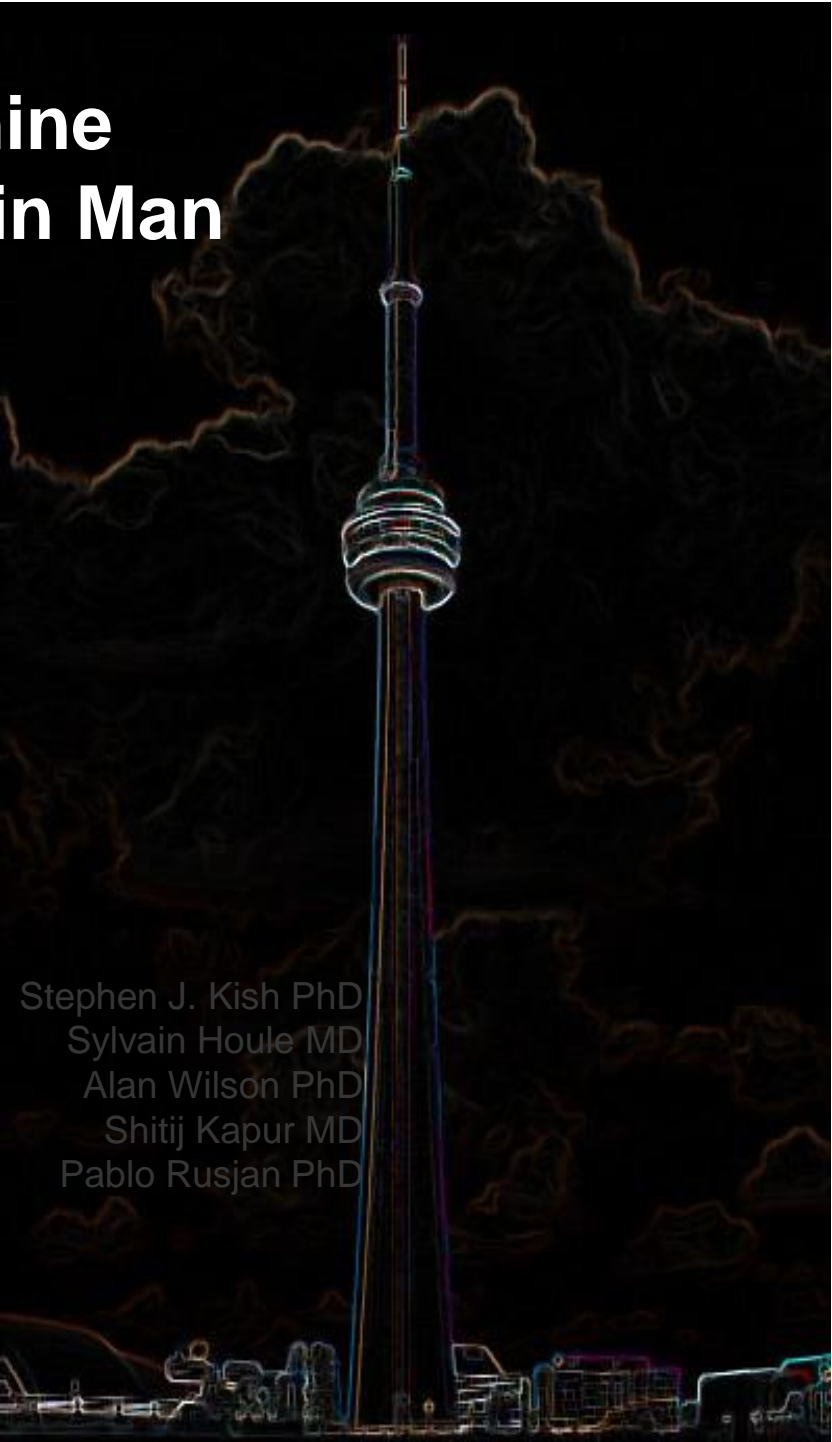


Amphetamine Sensitization in Man



Chawki Benkelfat MD
Alain Dagher MD
Marco Leyton PhD
Linda Booij PhD
Krzysztof Welfeld



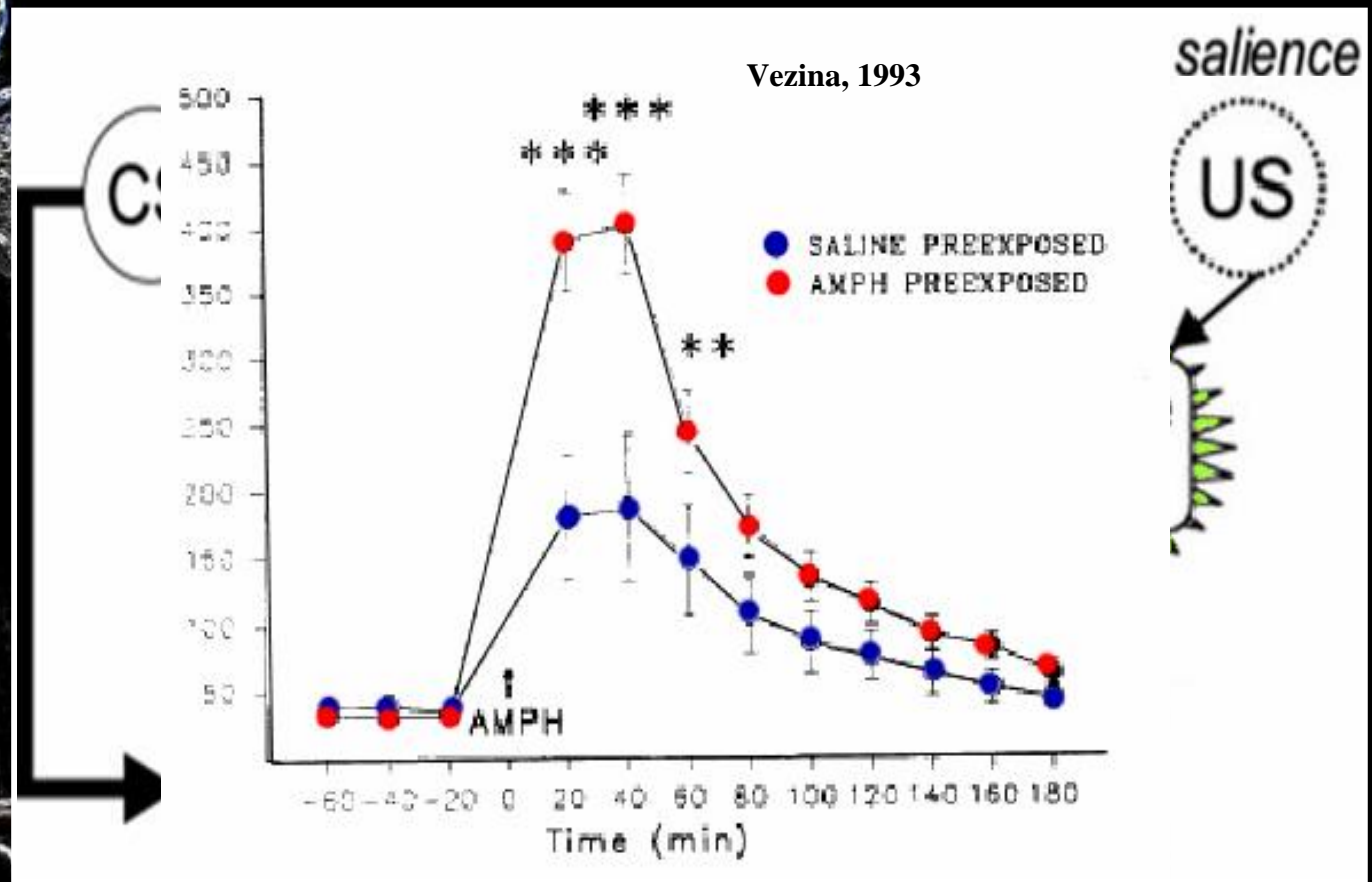
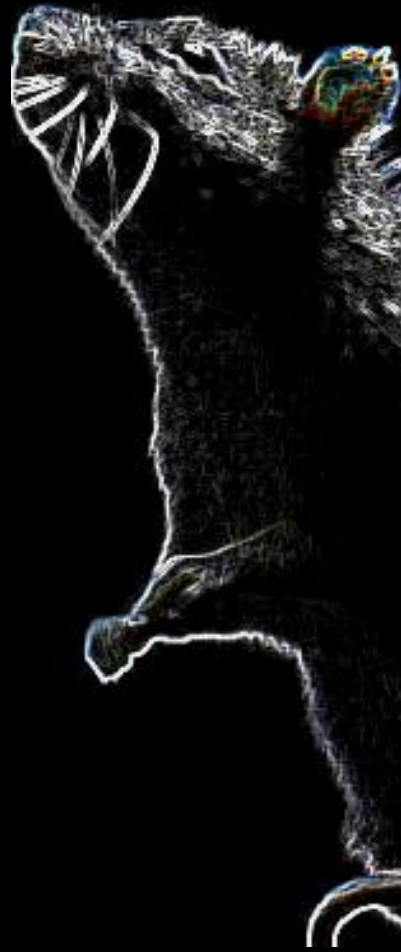
Stephen J. Kish PhD
Sylvain Houle MD
Alan Wilson PhD
Shitij Kapur MD
Pablo Rusjan PhD

