Detecting synaptogenesis induced by ketamine and motor learning using the PET tracer [^{11}C] UCB-J in an integrated PET-fMRI paradigm

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Table of contents

Mental Health

- 1 in every 8 people in the world live with a mental disorder
- Mental disorders involve significant disturbances in thinking, emotional regulation, or behaviour
- Currently, approximately a third of patients are treatment resistant.

Novel Therapeutics

Ketamine Psychiatric History

1962
First synthesised

1970's
Iran, Argentina, Mexico Psycho-therapeutic

1990's
Pre-clinical work

2000
First open label - TRD

2000-23
Clinical studies

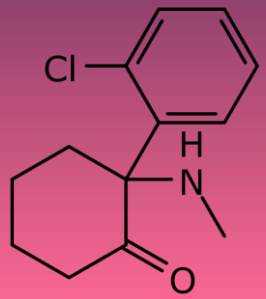
2023
Ketamine treatment models

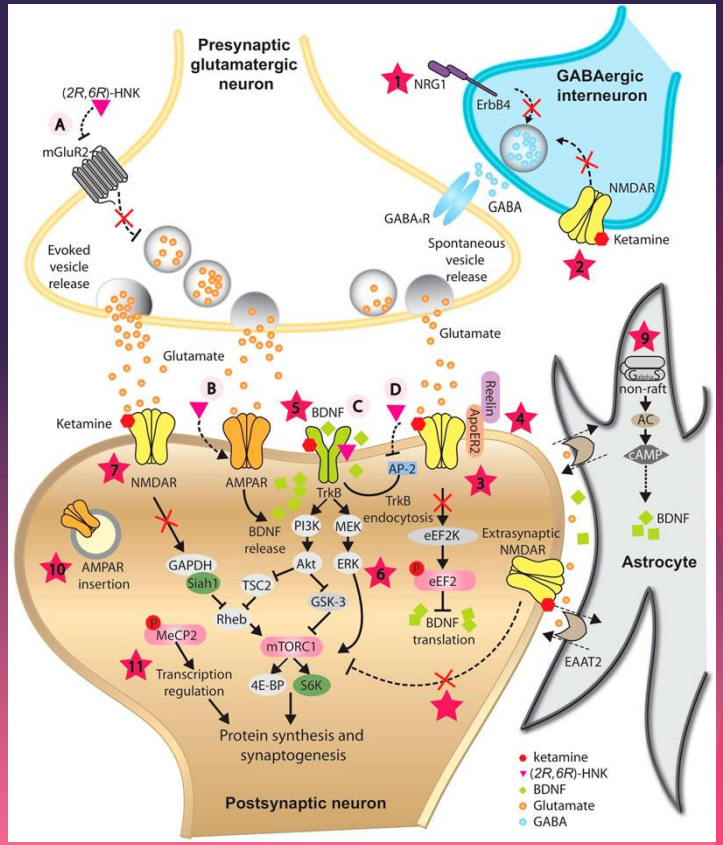
Effects of ketamine peak 1-7 days

Efficacy for depression, PTSD, anxiety, Substance-use disorder

What is Ketamine

- NMDA receptor antagonist
- Multiple downstream effects
- Dose response curve demonstrates sub anesthetic at low to medium doses and anesthetic at high doses
- First ‘hallucinogen’ to be approved by FDA – intranasal
- Main effects seem to be on neuroplasticity





Xu et al., 2022

Neuroplasticity

- The ability for nervous tissue to modify and change is termed neuroplasticity
- Time-windows of neuroplasticity or ‘critical periods’ close before adulthood
- Dysregulation of signalling pathways critical to synaptogenesis thought to be implicated mental health disorders, such as PTSD and MDD

