XXXI CONGRESSO NAZIONALE SIPF

Past, Present and Future Brains

Siena 9-11 novembre 2023

Museo Santa Maria della Scala

BIOMARKERS OF MOOD DISORDERS AND NOVEL THERAPEUTICS

Chairs: Alessandra Cinti (Siena) and Claudio Agnorelli (Siena)

Brain Serotonin Release Is Reduced in Patients With Depression: A [11C]Cimbi-36 Positron Emission Tomography Study With a d-Amphetamine Challenge
Claudio Agnorelli (Siena)

Detecting synaptogenesis induced by Ketamine and motor learning using the PET tracer [11C]UCB-J in an integrated PET-fMRI paradigm
Joseph Peill (Regno Unito)

EEG correlates of ketamine-induced dissociative state
Alessandra Cinti (Siena)

DISCUSSIONE

XXXI Congresso Nazionale SIPF, Siena 9-11 novembre 2023

Brain Serotonin Release Is Reduced in Patients With Depression: A [11C]Cimbi-36 Positron Emission Tomography Study with a d-Amphetamine Challenge

Speaker: Claudio Agnorelli, PhD student, University of Siena

David Erritzoe[1], Beata R. Godlewska[2], Gaia Rizzo[3], Graham E. Searle[3], Claudio Agnorelli[1,4], Yvonne Lewis[3], Abhishekh H. Ashok[5,6], Alessandro Colasanti[7], Iro Boura[5], Chloe Farrell[5], Hollie Parfit[1], Oliver Howes[5], Jan Passchier[3], Roger N. Gunn[3], David J. Nutt[1], Philip J Cowen[2], Gitte Knudsen[8], Eugenii A. Rabiner[3, 5]

[1] Imperial College, London, UK, [2] University of Oxford, Oxford, UK, [3] Invicro, London, UK, [4] University of Siena, Italy
[5] King's College, London, UK, [6] University of Cambridge & Addenbrooke's Hospital, [7] University of Sussex, UK,
[8] Neurobiology Research Unit, University Hospital Rigshospitalet and Dept. Clinical Medicine, University of Copenhagen, Denmark

