Precuneus, extending to cuneus, lingual, middle occipital and fusiform gyri and cerebellum	25	-74	7	176	0.0001
Cerebellum, extending to fusiform, lingual and inferior occipital gyri	-36	-63	-13	73	0.0019
CHR-PLB < CHR-CBD < HC					
Parahippocampal gyrus, extending to midbrain and cerebellum	-18	-26	-13	82	0.0008
Thalamus	-7	-26	-3	33	0.0032
Transverse temporal gyrus, extending to superior temporal gyrus	-50	-26	13	33	0.0037
Precentral gyrus, extending to cingulate gyrus and body of caudate	-36	18	36	60	0.0016

709 TAL = Talairach coordinate system. *Corrected for less than 1 false positive cluster.
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715 **Figure Legends:**

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718 Figure 1. Altered brain activation in CHR (CHR-PLB vs HC)

719 A. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to HC
720 during the encoding condition.

721 B. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to HC
722 during the recall condition.

723 C. Clusters showing greater (red/yellow) or reduced (blue/ green) activation in CHR-PLB compared to CHR-
724 CBD during verbal encoding.

725 D. Clusters showing greater (red/yellow) activation in CHR-PLB compared to CHR-CBD during the recall
726 condition.

727 The right side of the brain is shown on the right of the images.

728

729 Figure 2. Effect of CBD on brain activation compared to placebo in CHR and healthy controls

730 A. Clusters where activation during encoding differed across the 3 groups in a linear relationship. In the
731 head of caudate (red/yellow), activation was greatest in HC, lowest in CHR-PLB and intermediate in
732 CHR-CBD. The opposite pattern (CHR-PLB>CHR-CBD>HC) was seen in occipital regions (blue).

733 B. Activation in each group in the right caudate head during encoding (arbitrary units; as indexed using
734 median SSQ ratio)

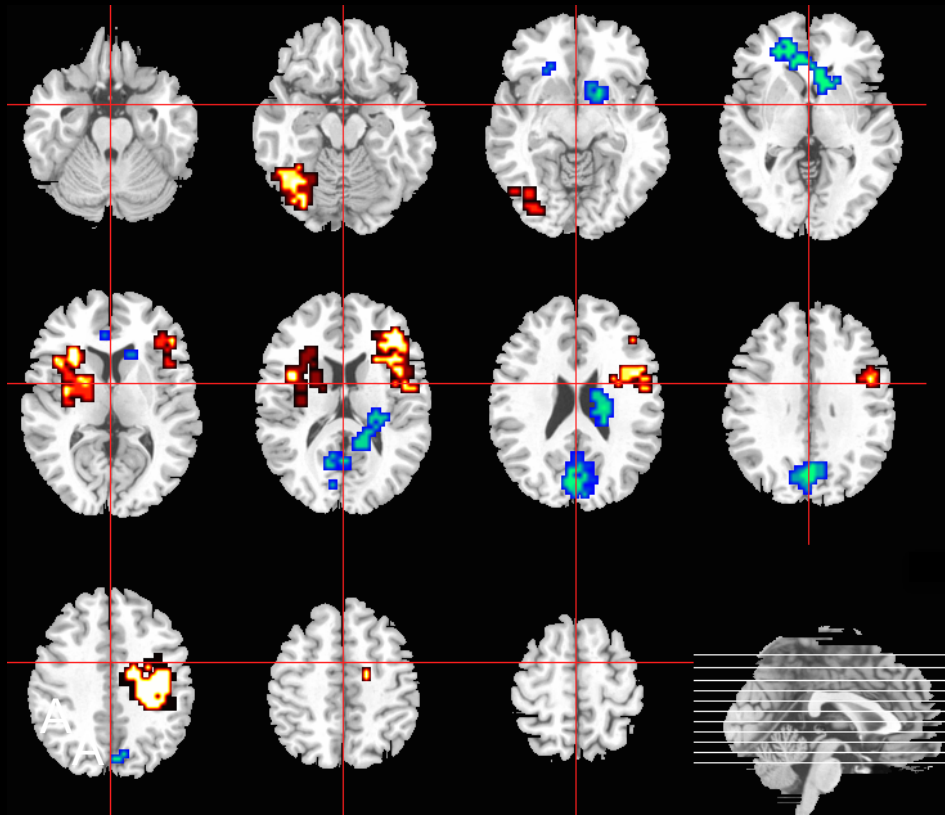
735 C. Clusters where there was a linear group difference in activation during recall. In the parahippocampal
736 region and midbrain (red/yellow), activation was greatest in HC, lowest in CHR-PLB and intermediate
737 in CHR-CBD. The opposite pattern (CHR-PLB>CHR-CBD>HC) was seen in occipital regions (blue).

