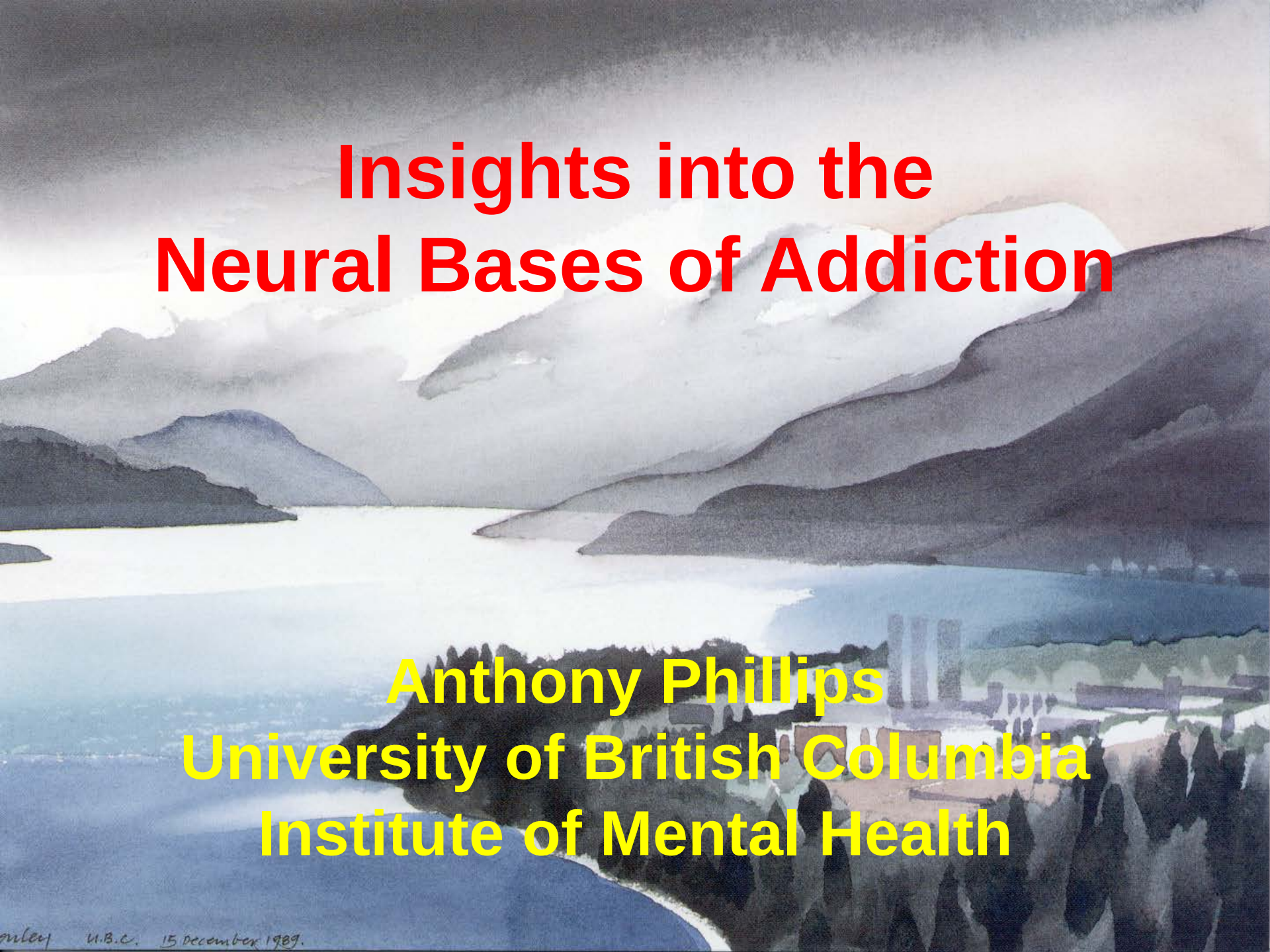

Insights into the
Neural Bases of Addiction
Anthony Phillips
University of British Columbia
Institute of Mental Health
U.B.C. 15 December 1989.

# Drug addiction is a brain disease with the following cardinal features:

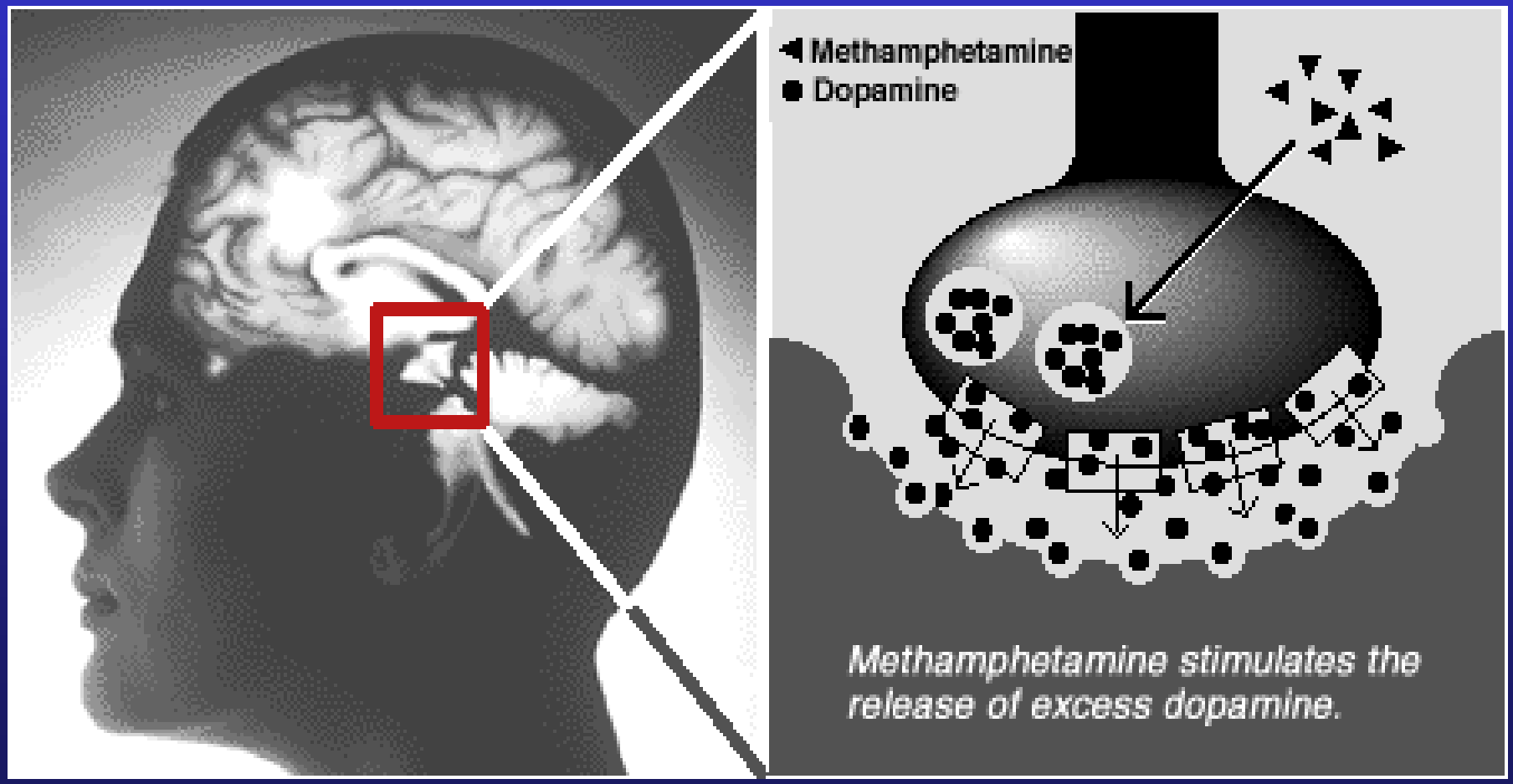
- Compulsive thoughts and actions directed towards procuring and administering a drug of choice
- A very strong tendency to reinstate drug seeking behaviours to such a degree that addiction appears to be a “chronic relapsing disorder”
- Relapse can be induced by:
  - **re-exposure to the drug**
  - **re-exposure to conditional stimuli**
  - **exposure to stressors**
- Relapse may be subserved by dopamine-glutamate interaction

# Key Assumptions

- All drugs of abuse exert powerful effects on brain neurochemistry
- All drugs of abuse ‘high-jack’ brain function related to natural motivation and reward processes
- Repeated exposure to drugs of abuse causes long-lasting modification of brain structure and function.
- Environmental stimuli and direct pharmacological effects of drugs of abuse in combination are major determinants of addiction