THE CENTRE FOR PSYCHEDELIC RESEARCH

Invicro

Imperial College London

UNIVERSITÀ DI SIENA 1240

Table of Contents

Depression

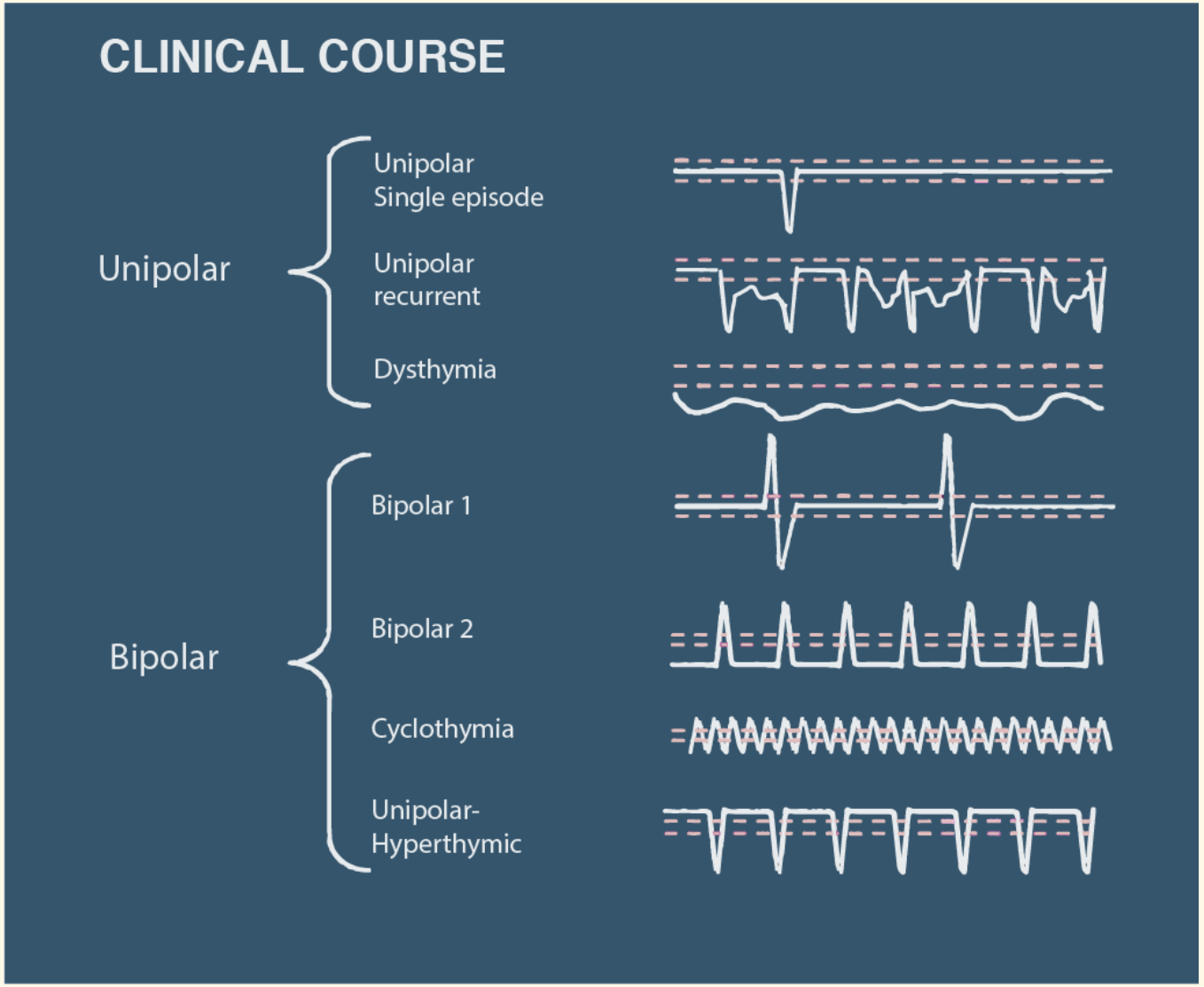
Background

Approximately 280 million people in the world have depression. More than 700 000 people die due to suicide every year.

Mood Disorders are severe psychatirc ilness which affects mood, thoughts, behavior, and ability to function.

Current antidepressant are effective in about 40% of patients. More than 75% of people in low- and middle-income countries receive no treatment.

The sixth leading cause of disability in the world.



Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). https://vizhub.healthdata.org/gbd-results/ (Accessed 4 March 2023).

The serotonin (5-HT) hypothesis of depression

Background

The “monoamine deficiency hypothesis” of depression postulates that depressive symptoms arise in part from insufficient levels of monoamine neurotransmitters such as serotonin (or 5 hydroxytryptamine, 5-HT).

The 5-HT receptors

5-HT_1 5-HT_2 5-HT_3 5-HT_4

5-HT_5 5-HT_6 5-HT_7

↓

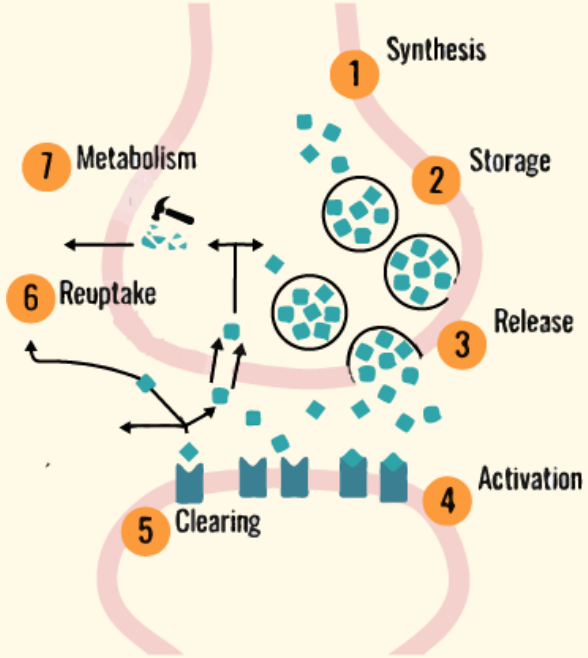
e.g., 5-HT_{2A}

↑

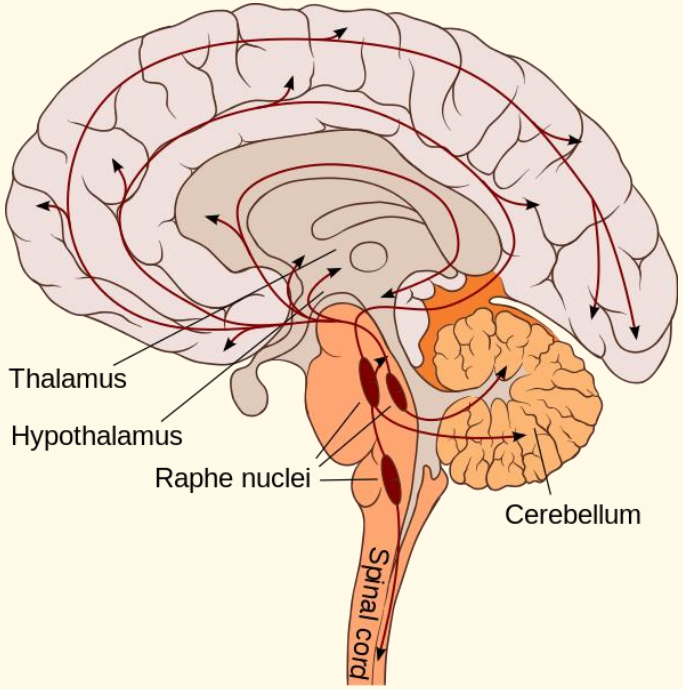
A B C

D E F

The 5-HT synapse



The 5-HT system



Cowen, Philip J., and Michael Browning. "What has serotonin to do with depression?." *World Psychiatry* 14.2 (2015): 158.

