Acute effects of cannabidiol on brain function during verbal learning in individuals at clinical high risk for psychosis: an fMRI-MRS study

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Introduction

➢ New treatments are needed for people with CHR

- Many individuals who eventually develop a psychotic disorder go through a prodromal phase characterized by attenuated or milder psychotic symptoms (Fusar-poli et al,2020), which are referred to as the clinical high risk(CHR) state for psychosis.
- Early intervention in people with CHR may help to reduce the risk of progression to psychotic disorder.
- Various pharmacological and psychological interventions have been studied for treating psychosis. However, there are no currently effective pharmacological treatments for people with CHR.

➢ CBD as a promising new treatment

- Although evidence is mixed, CBD has potential antipsychotic properties and can provide relief for both positive and negative symptoms of psychosis (Leweke et al., 2012, McGuire et al., 2018)
- CBD is well tolerated and has few adverse effects (Chesney et al., 2022)

➢ Mechanisms underlying antipsychotic effect

- CBD may act on hippocampal glutamate levels as a potential target for its antipsychotic effects (O'Neil et al. 2021), and may also modulate glutamate in people with CHR (Davies et al., 2023)
- 600mg CBD modulates medial temporal, midbrain and striatal function in People at Clinical High Risk of Psychosis (Bhattacharyya et al., 2018)

However, whether hippocampal glutamate is related to regional brain activation during memory processing, and whether CBD has effects on this relationship, remains unclear.

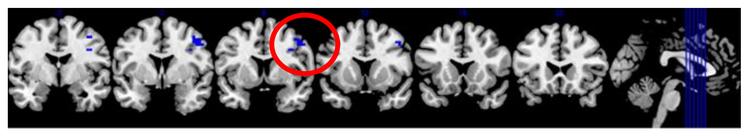
Results

Glutamate level X BOLD X Group

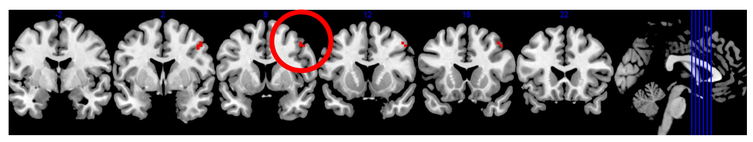
(Opposite correlation between activation and hippocampal glutamate levels)

➢ ENCODING

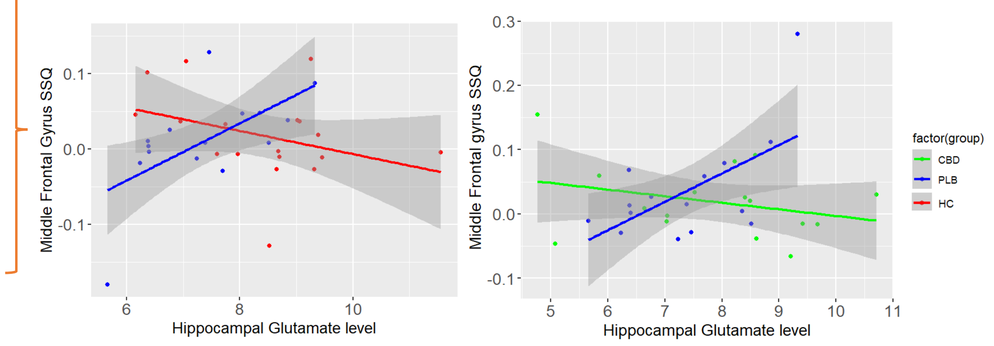
HC versus CHR-Placebo



CBD versus CHR-Placebo

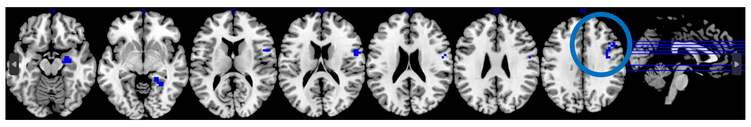


Scatter plots of the association between hippocampal glutamate levels and clusters identified in Glutamate level X BOLD X Group analysis