738 D. Median activation in each group in the midbrain during recall (arbitrary units; as indexed using median
739 SSQ ratio)

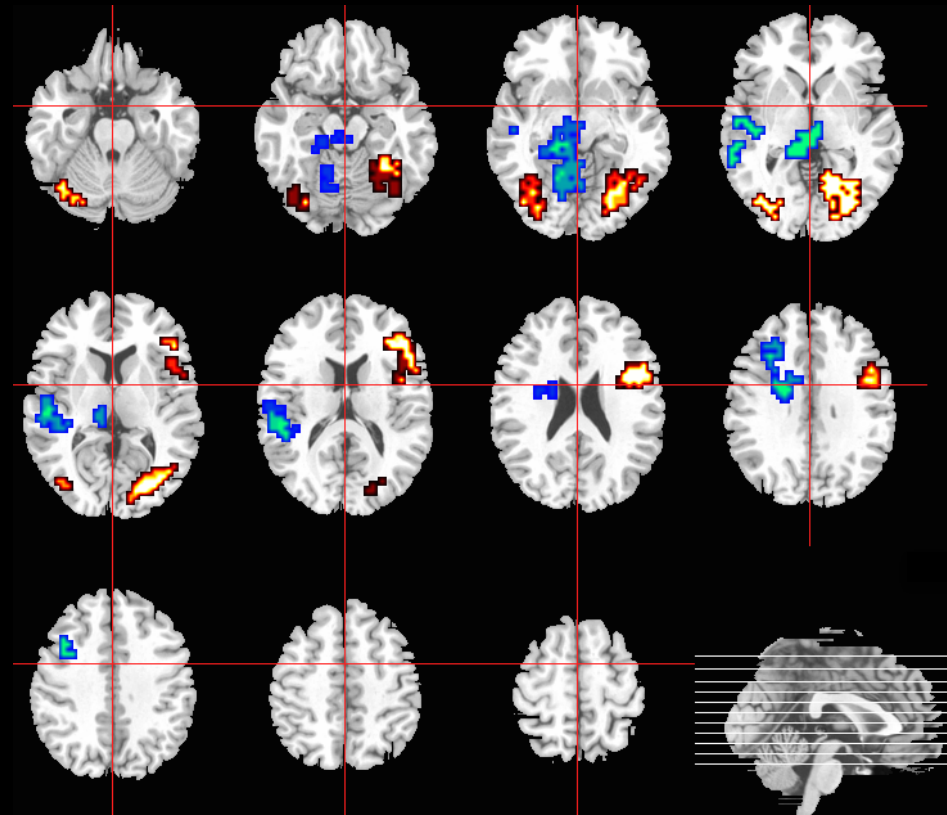
740 SSQ ratio statistic refers to the ratio of sum of squares (SSQ) of deviations from the mean image intensity due
741 to the model (over the whole time series), to the SSQ of deviations due to the residuals. The right side of the
742 brain is shown on the right of the images.