Testing the 5-HT hypothesis of depression in patients

Study Aim

Molecular Psychiatry www.nature.com/mp

SYSTEMATIC REVIEW OPEN Check for updates

The serotonin theory of depression: a systematic umbrella review of the evidence

Joanna Moncrieff[1,2]✉, Ruth E. Cooper[3], Tom Stockmann[4], Simone Amendola[5], Michael P. Hengartner[6] and Mark A. Horowitz[1,2]

© The Author(s) 2022

"The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations"

Molecular Psychiatry www.nature.com/mp

COMMENT OPEN Check for updates

A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression

Sameer Jauhar[1]✉, Danilo Arnone[2], David S. Baldwin[3], Michael Bloomfield[4], Michael Browning[5], Anthony J. Cleare[1], Phillip Corlett[6], J. F. William Deakin[7], David Erritzoe[8], Cynthia Fu[9], Paolo Fusar-Poli[10], Guy M. Goodwin[5], Joseph Hayes[4], Robert Howard[4], Oliver D. Howes[10,11,12], Mario F. Juruena[1], Raymond W. Lam[13], Stephen M. Lawrie[14], Hamish McAllister-Williams[15,16], Steven Marwaha[17], David Matuskey[18], Robert A. McCutcheon[5], David J. Nutt[8], Carmine Pariante[1], Toby Pillinger[10], Rajiv Radhakrishnan[19], James Rucker[1], Sudhakar Selvaraj[20,21], Paul Stokes[1], Rachel Upthegrove[17], Nefize Yalin[1], Lakshmi Yatham[13], Allan H. Young[1], Roland Zahn[1] and Philip J. Cowen[5]

© The Author(s) 2023

- **Some evidence of impaired 5-HT system in depression.**
- **All available evidence is indirect.**
- **No in-vivo human studies measured 5-HT in patients.**

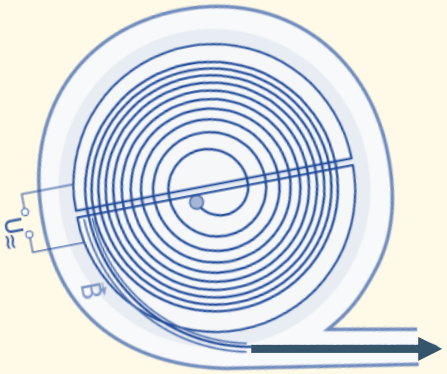
Objective

To compare the release of 5-HT in the living human brain between patients with depression and healthy controls

Positron Emission Tomography (PET)

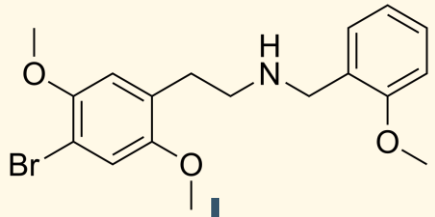
Materials and Methods

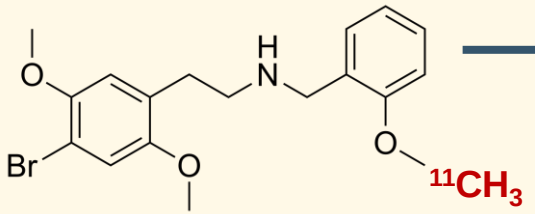
Cyclotron



$^{14}N(p,\alpha)^{11}C$

Radiochemistry





PET scan

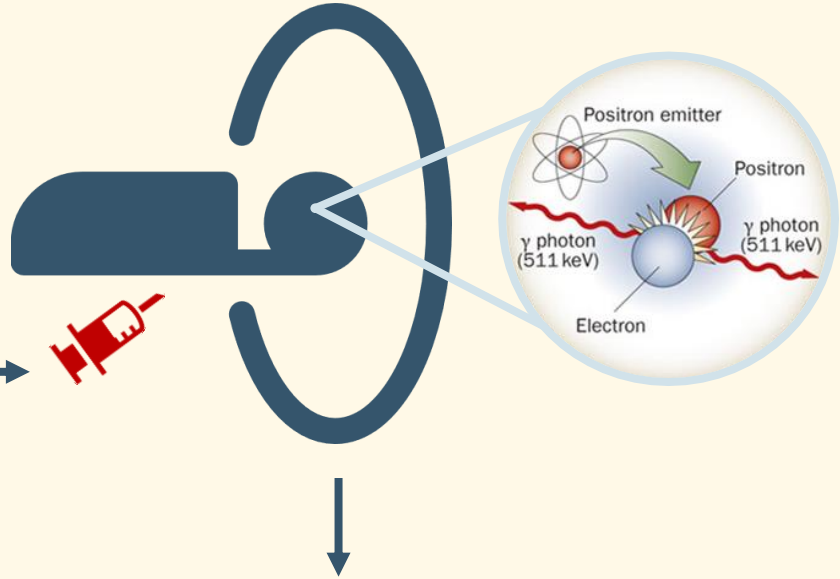
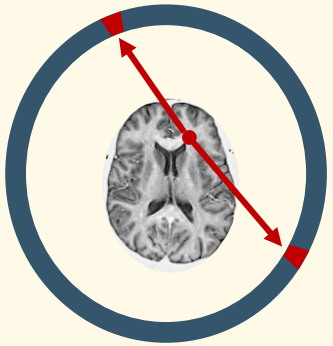
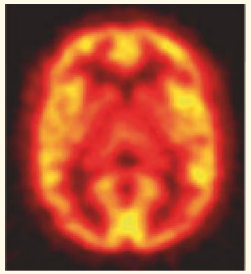


Image reconstruction



Kinetic modeling

PET image



Positron Emission Tomography (PET)

Materials and Methods

5-HT targets challenged in human PET studies:

Targets

SERT
- DASB

5-HT_{1A}
- WAY-analogues
- CUMI-101

5-HT_{1B}
- AZ10419369

5-HT_{2A}
- MDL
- Altanserin
- Setoperone

5-HT_{4}
- SB207145

All antagonists

Challenges

- SSRIs
- Ketamine
- Clomipramine
- d-Fenfluramine
- Tryptophan depletion

Studies with expected direction

1 of 6	5-HT_{1A}
0 of 1	5-HT_{1B}
0 of 6	5-HT_{2A}
1 of 2	5-HT_{4}
0 of 2	SERT

.