GENERAL OBJECTIVE

- Does sensitization occur in humans?
- Is it measurable in the laboratory?
- Why are we interested in measuring it?



Sensitization as a Model of Addiction

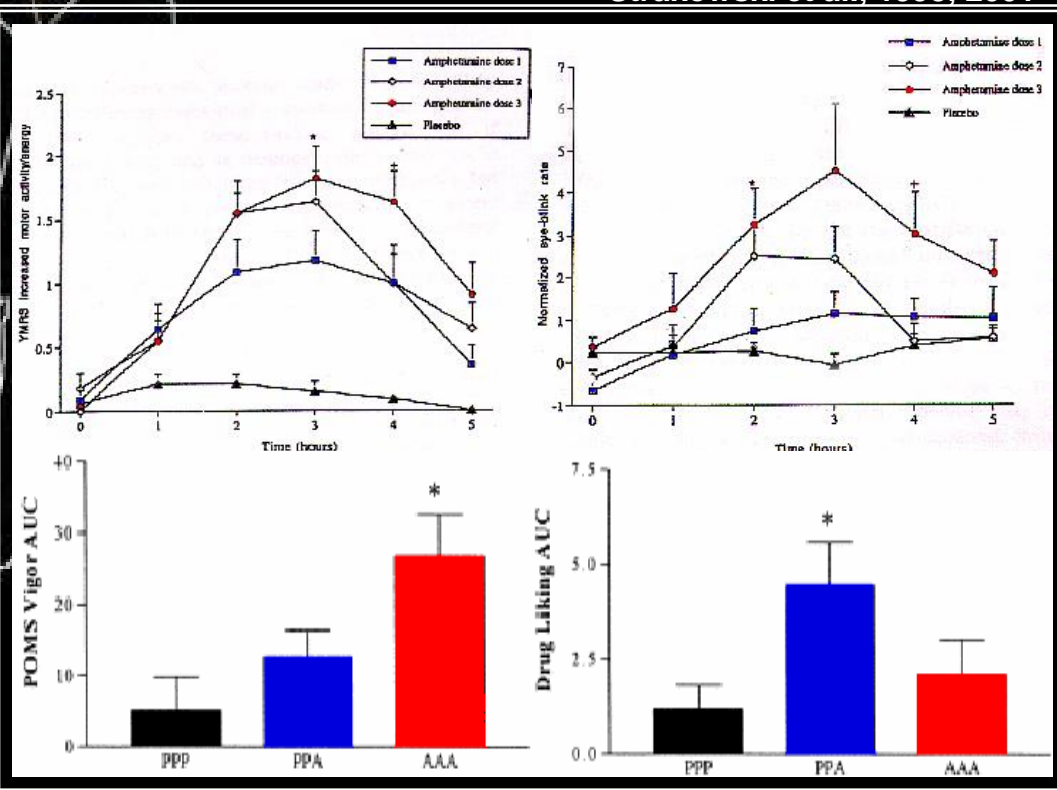


In controlled Studies

Strakowski et al., 1998, 2001



0.25 mg/kg per 48 hours



motor activity, # self-reported vigor, # eye-blink rate but not drug-liking

Sensitization as a Model of Psychosis



K. Yui · T. Ishiguro · K. Goto · S. Ikemoto · Y. Kamata

**Spontaneous recurrence of methamphetamine psychosis:
increased sensitivity to stress associated
with noradrenergic hyperactivity and dopaminergic change**

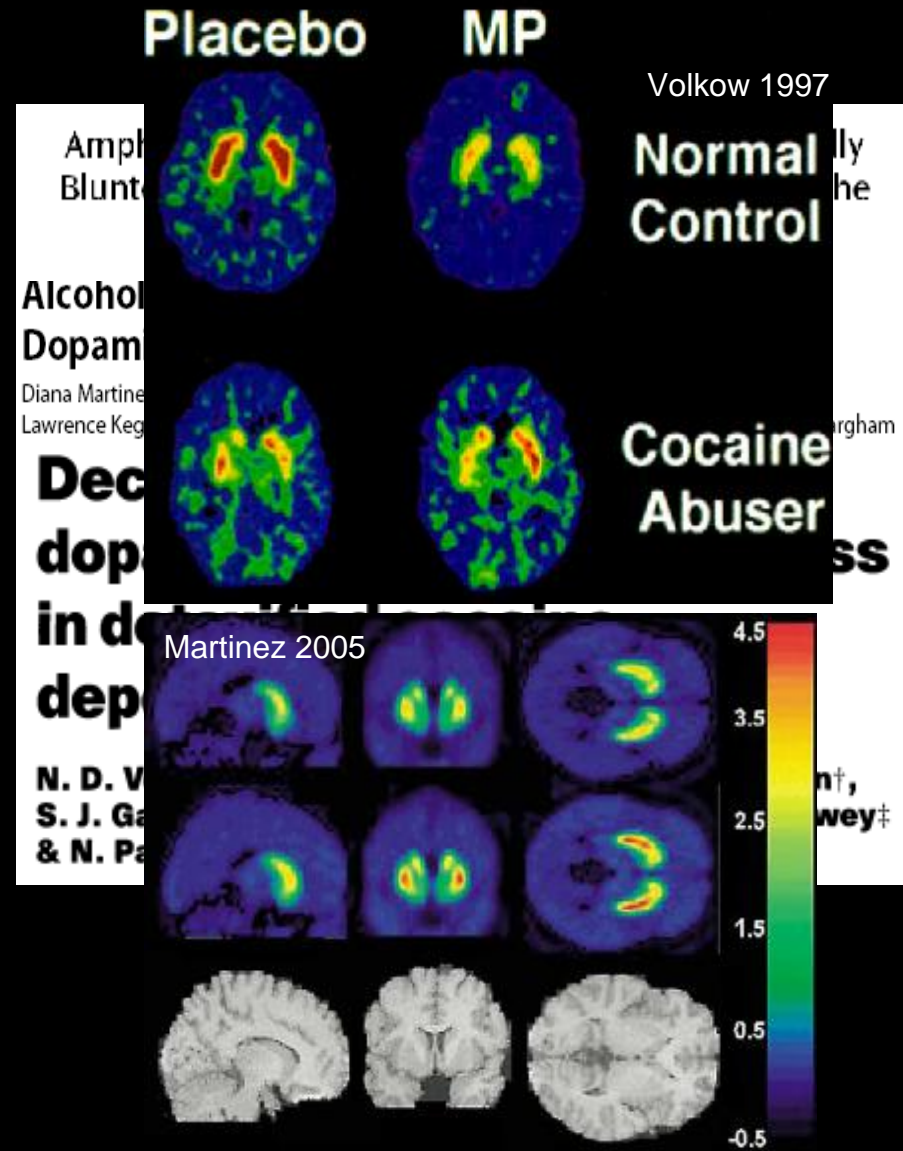
**Neurobiological basis of relapse prediction in stimulant-
induced psychosis and schizophrenia: the role of
sensitization**

K Yui¹, K Goto², S Ikemoto³, T Ishiguro¹, B Angrist¹, GE Duncan², BB Sheitman², JA Lieberman², SH Bracha^{1*} and SF Ali¹

