Understanding Brain Function in Psychiatric Disease

MEDAMI 2022 – 5th September 2022

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EVP, Head of Translational Applications

Invicro

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Pharmacokinetic and Pharmacodynamic Biomarkers

- Concentration of drug in tissue
- Drug-target interaction
- Change in molecular target density
- Change in molecular target affinity (allosteric modulation)
- Change in neurotransmitter release
- Change in brain activity and/or metabolism

Applications of Imaging in Translational Medicine

- Investigate Normal State
  - Normal Function
  - Link to Individual Differences
    - Genetic
    - Environmental
- Investigate Disease
  - Evaluate Pathological Changes
  - Disease Progression
  - Effects of Treatment
- Evaluate Pharmacology
  - Drug/Target Interaction
  - Dose Selection
  - Off-target interactions

Anatomy

X-ray
Computerised Tomography (CT)
Structural Magnetic Resonance Imaging (MRI)
Ultra-sound (US)
Light Photography

Evaluates anatomical features e.g. organ size, shape, tissue density, water/fat content

Physiology/Biochemistry/Pharmacology

Positron Emission Tomography (PET)
Single Photon Tomography (SPET)
2D γ-Scintigraphy
Magnetic Resonance Spectroscopy (MRS)
Functional Magnetic Resonance (BOLD/ALS)
Near Infrared Spectroscopy (NIRS)

Evaluates specific molecules in tissue. Exogenous probes or endogenous molecular markers

Electroencephalography (EEG)
Electrocardiography (ECG)
Magnetoencephalography (MEG)

Evaluates electromagnetic fields generated by excitable tissues

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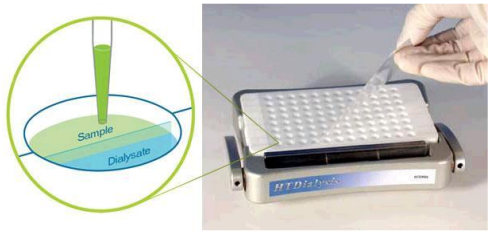
Biodistribution+- Assessing Free Drug Brain Concentrations

Biodistribution+

- Measuring Free Drug Concentration in Brain
- Assessing Active Transport Liability

Equilibrium Dialysis



Plasma Sampling

$$C_{FT} = f_{ND} V_{ND} C_P$$

Journal of Cerebral Blood Flow & Metabolism (2012) 32, 874–883
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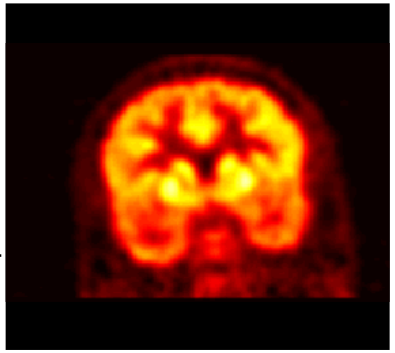
www.jcbfm.com

Combining PET biodistribution and equilibrium dialysis assays to assess the free brain concentration and BBB transport of CNS drugs

Roger N Gunn[1,2,3], Scott G Summerfield[4], Cristian A Salinas[1], Kevin D Read[5], Qi Guo[1,3], Graham E Searle[1], Christine A Parker[1,3], Phil Jeffrey[6] and Marc Laruelle[3,7]

PET



BBB Transport Assessment

$$C_P = \frac{C_{FT}}{f_P} \therefore$$

$$V_{ND} = \frac{C_T}{C_P} = \frac{f_P}{f_{ND}}$$

Passive Diffusion

$$V_{ND} < \frac{f_P}{f_{ND}}$$

Efflux Gradient

$$V_{ND} > \frac{f_P}{f_{ND}}$$

Influx Gradient

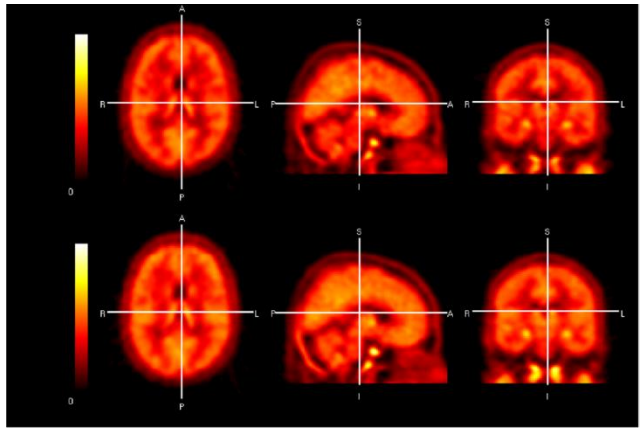
BBB Transport Assessment

$$Occ = \frac{C_{FT}}{C_{FT} + K_D}$$

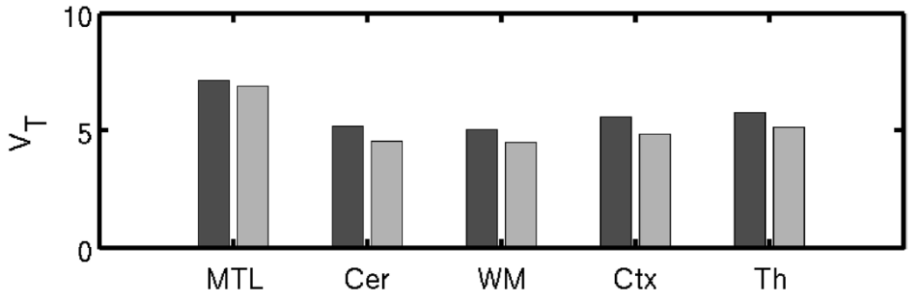
Assuming in vitro K_D = in vivo K_D

Characterising BBB transport of GSK1034702

- A novel $mAChR_1$ PAM that is a weak PgP substrate *in vitro*
  - efflux ratio 2.6:1 in MDCK cell line expressing human MDR1
- Species variability in brain-to-plasma ratios
  - mouse, rat and marmoset ratios of 0.4, 0.6 and 2.0
- Human PET study investigated the brain penetration of [^{11}C]GSK1034702 in 4 subjects before and after a single oral dose of 5mg of GSK1034702



[^{11}C] GSK1034702 distribution in the brain of a representative subject



[^{11}C] GSK1034702 regional V_T

Results: Human brain V_T ~ 4.9 broadly similar to NHP brain V_T ~ 3.9 & f_P/f_{ND} ~ 2.6

Conclusion: No evidence of liability to efflux pumps

Ridler et al. EJNMMI Research 2014

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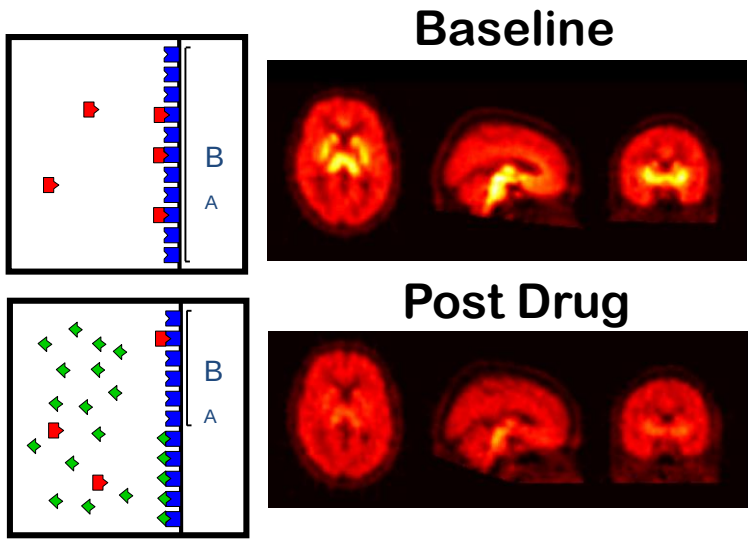
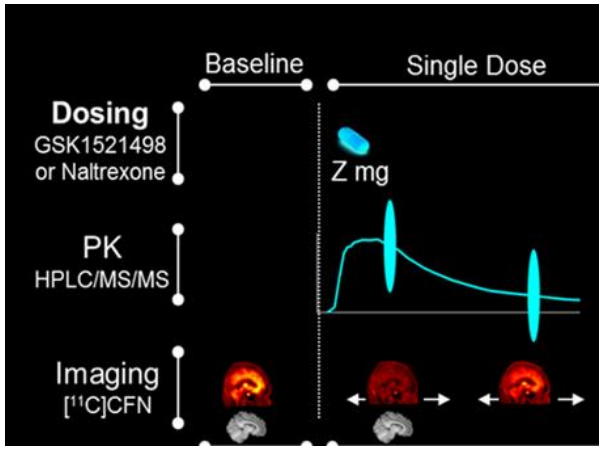
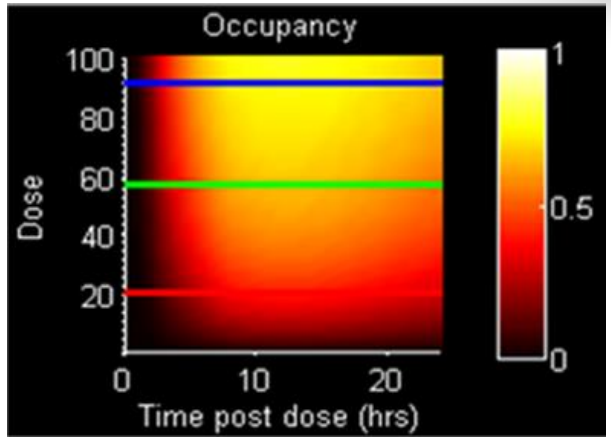
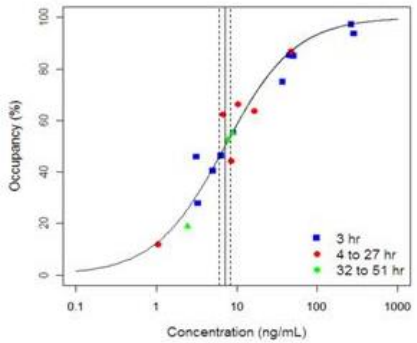
Quantifying Target Engagement to Optimise Dose Selection

Better, Faster and Cheaper Clinical Trials



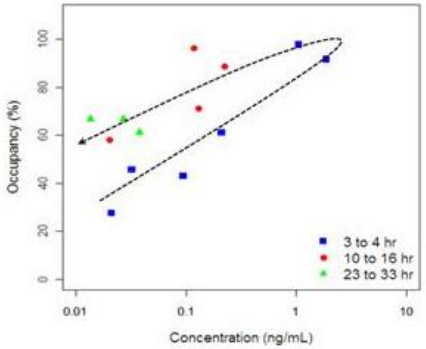


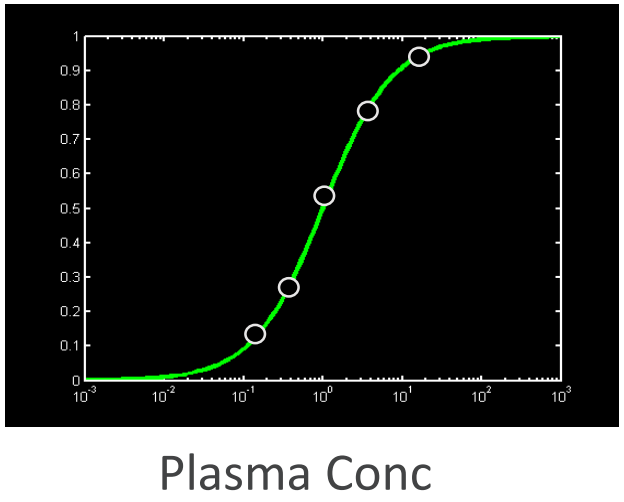


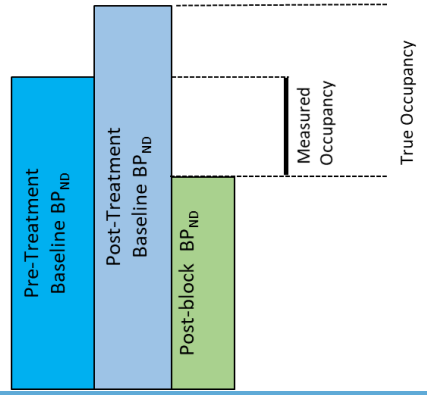


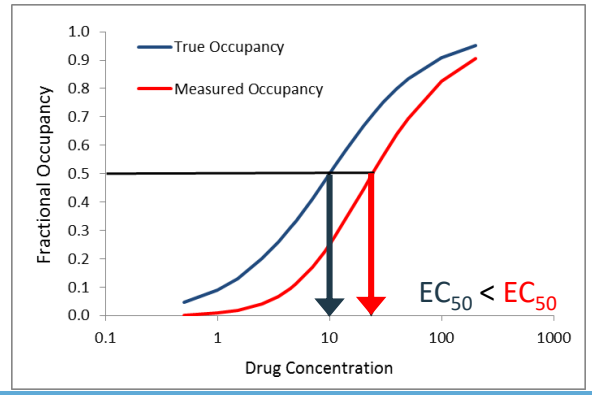
Invicro Target Engagement+

- *Adaptive Design*
- *PK-RO Modelling Indirect Kinetics*
- *RD Prediction from SD*
- *Upregulation RD Modelling*









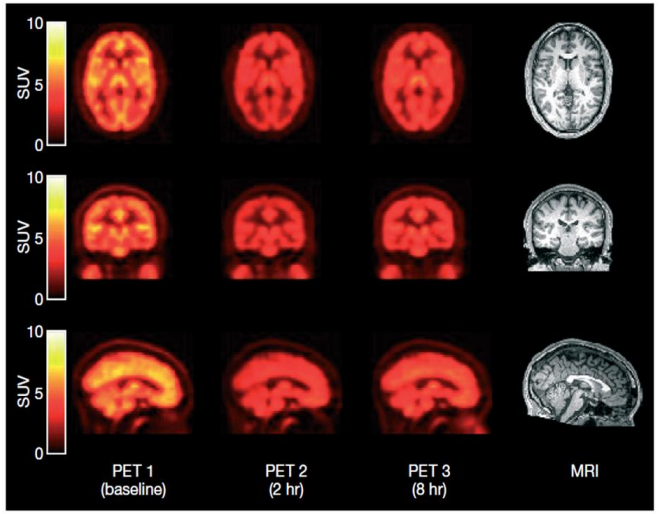
Target occupancy of a novel σ1 receptor antagonist

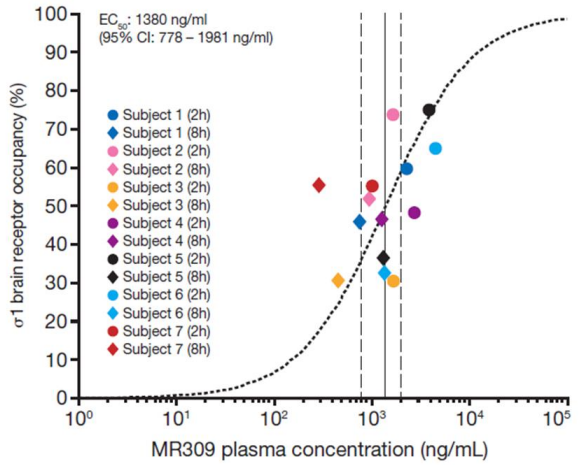
MR309, a selective σ1R antagonist in development for the treatment of neuropathic pain

PET study used the selective σ1R radioligand [^{11}C]SA-4503 to establish the relationship between plasma concentration and σ1R occupancy of MR309

Conclusions: MR309 200 mg BID dose produced σ1R occupancy below the 75% occupancy threshold expected to elicit maximal antinociceptive effect as observed in neuropathic pain models.