Active vs Inacitve receptor states

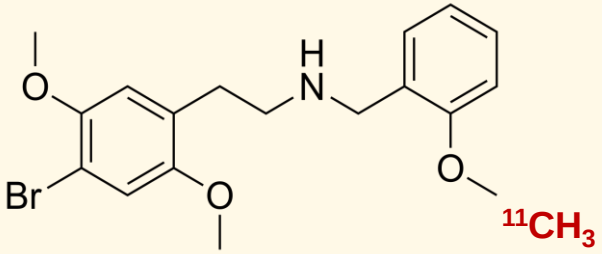
In dopamine research it was found that the D2/D3 agonist [11C]PHNO is 1.5 times more sensitive to acute fluctuations in synaptic dopamine induced by d-amphetamine challenge than the D2/D3 antagonist [11C]raclopride.

Shotbolt, Paul, et al. "Within-subject comparison of [11C]-(+)-PHNO and [11C] raclopride sensitivity to acute amphetamine challenge in healthy humans." Journal of Cerebral Blood Flow & Metabolism 32.1 (2012): 127-136.

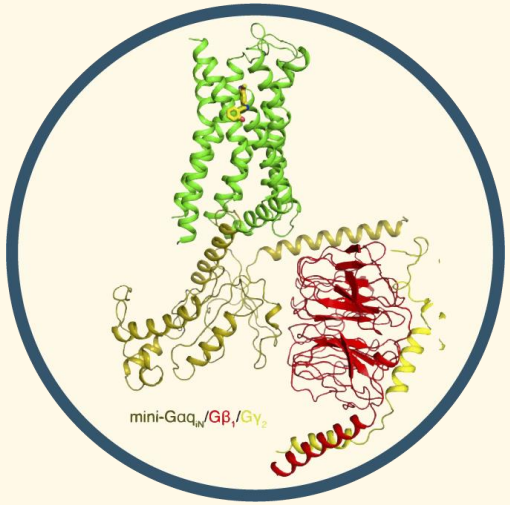
The radioligand [11C]Cimbi-36

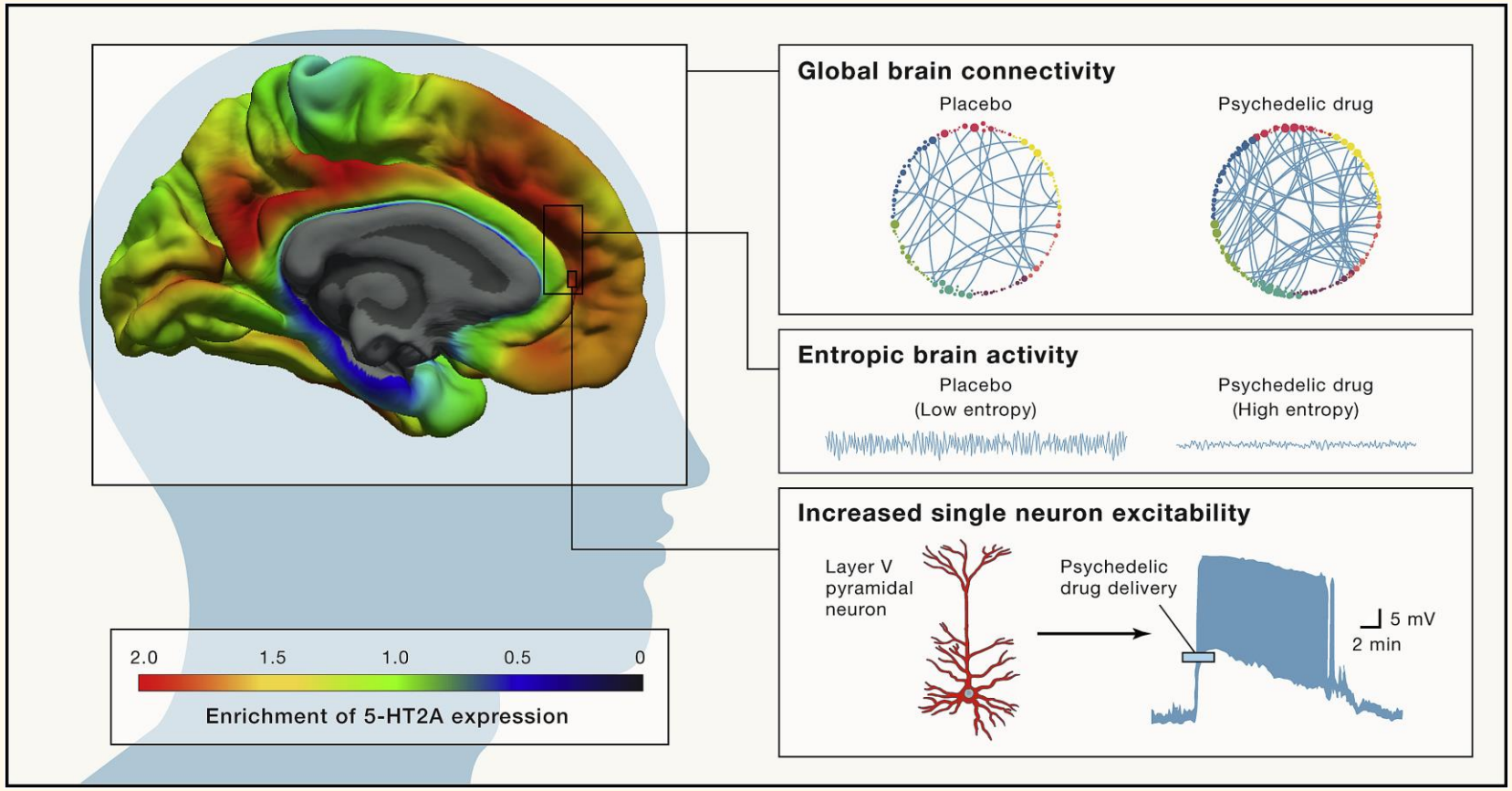
Materials and Methods

[11C]Cimbi-36 (25B-NBOMe)



5-HT type 2A receptor (5-HT2AR)