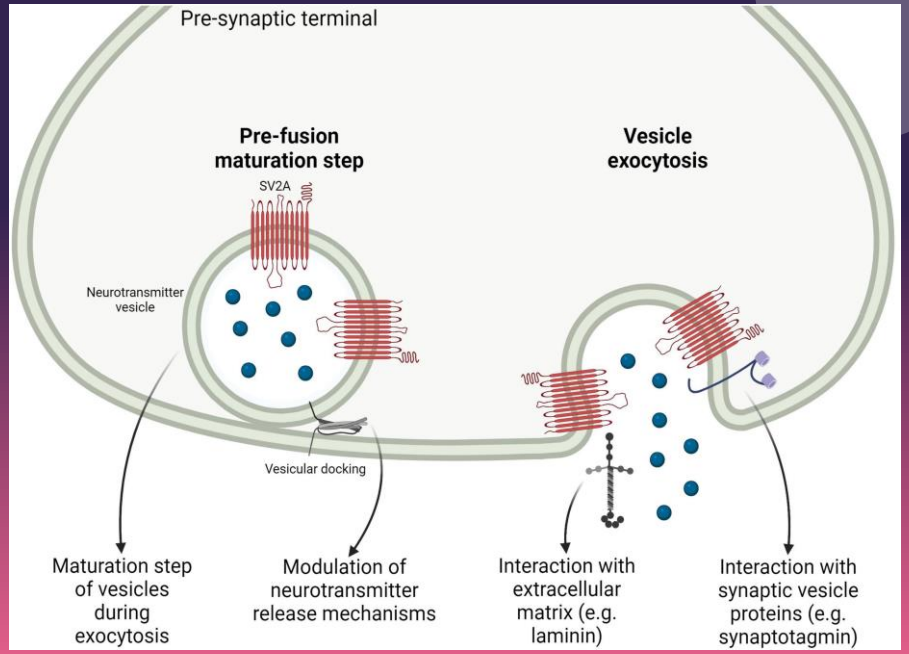
(Kays, Hurley & Taber., 2012; Williams & Umemori., 2014)

Neuroplasticity

- In vitro and in vivo, enhancement of synaptogenesis (Li et al., 2010; Ly et al., 2019)
- In humans, ketamine enhances an indirect EEG measure of LTP, serving as a marker of neural plasticity (Sumner et al., 2019).
- This research suggests that ketamine enhances synaptogenesis

[11C] UCB-J tracer and SV2A

- (11)C-UCB-J ((R)-1-((3-((11)C-methyl-(11)C)pyridin-4-yl)methyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one)
- The UCB-J tracer binds to SV2A – presynaptic vesicle
- SV2A is essential to the maintenance of normal neurotransmission, and altered SV2A expression can affect the balance between excitation and inhibition.
- Originally used in Alzheimers – demonstrating efficacy for detecting lower SV2A in cortical and Hippocampal regions (for review, Carson et al., 2022).
- Used in Pigs following psilocybin administration and we see an increase in synaptic density (Hipp and PFC) as measured using VT of SV2A (Raval et al., 2021).



Taken from Rossi et al 2022

The wider picture

- Ketamine appears to be useful for multiple psychiatric disorders
- Dysregulation of signaling pathways relevant to synaptogenesis in psychiatric disorders
- In vitro and in vivo we have increased synaptogenesis after ketamine administration
- Classic psychedelics enhancing synaptogenesis in the pig brain in key areas such as Hipp and PFC
- Let’s have a look at this in the human brain!

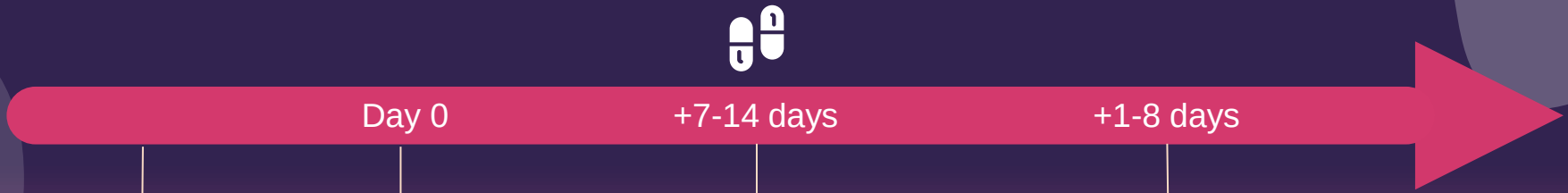
Hypotheses

1. Increased [11C]UCB-J Vt in pre-frontal cortex, hippocampus, anterior cingulate cortices and amygdala from baseline (scan 1) to 1-7 days post-ketamine infusion (scan 2) in healthy participants

2. Increases in VT are associated with improvements in psychometric measures of mood

Methods

Study design



Recruitment and screening

Baseline PET scan

Ketamine administration & Acute Questionnaires

Pet scan 2

Blood derived measures of BDNF/immune markers and fMRI/EEG were also part of the study design

Volume distribution, Binding Potential and Free fraction

Volume distribution (VT): in PET imaging is a pharmacokinetic parameter that describes the distribution of a radioligand between the plasma and the tissues. It's a measure of how extensively a drug or radioligand is distributed throughout the body tissues relative to the plasma.