Further investigations of MR309 for neuropathic pain will require higher brain σ1R occupancy

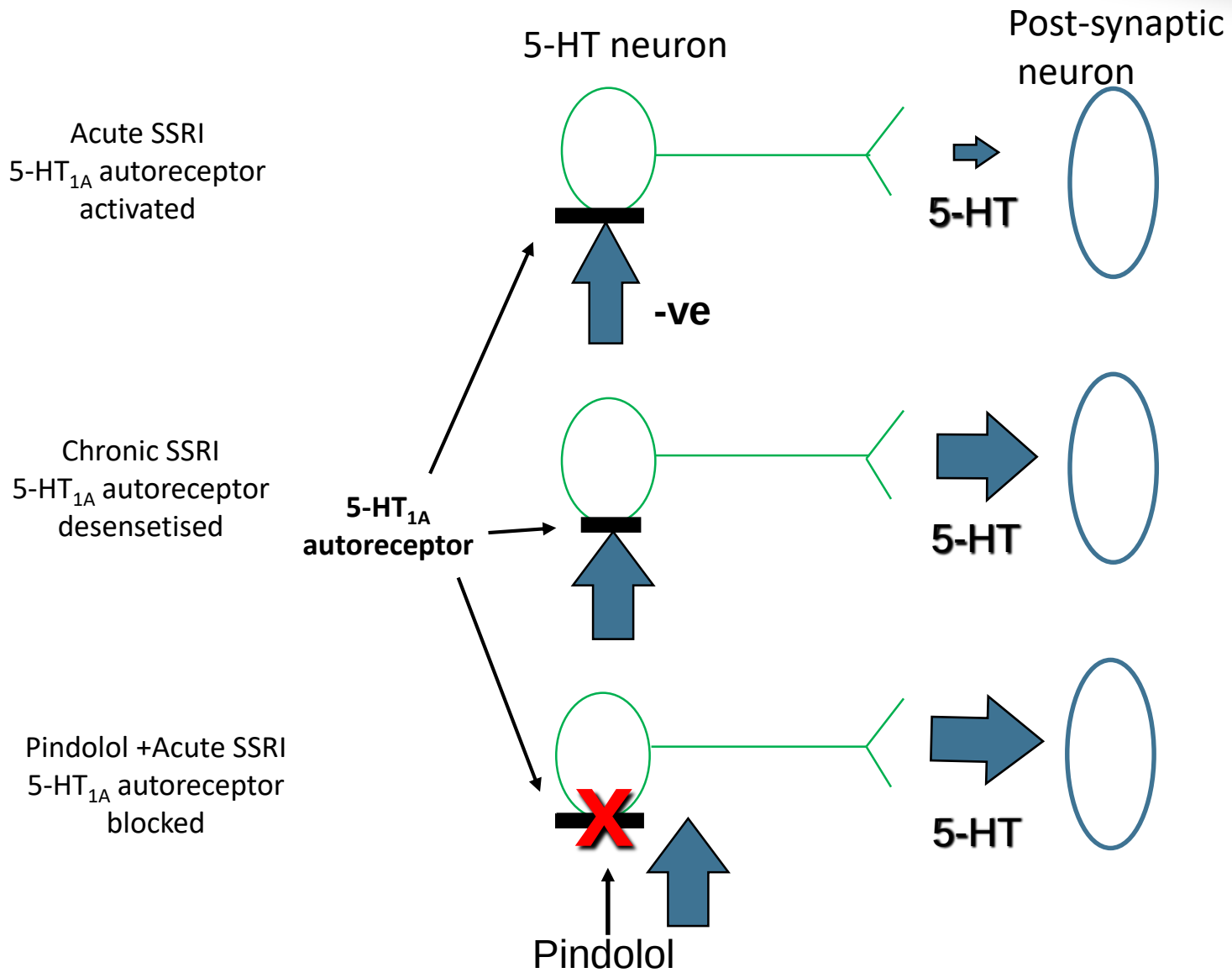




Pharmacokinetics and brain sigma 1 (σ1) receptor occupancy of MR309, a selective σ1 receptor antagonist, Rabiner et al, British Journal of Clinical Pharmacology, In Press

5-HT release in the treatment of depressive disorders

- Antidepressants block the 5-HT transporter or MAO within hours/days of administration
- Clinical effect of antidepressants requires 4-6 weeks of treatment
- The activation by increased 5-HT concentration of 5-$HT_{1A/B}$ autoreceptors is proposed to reduce 5-HT release and delay onset of clinical efficacy
- Blockade of 5-$HT_{1A/B}$ autoreceptors was proposed as a strategy to accelerate and augment SSRI treatment



Evaluation of pindolol augmentation of SSRI in depression – evaluation of 5-HT$_{1A}$ autoreceptor blockade

Brief Report

Pindolol Augmentation of Selective Serotonin Reuptake Inhibitors: PET Evidence That the Dose Used in Clinical Trials Is Too Low

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Roger N. Gunn, Ph.D.
Peter A. Sargent, M.R.C.Psych.
Christopher J. Bench, M.R.C.Psych.
Philip J. Cowen, F.R.C.Psych.
Paul M. Grasby, M.R.C.Psych.

Objective: Positron emission tomography (PET) was used to examine whether the dose of pindolol used to augment antidepressant medication achieves a significant occupancy of the serotonin type 1A (5-HT$_{1A}$) autoreceptor in depressed patients receiving medication.

Method: The authors examined eight depressed patients on one of two regimes of pindolol (2.5 mg t.i.d. and 5.0 mg t.i.d.) with PET and [^{11}C]WAY-100635.

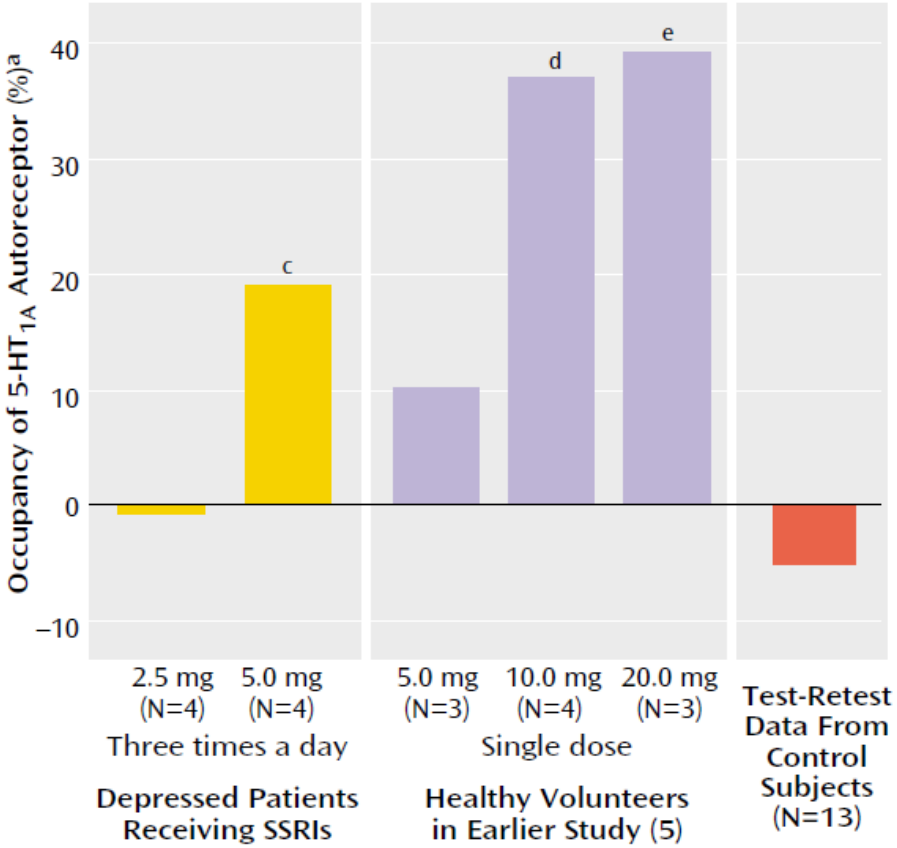
Results: The 5-mg t.i.d. regime achieved a modest (19%) but significant occupancy of the 5-HT$_{1A}$ autoreceptor, while the regime used in the vast majority of clinical trials (2.5 mg t.i.d.) did not achieve a significant occupancy.

Conclusions: The dose of pindolol used in clinical trials is suboptimal and may explain the inconsistent results. Therefore, a thorough test of pindolol's efficacy will necessitate doses higher than those used in present clinical trials.

(Am J Psychiatry 2001; 158:2080–2082)

- Pindolol (a β-blocker with 5-HT$_{1A}$ affinity) proposed to accelerate and augment SSRI treatment in depression
- Clinical trials of 2.5 mg dose provided disappointing results
- A PET study using [^{11}C]WAY-100635 evaluated pindolol occupancy of the 5-HT$_{1A}$ receptor and found occupancy of 2.5 mg dose to be too low for clinical efficacy

FIGURE 1. Mean Occupancy[a] of the 5-HT$_{1A}$ Receptor in Depressed Patients Receiving SSRIs and Two Doses of Pindolol, in Healthy Volunteers Receiving Three Doses of Pindolol, and in Healthy Control Subjects Tested Twice[b]



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- Change in brain activity and/or metabolism

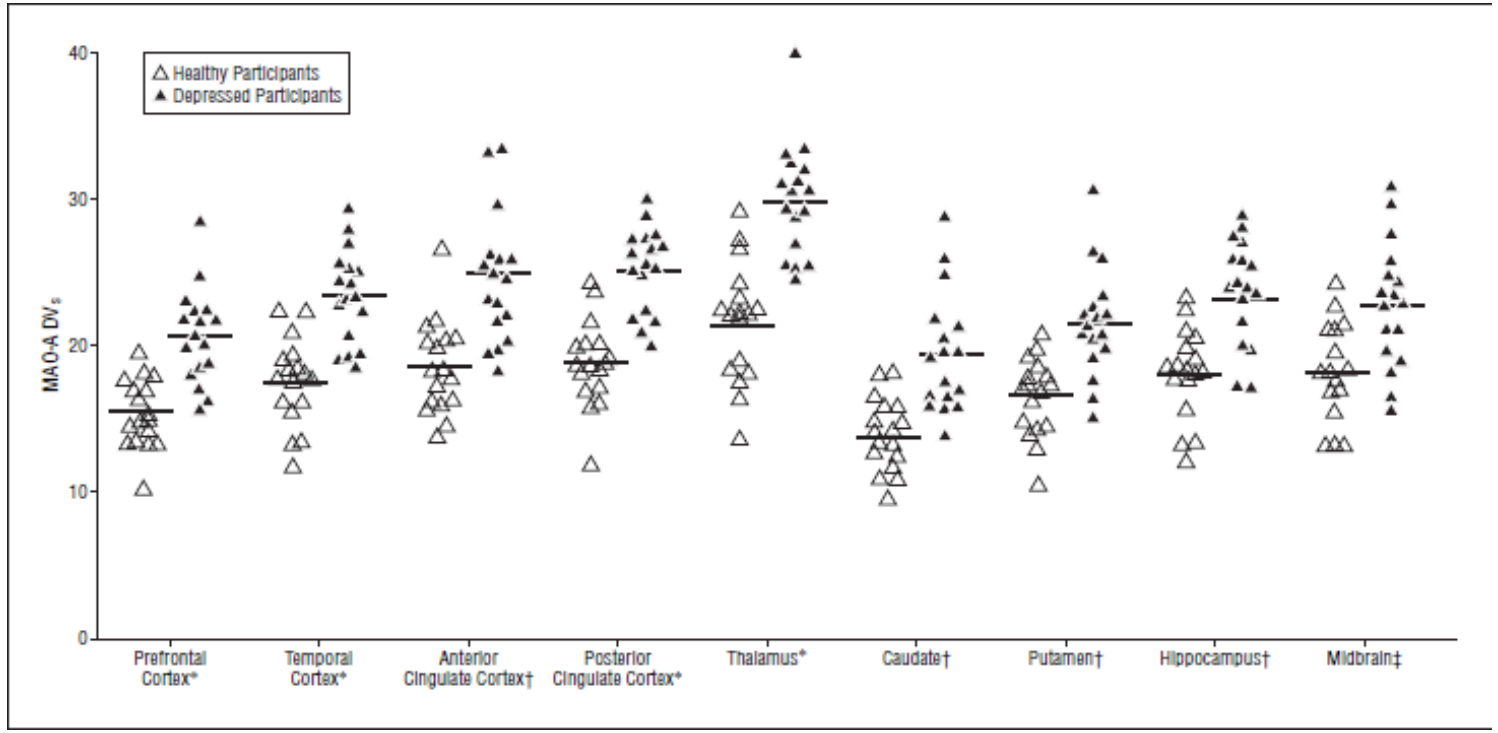
5-HT neurotransmission in depression – MAO-A