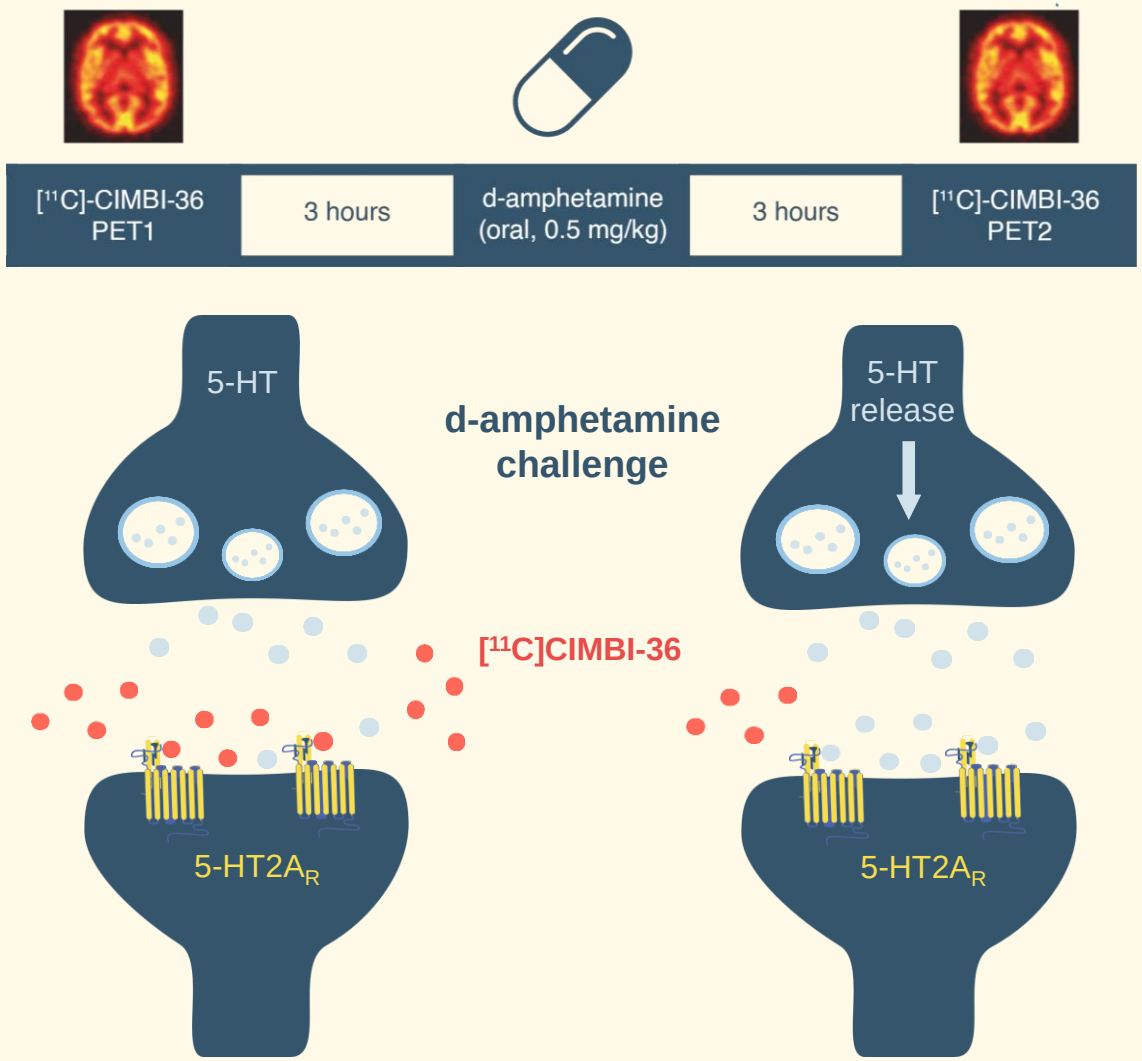


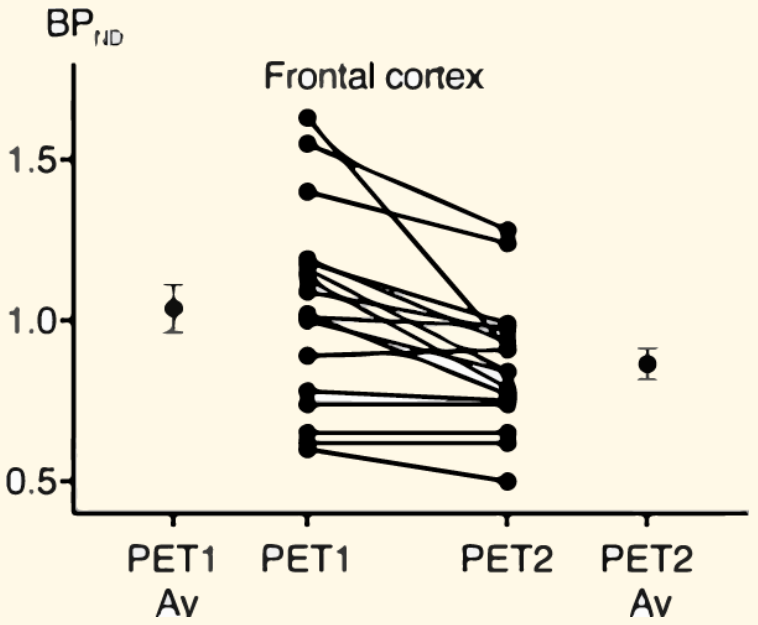
- 5-HT2AR highly expressed in cortical regions
- Agonism at the 5-HT2AR induces alteration of consciousness
- Main mechanism of action of classic psychedelics

Nutt, David, David Erritzoe, and Robin Carhart-Harris. "Psychedelic psychiatry's brave new world." *Cell* 181.1 (2020): 24-28.

Using d-amphetamine challenge to measure 5-HT release

Materials and Methods



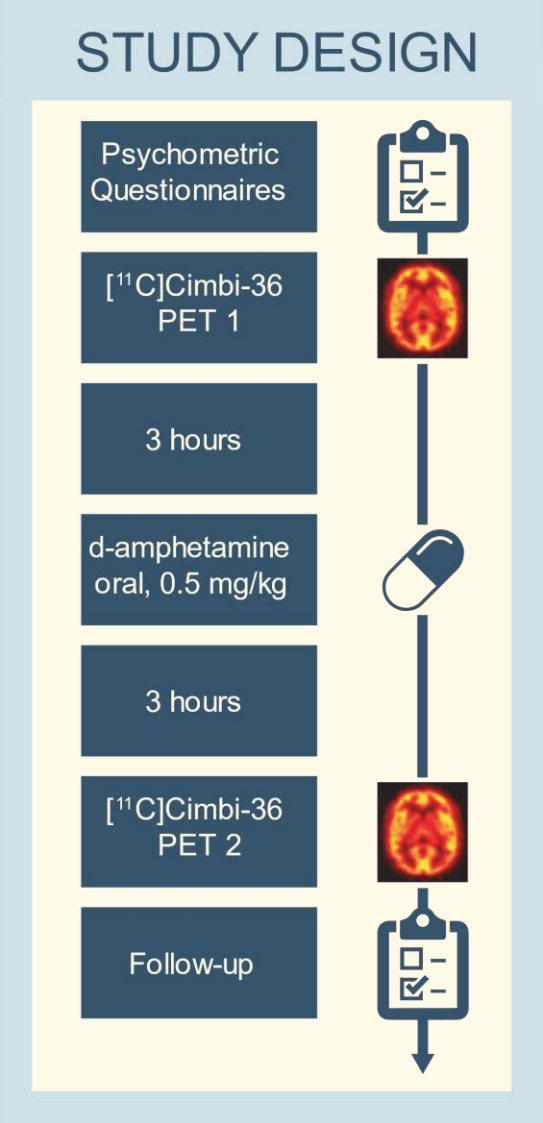


"Data from 17 healthy males suggest that [11C]Cimbi-36 is sensitive to synaptic 5-HT release in the human brain, and combined with a d-amphetamine challenge can enable the evaluation of the human brain 5-HT system in neuropsychiatric disorders"

Erritzoe, David, et al. "Serotonin release measured in the human brain: a PET study with [11C] CIMBI-36 and d-amphetamine challenge." *Neuropsychopharmacology* 45.5 (2020): 804-810.

Brain serotonin release is reduced in patients with depression

Materials and Methods