**Clinical Features of Sensitization to
Methamphetamine Observed in Patients with
Methamphetamine Dependence and Psychosis**

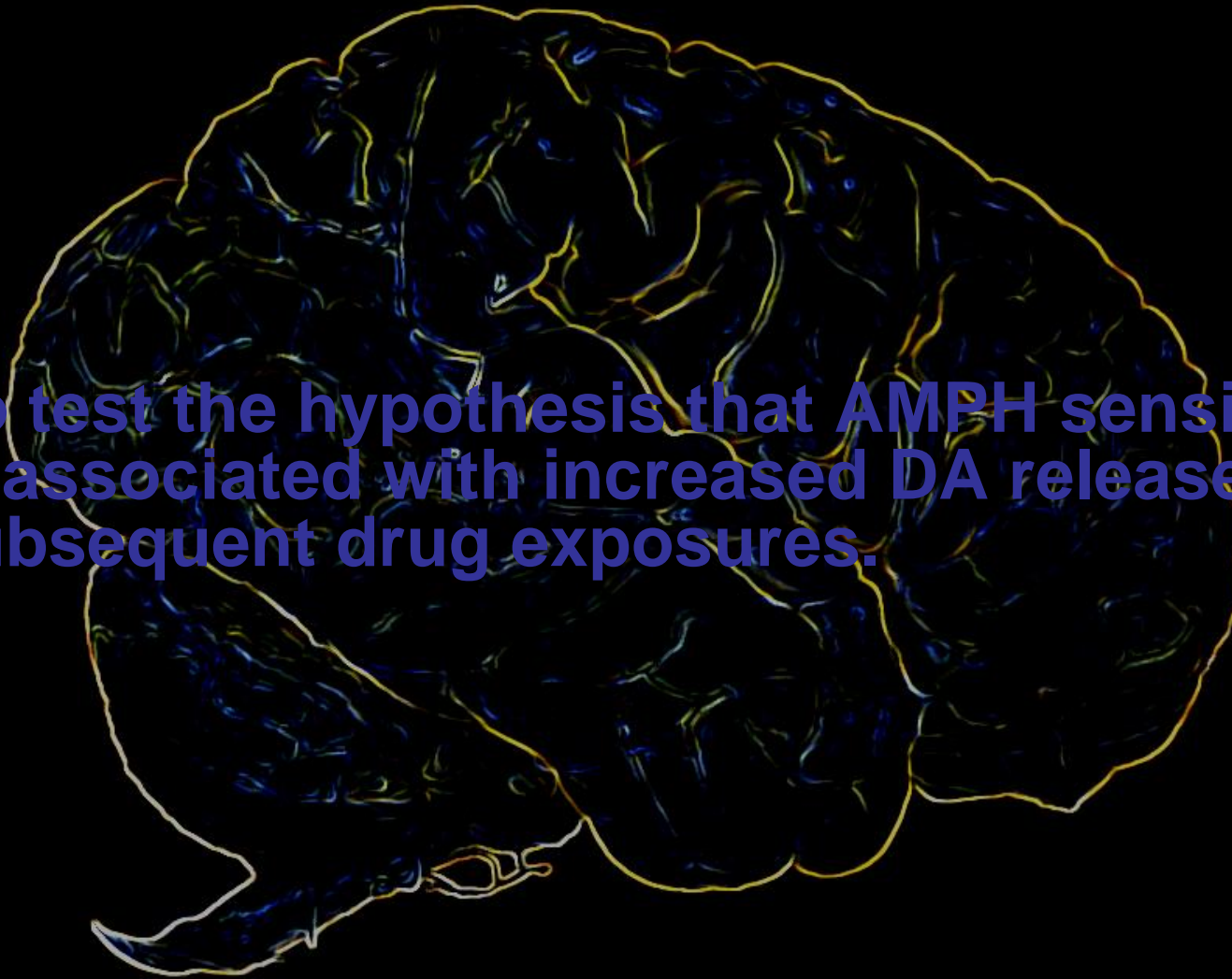
HIROSHI UJIKE^a AND MITSUMOTO SATO^b

Dopamine and Sensitization in Addiction

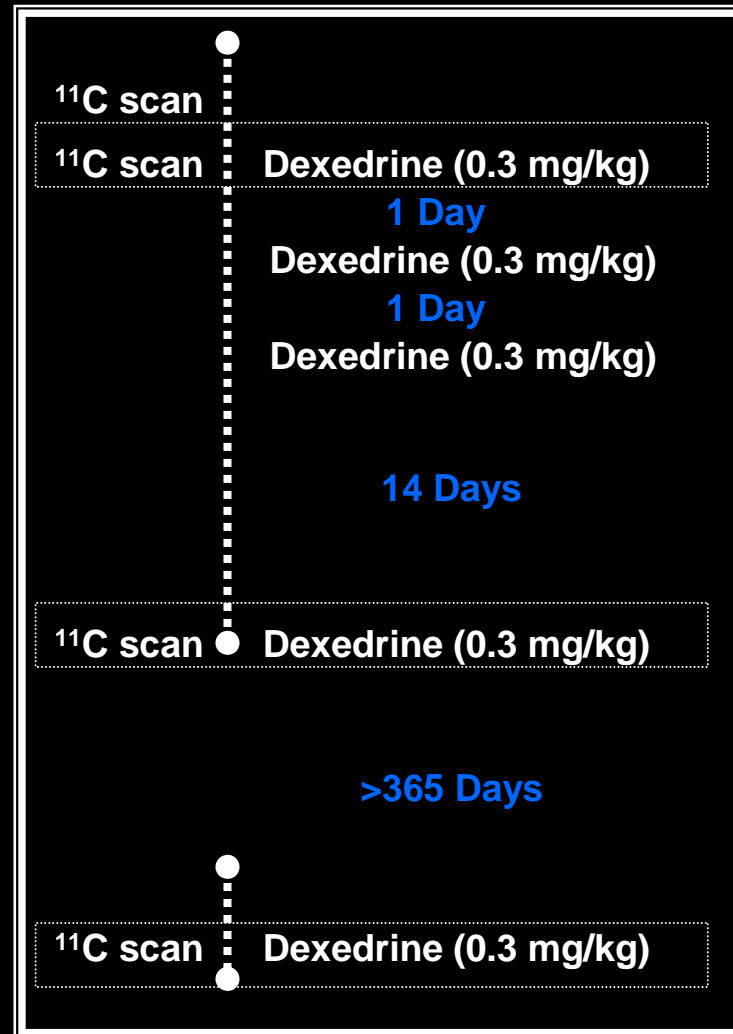


AIM of STUDY I

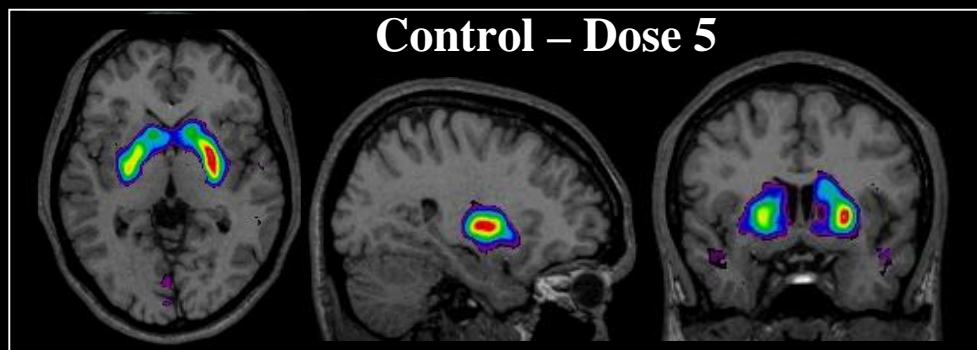
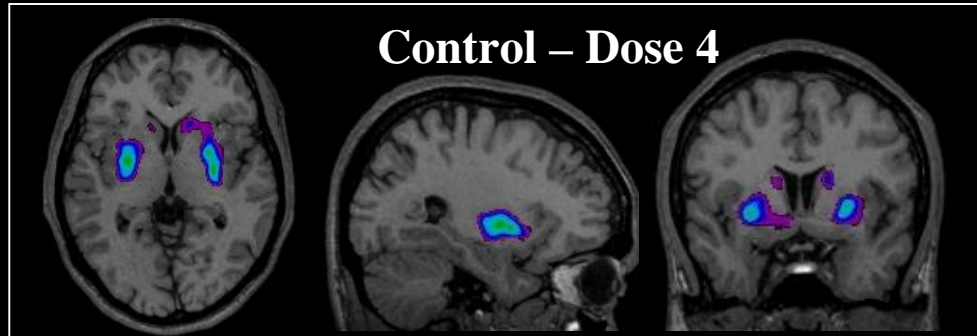