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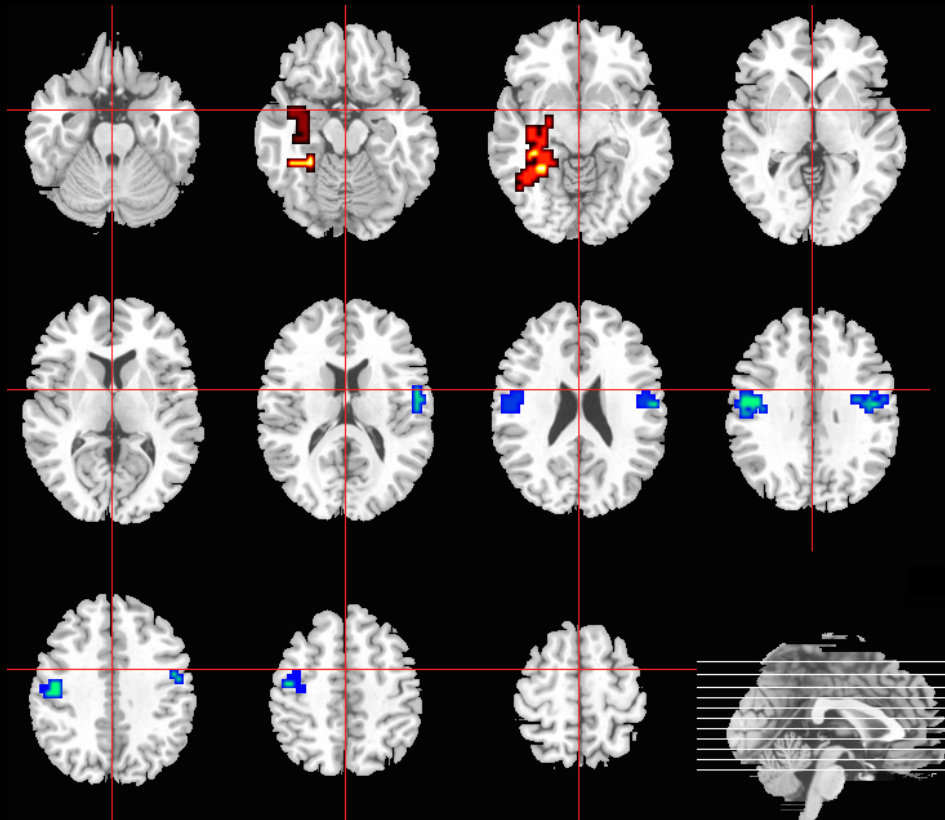
A. HC vs CHR-PLB: Encoding