Elevated Monoamine Oxidase A Levels in the Brain

An Explanation for the Monoamine Imbalance of Major Depression

Jeffrey H. Meyer, MD, PhD; Nathalie Ginovart, PhD; Anahita Boovariwala, BSc; Sandra Sagrati, BSc; Doug Hussey, BSc; Armando Garcia, BSc; Trevor Young, MD, PhD; Nicole Praschak-Rieder, MD; Alan A. Wilson, PhD; Sylvain Houle, MD, PhD

Arch Gen Psychiatry. 2006;63:1209-1216



- 5-HT dysregulation is implicated in the pathophysiology of depression
  - Most antidepressants increase brain 5-HT levels
- Monoamine Oxidase A (MAO-A) a major path for the breakdown of 5-HT
- [^{11}C]harmine is a PET ligand suitable to evaluate MAO-A density
- Patients with major depression demonstrated widespread increases in MAO-A expression implying reduction in brain 5-HT levels

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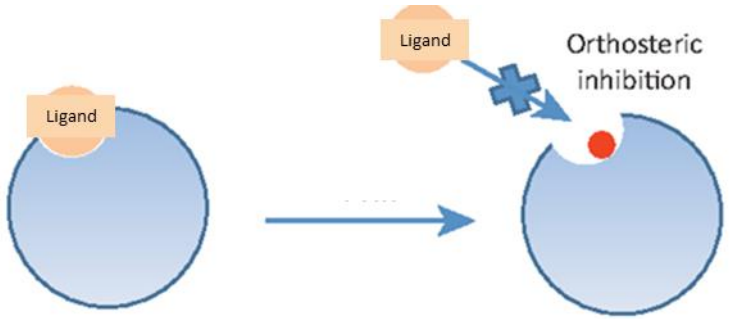
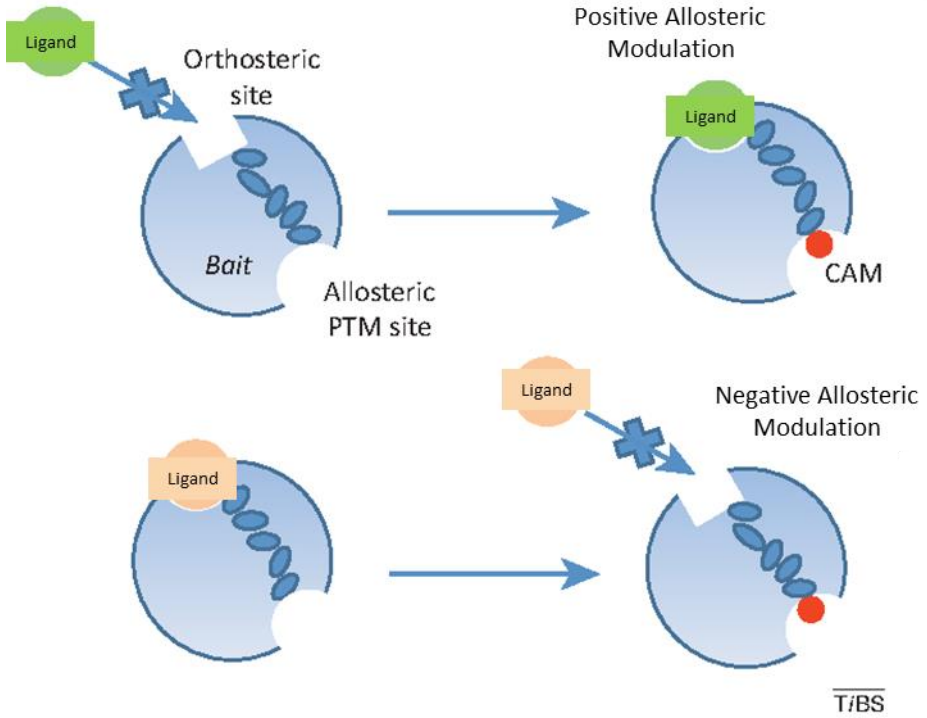
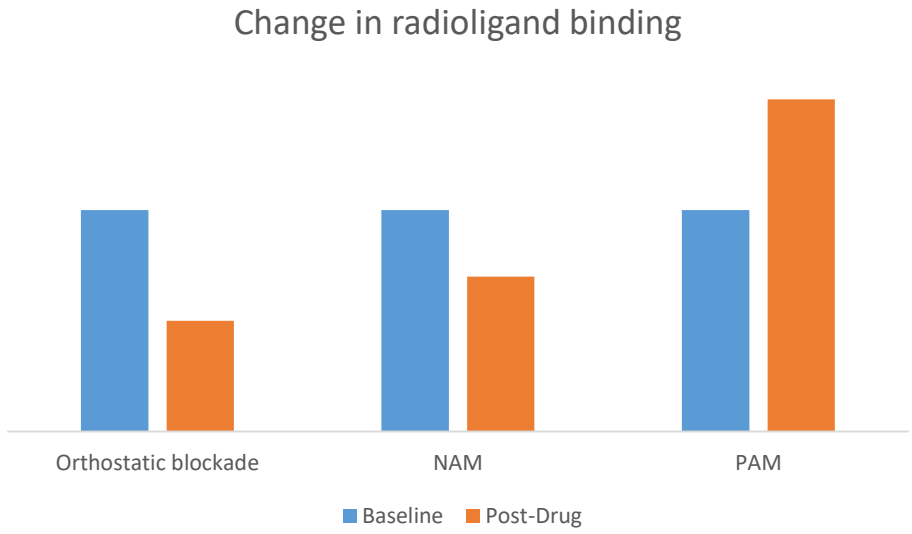
Allosteric Modulators

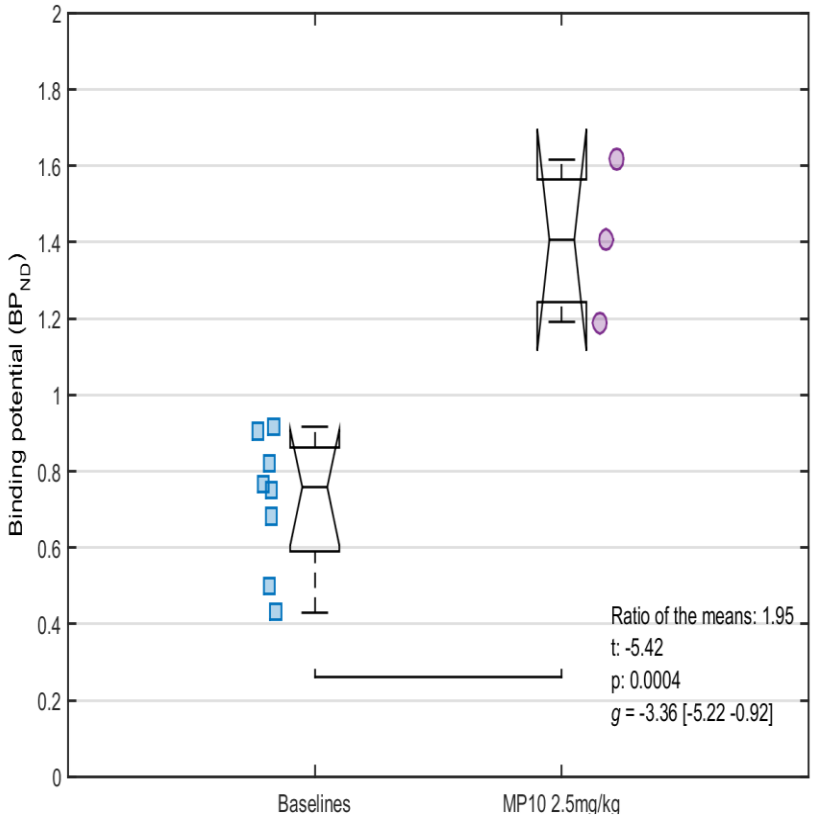






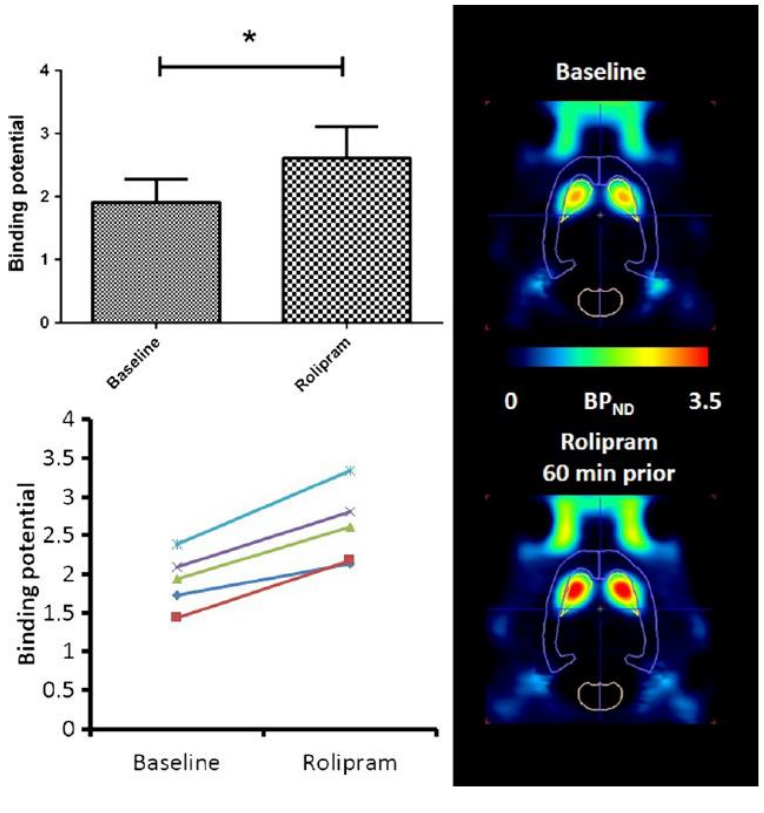
Modulation of PDE radioligand binding by cN's

PDE2 and [^{18}F]PF-05270430

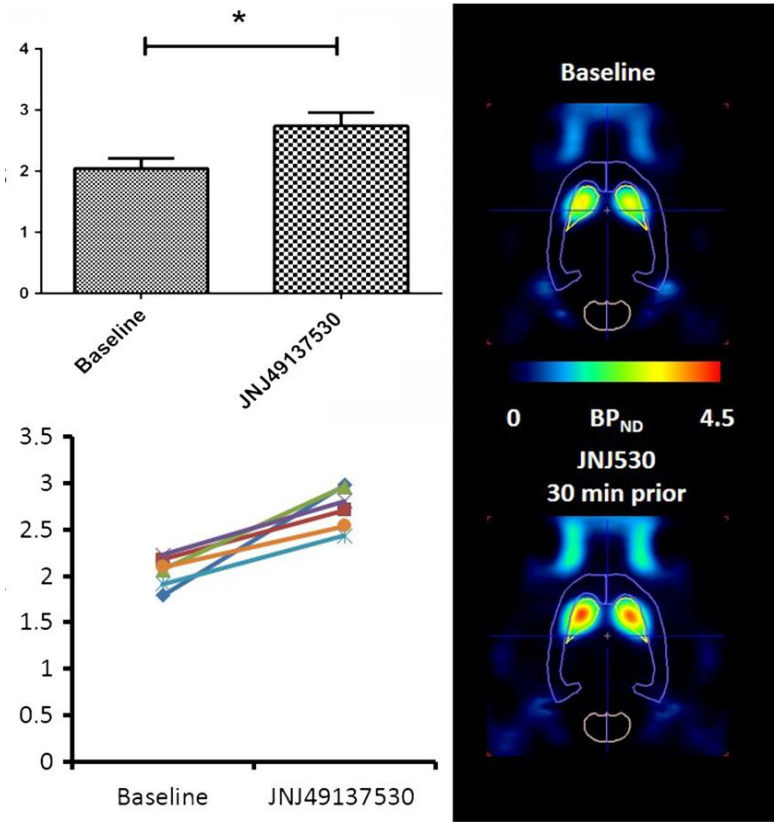


Effect of PDE10 blockade by MP-10

PDE10 and [^{18}F]JNJ42259152



PDE4 blockade by rolipram
Ooms et al, 2016

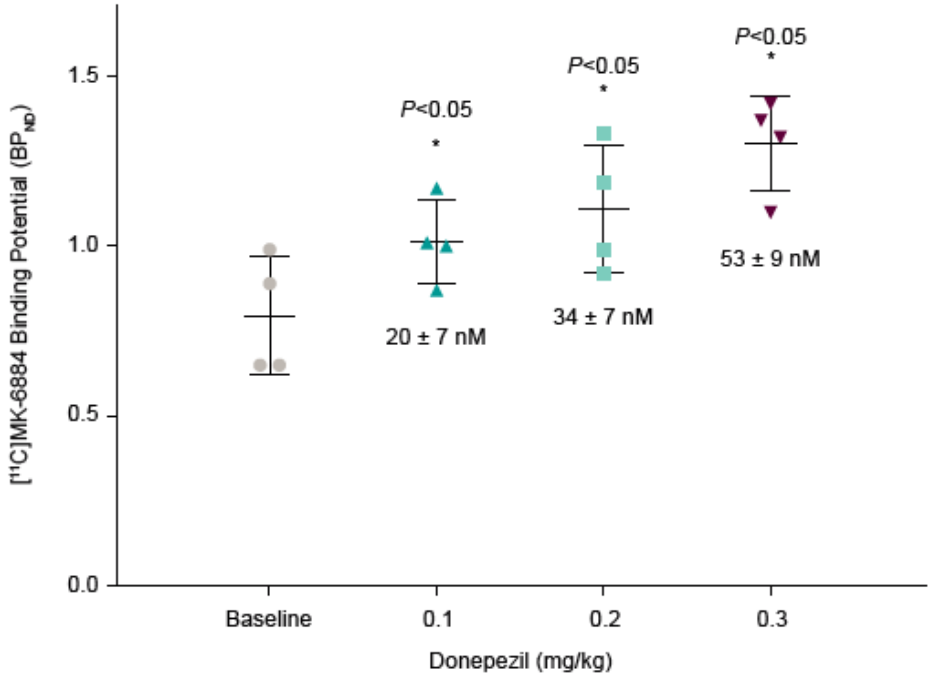


PDE2 blockade by JNJ49137530

Modulation of the affinity of m4AChR PAM by agonist stimulation

Impact of Cholinergic Tone on the Binding of PET Tracer [^{11}C]MK-6884, a Positive Allosteric Modulator of M4 Acetylcholine Receptor in Monkeys and Healthy Elderly Volunteers

Figure 1. Donepezil Increased Binding Potential of [^{11}C]MK-6884 in Rhesus Monkey



T Bueters[1]; AM Hussain[1]; Y Wang[2]; TG Lohith[2]; HD Haley[2]; ML Purcell[2]; MA Holahan[2]; ED Hostetler[2]; PJ Coleman[6a]; RD Mazzola, Jr[6b]; L Tong[6b]; JA Morrow[3]; JM Uslaner[3]; G Bormans[7]; M Koole[8]; K Van Laere[8]; K Serdons[7]; A Van Hecken[9]; JN de Hoon[9]; C Vandermeulen[9]; R Declercq[10]; I De Lepeleire[10]; Y Li[4]; AS Basile[5]; W Li[2]

Presented at the ASCPT 2019 Annual Meeting; Washington, DC, USA; March 13-16, 2019.