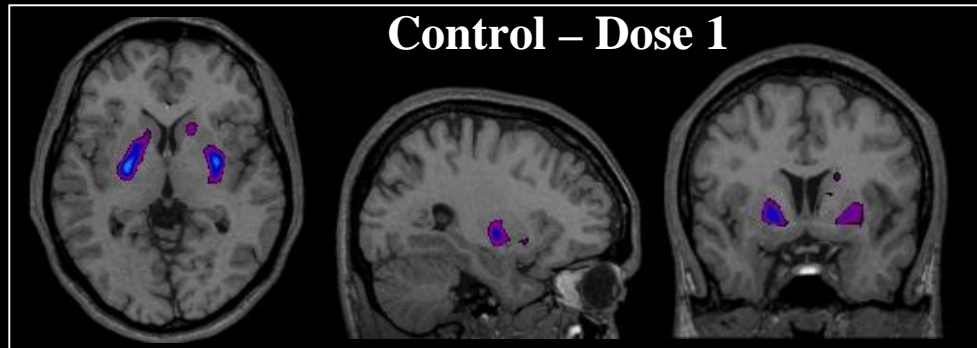
- To test the hypothesis that AMPH sensitization is associated with increased DA release at subsequent drug exposures.



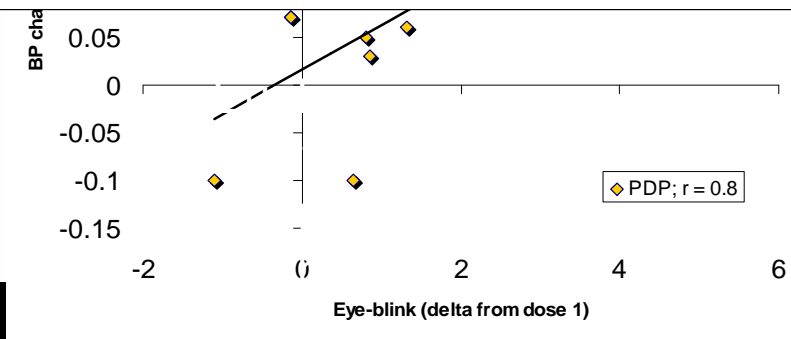
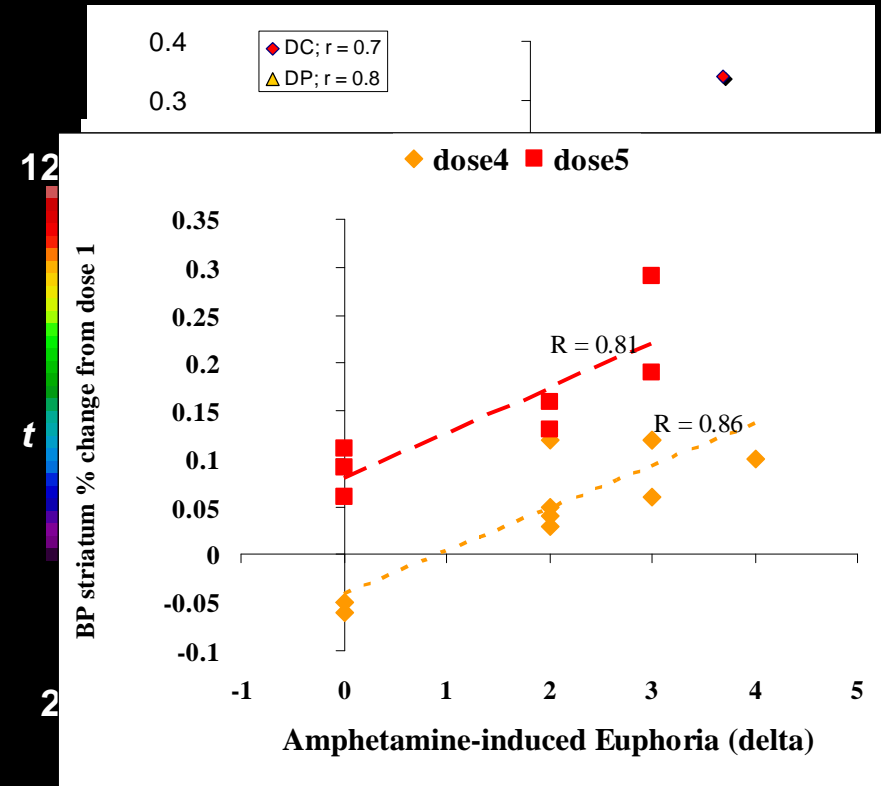
Experimental design



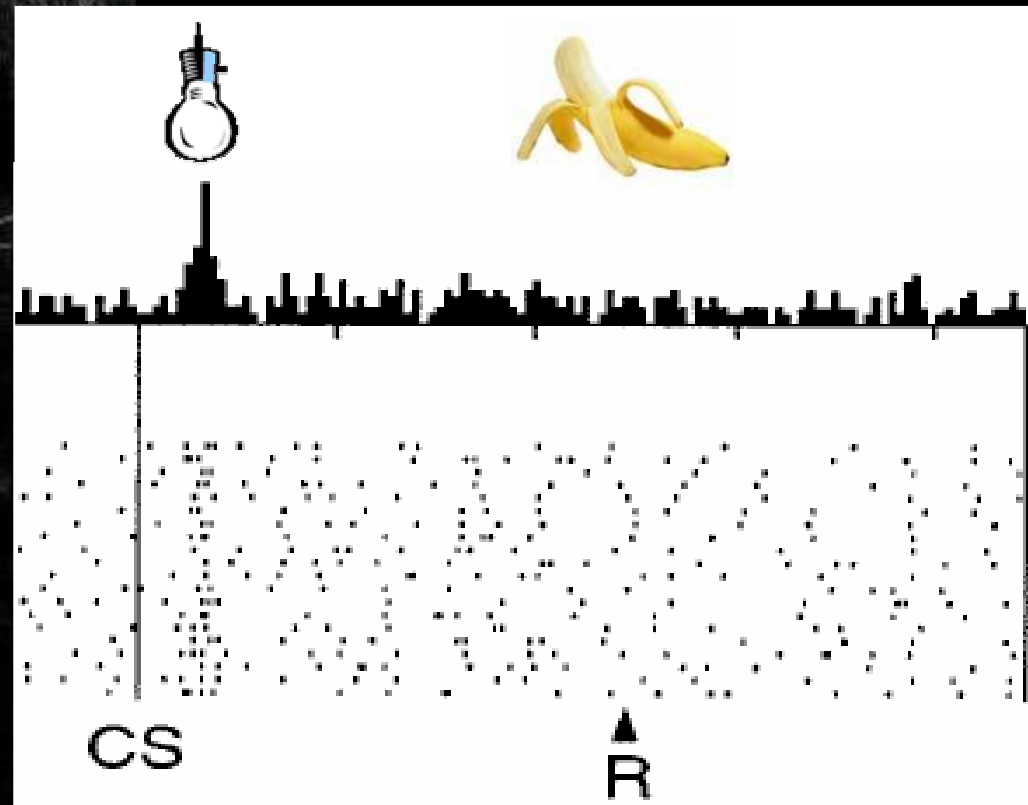
RESULTS



x: 28; y:2; z: 0



Anticipation of reward?