# All Drugs of Abuse Exert Powerful Effects on Brain Neurochemistry

## Methamphetamine at the synapse



Reprinted from
9 February 1973, Volume 179, pp. 575-577

SCIENCE

# Dopaminergic and Noradrenergic Substrates of Positive Reinforcement: Differential Effects of d- and l-Amphetamine

Anthony G. Phillips and Hans C. Fibiger

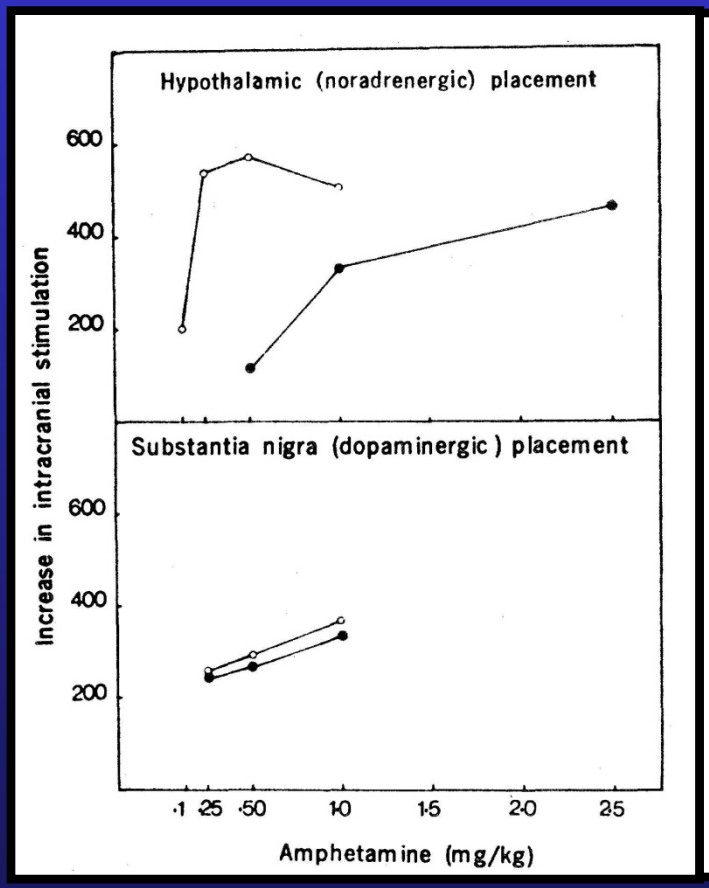



Fig.1 Increase in intracranial self-stimulation (ICS) above control levels from two electrode placements in the brain, produced by different doses of *d*- (○--○) and *l*-amphetamine (●--●). Control levels were obtained for each animal by determining the difference between two daily 15-minute test sessions on each of the 6 or 7 days before the drug was given. The abscissa represents the drug induced increase in ICS relative to the average change observed on control days.

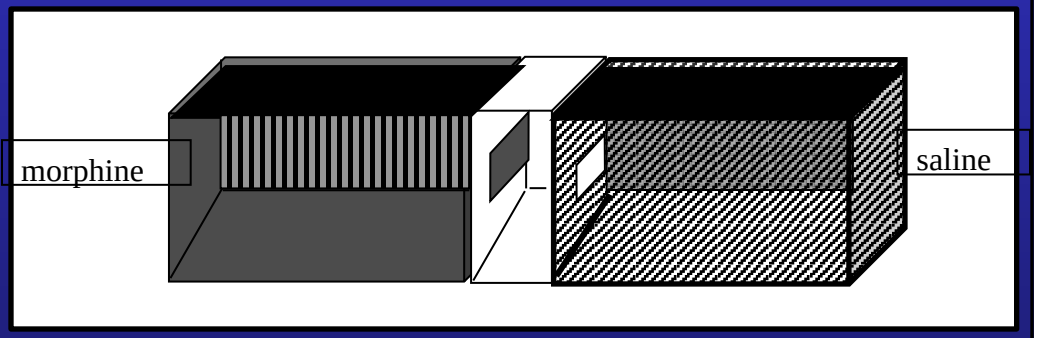
*Behavioral Brain Research*, 5 (1982) 225-229
Elsevier Biomedical Press

# Reward produced by microinjection of (D-Ala²),Met⁵-enkephalinamide into the ventral tegmental area

ANTHONY G. PHILLIPS and FREDRIC G. LePIANE

*Department of Psychology, University of British Columbia, Vancouver V6T 1W5 (Canada)*

## Conditioned place preference




Measure the rewarding effects of a drug by measuring the contextual association with the drug injection

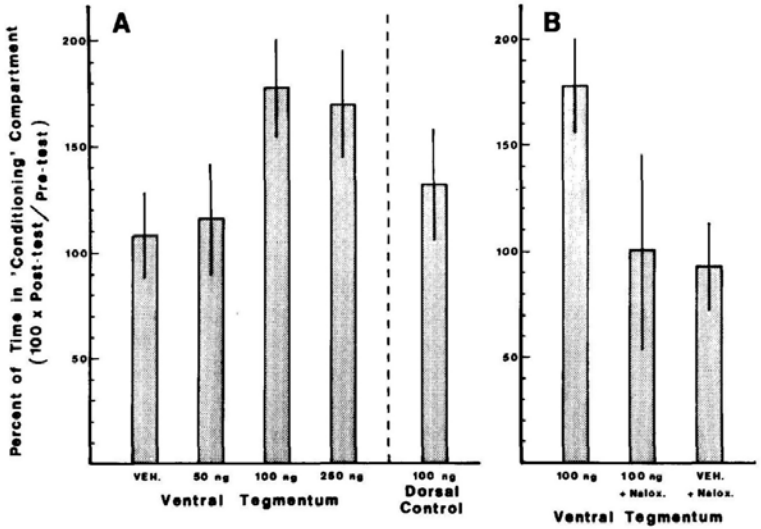


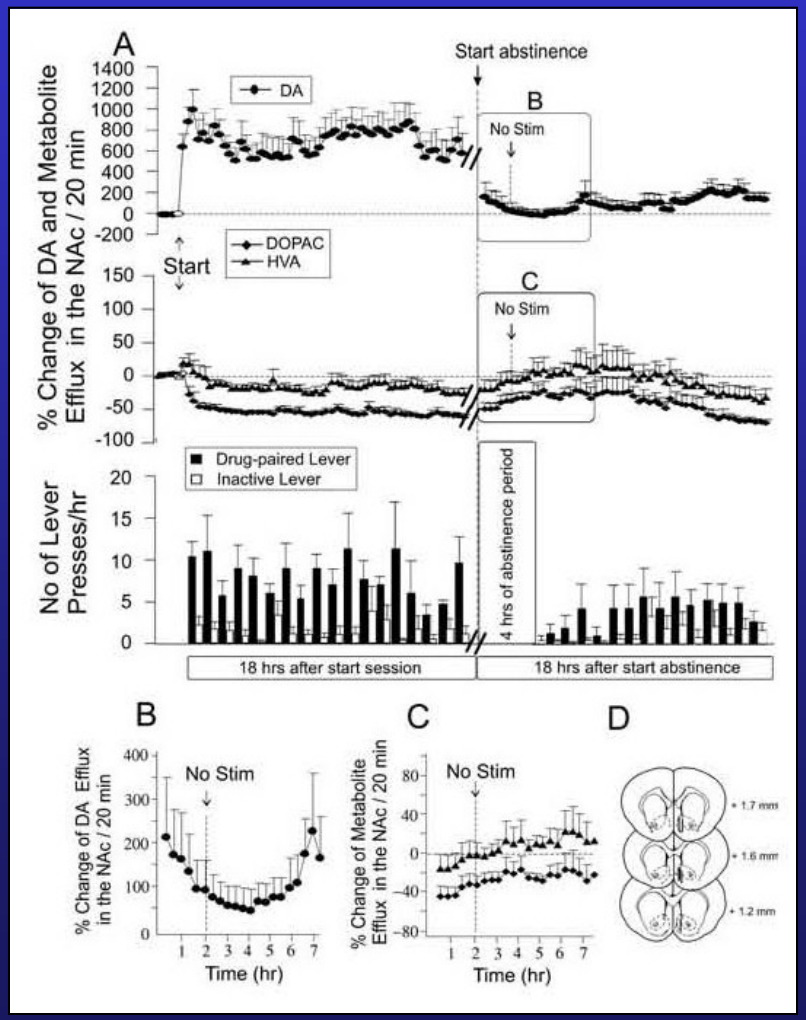

Fig. 1. A: preference scores for a compartment paired with microinjection of D-Ala (50, 100, 250 ng) or vehicle into the ventral tegmental area or control placements in central grey (D-Ala, 100 ng). Data are expressed as post-conditioning scores/pre-conditioning scores × 100. B: effects of naloxone (2 mg/kg) on place preference produced by microinjection of D-Ala (100 ng) into ventral tegmental area.