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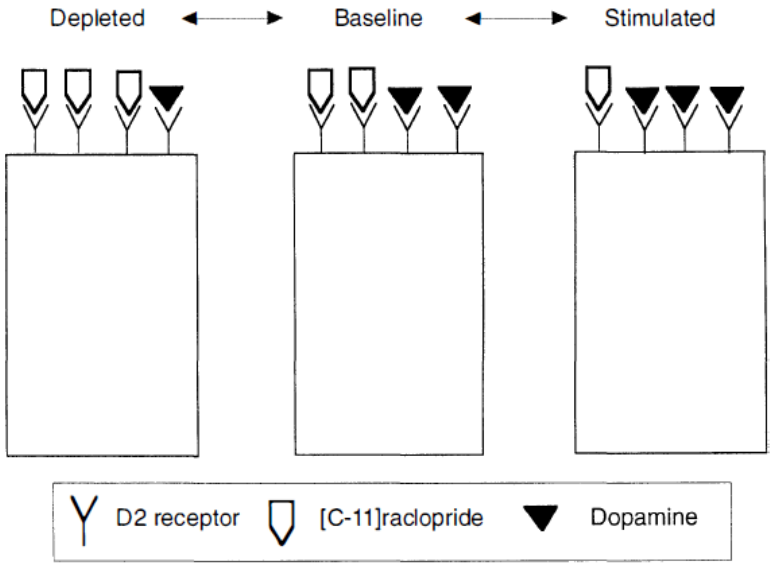
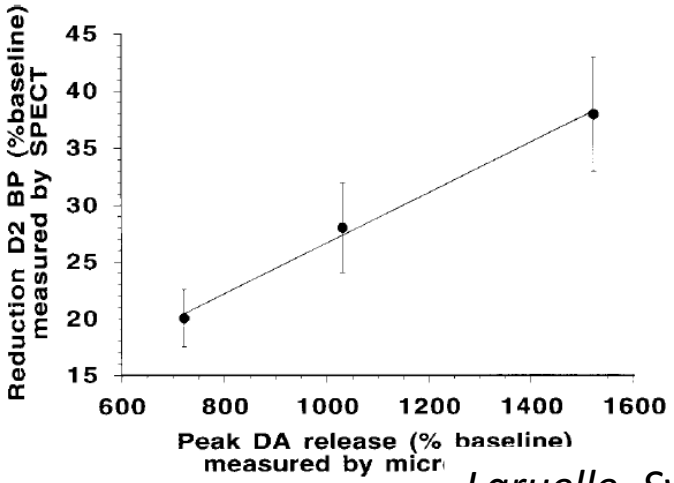
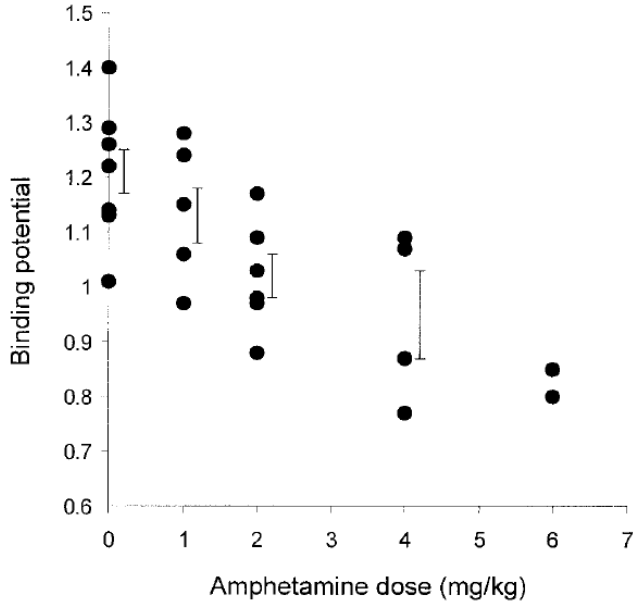
Measuring Neurotransmitter Release - Dopamine



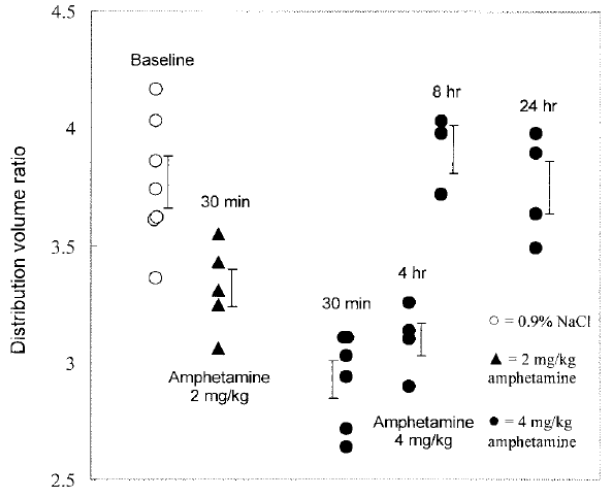
Laruelle, JCBFM 2000



Laruelle, Synapse 1997

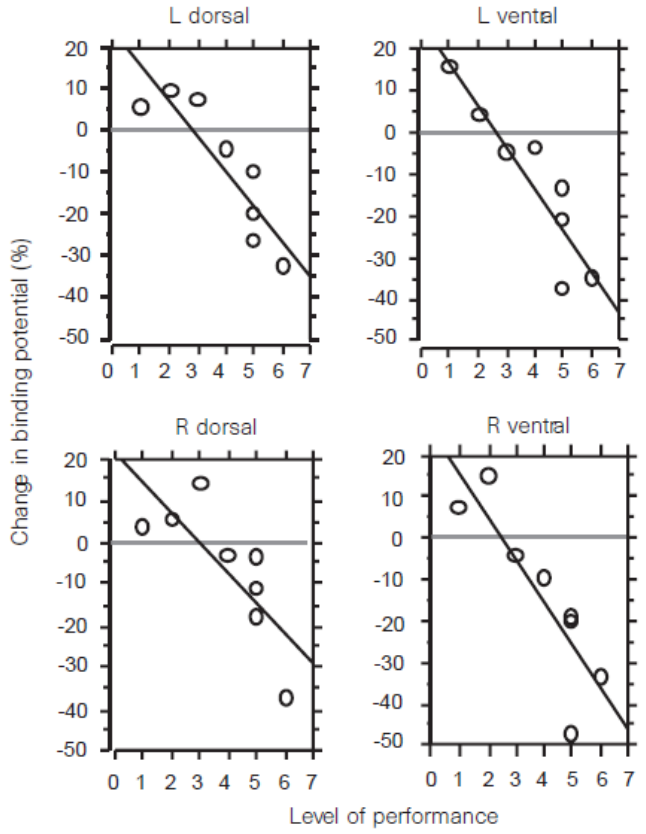


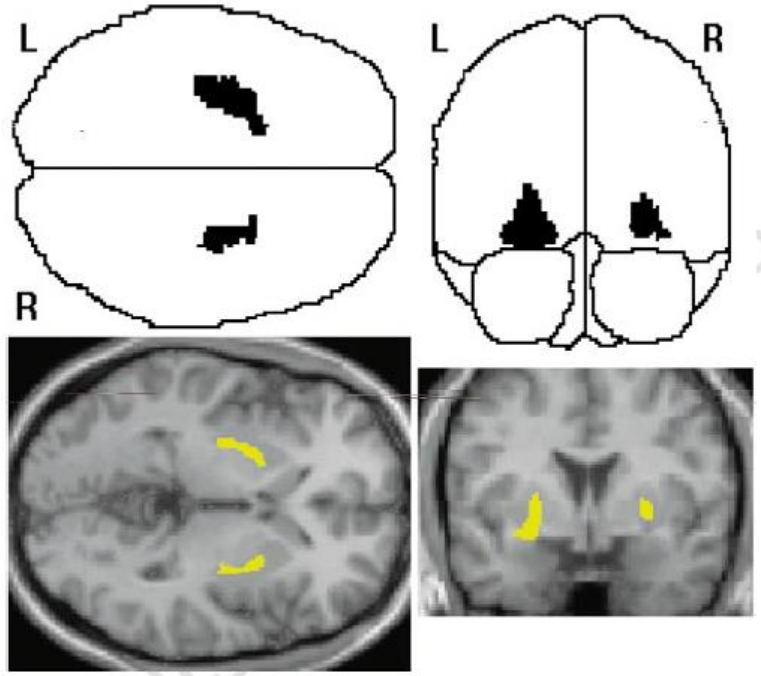
Houston, Synapse 2004



Evaluation of Dopamine Involvement in Reward

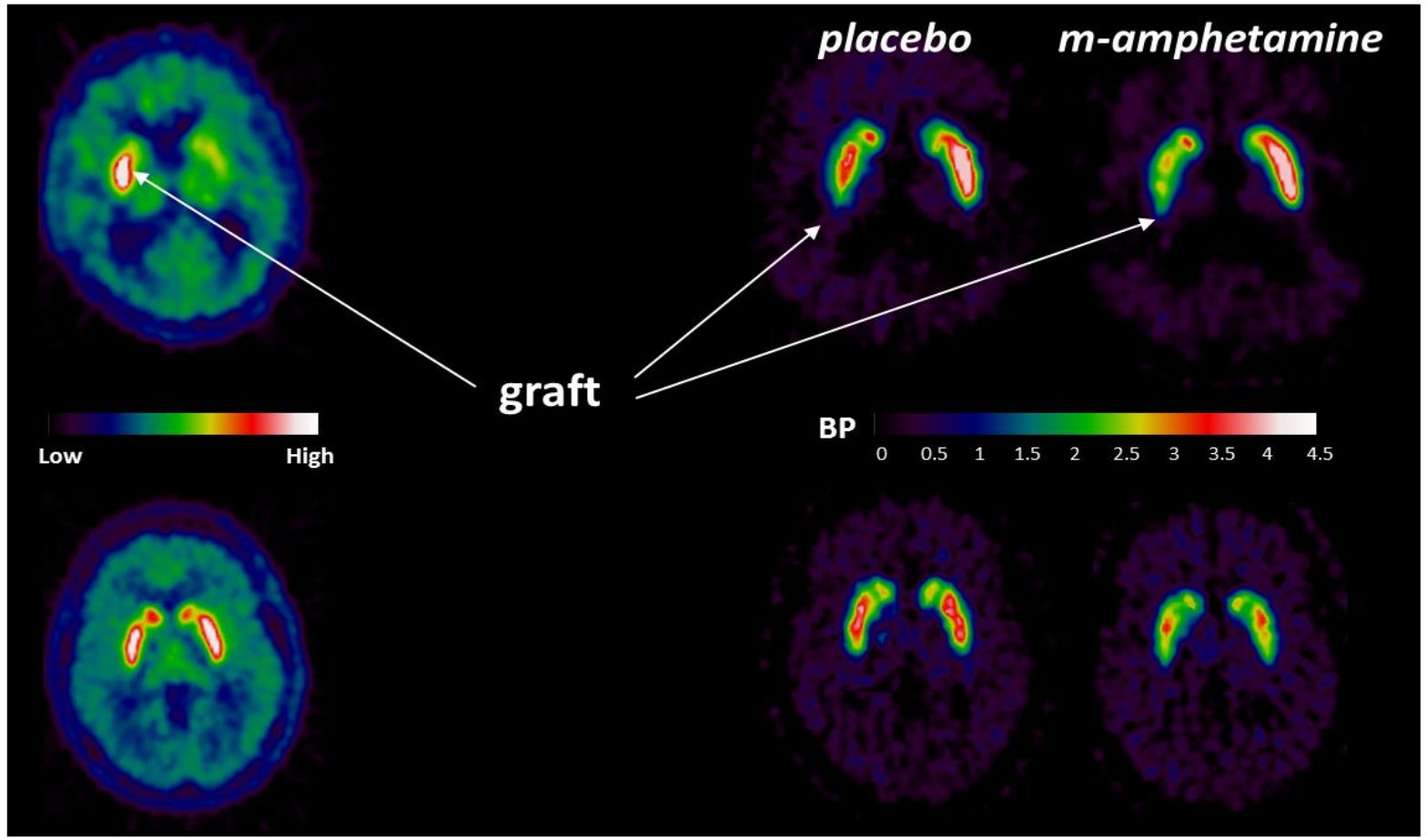
- Reward was postulated to be mediated by dopamine released in the striatum
- First direct evaluation of the relationship between reward and dopamine release in the human brain using [^{11}C]raclopride PET
- Individuals playing a video game demonstrated dopamine release that correlated with the performance level and the monetary reward received