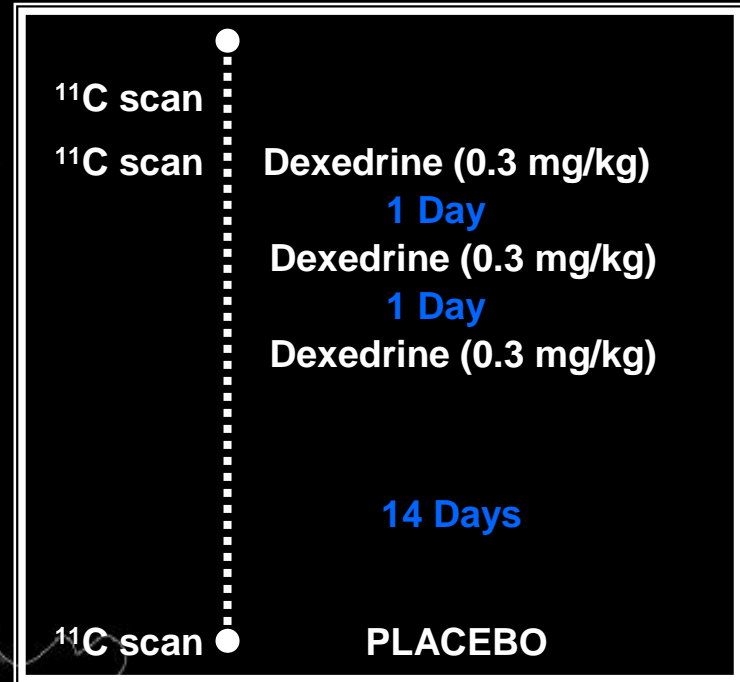
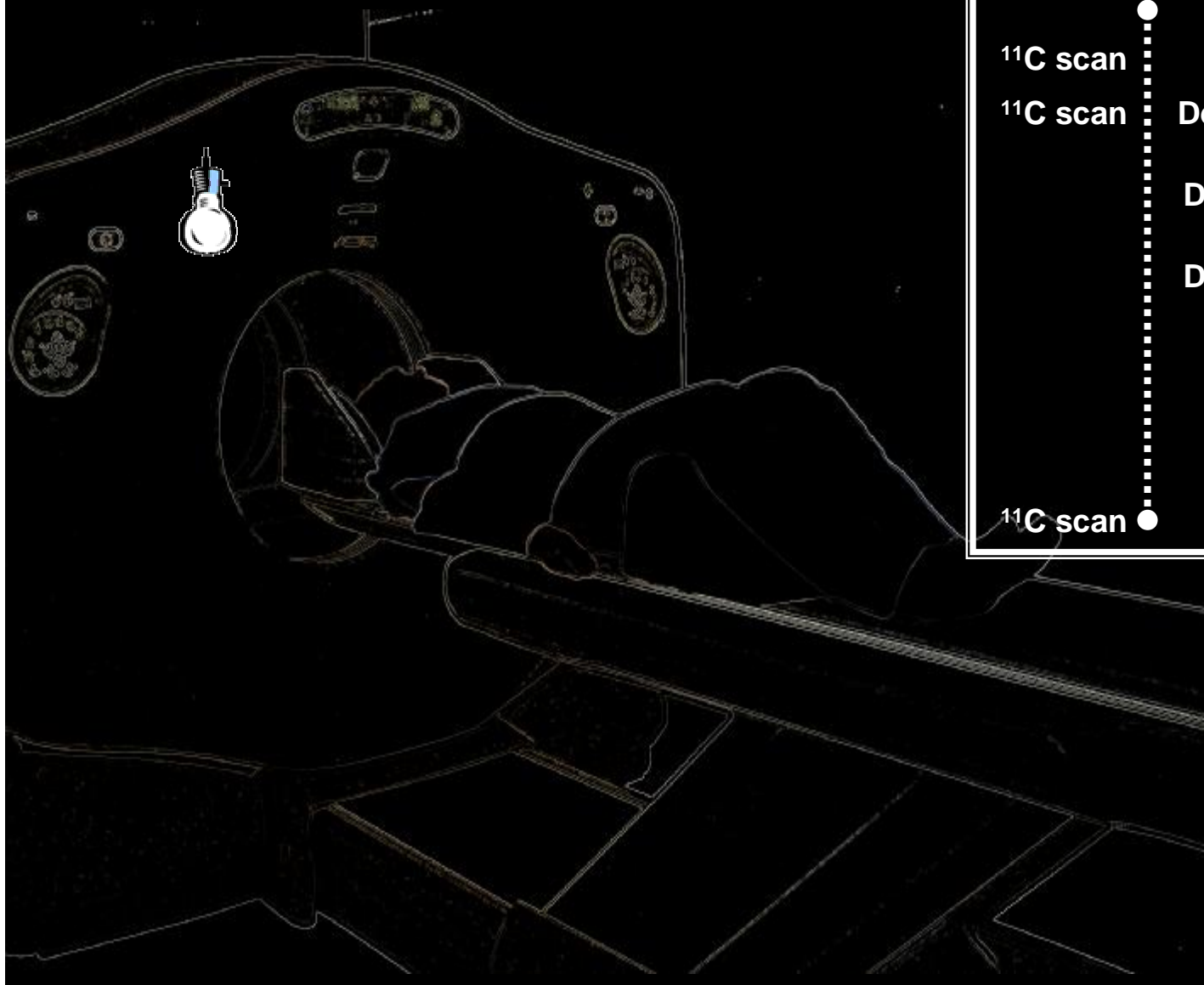


AIM of STUDY II

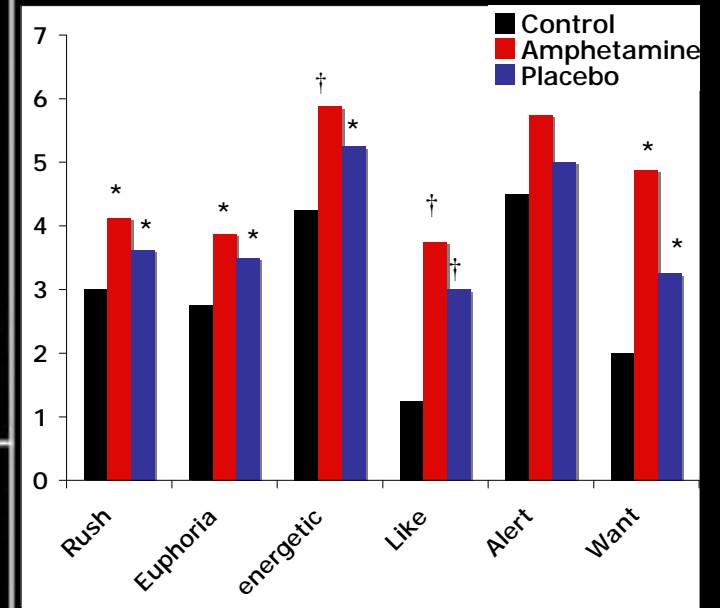
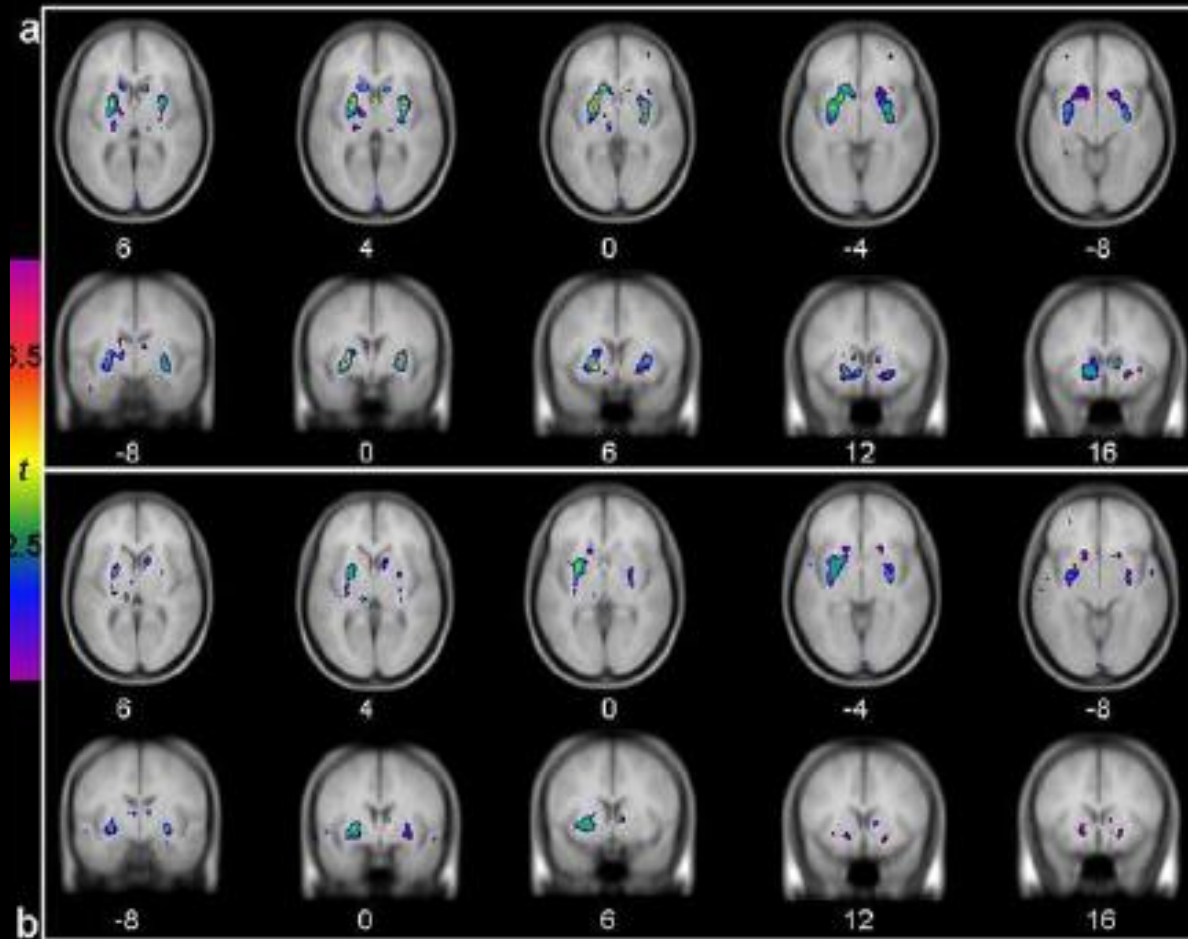
§To investigate whether conditioned reinforcer increases DA release in human.