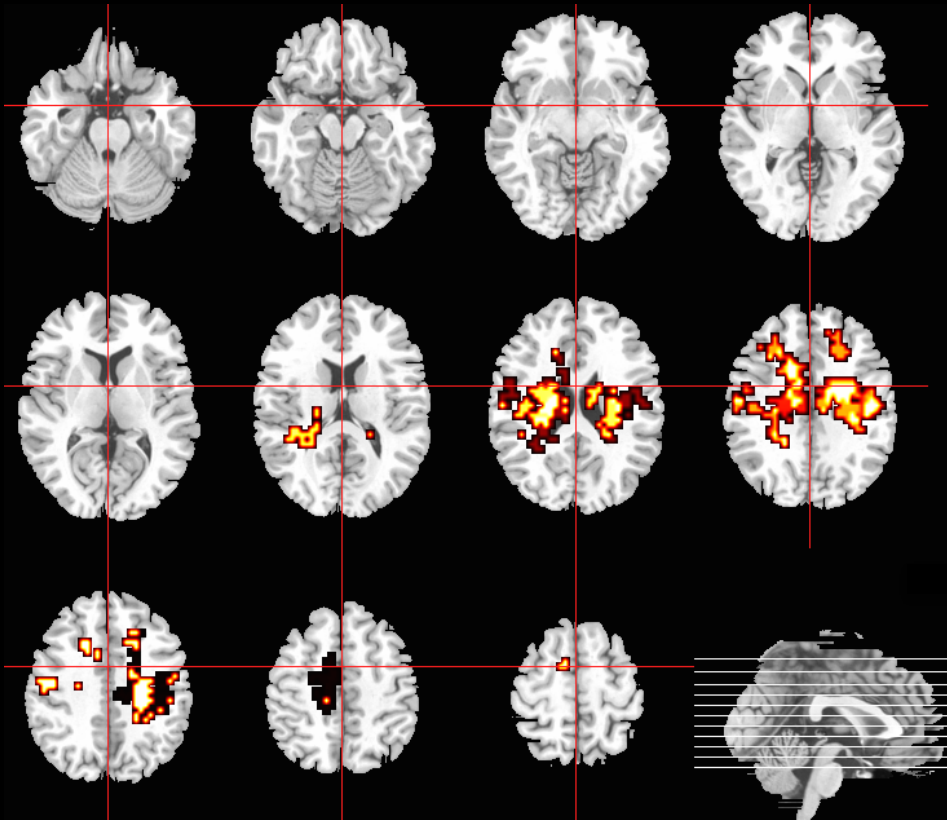
B. HC vs CHR-PLB: Recall



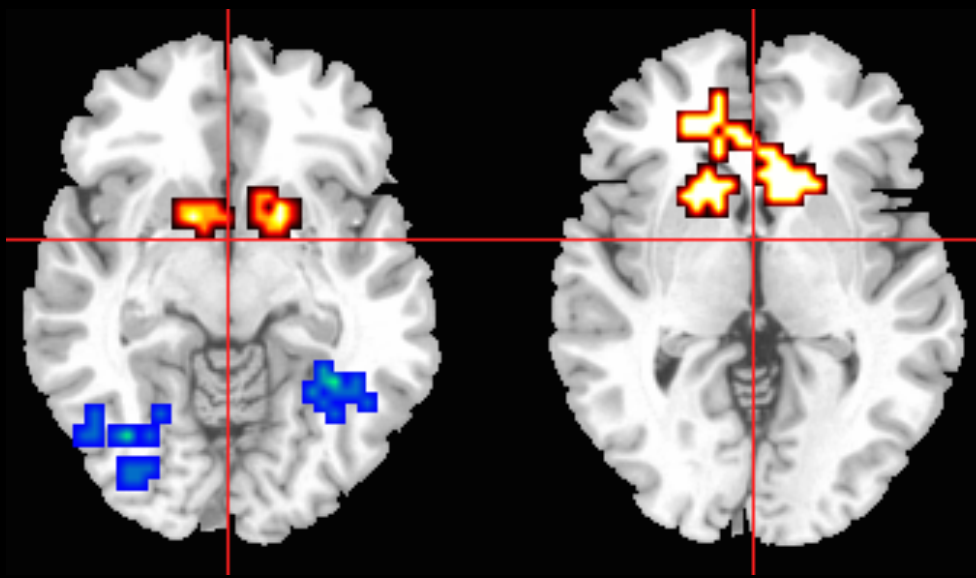
C. CHR-PLB vs CHR-CBD: Encoding



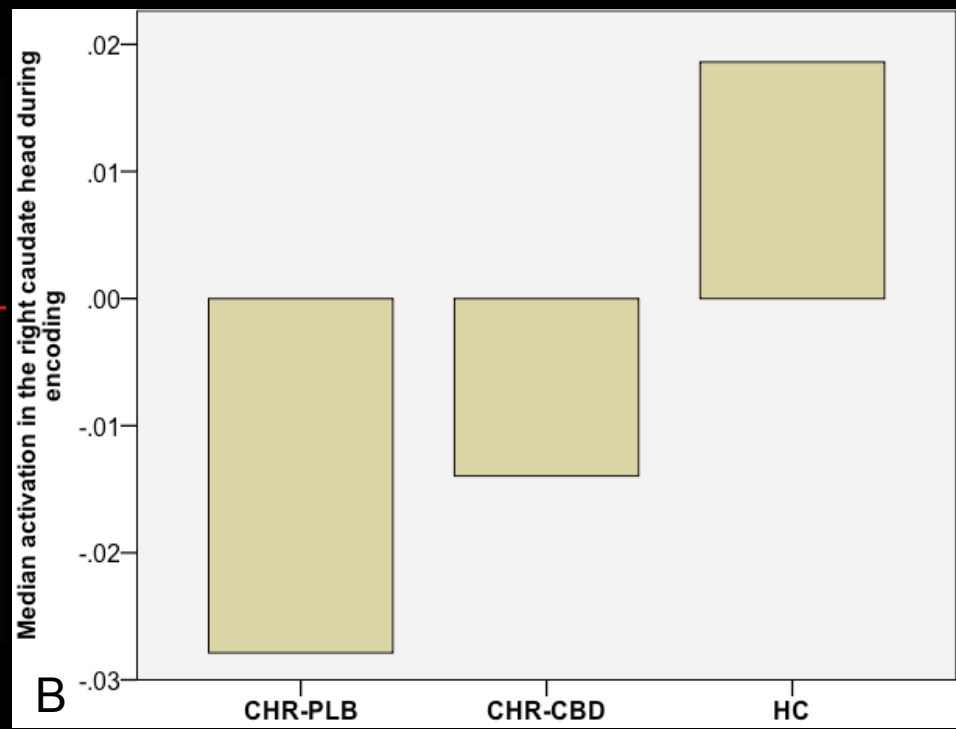