Binding Potential (BP): It is a ratio that compares the amount of radioligand bound to the target receptors to the amount of radioligand that is not bound in the brain. The binding potential is a unitless measure that reflects the density of available receptors for the radioligand. It can be thought of as an indicator of receptor availability in the tissue of interest.

Free Fraction (FP): Free fraction is the fraction of the total radioligand in the blood that is unbound to blood components, such as plasma proteins, and is available for interaction with target sites.

Demographics and dose

	All participants (N = 11)
Age	**32 ± 10**
Psychedelic naive	**0**
Last psychedelic use (years)	**7 ± 10**
Ketamine naive	**7**
Last ketamine use (years)	**8 ± 5**
Ketamine administered	**78 ± 13 mg**
CADSS	**16 ± 5**
MOAA/S	**19 ± 2**

Modified Observer's Assessment of Alertness and sedation (MOAA/S)
Clinician Administered Dissociative States Scale (CADSS)

CADDS

- Do things seem to be moving in slow motion?
- Do things seem to be unreal to you, as if you are in a dream?
- Do you feel disconnected from your own body
- Does your sense of your own body feel changed: for instance, does your own body feel
- Have you spaced out, or in some other way lost track of what was going on during this experience?
- Do you have gaps in your memory?

0 - Not at all

1 - Mild, things seem slightly slowed donw, but not very noticeable.

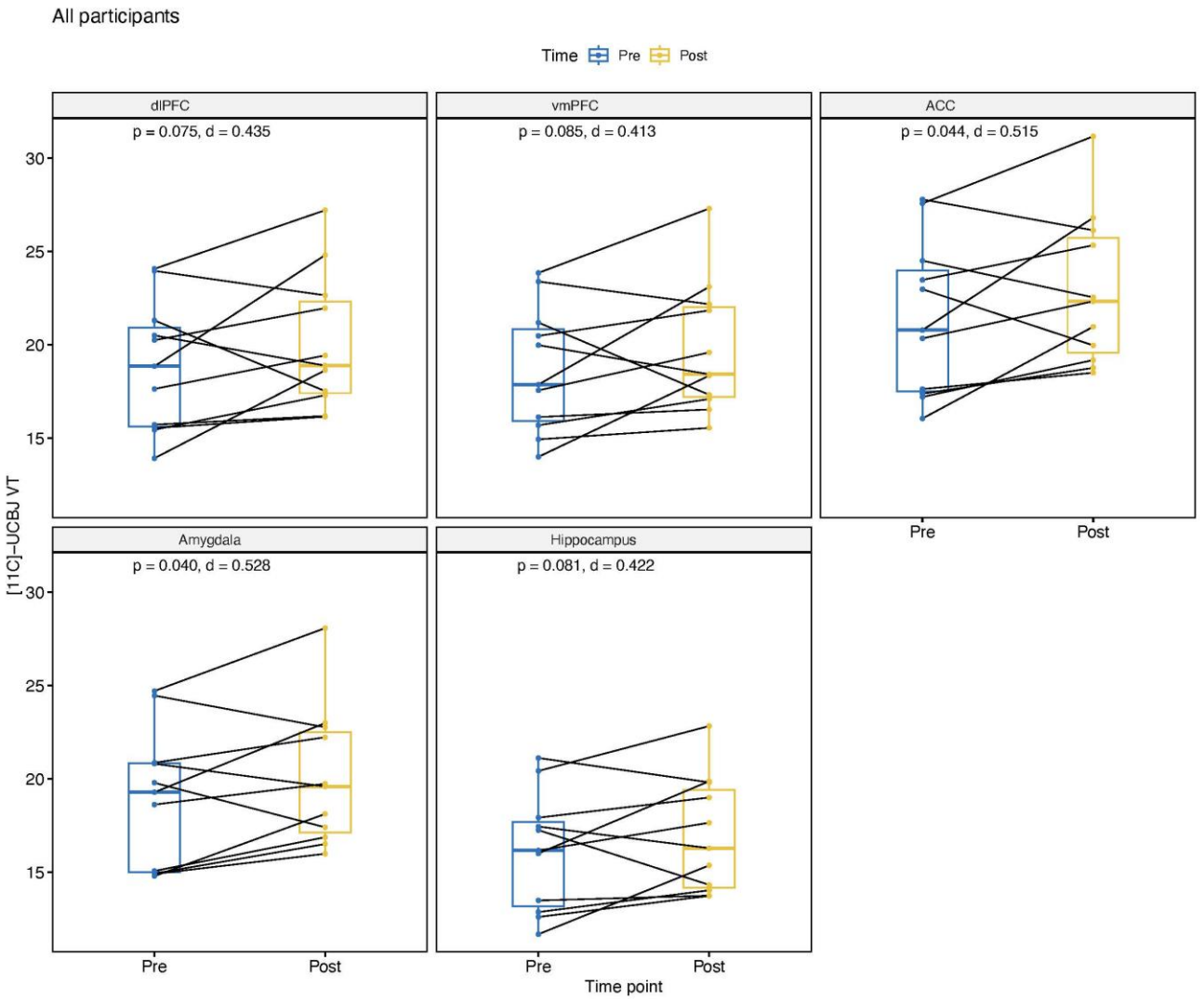
2 - Moderate, things are moving about twice as slow as normally.