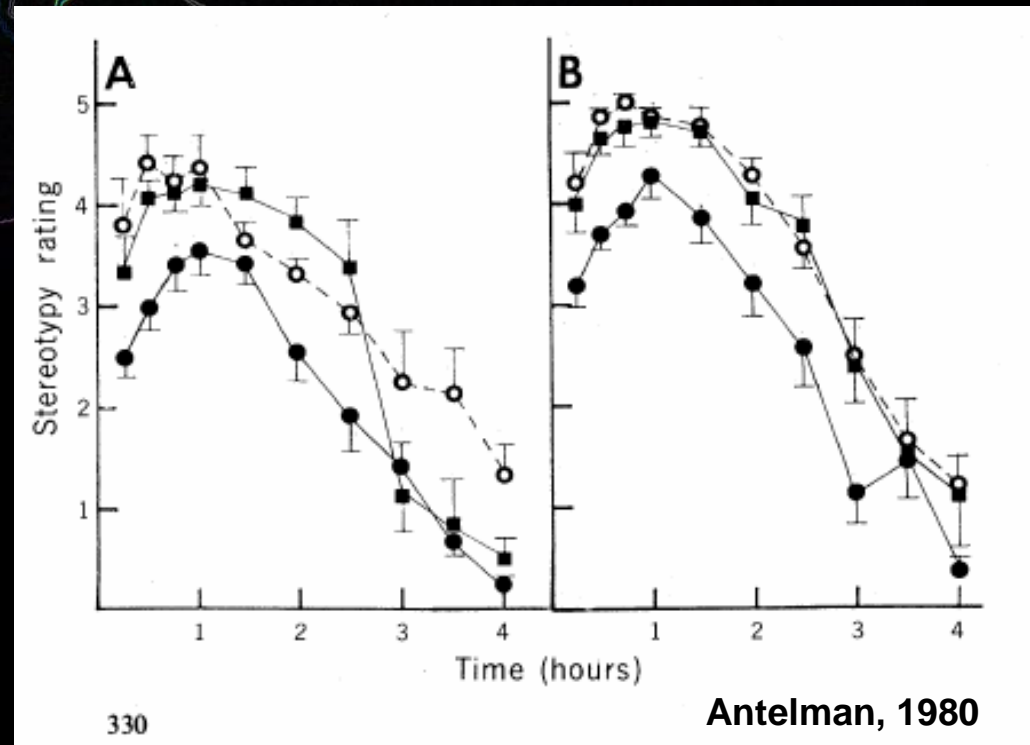
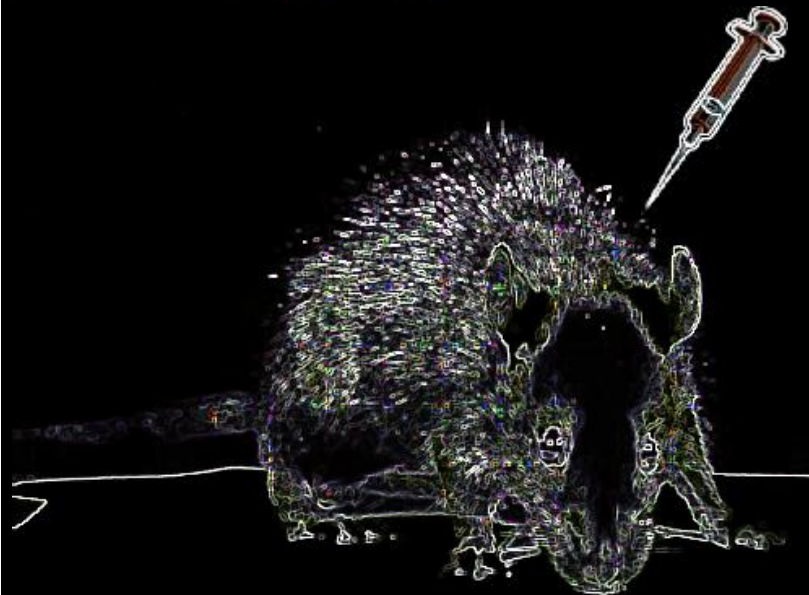
Experimental design



RESULTS



Stress Cross-sensitization



330

Antelman, 1980

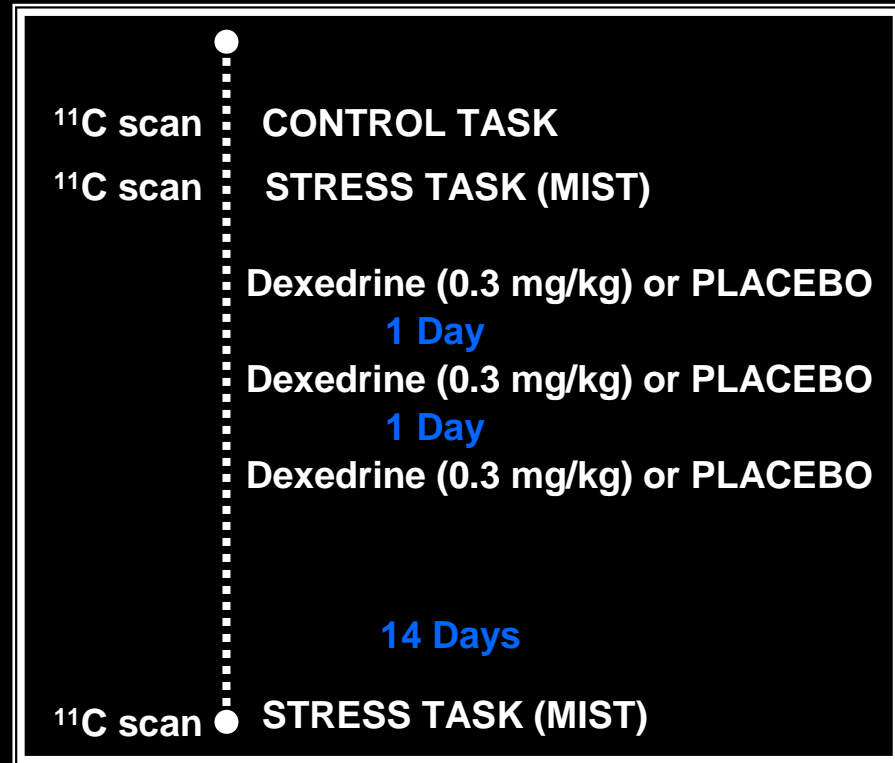
AIM of STUDY III

§To investigate whether amphetamine increases DA release during stress in human



Experimental design

$$\frac{\partial}{\partial \theta} M(r(\xi)) = \frac{\partial}{\partial \theta} \int T(x) f(x, \theta) dx = \int \frac{\partial}{\partial \theta} T(x) f(x, \theta) dx$$
$$\frac{\partial}{\partial a} \ln f_{a, \sigma^2}(\xi_1) = \frac{(\xi_1 - a)}{\sigma^2} f_{a, \sigma^2}(\xi_1) = \frac{1}{\sigma^2} \left(\frac{\xi_1 - a}{\sigma^2} \right) f_{a, \sigma^2}(\xi_1)$$
$$\int T(x) \cdot \frac{\partial}{\partial \theta} f(x, \theta) dx - M(r(\xi)) \cdot \frac{\partial}{\partial \theta} \ln f(\xi)$$



