Medication status modulates metabotropic glutamate receptor 5 availability in Bipolar Disorder and its associations with attention, anhedonia, and cognition

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BACKGROUND

•Dysregulation of glutamatergic signaling via the **metabotropic glutamate receptor subtype 5 (mGlu5)** has been implicated in the pathophysiology of bipolar disorder (BD).
•Postmortem and preclinical studies suggest that **altered mGlu5 availability** may contribute to mood dysregulation and suicidality.
•**Positron emission tomography (PET)** using the radioligand [^{18}F]FPEB enables *in vivo* quantification of mGlu5 receptor availability.

AIMS:

•To examine mGlu5 receptor availability across frontolimbic regions (vmPFC, dlPFC, OFC, hippocampus, amygdala) among unmedicated BD, medicated BD, and healthy controls (HC).

•Assess the influence of medication status on mGlu5 availability in BD.

METHODS

Participants
• N = 96 adults: 21 unmedicated BD, 27 medicated BD, 48 HC; matched for age and sex.
• Diagnoses confirmed using SCID-5.
• Clinical measures: HAMD-21, MADRS, Attention (BIS subscale), GMLT, SHAPS

PET Imaging & Processing
• [^{18}F]FPEB PET (bolus + infusion; K_{bol} = 190 min; 120 min total) acquired on HRRT scanner; MRI on 3 T Siemens Prisma.
• Venous sampling used for metabolite correction (*validated; TRV ≈ 12%*).
• V_T (estimated using equilibrium analysis with venous input).

Statistical Analysis
• Group effects tested via ANCOVA controlling for cannabis and nicotine.
• Bonferroni-corrected post hoc tests
• Pearson correlations and multiple linear regression examined associations between mGlu5 V_T and clinical measures ($p < 0.05$).

Table 1. Participant Demographic, Clinical, and PET Characteristics.

	HC (n=48)	BD unmedicated (n=21)	BD medicated (n=27)	Statistical test (F or Chi², p)
DEMOGRAPHIC CHARACTERISTICS				
Age, years (mean±SD)	36.9±14.3	39.1±11.8	36.8±13.6	F = 0.21, p = 0.81
Sex, female (n,%)	29 (60.4%)	11 (52.4)	18 (66.7)	χ^2 = 1.01, p = 0.60
Current cannabis users (n,%)	3 (6.3%)	7 (33.3%)	8 (29.6%)	χ^2 = 11.42, **p = 0.02***
Current nicotine users (n,%)	5 (10.4%)	7 (33.3%)	4 (14.8%)	χ^2 = 5.62, p = 0.06
CLINICAL MEASURES				
Mood state at scan (E/D/M), n	—	12/6/3	12/14/1	
HAMD-21(mean±SD)	1.15±2.66	10.27±6.51	9.08±6.93	F = 23.32, **p<0.001****
MADRS (mean±SD)	1.05±3.43	13.43±9.21	11.78±8.36	F = 28.82, **p<0.001****
Attention (BIS subscale) (mean±SD)	13.69±2.92	18.93±3.49	18.12±3.00	F = 18.97, **p<0.001****
GMLT (mean±SD)	45.00±18.88	63.00±30.60	58.68±25.12	F = 3.399, **p<0.04***
SHAPS (mean±SD)	0.49±0.98	3.00±3.65	1.59±2.31	F = 7.192, **p<0.001****
PET PARAMETERS				
Injected tracer dose (MBq) (mean ± SD)	4.35±0.70	4.25±1.00	4.32±0.87	F = 0.11, p = 0.95
Injected tracer mass (μg) (mean±SD)	0.37±0.23	0.28±0.17	0.39±0.21	F = 1.67, p = 0.20
Plasma Free Fraction (f_p) (mean±SD)	0.04±0.01	0.046±0.00	0.041±0.01	F = 0.80, p = 0.47

Abbreviations: **E** = euthymic, **D** = depressed, **M** = manic/mixed. Mood state was determined at the time of PET scanning based on MADRS and YMRS scores.