D. CHR-PLB vs CHR-CBD: Recall



Encoding: CHR-PLB vs CHR-CBD vs HC

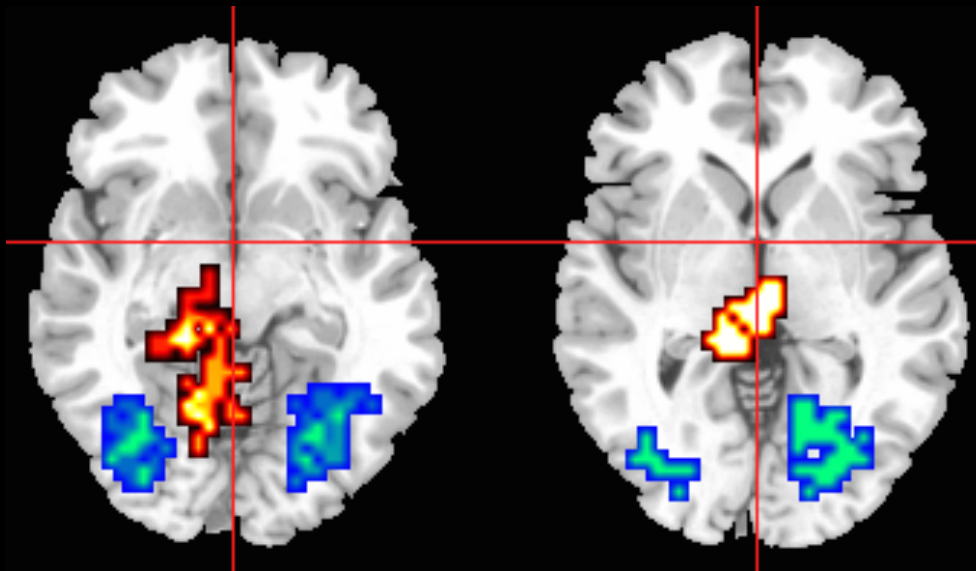


A

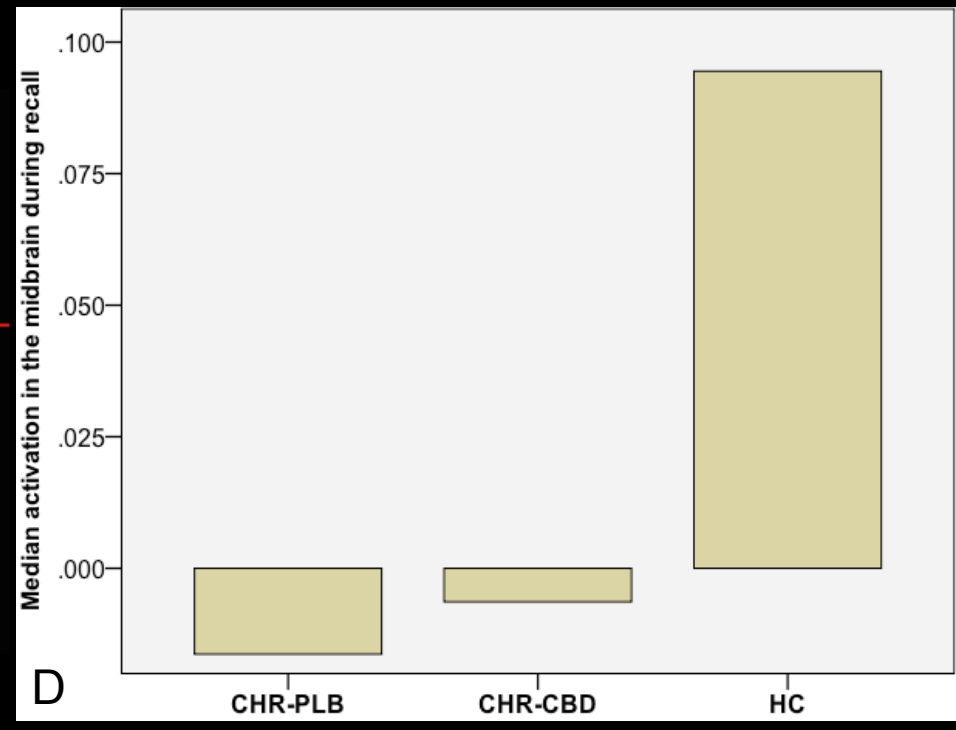


B

Recall: CHR-PLB vs CHR-CBD vs HC



C



D