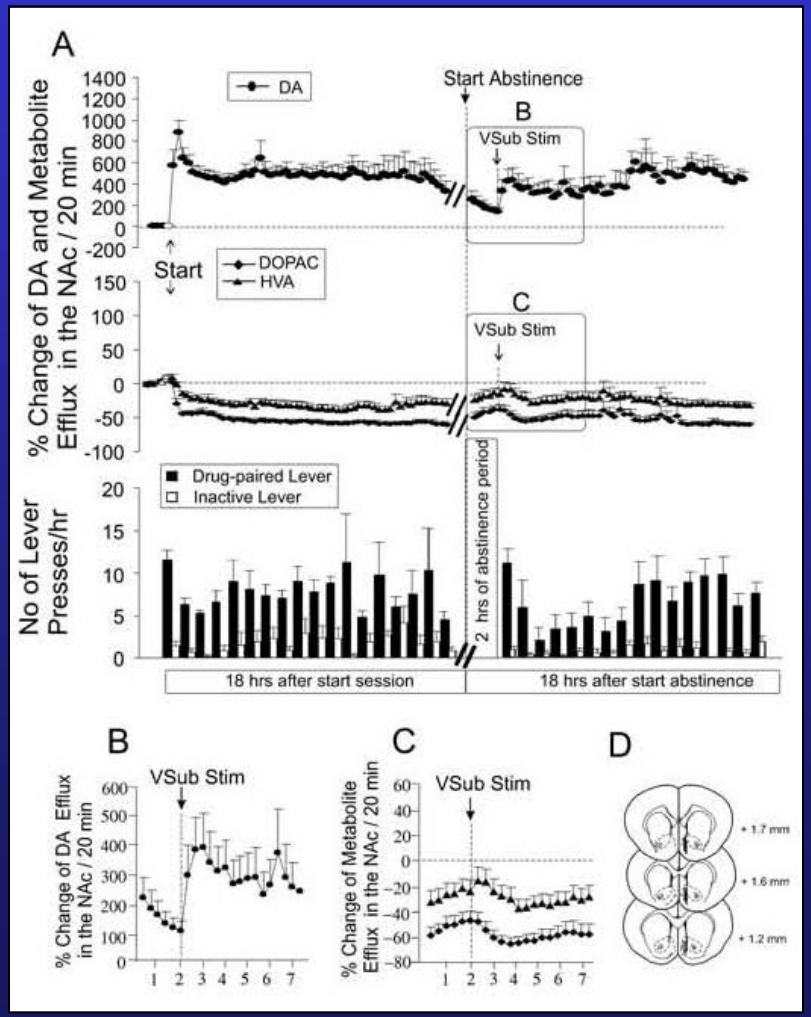
Psychopharmacology (2003) 168:99-108

ORIGINAL INVESTIGATION

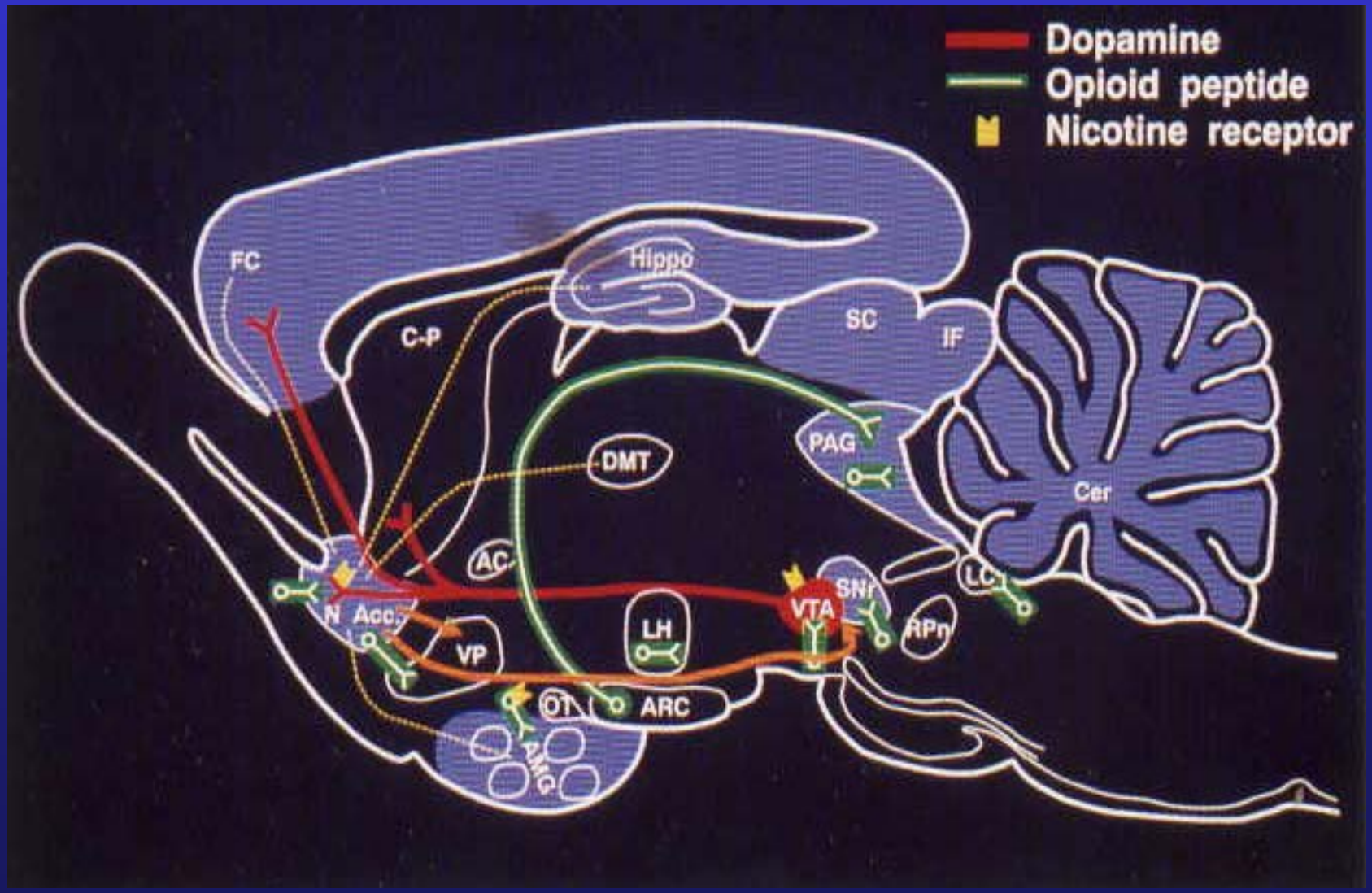
**Pornnarin Taepavarapruk · Anthony G. Phillips**

# Neurochemical correlates of relapse to D-amphetamine self-administration by rats induced by stimulation of the ventral subiculum



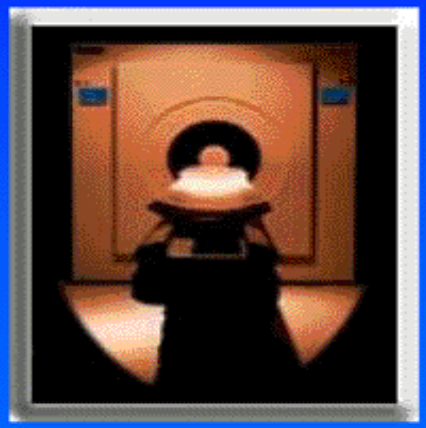



# All drugs of abuse ‘usurp’ brain function related to natural motivation and reward processes

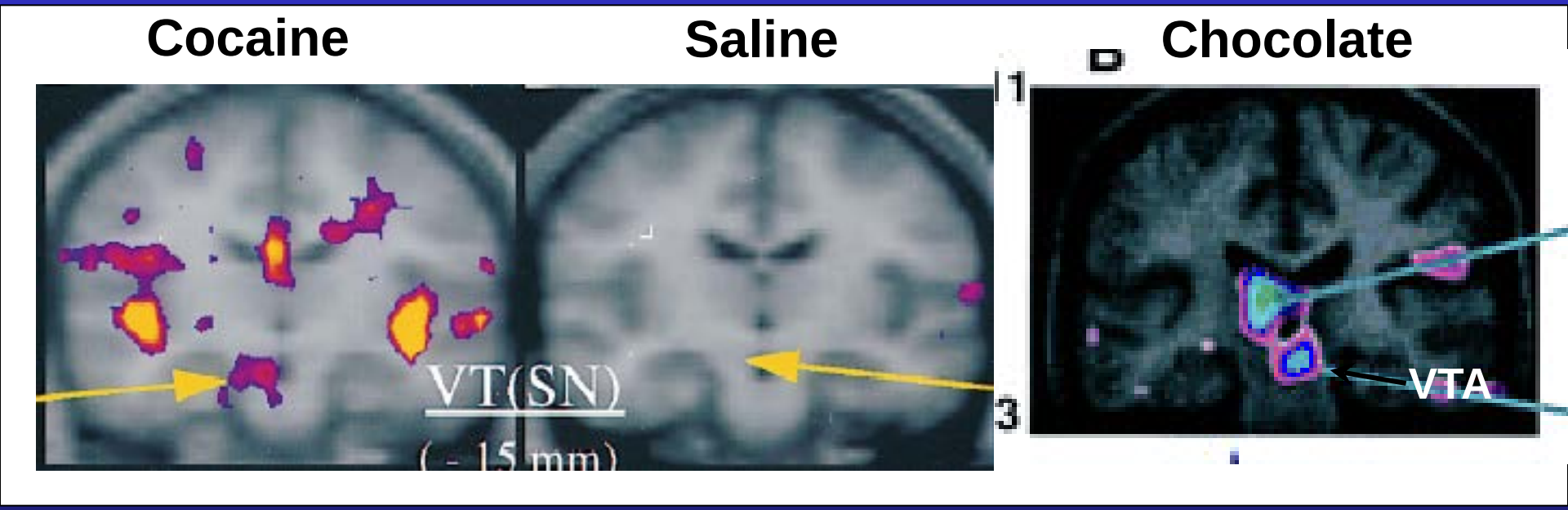


# In humans, (PET) imaging studies have established a relationship between dopamine transporter occupancy by cocaine & subjective effects of the drug [Volkow et al, 1997].