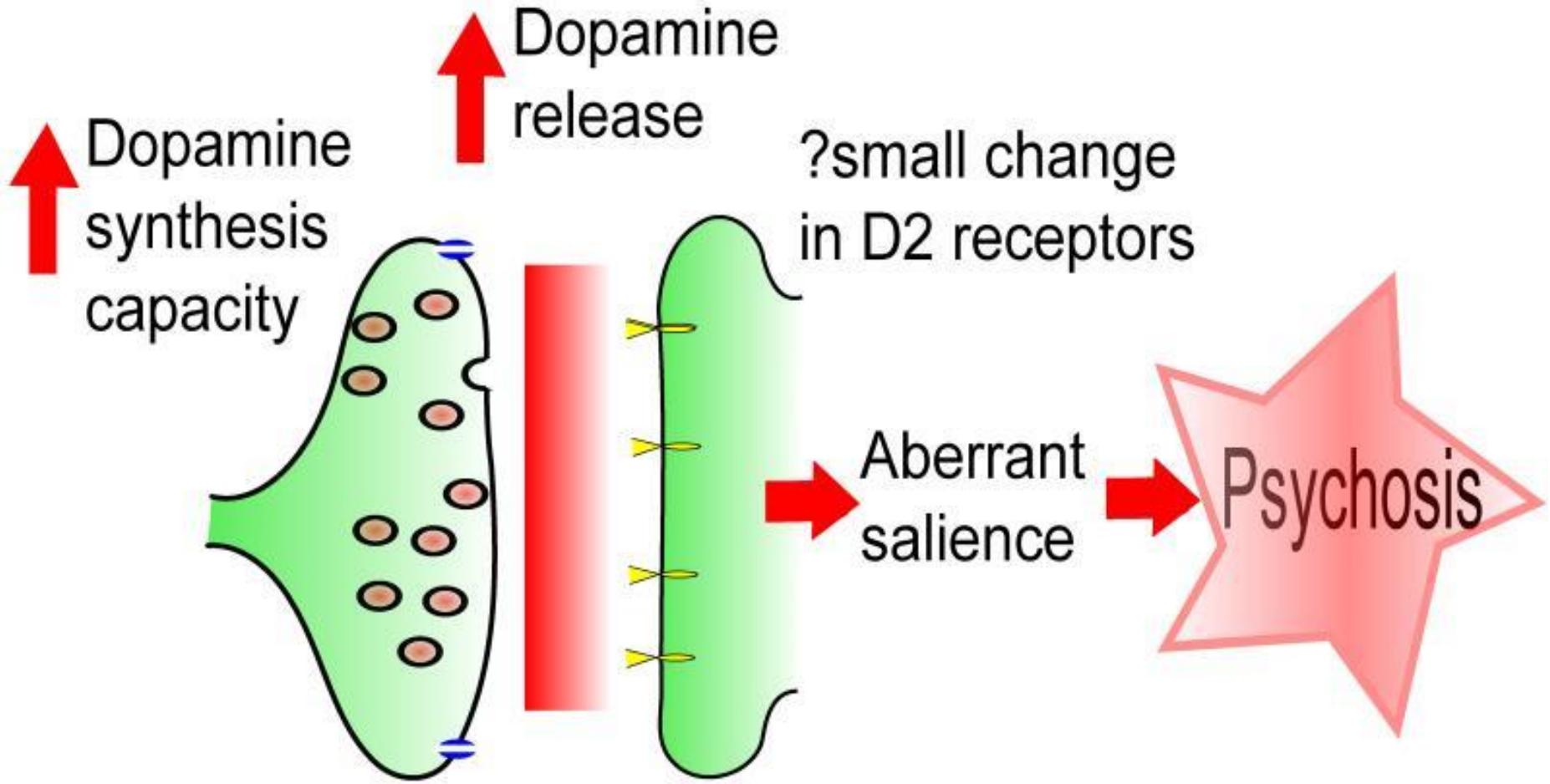
Koepp et al, Evidence for striatal dopamine release during a video game. Nature **393**, 266–268; *1998*

Imaging Neuronal Viability & Function



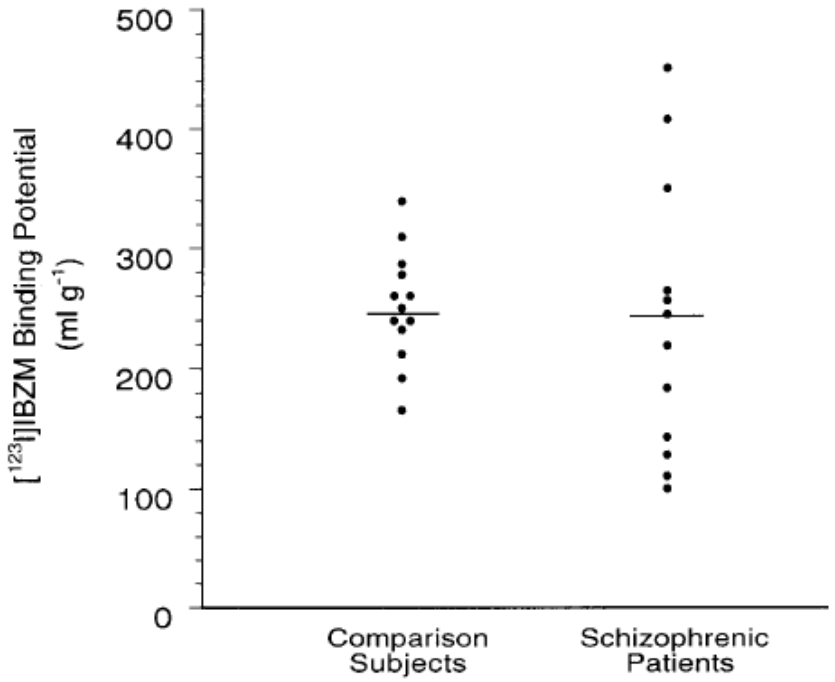
Piccini, Nature 1999

Dopaminergic Abnormalities in Schizophrenia



Howes, Current Pharm Des, 2009

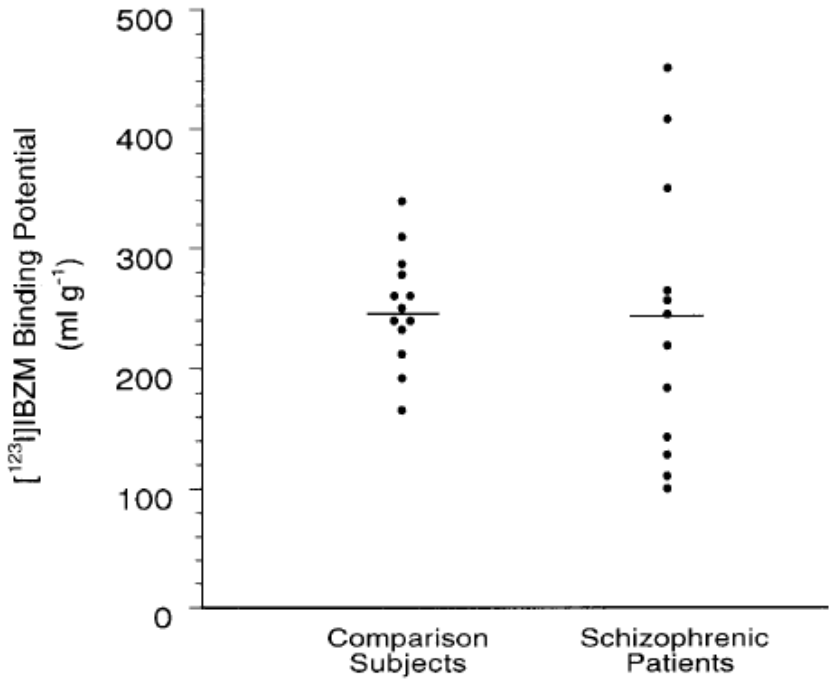
Dopaminergic Neurotransmission in Schizophrenia



D_2 receptor density does not differ between patients with schizophrenia and healthy individuals

Abi-Dargham et al, Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 155 (6), 761-7; 1998

Dopaminergic Neurotransmission in Schizophrenia



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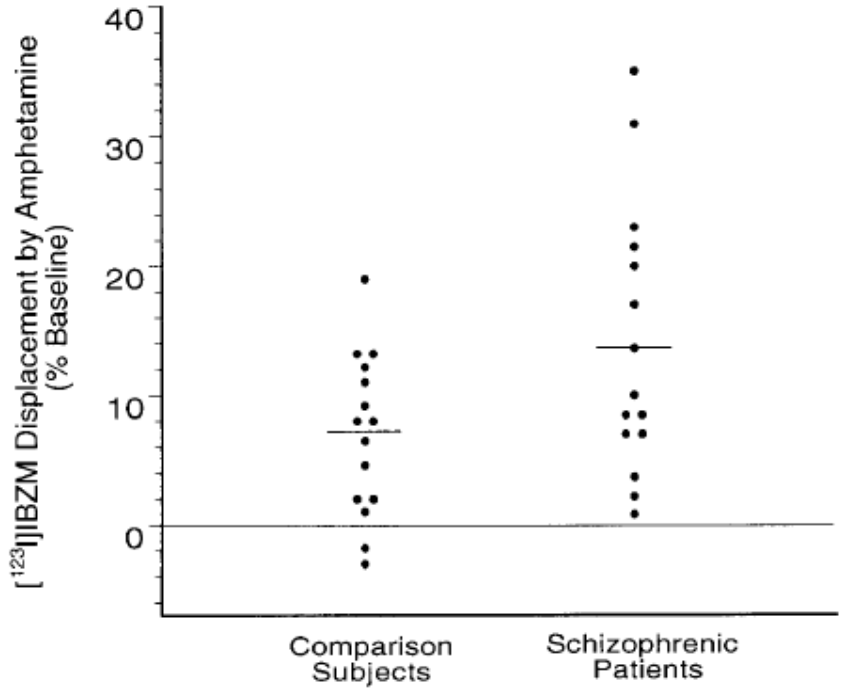
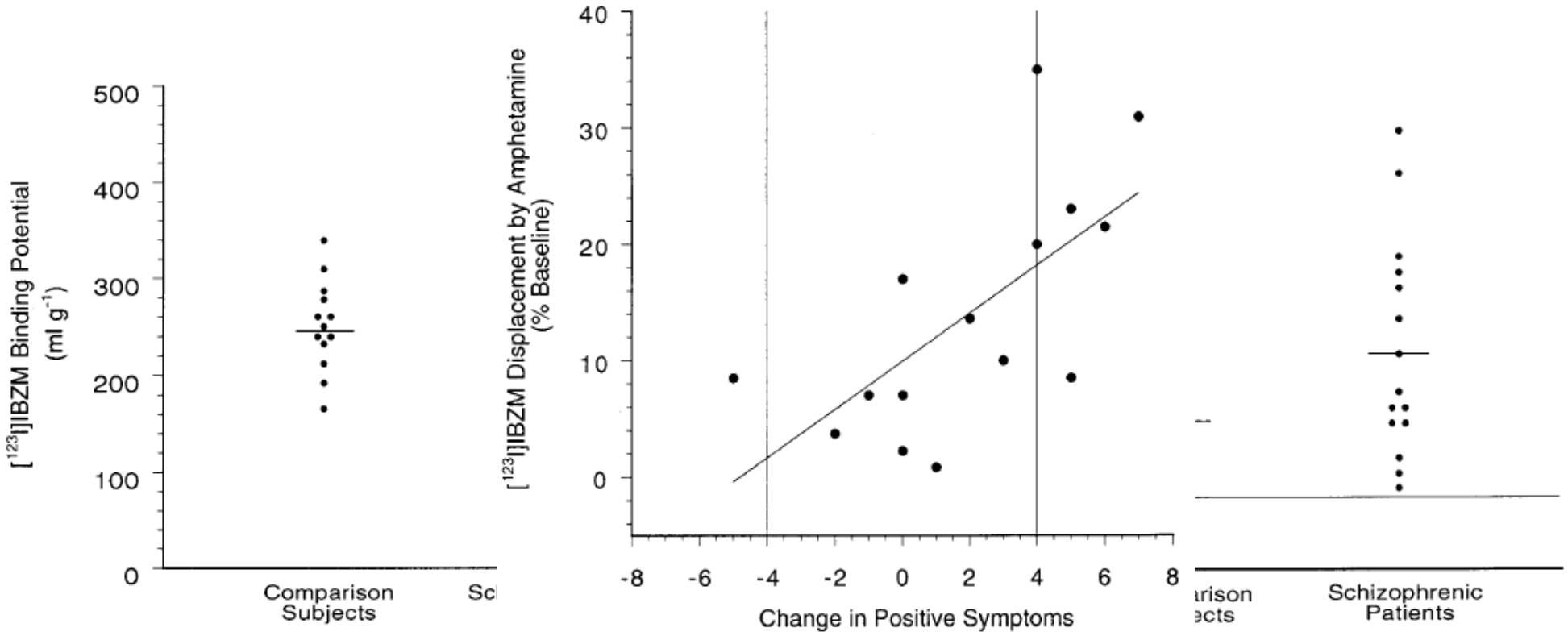


Dopamine release capacity is significantly higher in patients with schizophrenia compared to healthy individuals

Abi-Dargham et al, Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 155 (6), 761-7; 1998