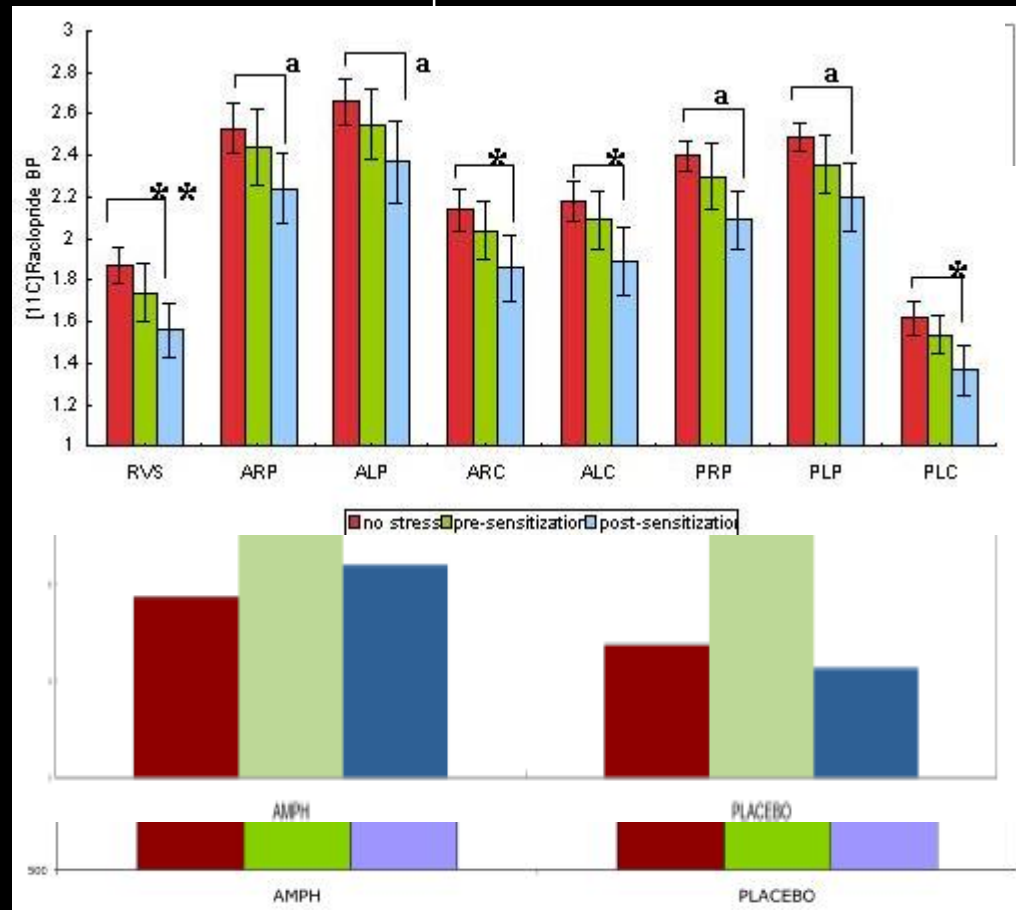
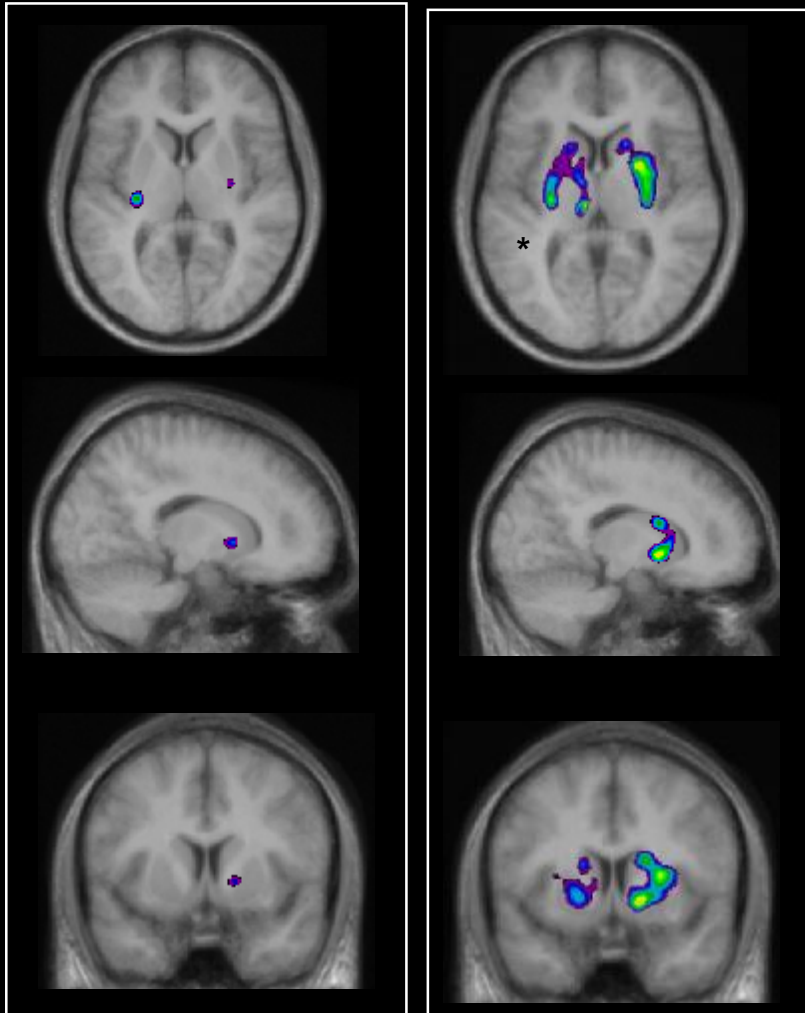
RESULTS