3 - Severe, things are moving so slowly that they are barely moving.

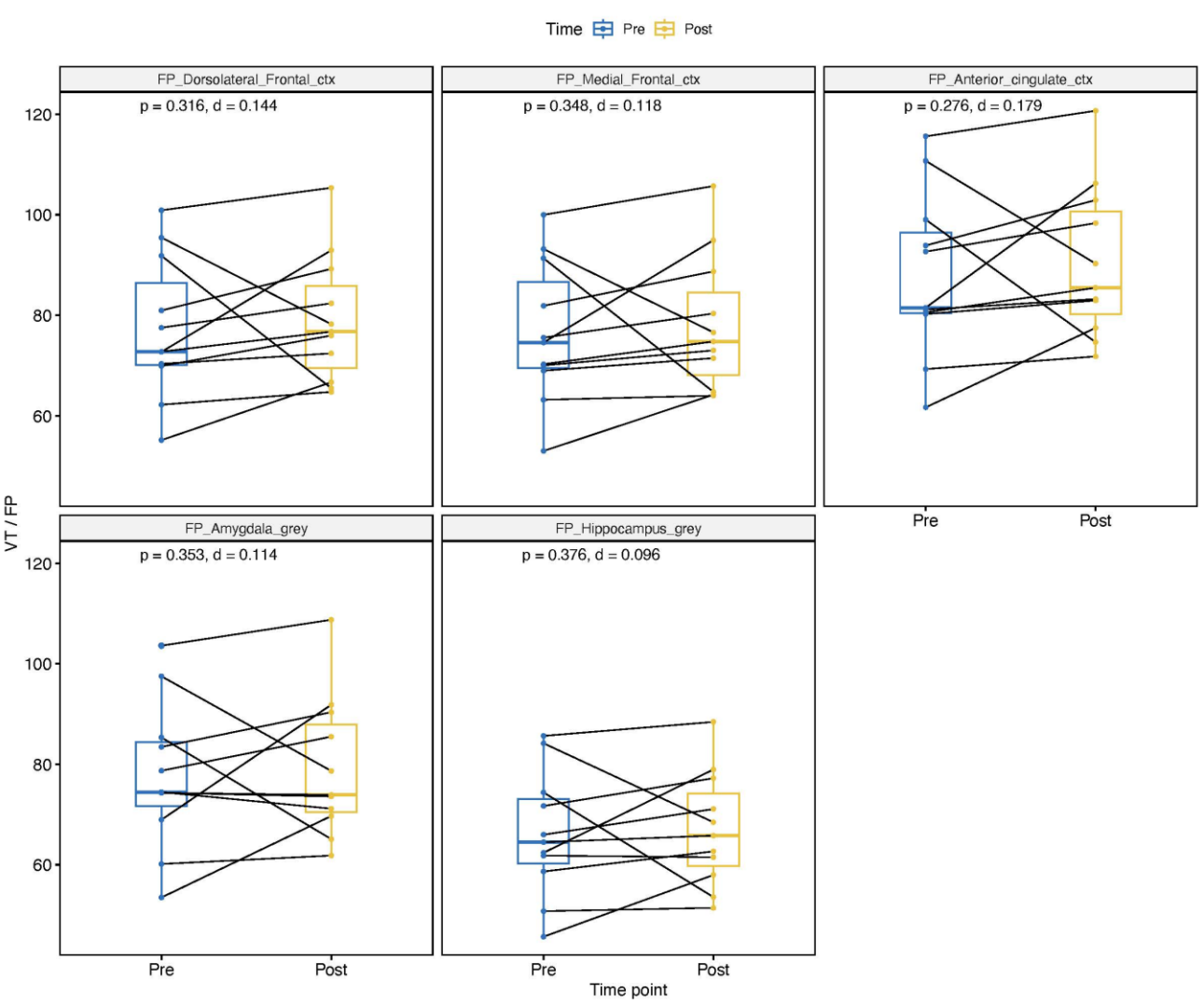
4 - Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still