Dopaminergic Neurotransmission in Schizophrenia

Dopamine release capacity is related to the intensity of positive symptoms

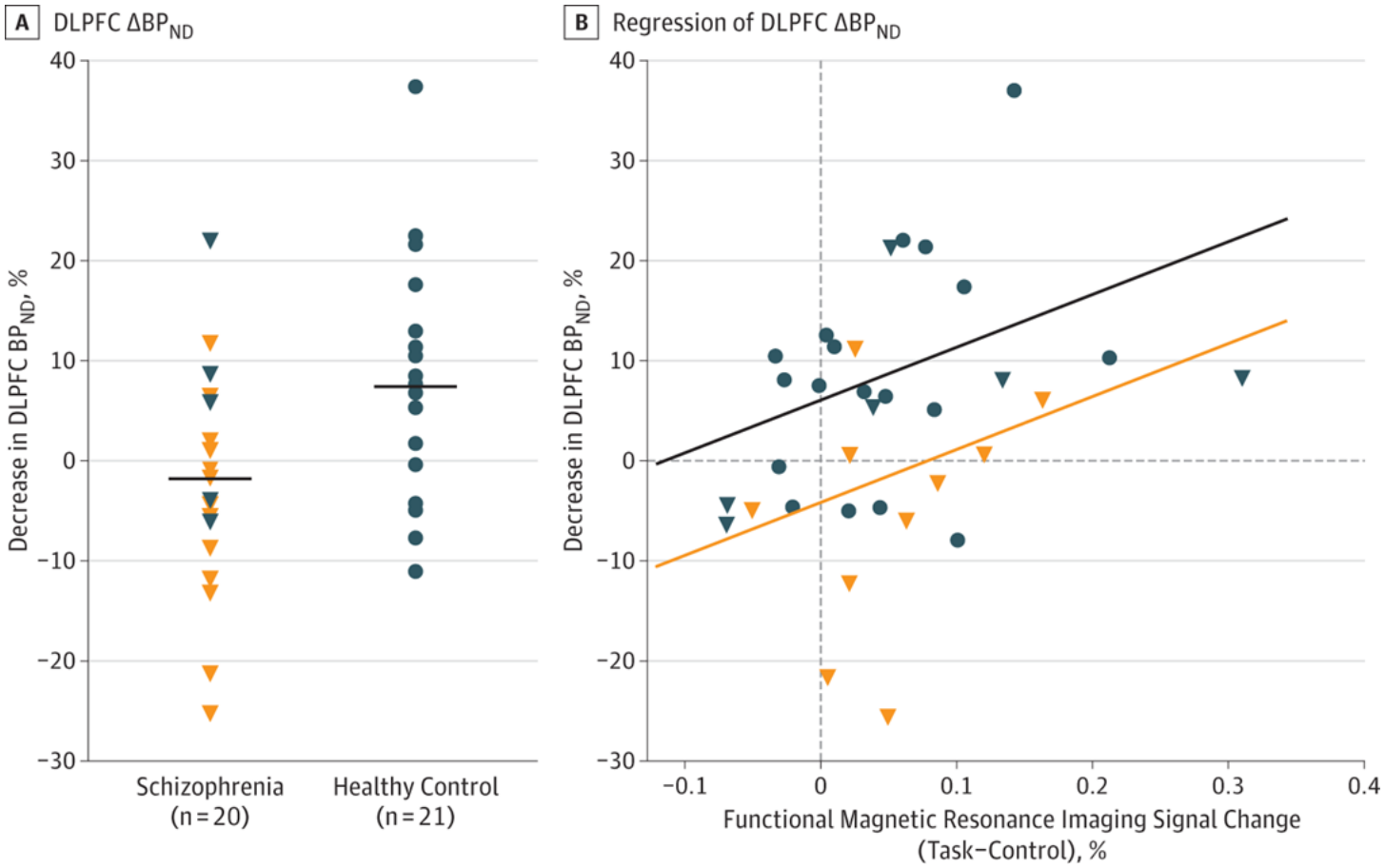


D_2 receptor density does not differ between patients with schizophrenia and healthy individuals

Dopamine release capacity is significantly higher in patients with schizophrenia compared to healthy individuals

Abi-Dargham et al, Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. Am J Psychiatry 155 (6), 761-7; 1998

Dopaminergic Neurotransmission in Schizophrenia



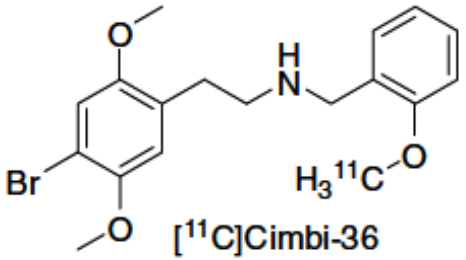
Scatterplot and Regression of Dorsolateral Prefrontal Cortex (DLPFC) Binding Potential (ΔBP_{ND})Scatterplot of DLPFC ΔBP_{ND} (A) and regression of DLPFC ΔBP_{ND} onto functional magnetic resonance imaging blood oxygenation level–dependent increase during the self-ordered working memory task (B). In A, group means are given by horizontal lines; in B, the lines represent the best linear model fit of the data, with slope equal to 53% for both groups and intercepts of 6% in the healthy control and −4% in the schizophrenia groups. Sixteen patients with schizophrenia and 18 healthy control individuals in B. The circles indicate data for healthy control individuals; orange triangles, drug-free patients with schizophrenia; and dark triangles, drug-naive patients with schizophrenia.

JAMA Network

From: **Deficits in Prefrontal Cortical and Extrastriatal Dopamine Release in Schizophrenia: A Positron Emission Tomographic Functional Magnetic Resonance Imaging Study**

JAMA Psychiatry. 2015;72(4):316-324. doi:10.1001/jamapsychiatry.2014.2414

Measuring Neurotransmitter Release – 5-HT



High affinity 5-HT_2 agonist

Demonstrated sensitivity to 5-HT fluctuation in preclinical species

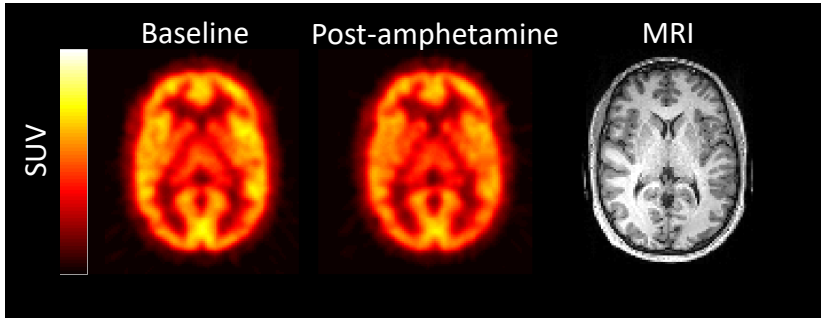
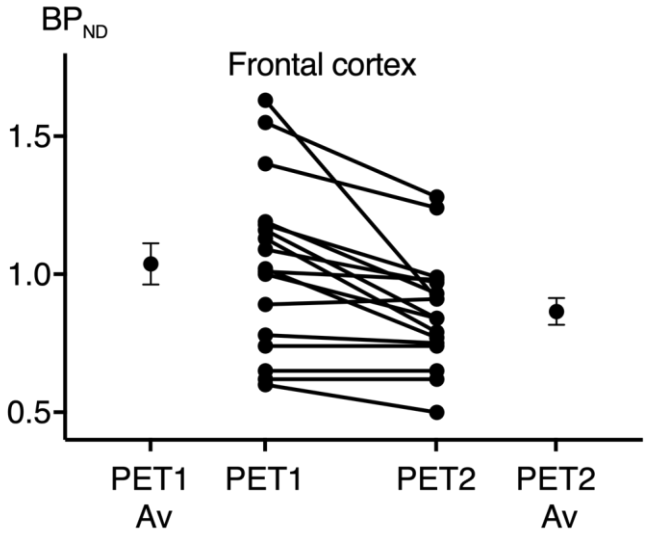


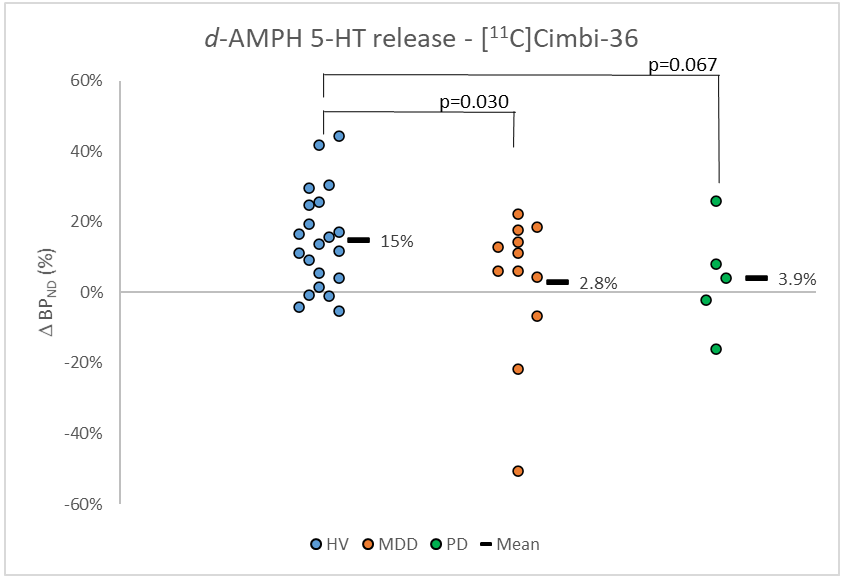
Fig 1: *[11C]Cimbi-36 binding before and after d-amphetamine in a male HC*

Effect of d-amphetamine on [11C]Cimbi-36 BP_{ND} in healthy volunteers



Erritzoe, Neuropsychopharmacology 2020

Comparison of d-amphetamine on [11C]Cimbi-36 BP_{ND} in healthy volunteers and depressed patients



[11C]Cimbi-36 Δ $BP^{FCx}{}_{ND}$ in HC, MDD & PD

Measuring Endogenous Neurotransmitter Release

Dopamine

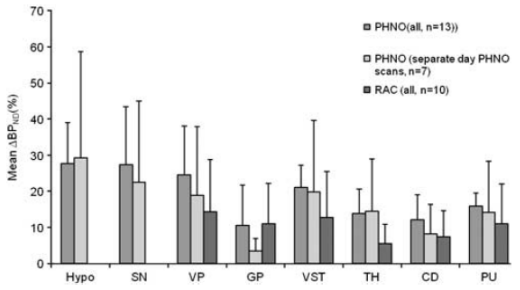
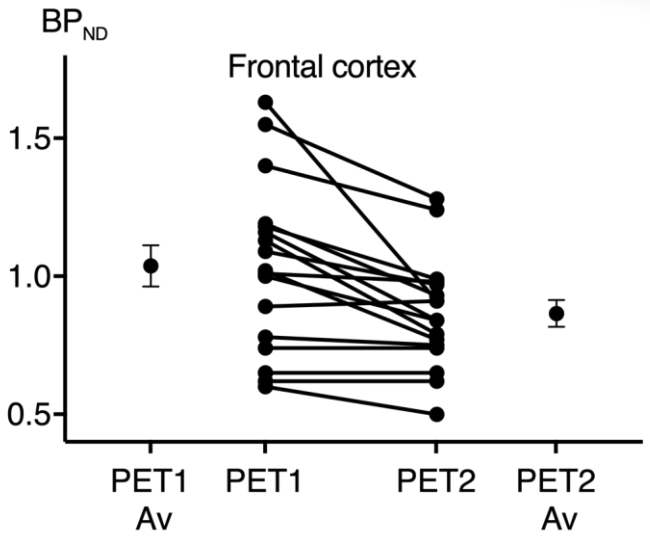


Figure 2 Reduction in BP_{ND} for [^{11}C]-(+)-PHNO and [^{11}C] raclopride after amphetamine. Columns represent mean values with associated s.d. error bars.

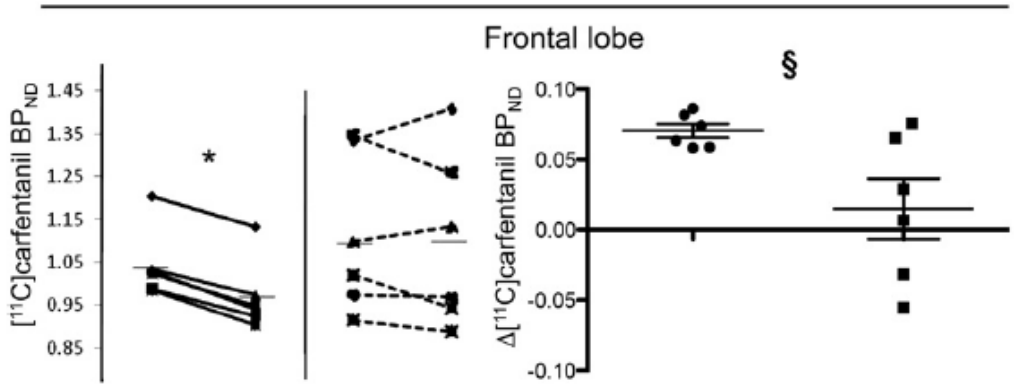
Shotbolt, JCBFM 2012

5-HT



Erritzoe, Neuropsychopharmacology 2020

Opioids



Colasanti, Biol Psychiatry 212

Acetylcholine

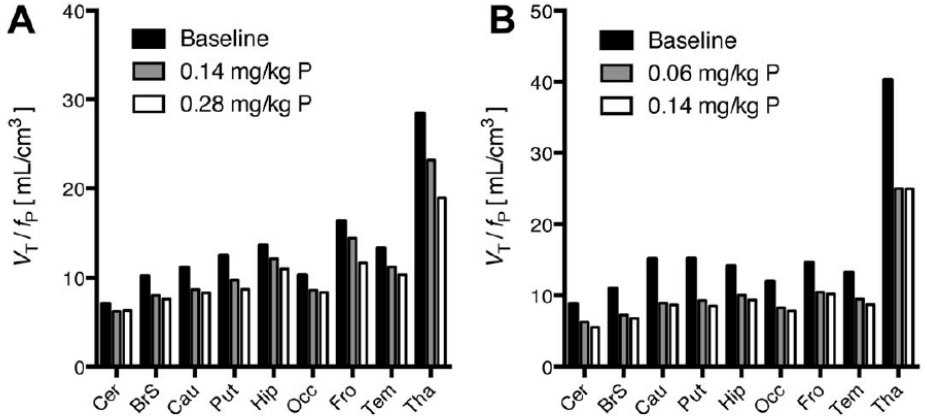


Fig. 3. Effect of physostigmine on ^{18}F-(-)-NCFHEB volumes of distribution: for each animal [(**A**) animal 1, (**B**) animal 2], physostigmine induced a dose-dependent reduction of ^{18}F-(-)-NCFHEB V_T/f_p estimates