STRESS VS CONTROL TASK

Pre-sensitization

Post-sensitization

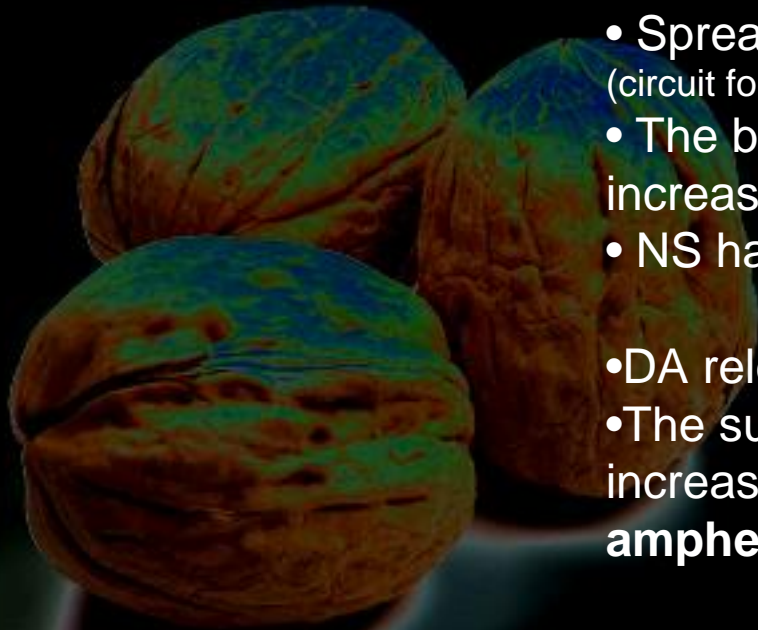
Placebo Condition

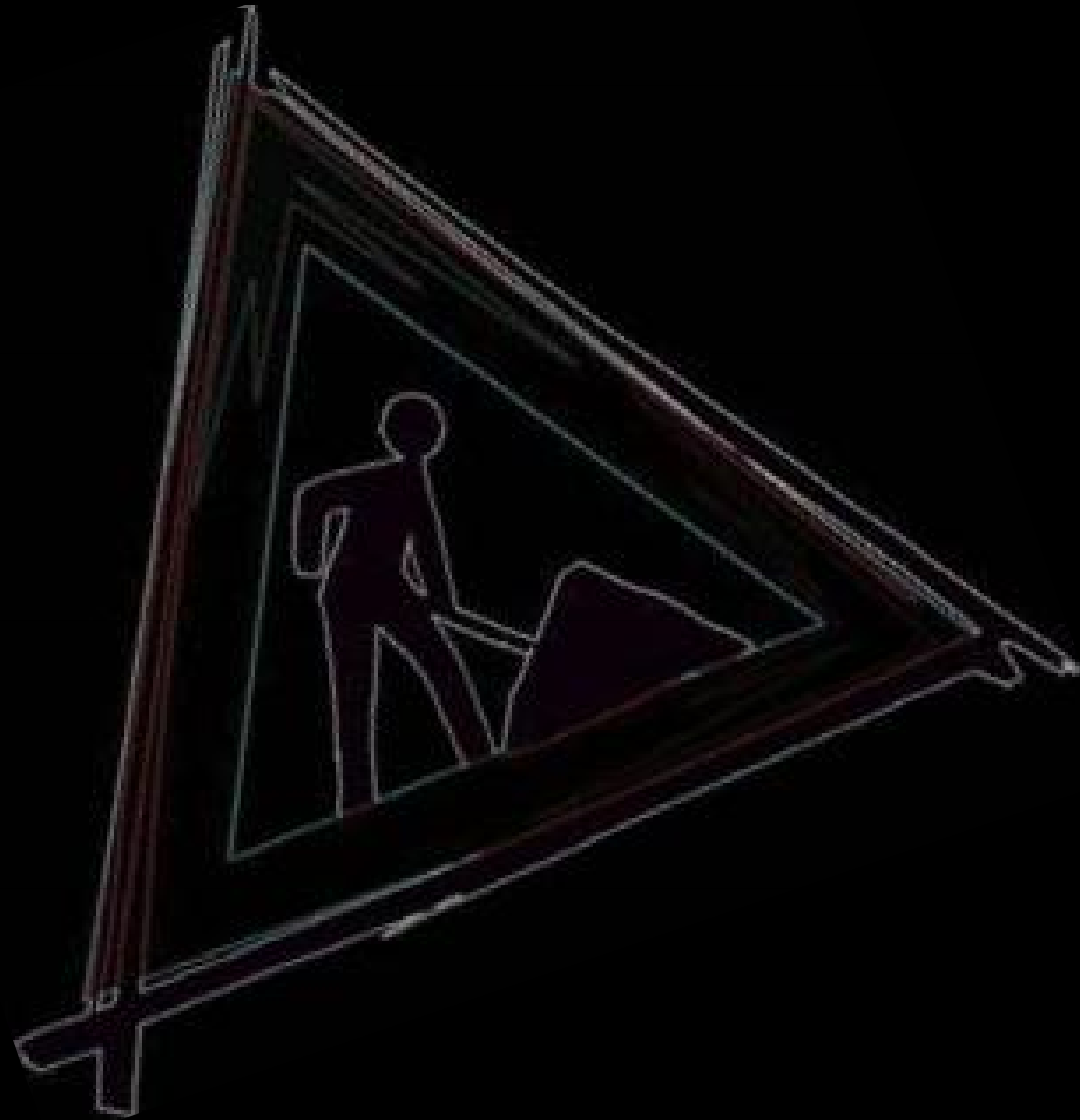


Summary of Main Findings

As drug exposure is repeated...

- The effects on DA progressively get bigger (50%)
- Enduring (after 1 year)
- Spread dorsally to include the dorsal striatum (circuit for habit formation?)
- The behavioral correlates of sensitization = increased *alertness, energy*
- NS have a higher propensity to sensitize
- DA release is modulated by **anticipation**
- The substitution of the amphetamine for a placebo increased **DA to the same extent as amphetamine**
- A sensitizing amphetamine regimen seems to potentiate the response to the laboratory **stress** task





Increased expression of D₃ receptors in MA users?

Induction of dopamine D₃ receptor expression as a mechanism of behavioral sensitization to levodopa

(Parkinson disease/*l*-hydroxyamphetamine/rotation behavior/prodynorphin/preproenkephalin)

RÉGIS BORDET^{1,2}, SOPHIE RIDRAY¹, SUZANNA CARBONI², JORGE DIAZ³, PIERRE SOKOLOFF⁴, AND JÉRÔME FAURE^{1,2}

AND JÉRÔME FAURE^{1,2}

¹Laboratoire de Neurobiologie de l'Université de la Méditerranée

BD

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Jean

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Marie

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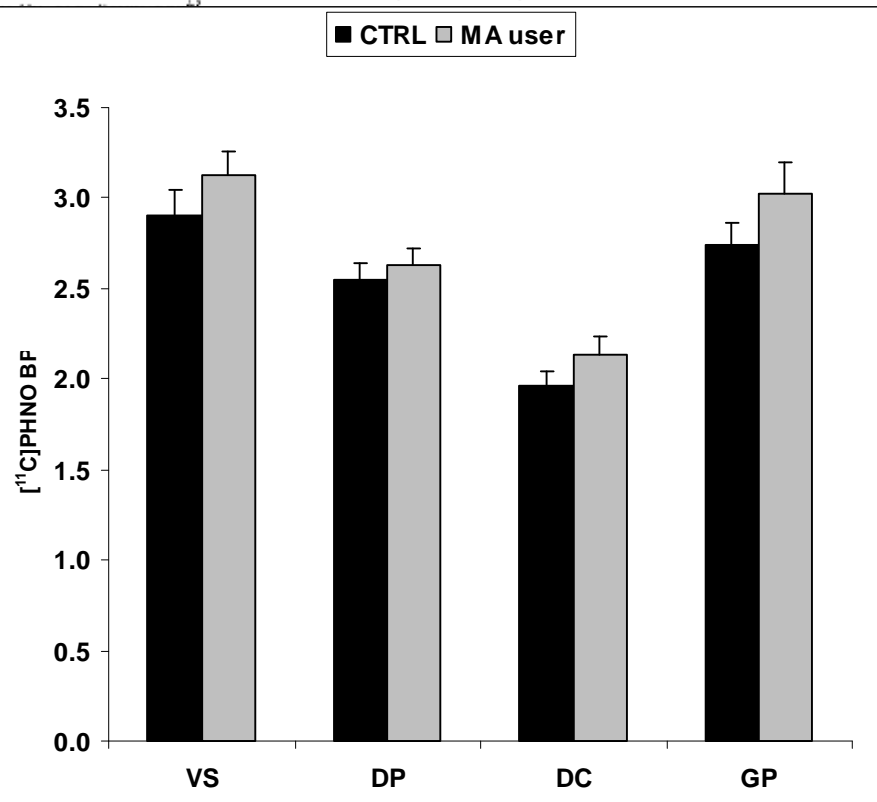
Jean

Be

Do

Dopamine (D_{2/3}) Receptor Agonist Position Emission Tomography Radiotracer [¹¹C]-(+)-PHNO is a D₃ Receptor Preferring Agonist In Vivo

RAJESH NARENDRA^{1,2}, MARK SLIFSTEIN^{1,2}, OLIVIER GUILLEN^{1,2}, YUYING HWANG^{1,2}, DAH-REN HWANG^{1,2,3}, ERICA SCHER^{1,2}, STEPHANIE REEDER^{1,2}, EUGENII RABINER³, AND MARIE-LAURELLE^{1,2,3}



Thank you!