- 12 medication-free patients with Major Depressive Disorder (MDD) [9 males, mean age 40 ± 11].
- 5 medication-free patients with comorbid Major Depressive Disorder and Parkinson's Disease (MDPD) [All males, mean age 55 ± 9].
- 20 Healthy Controls (HC) [17 males, mean age 32 ± 9].
- [^{11}C]CIMBI-36 PET pre and 3 hours post oral d-amphetamine [0.5 mg/kg, p.o.].
- Scale: Beck Depression Inventory (BDI).
- Dynamic PET data with metabolite, arterial plasma input function, acquired over 90 minutes, corrected for attenuation, scatter and motion.

$$BP_{ND} = \frac{V_T^{FCx}}{V_T^{Cb}} - 1$$

$$\Delta BP_{ND} = 100 \times (1 - \frac{BP_{ND}^{post-dose}}{BP_{ND}^{baseline}})$$

Outlier exclusion

1 participant in the MDD group was identified as an outlier for ΔBP_{ND} using the Tukey's rule and was not included in all the parametric statistics involving ΔBP_{ND}

Erritzoe, David, et al. "BRAIN SEROTONIN RELEASE IS REDUCED IN PATIENTS WITH DEPRESSION: A [11C] Cimbi-36 PET STUDY WITH A D-AMPHETAMINE CHALLENGE." Biological Psychiatry (2022).