Results

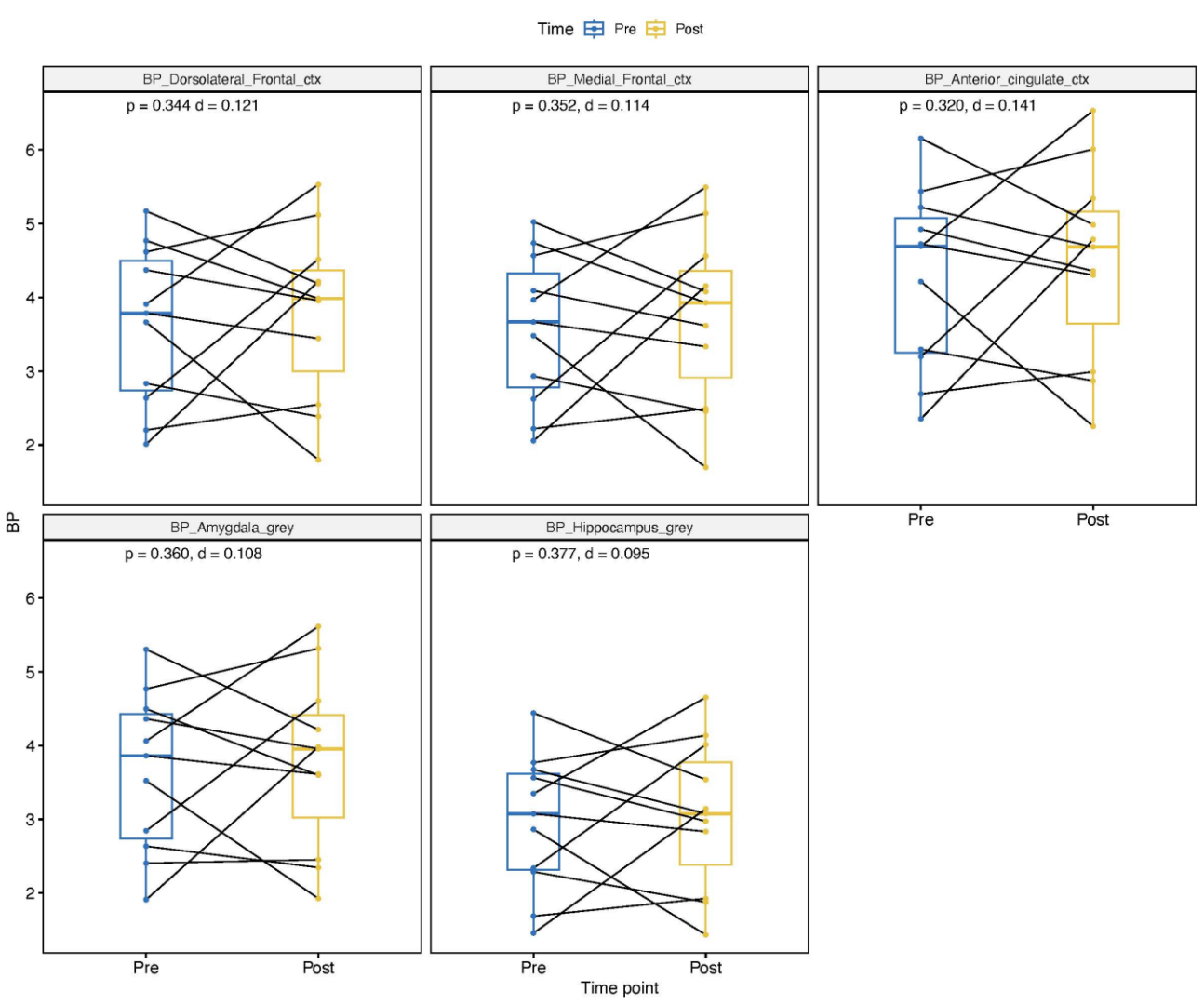
Results – volume distribution change

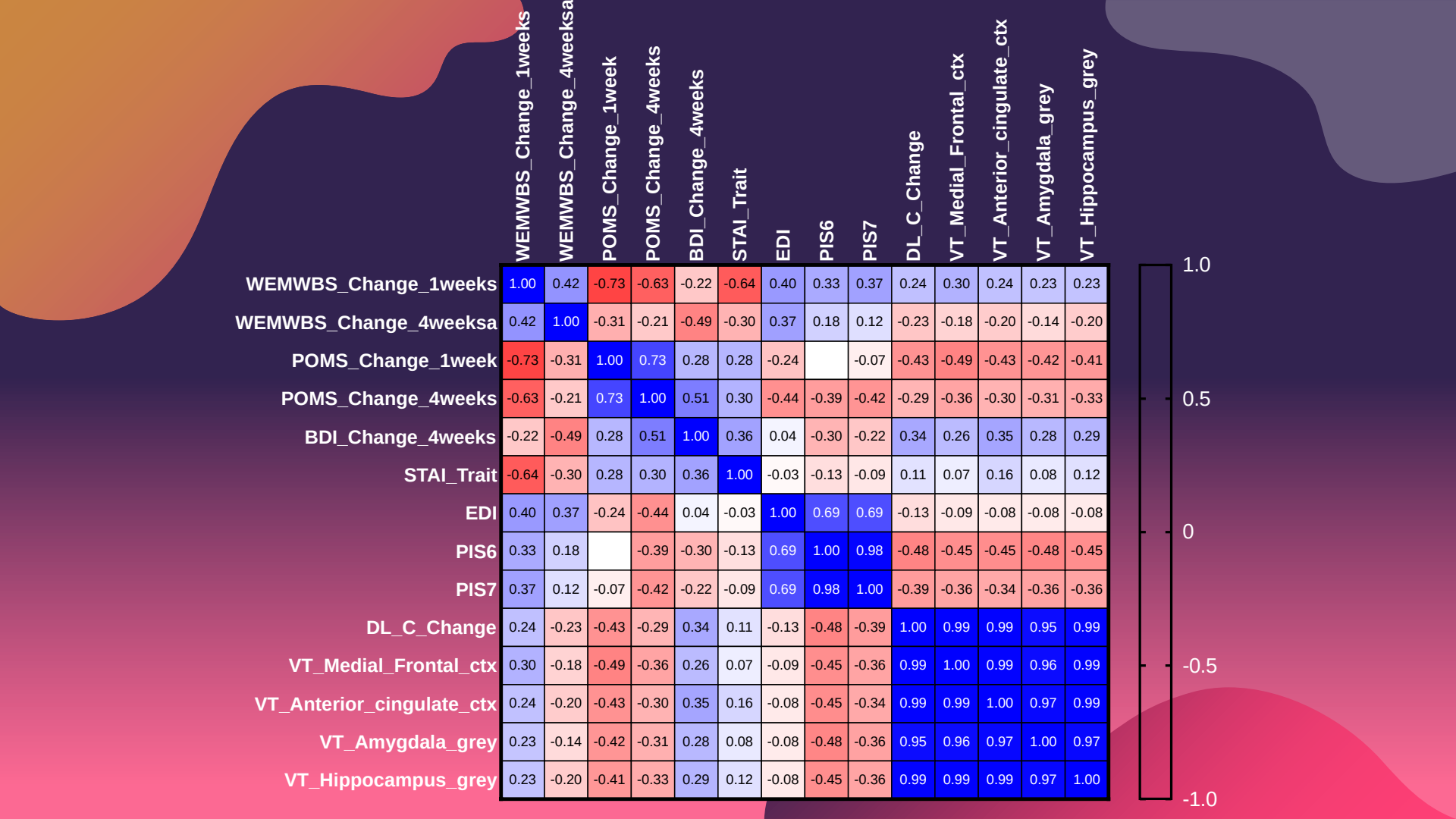


Results – Free fraction corrected



Results – Binding potential corrected




WEMWBS_Change_1weeks
WEMWBS_Change_4weeksa
POMS_Change_1week
POMS_Change_4weeks
BDI_Change_4weeks
STAI_Trait
EDI
PIS6
PIS7
DL_C_Change
VT_Medial_Frontal_ctx
VT_Anterior_cingulate_ctx
VT_Amygdala_grey
VT_Hippocampus_grey
WEMWBS_Change_1weeks 1.00 0.42 -0.73 -0.63 -0.22 -0.64 0.40 0.33 0.37 0.24 0.30 0.24 0.23 0.23
WEMWBS_Change_4weeksa 0.42 1.00 -0.31 -0.21 -0.49 -0.30 0.37 0.18 0.12 -0.23 -0.18 -0.20 -0.14 -0.20
POMS_Change_1week -0.73 -0.31 1.00 0.73 0.28 0.28 -0.24 -0.07 -0.43 -0.49 -0.43 -0.42 -0.41
POMS_Change_4weeks -0.63 -0.21 0.73 1.00 0.51 0.30 -0.44 -0.39 -0.42 -0.29 -0.36 -0.30 -0.31 -0.33
BDI_Change_4weeks -0.22 -0.49 0.28 0.51 1.00 0.36 0.04 -0.30 -0.22 0.34 0.26 0.35 0.28 0.29
STAI_Trait -0.64 -0.30 0.28 0.30 0.36 1.00 -0.03 -0.13 -0.09 0.11 0.07 0.16 0.08 0.12
EDI 0.40 0.37 -0.24 -0.44 0.04 -0.03 1.00 0.69 0.69 -0.13 -0.09 -0.08 -0.08 -0.08