## Positron Emission Tomography (PET)



# VTA activation is associated with the “rush” experienced following cocaine administration in addicts and with experienced pleasure from eating chocolate in chocoholics

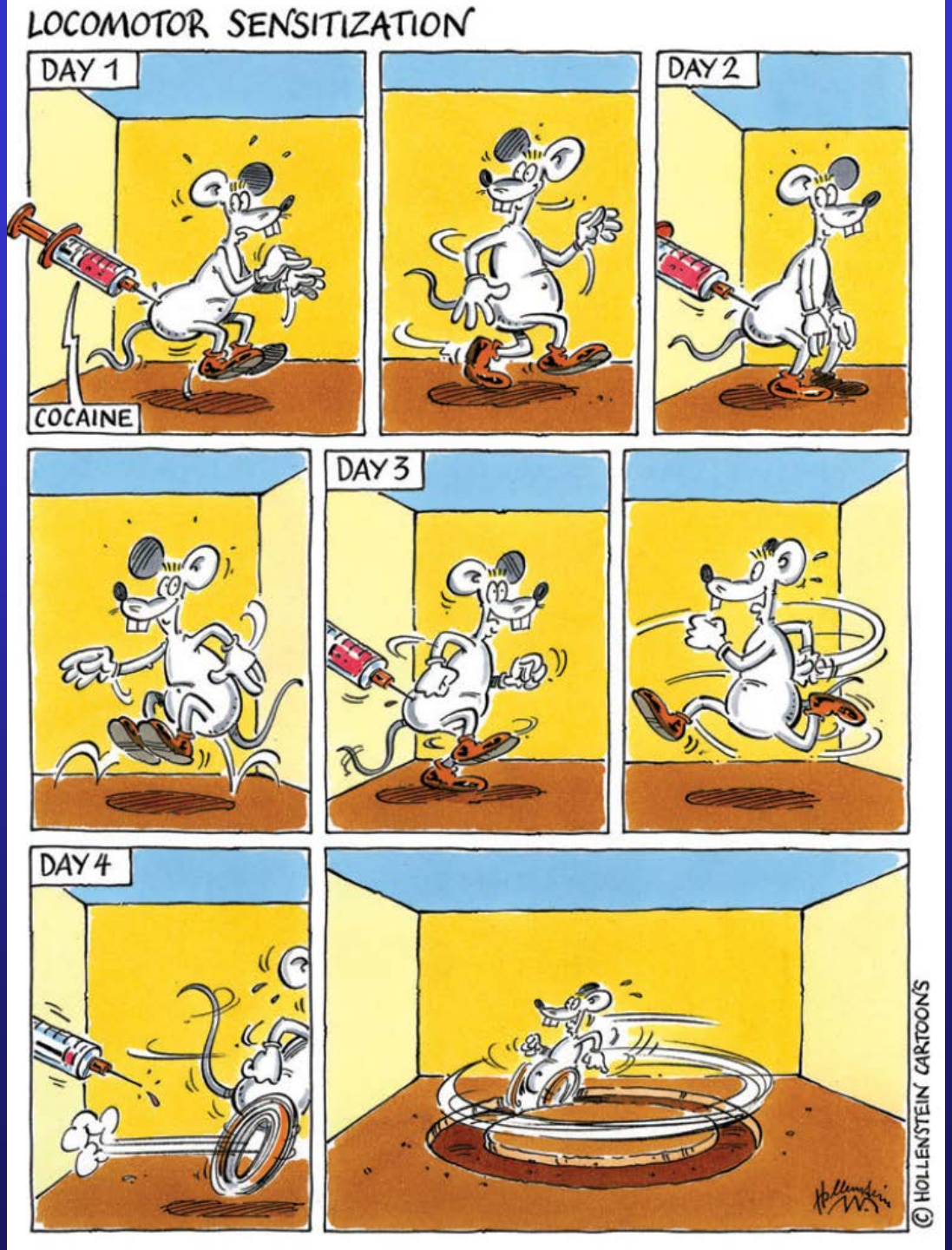



Breiter et al., 1997 Neuron

Small et al., 2001 Brain

# Behavioural sensitization as a model of drug-craving in human drug addicts

- Hallmarks of addiction are ‘craving’ and ‘relapse.’
- Craving, defined as compulsive thoughts and actions related to procurement of drugs of abuse that persist for extended periods of time.
- Behavioural sensitization is manifested in rodents as increased exploratory activity or focused repetitive motor stereotypies.
- In common with the development of ‘craving,’ these effects increase in magnitude and persist for long periods once manifested.
- Robinson and Berridge (1993) hypothesize that sensitization of the mesocorticolimbic dopamine system can enhance and distort motivational processes related to both natural rewards and drugs of abuse.




Sanchis-Segura & Spanagel, 2007

# Neurochemical and Behavioural Measures of D-Amphetamine Sensitization

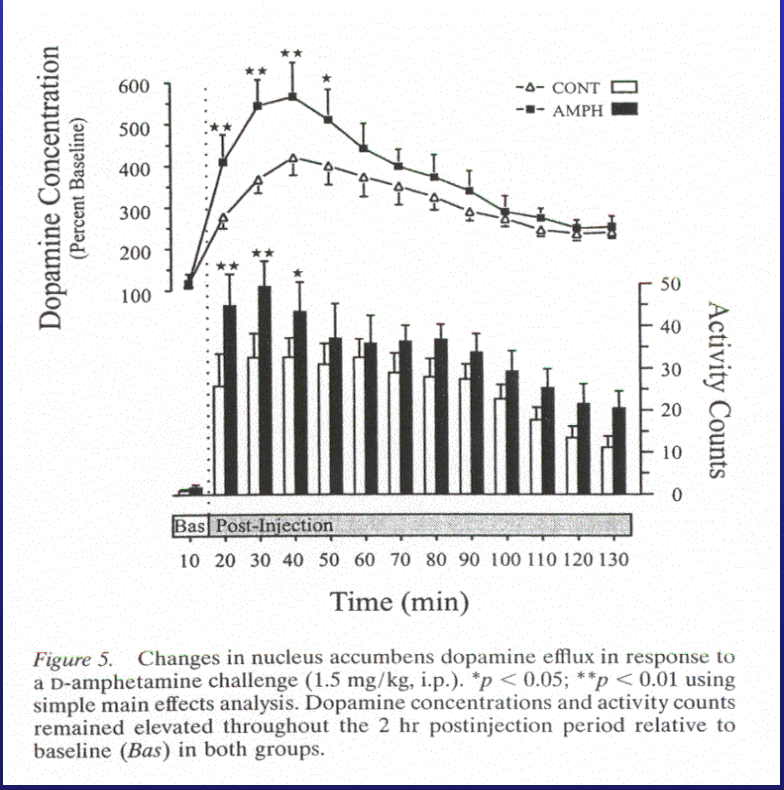
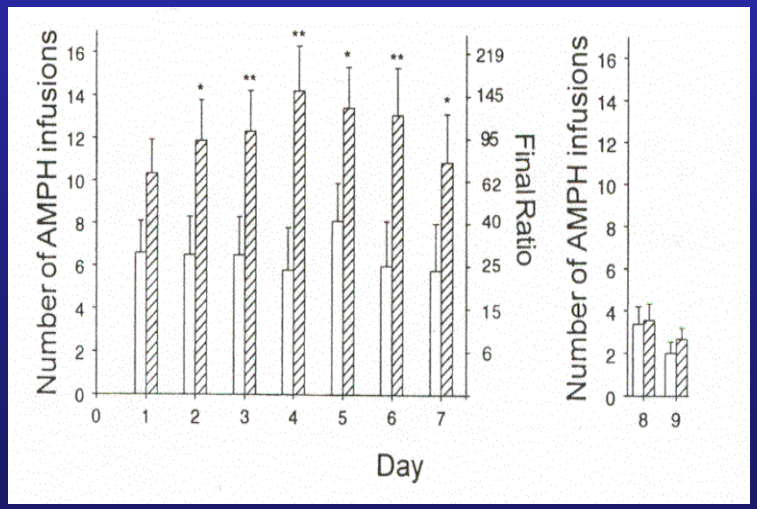



*Figure 5.* Changes in nucleus accumbens dopamine efflux in response to a D-amphetamine challenge (1.5 mg/kg, i.p.). $*p < 0.05$; $**p < 0.01$ using simple main effects analysis. Dopamine concentrations and activity counts remained elevated throughout the 2 hr postinjection period relative to baseline (*Bas*) in both groups.