Brain serotonin release is reduced in patients with depression

Results

Reduced [^{11}C]CIMBI-36 displacement in patients with major depressive episode (MDE)

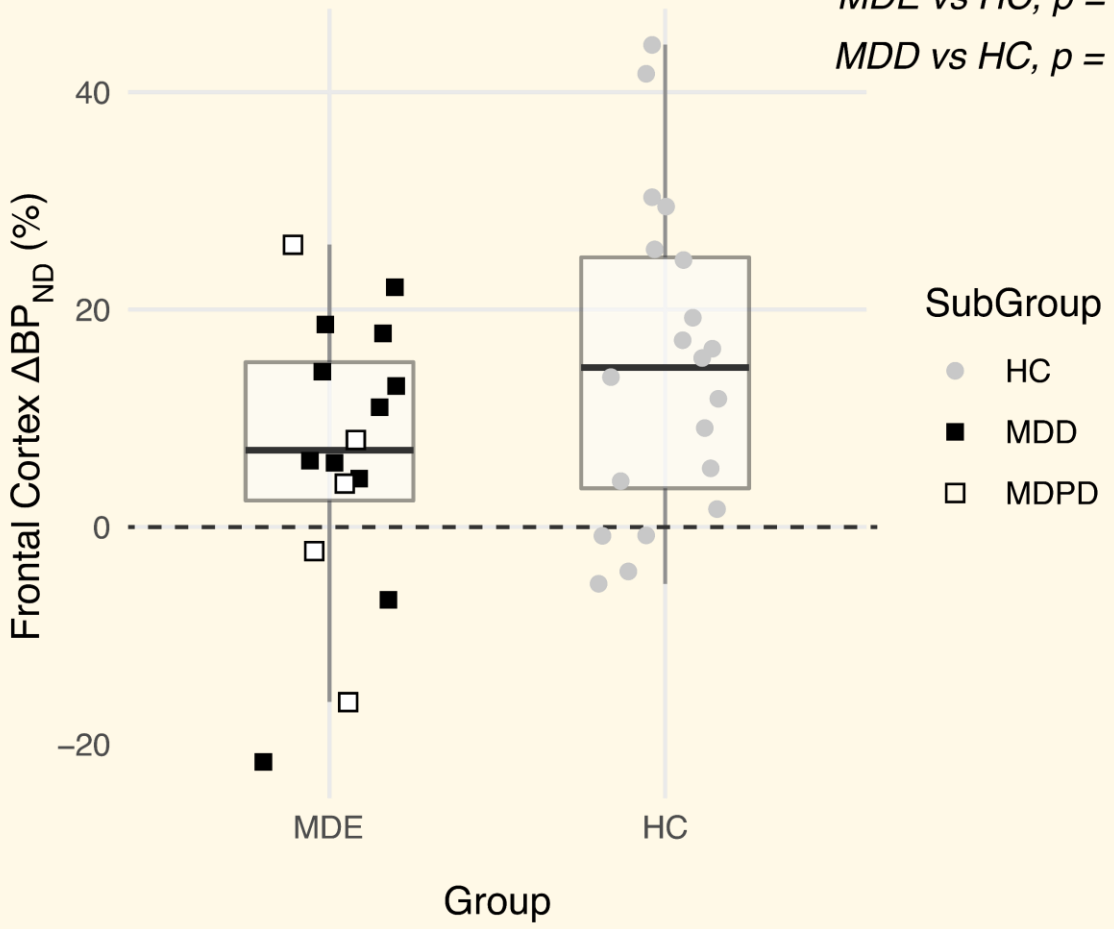
1. 5-HT release (or ΔBP_{ND}) in Frontal Cortex:
   - In 20 HC : 15±14%, p<0.001
   - In 12 MDD: 3±20%, ns
   - In 5 MDPD: 4±15%, ns

Conclusion – MDE patients have lower serotonin release capacity (SRC) in the frontal cortex than non-depressed controls