Gallezot, Synapse 2014

Agonist Radioligands – Improved Sensitivity

[^{11}C]PHNO and 0.3 mg/kg d-amphetamine p.o. in the human brain

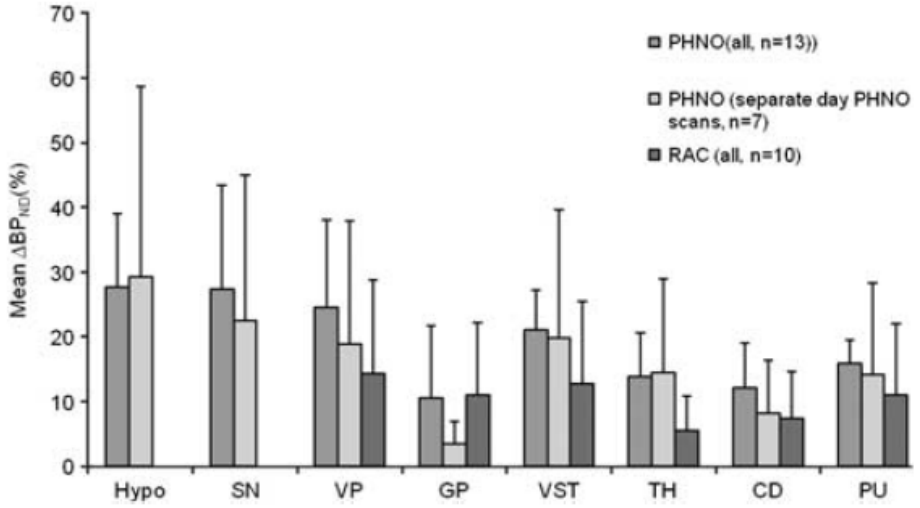
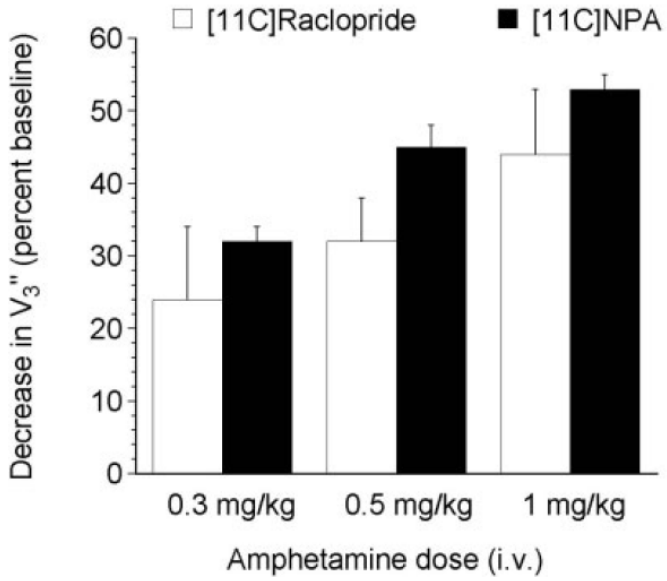


Figure 2 Reduction in BP_{ND} for [^{11}C]-(+)-PHNO and [^{11}C] raclopride after amphetamine. Columns represent mean values with associated s.d. error bars.

Shotbolt, JCBFM 2012

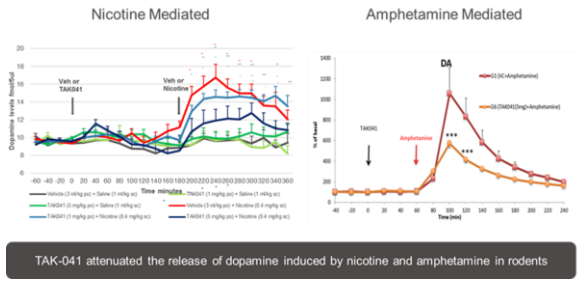
[^{11}C]NPA and d-amphetamine i.v. in the NHP brain



Narendran, Synapse 2004

Dopamine Modulation – Drug modified NT release

TAK-041 – Targets GPR-139 (orphan receptor) – no selective ligands identified



TAK-041 attenuated the release of dopamine induced by nicotine and amphetamine in rodents

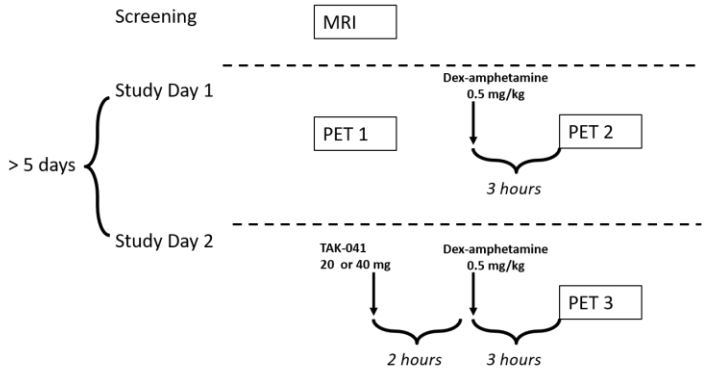
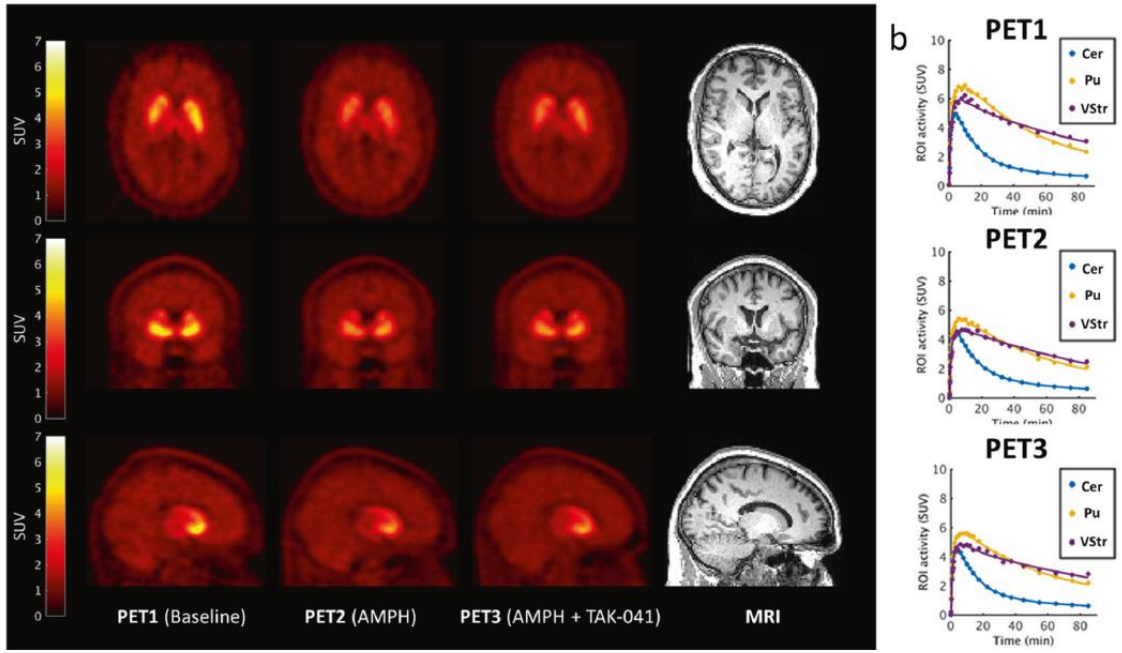
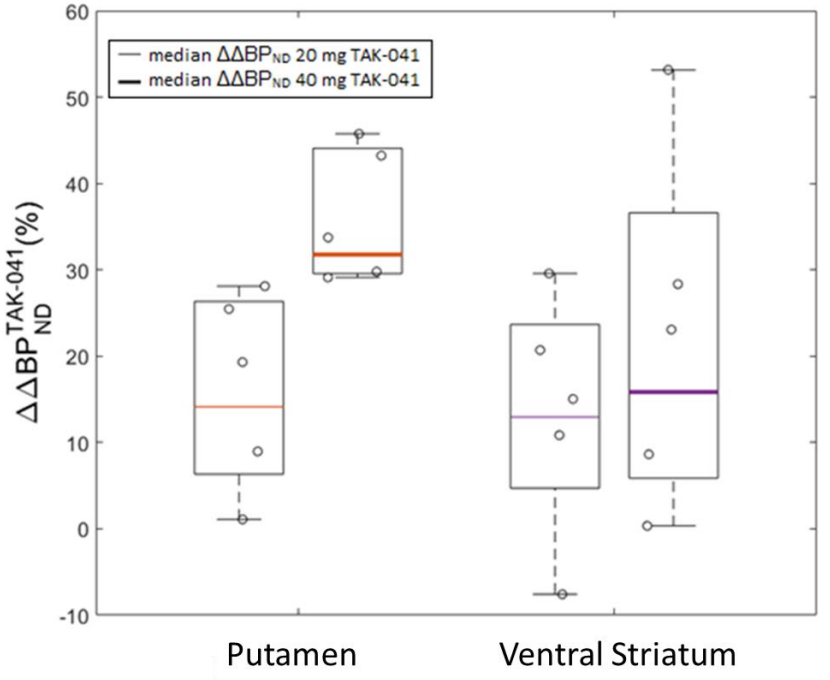


Fig. 1 Schematic of study design.





Rabiner et al, Neuropsychopharmacology, 2021

Pharmacokinetic and Pharmacodynamic Biomarkers

- Concentration of drug in tissue
- Drug-target interaction
- Change in molecular target density
- Change in molecular target affinity (allosteric modulation)
- Change in neurotransmitter release
- Change in brain activity and/or metabolism

Evaluation of Target Engagement and Target Modulation in Phase I

Invicro
A Konica Minolta Company

Background:

- GSK1521498 a novel m-opioid receptor (mOR) antagonist/inverse agonist in development for appetite dysregulation
- Modulation of mOR neurotransmission hypothesised to modulate brain reward mechanisms associated with eating behaviour
- Naltrexone – a relatively unselective mOR antagonist (affinity for dOR and kOR) is on the market

Aim:

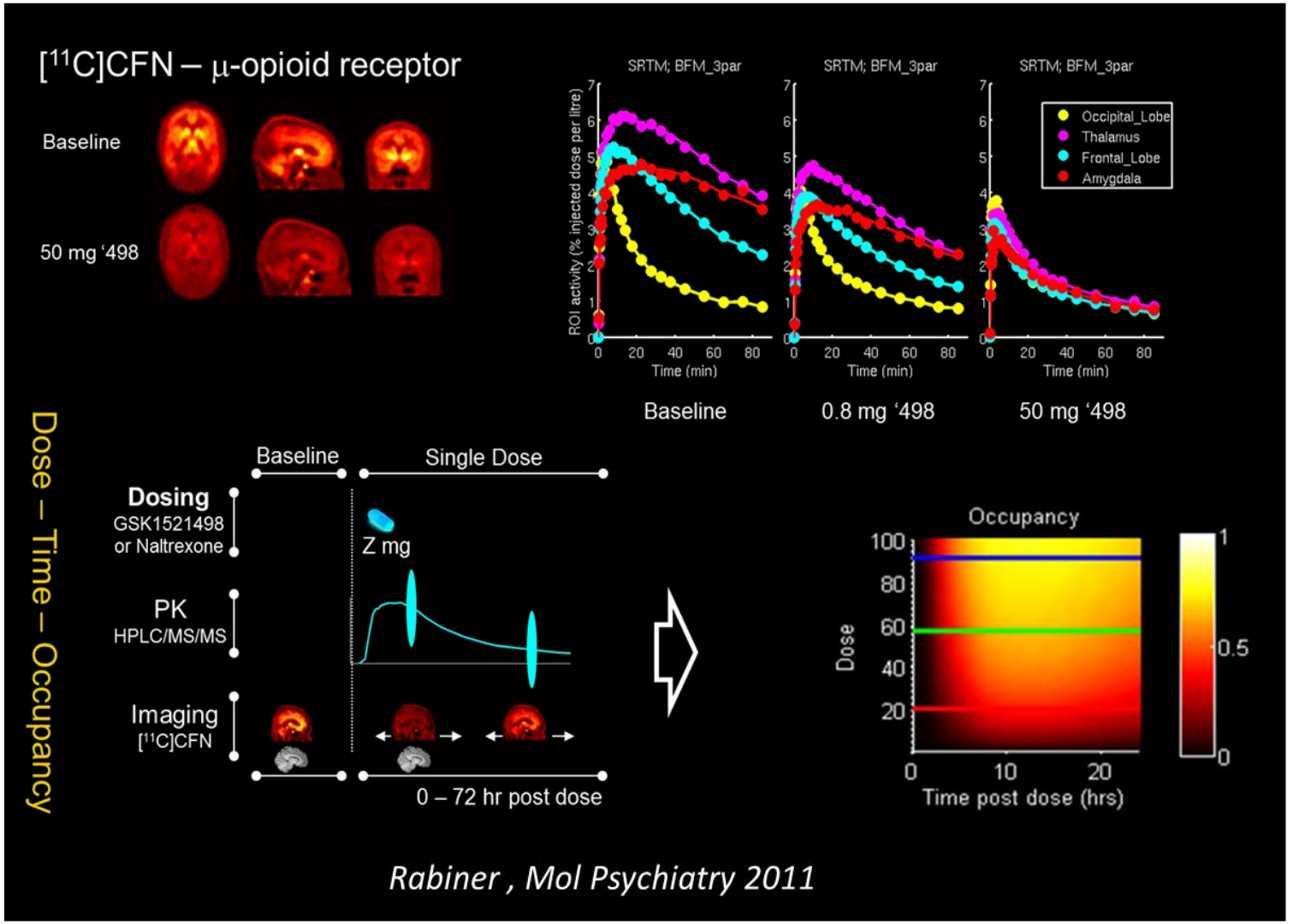
- Demonstrate the relationship between plasma drug concentration and mOR occupancy over time following a single oral dose, to enable the prediction of plasma concentration : mOR occupancy relationship following repeat dosing in clinical populations
- Demonstrate modulation of brain activity following mOR engagement by GSK1521498
- Compare GSK1521498 to Naltrexone