RESULTS

Unmedicated BD showed significantly lower mGlu5 V_T across frontolimbic regions

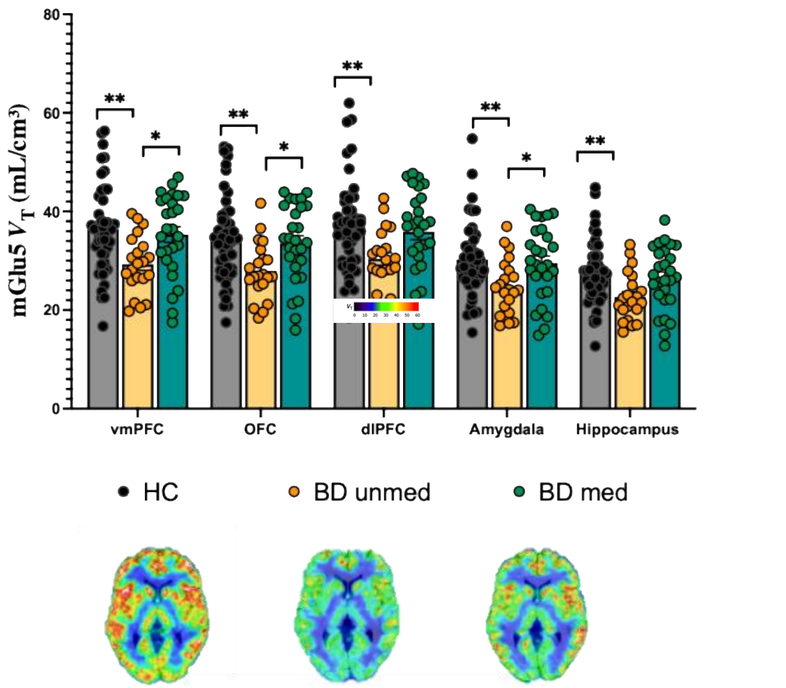

Figure 1. Significantly lower mGlu5 availability in the unmedicated BD as compared to other groups. Estimated marginal means of [^{18}F]FPEB V_T across frontolimbic regions (vmPFC, OFC, dlPFC, amygdala, hippocampus) for HC (gray), unmedicated BD (orange), and medicated BD (teal). Dots represent individuals. ANCOVA controlling for cannabis and nicotine use (*p<0.05, **p<0.01).

Greater Attentional Difficulties are associated with lower mGlu5 availability in unmedicated bipolar disorder

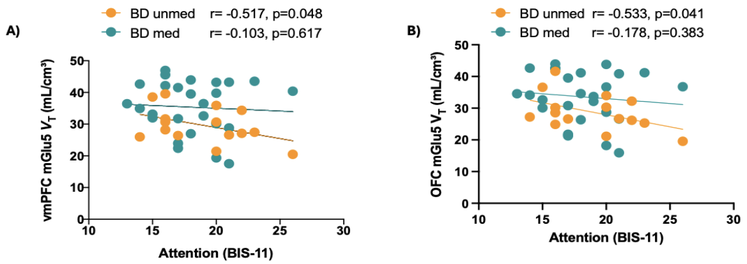

Figure 3. Significant negative correlations were observed in unmedicated participants (orange) but not in medicated participants (teal). Panels show vmPFC (A), OFC (B)

Lower OFC mGlu5 V_T associated with worse executive function performance

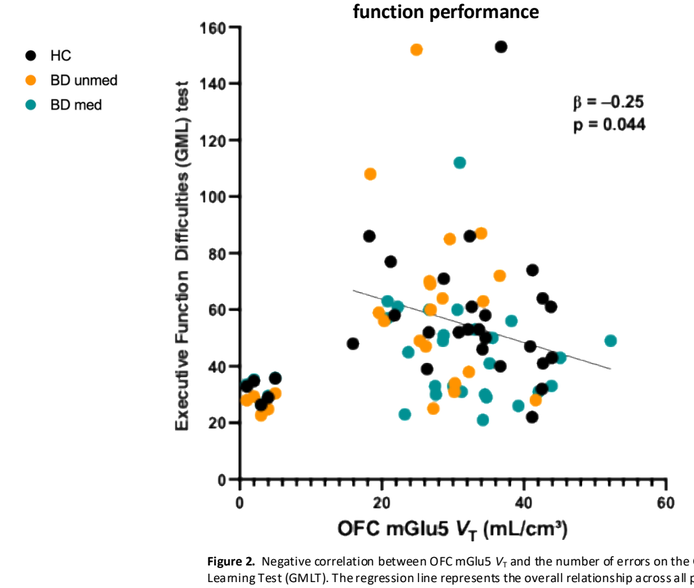

Figure 2. Negative correlation between OFC mGlu5 V_T and the number of errors on the Groton Maze Learning Test (GMLT). The regression line represents the overall relationship across all participants, adjusting for nicotine and cannabis use.

CONCLUSIONS

• **Unmedicated BD** participants show **lower mGlu5 availability** across frontolimbic regions as compared to other groups.

• Data suggest **medication may normalize mGlu5** availability.

• **Lower OFC mGlu5 V_T is linked to worse executive function**, while **greater attentional difficulties are associated with lower mGlu5 availability in unmedicated BD**.

• **mGlu5** may represent a **biomarker and treatment target** for mood stabilization in BD.

References

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