*One-way ANCOVA**

MDE vs HC, p = 0.041

MDD vs HC, p = 0.043

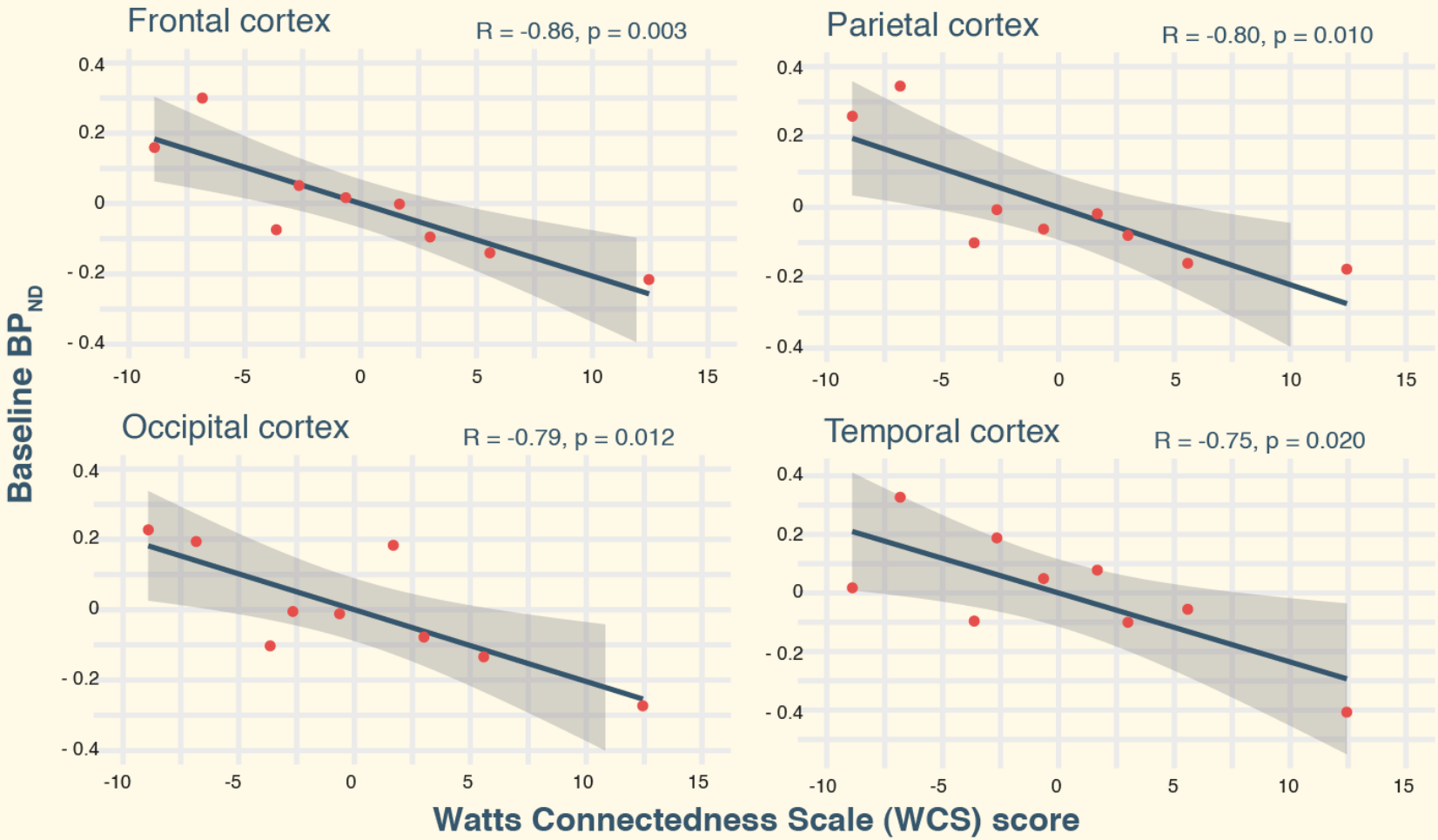


Erritzoe, David, et al. "BRAIN SEROTONIN RELEASE IS REDUCED IN PATIENTS WITH DEPRESSION: A [11C] Cimbi-36 PET STUDY WITH A D-AMPHETAMINE CHALLENGE." Biological Psychiatry (2022).

Brain serotonin release is reduced in patients with depression

Results

Relationship between 5-HT2A receptor availability (Baseline BP_{ND}) and SRC (ΔBP_{ND}) with psychometric measures in the MDD sub-group.



- A statistically signficant negative correlation was found between the baseline BP_{ND} and connectedness scores (i.e., WCS, 3 missing data points) in all analysed ROIs.
- No statistically significant relationship was found between the psychometric measures of mood (i.e., BDI, RS, SHAPS, and SSAI), wellbeing (i.e., WEMWBS) and personality (i.e., BFI) with either baseline BP_{ND} or SRC in any of the analysed ROIs.

** data points correspond to residuals after inculding age as a covariate as a positive correlation existed in our data between age and baseline BP_{ND}*

UNPUBLISHED

Brain serotonin release is reduced in patients with depression

Discussion

Summary

1. Reduced serotonin release capacity (SRC) in the frontal cortex of depressed patients as compared to healthy controls.
2. No correlation with severity of depression or treatment outcome.
3. Negative correlation between baseline 5-HT2AR availability and trait connectedness among depressed patients (scale not administered to healthy controls).

Limitations

- Small effect size of the between-group difference in ΔBP_{ND}.
- Study underpowered to detect interpretable correlations.
- Results to be replicated in a bigger sample size and using a selective 5-HT pharmacological challenge.

Acknowledgments

Dr. David Erritoze,
Centre for Psychedelic Research:
Secondary supervisor of the PhD,
First author of the study

Dr. Eugenii (Ilan) Rabiner,
Invicro Imaging Centre:
Last author of the study

Prof. Andrea Fagiolini,
University of Siena:
Primary supervisor of the PhD

Co-Authors:

Beata R. Godlewska, Gaia Rizzo, Graham E. Searle, Yvonne Lewis, Abhishekh H. Ashok, Alessandro Colasanti, Iro Boura, Chloe Farrell, Hollie Parfit, Oliver Howes, Jan Passchier, Roger N. Gunn, David J. Nutt, Philip J Cowen, Gitte Knudsen

THE CENTRE FOR PSYCHEDELIC RESEARCH

Invicro

Imperial College London

UNIVERSITÀ DI SIENA 1240

Questions