Study:

- Healthy volunteers, in parallel with first in human safety study
- Use [^{11}C]carfentanil PET to evaluate mOR time-occupancy relationship
- Use fMRI with a palatable food stimulus to evaluate brain reward mechanisms following drug administration

Rabiner et al, Mol Psychiatry 2011

Study Design

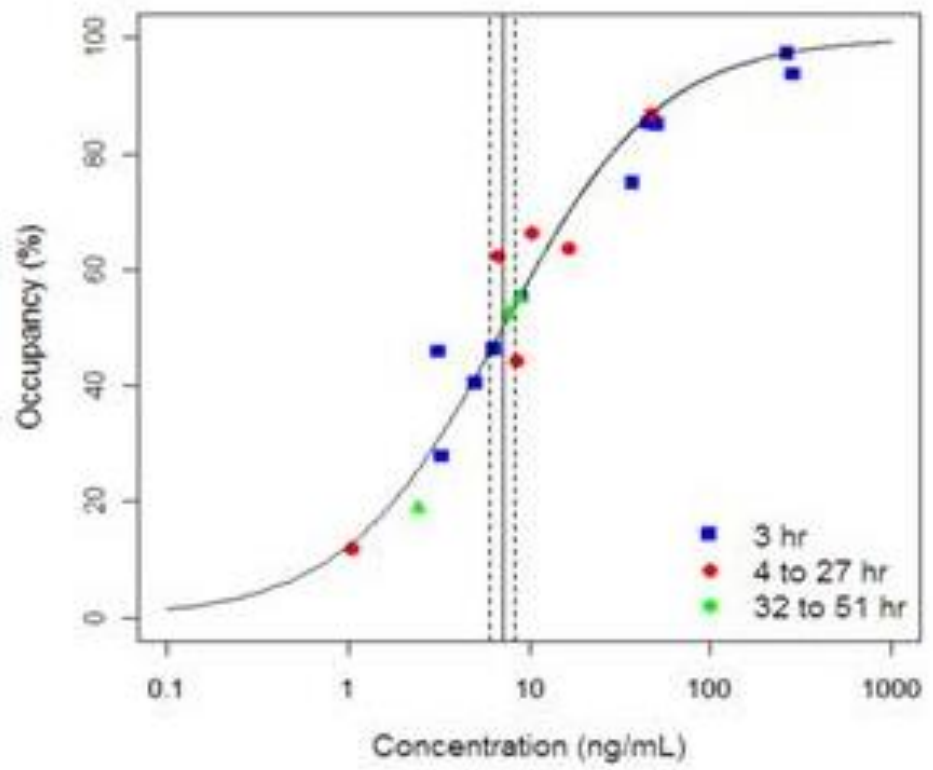


Rabiner et al, Mol Psychiatry 2011

Evaluation of the relationship between plasma concentration and target occupancy

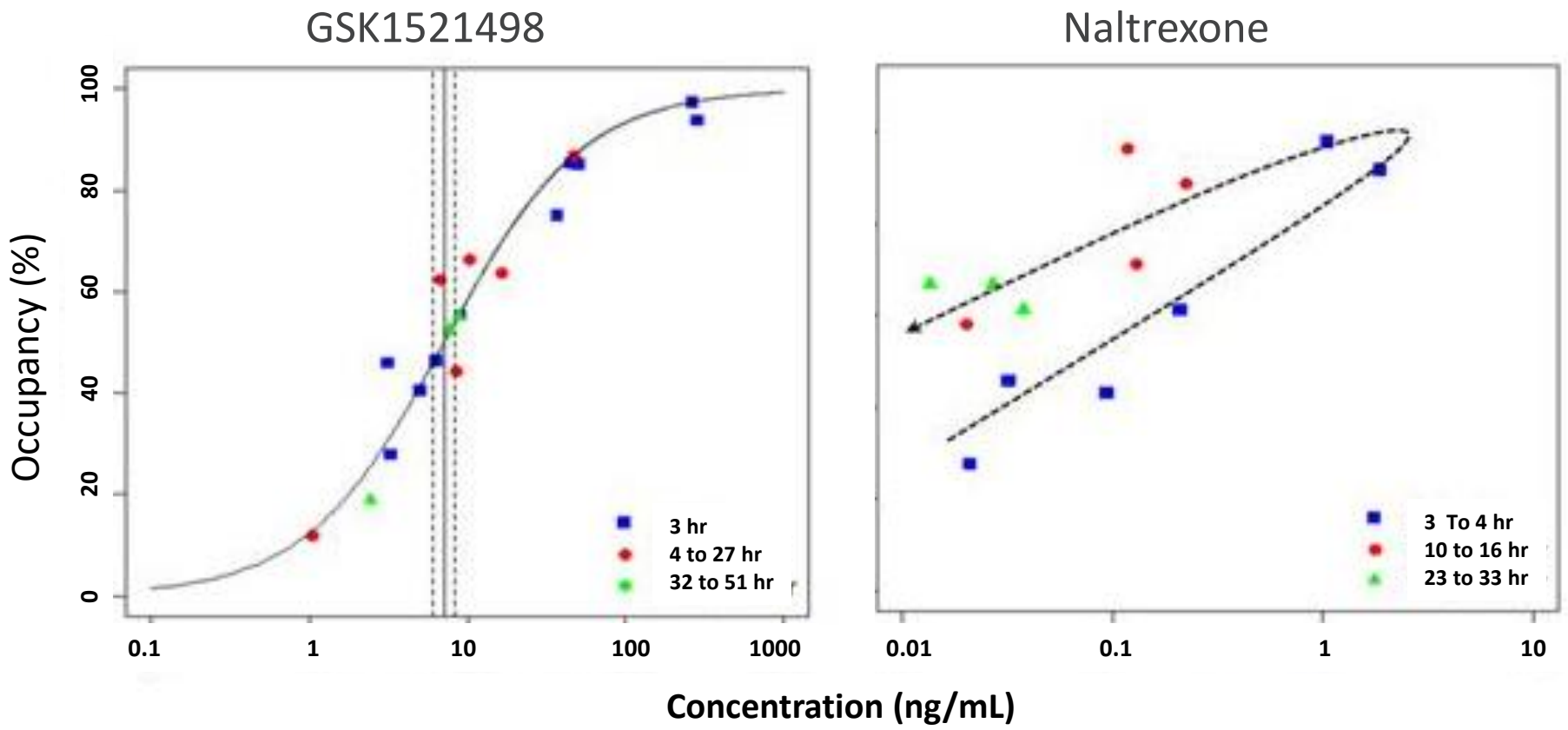
Quantification of Target Engagement

GSK1521498



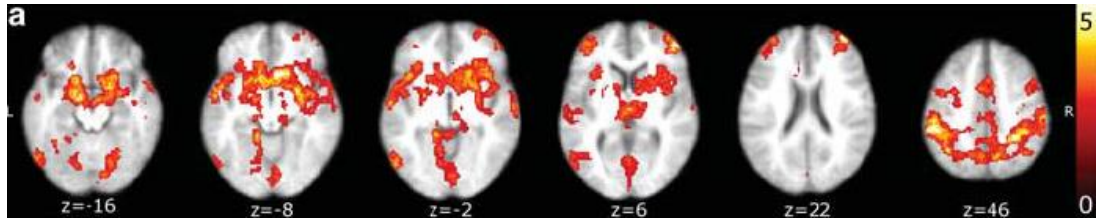
Evaluation of the relationship between plasma concentration and target occupancy

Quantification of Target Engagement

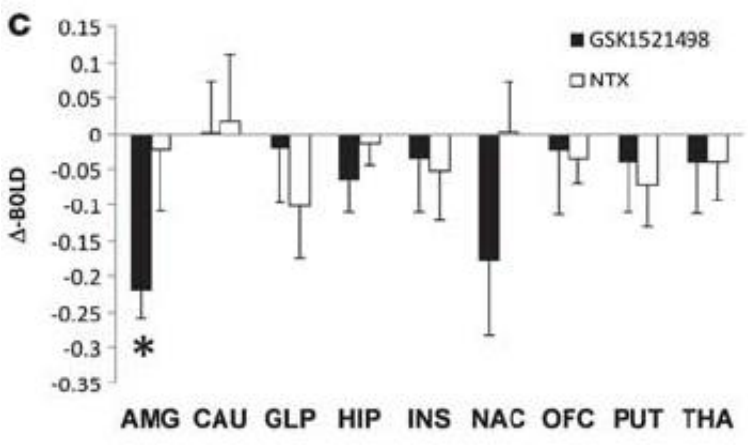


Synergies between Target Engagement and Target Modulation Evaluation

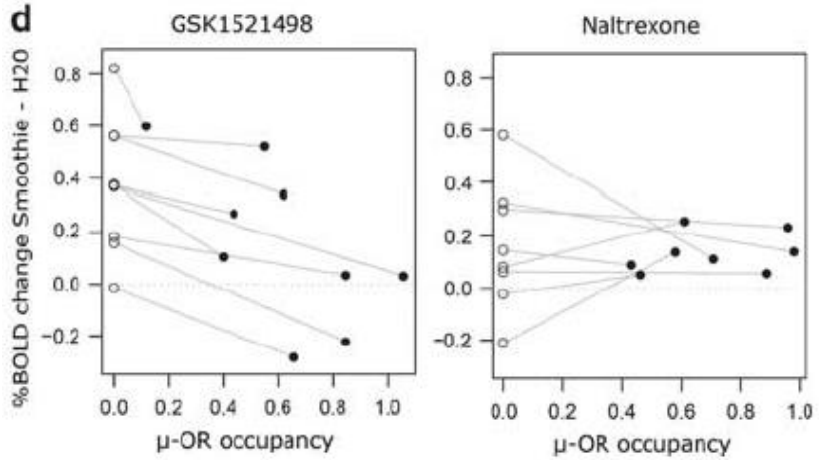
Assessment of Functional Modulation



Whole Brain Activation by High Fat/High Sugar Smoothie vs Water



Effects of m-OR Blockade on Brain Activation in Response to Palatable Food

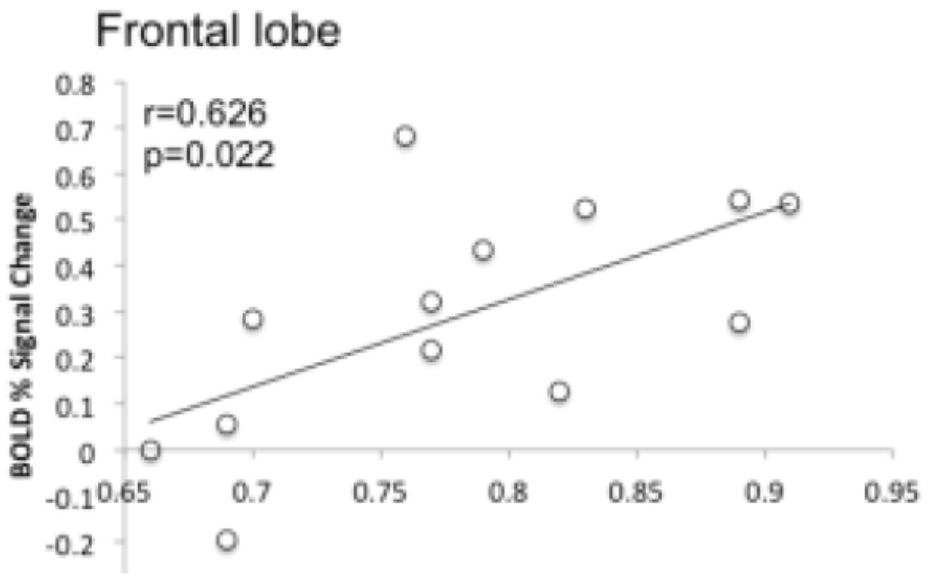


Relationship Between m-OR Occupancy and Amygdala Activation by Palatable Food

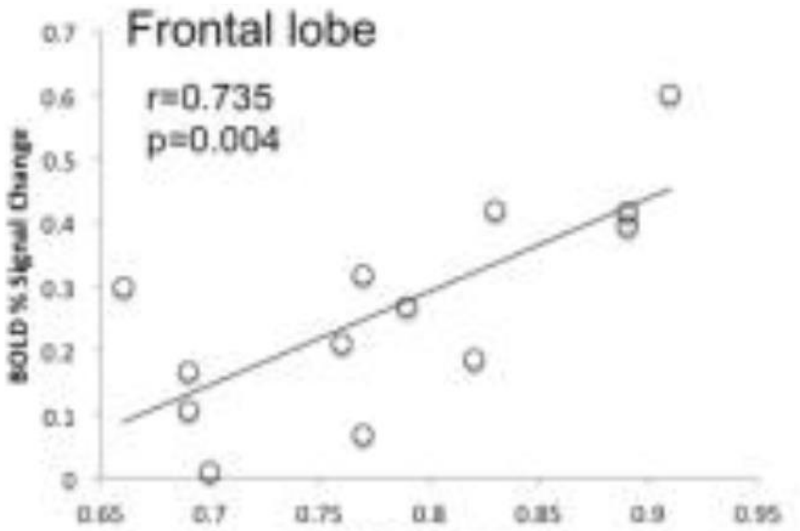
Rabiner et al, Mol Psychiatry 2011

Relationship of BOLD fMRI signal change and occupancy of a novel target

N-Back task



"switching" task



THANK YOU