Fiorino & Phillips, *J Neurosci* 19(1): 456-463 (1999)

## Amphetamine Self-Administration: Progressive Ratio




Mendrek, Blaha, Phillips. *Psychopharmacol* 135:416-422 (1998)

# Environmental stimuli and direct pharmacological effects of drugs of abuse are major determinants of addiction

*Self Portrait*
Rachel Strong

# Disruption of LTD blocks amphetamine-induced behavioral sensitization in a context-dependent manner

# Context-dependent sensitization

- Behavioural sensitization is context-specific (Robinson, 2001; Badiani & Robinson, 2004).

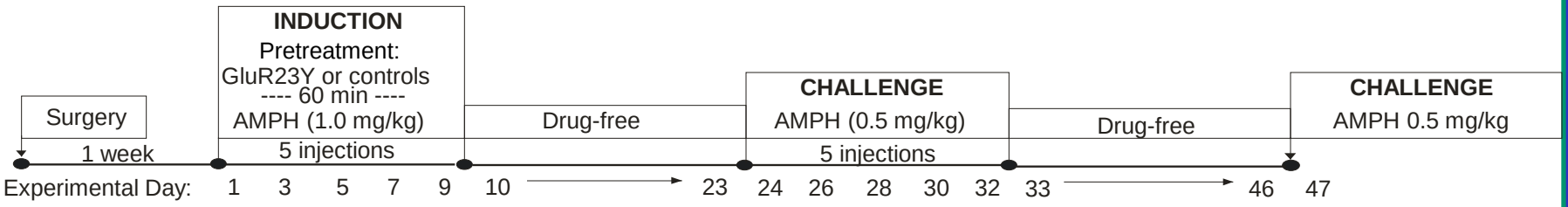
  Other models: Context-induced relapse, conditioned place preference

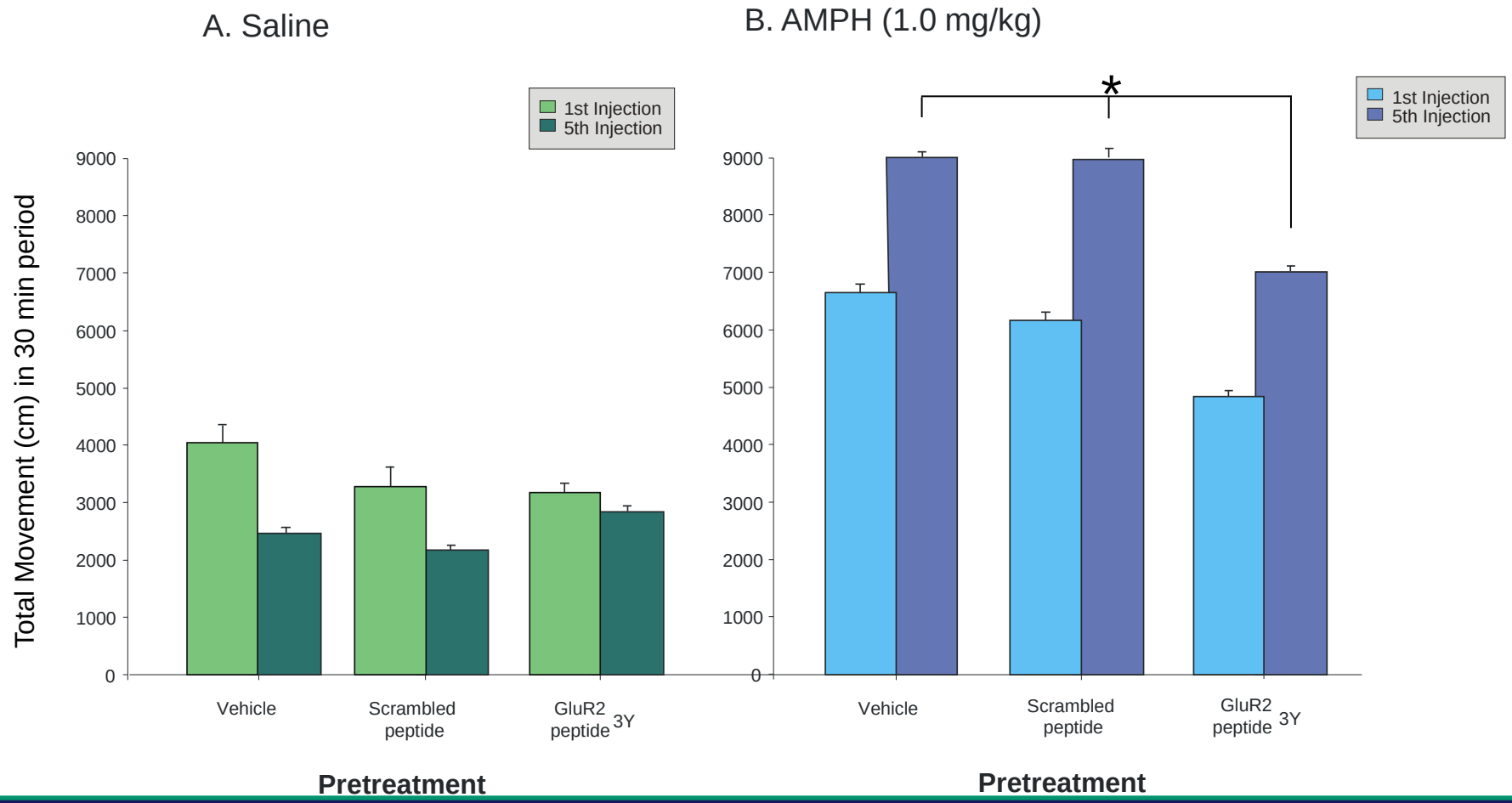
- 3 memory mechanisms may regulate context-specificity of AMPH sensitization:

  1. Sensitization of the neural substrate that mediates the unconditioned response (UR) to the drug
  2. An inhibitory process can block the expression of neural sensitization in contexts where the drug is not expected, involves a form of inhibitory *occasion-setting*
  3. An excitatory conditioned response (CR) can amplify the sensitized response in a context where the drug is expected

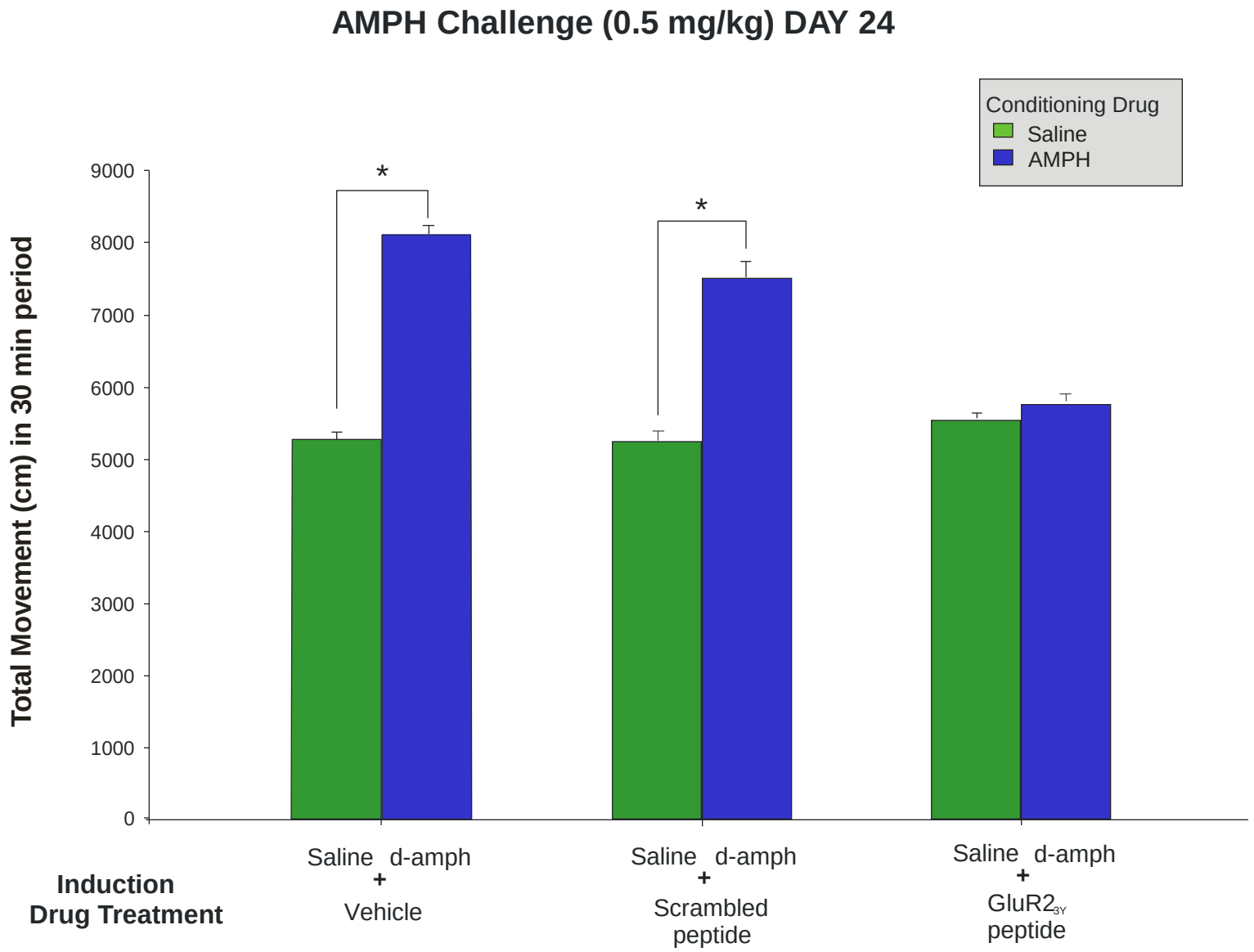
  - Taken together, the ability of drug-associated contexts to modulate expression of neural sensitization via occasion-setting may combine with the ability of a drug-associated context to produce conditioned responses, providing powerful associative control over not only behavioral sensitization, but in addicts, over craving and relapse.