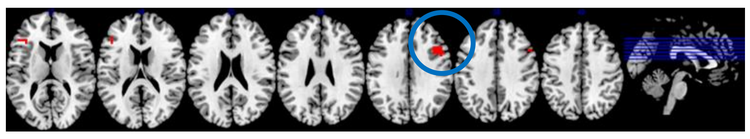


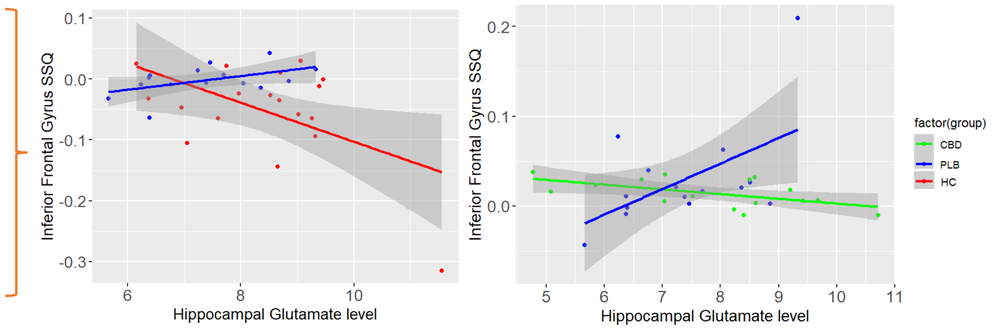
➢ RECALL

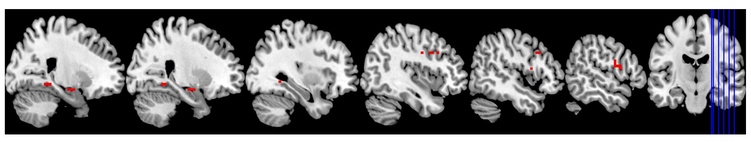
HC versus CHR-Placebo

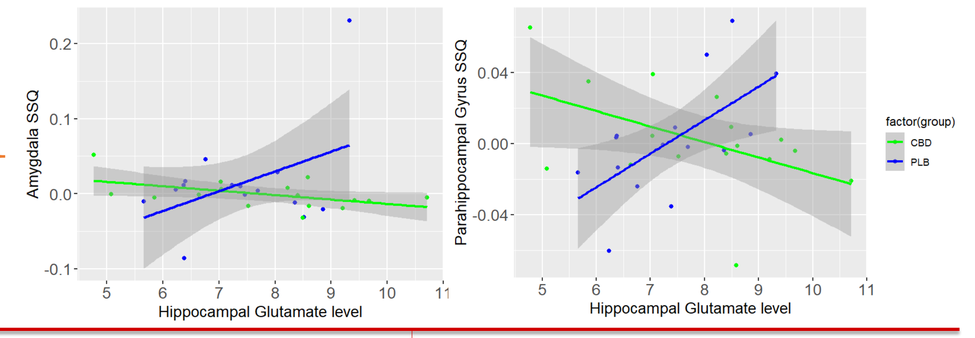


CBD versus CHR-Placebo









Methods

➢ Design

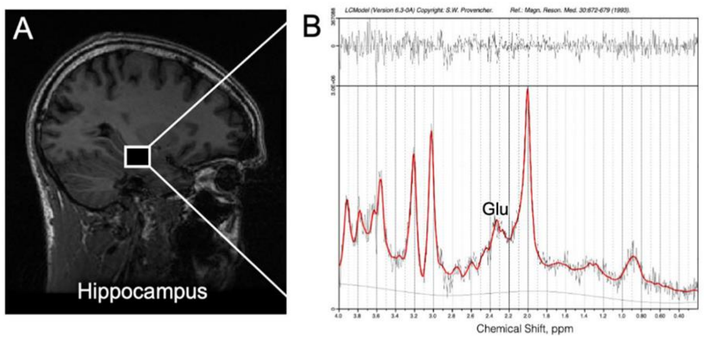
This is a parallel-group, double-blind, placebo-controlled randomized trial. Psychopathology was measured at baseline using the CAARMS (Comprehensive Assessment of At-Risk Mental States) scale. Three hours after a single dose of the study drug, trial participants underwent neuroimaging to measure hippocampal glutamate levels using 1H-MRS, followed by fMRI during a VPA task. Healthy controls did not receive any intervention but were studied under identical conditions.