PIS6 0.33 0.18 -0.39 -0.30 -0.13 0.69 1.00 0.98 -0.48 -0.45 -0.45 -0.48 -0.45
PIS7 0.37 0.12 -0.07 -0.42 -0.22 -0.09 0.69 0.98 1.00 -0.39 -0.36 -0.34 -0.36 -0.36
DL_C_Change 0.24 -0.23 -0.43 -0.29 0.34 0.11 -0.13 -0.48 -0.39 1.00 0.99 0.99 0.95 0.99
VT_Medial_Frontal_ctx 0.30 -0.18 -0.49 -0.36 0.26 0.07 -0.09 -0.45 -0.36 0.99 1.00 0.99 0.96 0.99
VT_Anterior_cingulate_ctx 0.24 -0.20 -0.43 -0.30 0.35 0.16 -0.08 -0.45 -0.34 0.99 0.99 1.00 0.97 0.99
VT_Amygdala_grey 0.23 -0.14 -0.42 -0.31 0.28 0.08 -0.08 -0.48 -0.36 0.95 0.96 0.97 1.00 0.97
VT_Hippocampus_grey 0.23 -0.20 -0.41 -0.33 0.29 0.12 -0.08 -0.45 -0.36 0.99 0.99 0.99 0.97 1.00
1.0
0.5
0
-0.5
-1.0

Discussion

Discussion

- Increased volume distribution in ACC and amygdala following ketamine administration
  - Following Binding potential/free fraction correction this effect does not hold.
  - Low number of participants
  - Not all participants measured at same timepoint
- Volume distribution change does not show associations with psychometric measures
- A [^{11}C]UCB-J PET study in rhesus macaques, HC and MDD/PTSD ketamine did not affect SV2A density measured synaptogenesis, at **24 hours,** 1 week or 4–6 weeks post-administration. (Holmes, 2022).
- In humans - increased SV2A density in those with low levels of baseline SV2A in ROIs (ACC and dlPFC) 24 hours after administration (Holmes, 2022).

Discussion

- In a healthy population given Serotonin Selective Reuptake Inhibitors (SSRIs), we see no change in SV2A on a group level for Hippocampus or Neocortex (Knudsen et al., 2023).
    - However, there was a time dependent effect of escitalopram on synaptic density in the neocortex but not Hippocampus

- Future directions
    - We need further information about the latent synaptogenic effects of psychiatric medication (including psychedelics and ketamine).
    - Multiple doses may be more effective
    - We need more direct/sensitive measurement of synaptogenesis – ubiquitous spread of SV2A
    - Individual variability - we need more studies in people who are demonstrating low baseline SV2A

Our team

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Thank you

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