# Experiment 1: Effects of GluR2$_{3Y}$ on induction of sensitization



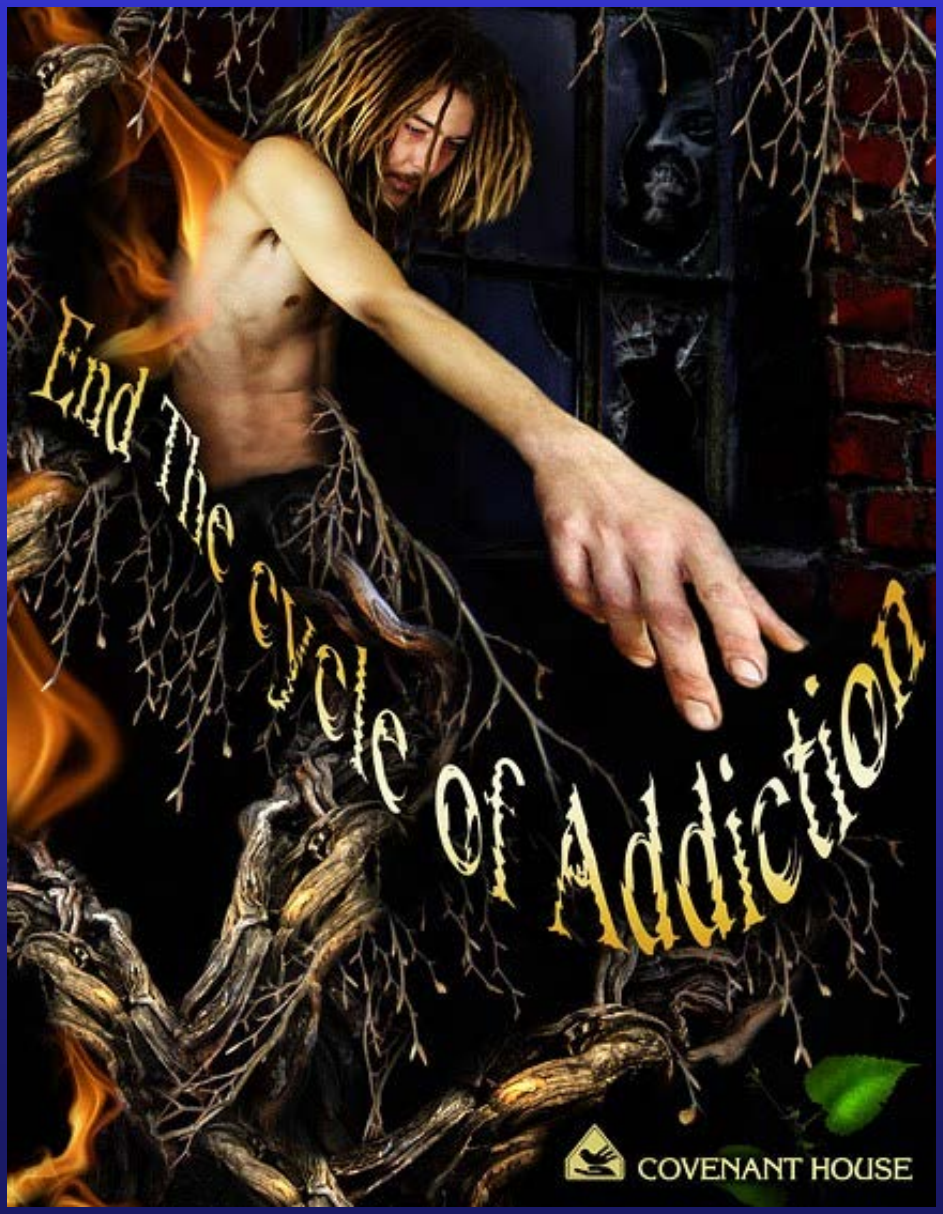



# Experiment 1: Effects of GluR2$_{3Y}$ on maintenance and expression of sensitization



# Concluding Remarks

- Behavioural sensitization models drug-craving in humans and pre-clinical animal models
- Behavioural sensitization is mediated by unique long-term memories linking environmental cues with the mood-altering properties of drugs of abuse
- Drugs of abuse change brain structure and function via modification of synaptic plasticity
- Long-term depression of synaptic activity plays a key role in context-dependent behavioural sensitization




- **Research is the key**
- **New paradigms required that link clinical and basic research in novel ways**
- **Research on trauma and addiction holds promise for meaningful breakthroughs**
- **For more information, please attend:**

*Lost in Translation: seeking answers in addiction and concurrent disorders*
*February 15 – 17, 2011*