Healthy Control (n=)	CHR-Placebo (n=)	CHR-CBD (n=)
19	16	15
No any intervention	Identical placebo capsule	600mg CBD capsule

➢ MRI and MRS acquisition/preprocessing

MRI: 3T MRI; gradient echo sequence axially; 39 × 3mm slices; 3.3mm slice gap; TE=30ms; compressed acquisition with TR=2s & 3s silence). Images were corrected for motion, spatially smoothed (filter kernel=5mm) and analysed with XBAM software (v. 4.1).

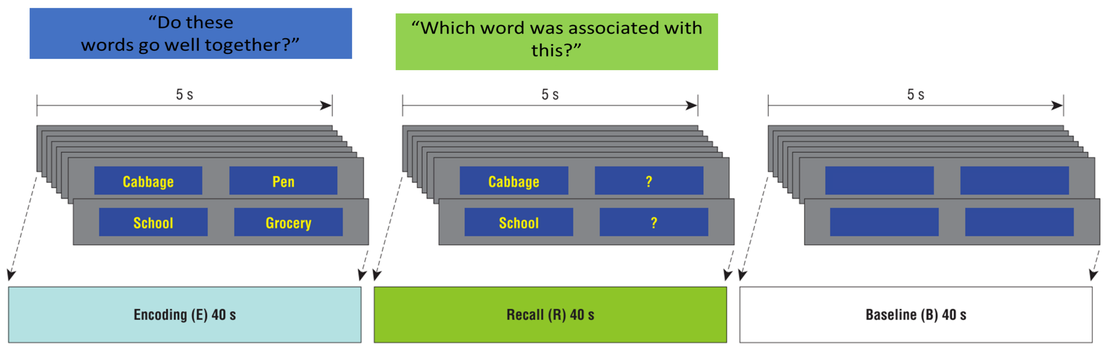
MRS: Proton magnetic resonance spectroscopy (1H-MRS) spectra were acquired in the left hippocampus (PRESS; TR= 3000ms; TE= 30ms; 96 averages at 3 Tesla) in a 6-min scans. We used the standard GE PROBE sequence with CHESS water suppression. Unsuppressed water reference spectra (16 averages) were also acquired for eddy current correction and water scaling. Shimming was optimised, with auto-prescan performed twice before each scan.



(Davies et al. 2023 preprint)

➢ fMRI task- verbal paired associate learning task

This block design task included 3 conditions **(Encoding, Recall, Baseline**), each presented 4 times.



➢ Data analysis

Glutamate x BOLD x Group Interactions

Subject level map
- Model the blood oxygen level-dependent (BOLD) response with experimental design
- Estimate sum of squares (SSQ) ratio statistic at each voxel.

Interact glutamate level
- ROI mask used (hippocampus, parahippocampus, striatum, inferior & medial frontal lobe
- The Pearson's correlation coefficient between glutamate levels and SSQ values at each voxel was calculated

Group comparison
- Non-parametric analysis of variance (ANOVA) was used to determine group difference
- Type I error control used to obtain less than 1 false-positive cluster over the whole map

Glutamate x Performance Interactions

- The dependent variable in the correlation analysis is the SSQ value, which is being correlated with the encoding accuracy rate and recalling accuracy rate. This correlation analysis is performed separately for each group

Conclusion

- There was a positive correlation between hippocampal glutamate and inferior and middle frontal activation in healthy controls, which was reversed in placebo-treated group.
- In CBD-treated CHR patients there was a positive correlation between hippocampal glutamate and inferior and middle frontal activations as well as parahippocampal/ amygdala activation in these regions in placebo-treated CHR patients.
- Overall, these findings may suggest that CBD could partially reverse the altered coupling between hippocampal glutamate and memory-related brain activity in people with clinical high risk of psychosis

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Reference [1]Fusar-poli eat al. (2020) Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiat ; ; [2]Leweke et al. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational Psychiatry;[3] McGuire et al., (2018). Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. American Journal of Psychiatry;[4] Chesney et al.(2020). Adverse effects of cannabidiol: A systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology; [5]Bhattacharyya et al. (2018). Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. JAMA Psychiatry; [6] Davies et al.(2023) Hippocampal Glutamate, Resting Perfusion and the Effects of Cannabidiol in Psychosis Risk. Preprint; [7]O'neil et al. (2021) Cannabidiol modulation of hippocampal glutamate in early psychosis. Journal of Psychopharmacology