*UBC – Life Sciences Centre*

*www.chess.ubc.ca*

# Acknowledgments

**Phillips Lab (UBC):**

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L.D. Liu

Tak Pan Wong

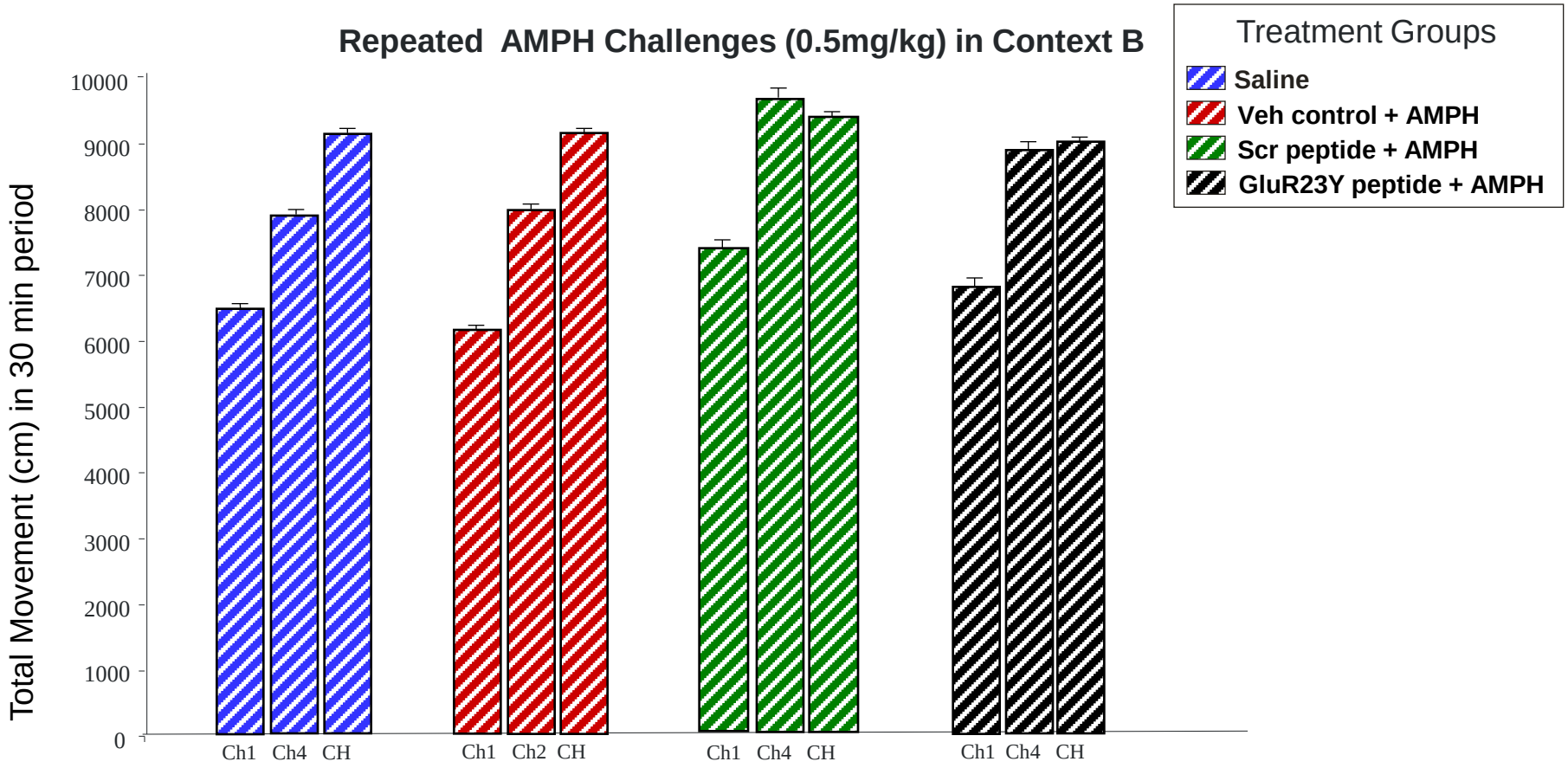
Zhifang Dong

Yu Tian Wang

CIHR IRSC

NeuroScience Canada

# Experiment 2: Effects of GluR2$_{3Y}$ on context-dependent sensitization



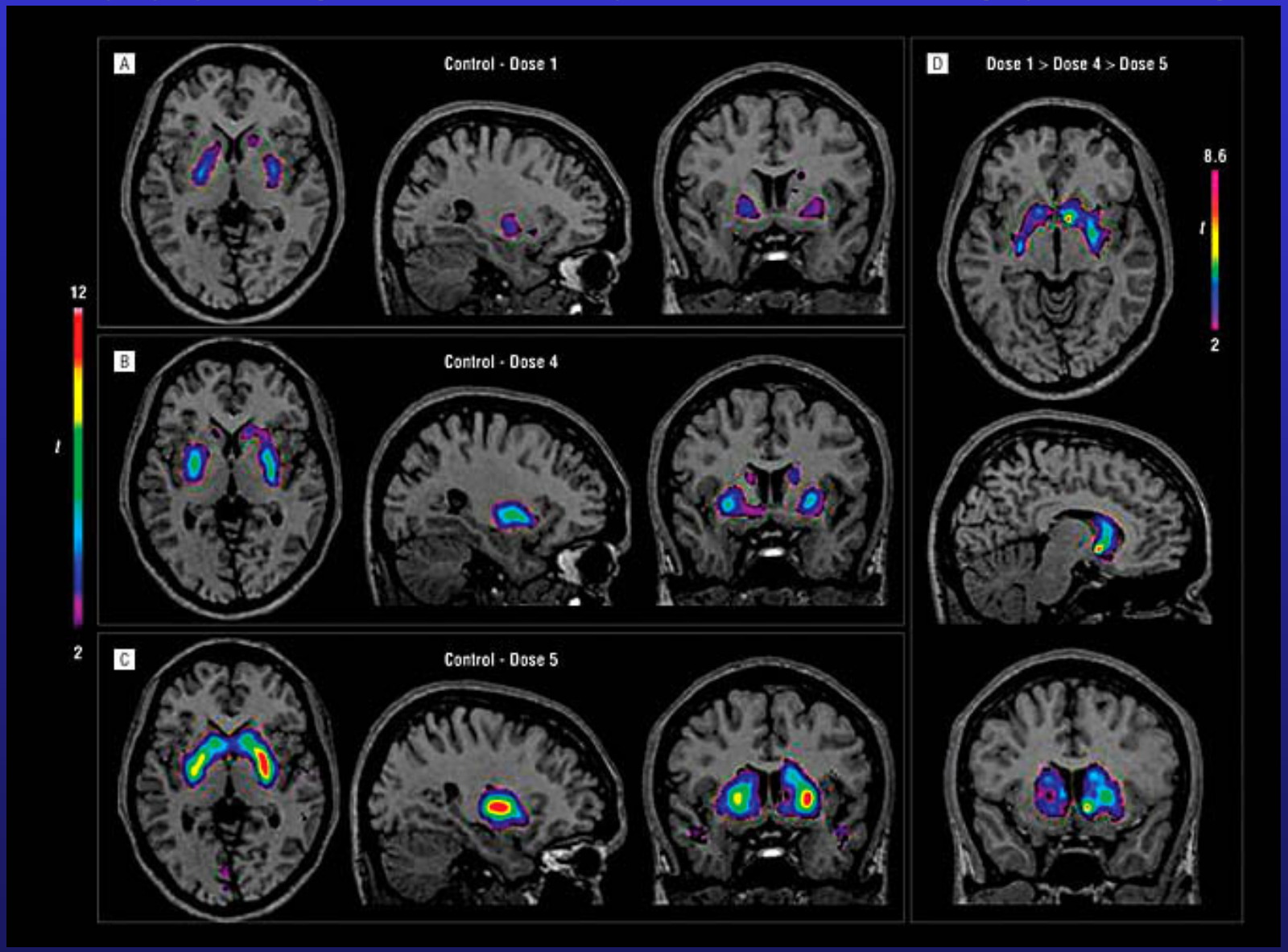

**Ch1**: AMPH Challenge (0.5 mg/kg) in Context B
**Ch4**: AMPH Challenge (0.5 mg/kg) in Context B
**CH**: Final Challenge (0.5 mg/kg) in Context B

# Modeling Sensitization to Stimulants in Humans An [$^{11}$C]Raclopride/Positron Emission Tomography Study in Healthy Men

**Isabelle Boileau, PhD; Alain Dagher, MD; Marco Leyton, PhD; Roger N. Gunn, PhD; Glen B. Baker, PhD; Mirko Diksic, PhD; Chawki Benkelfat, MD**

*Arch Gen Psychiatry.* 2006;63:1386-1395.

**t-Statistical maps of [11C]raclopride binding potential (BP) change illustrating a decrease in [11C]raclopride BP after dose 1 (A), dose 4 (B), and dose 5 (C) amphetamine administrations (0.3 mg/kg by mouth) relative to the drug-free control condition (x, y, z = 28, 2, 0)**

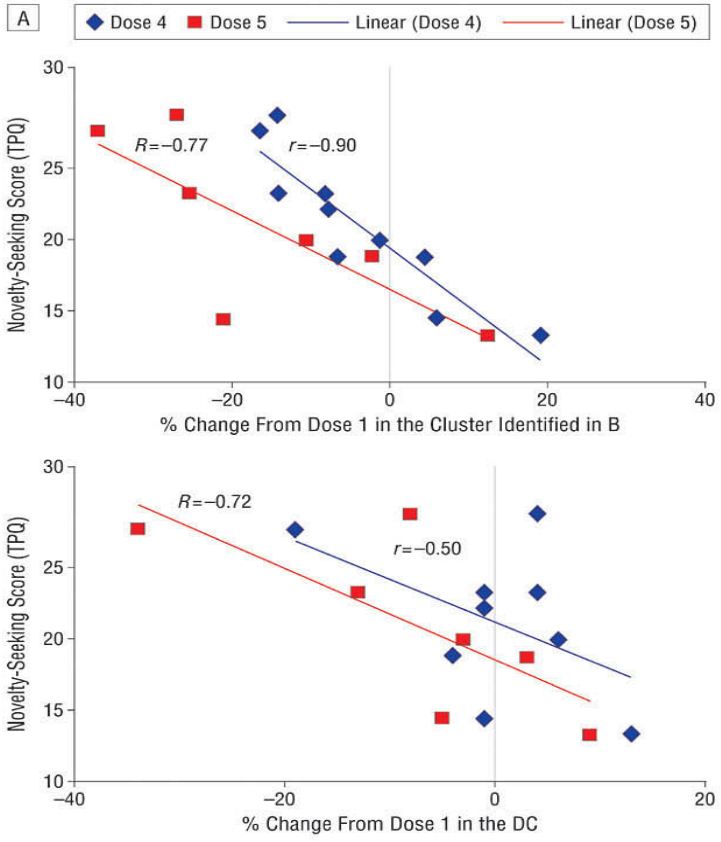



Boileau, I. et al. Arch Gen Psychiatry 2006;63:1386-1395.

# Behavioural Sensitization: an exemplar of drug induced long-term changes in brain function and behaviour

- Definition: a progressive augmentation of behavioural responses to psychomotor stimulants (amphetamines, cocaine, nicotine) that develops during their repeated administration and persists even after long periods of withdrawal.

# Relationship between dopamine sensitization and novelty-seeking personality




Boileau, I. et al. Arch Gen Psychiatry 2006;63:1386-1395.

# Compulsive Drug Use Linked to Sensitized Ventral Striatal Dopamine Transmission

Andrew H. Evans, FRACP, Nicola Pavese, MD, Andrew D. Lawrence, PhD, Yen F. Tai, MRCP, Silke Appel, MD, Miroslava Doder, David J. Brooks, MD, FRCP, DSc, Andrew J. Lees, MD, FRCP, and Paola Piccini, MD, PhD

**Ann Neurol 2006; 59:852-8**

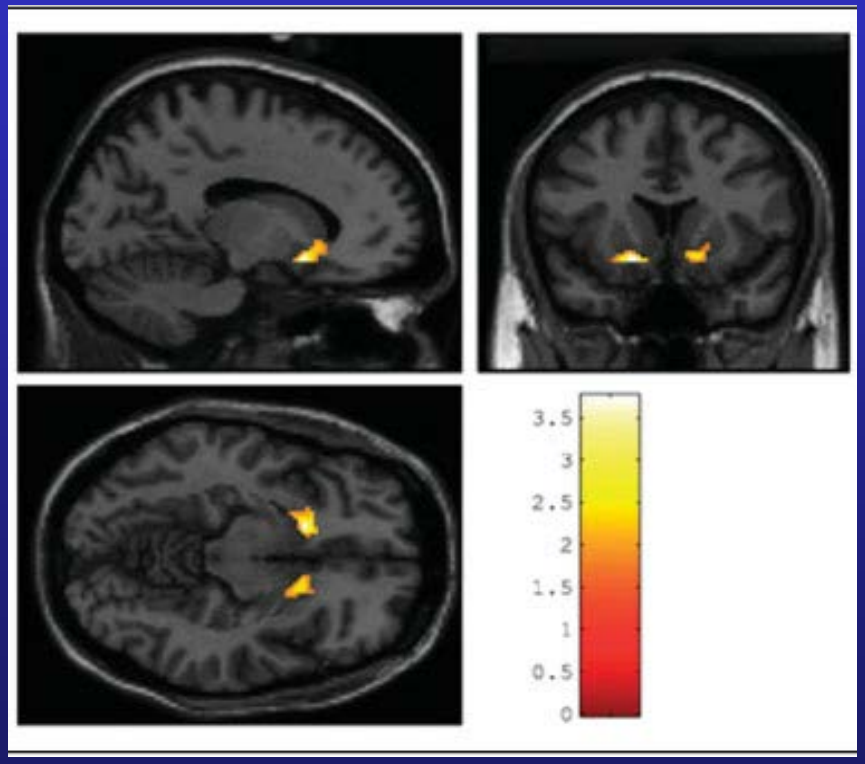
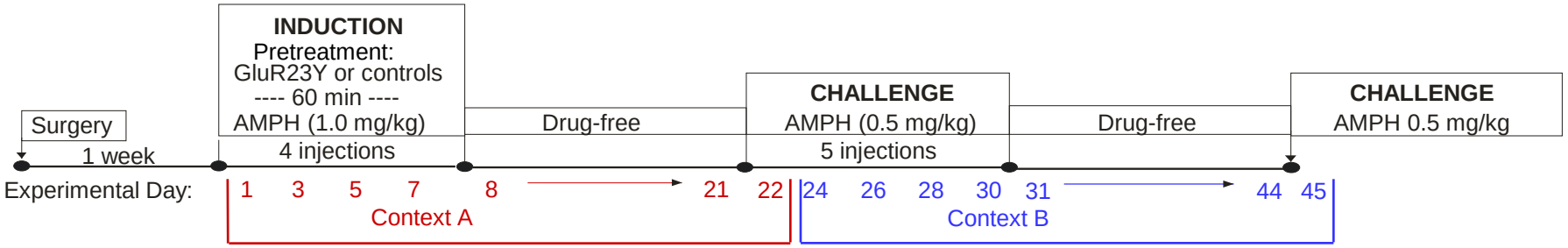
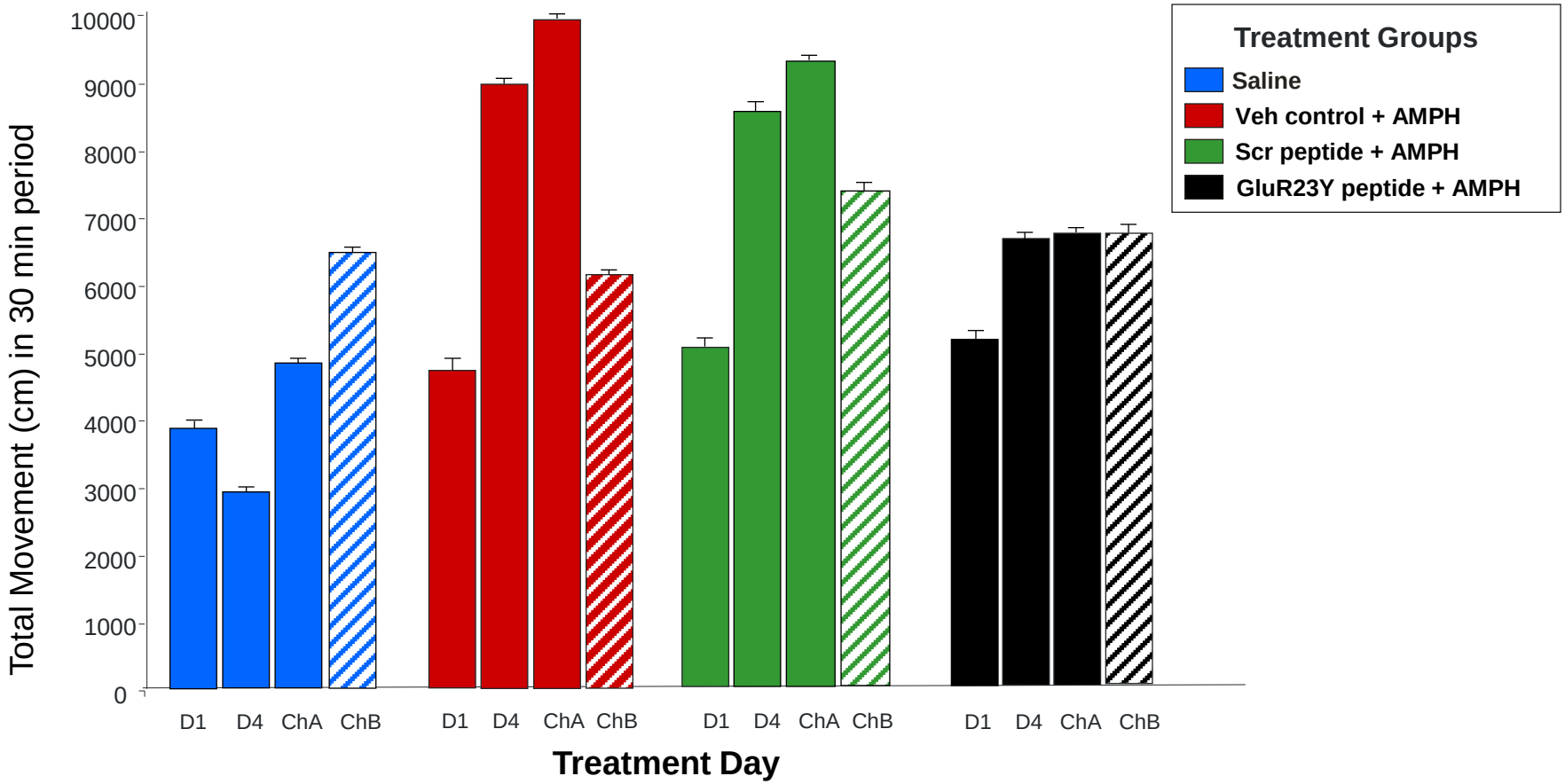



*Fig 2. Sagittal (*x = *17.40), coronal (*y = *14), and transaxial (*z = *-9.85) projections of statistical parametric maps superimposed on a standardized magnetic resonance imaging template. Shown is the localization of significant differences (in orange/yellow) in altered $^{11}$C-raclopride (RAC) binding potential after a single dose of L-dopa between control PD and dopamine dysregulation syndrome (DDS) groups. These areas were identified as right and left ventral striatum using Montreal Neurological Institute coordinates (right* x, y, z: *18, 12, -8;* p = *0.049;* z = *3.22; left* x, y, z: *-14, 14, -8;* p = *0.048;* z = *3.38), confirming the region of interest findings of higher dopamine release in ventral striatum in the DDS group.*

# Experiment 2: Effects of GluR2$_{3Y}$ on context-dependent sensitization




**D1**: AMPH Induction Day 1 (1.0 mg/kg) in Context A
**D4**: AMPH Induction Day 4 (1.0 mg/kg) in Context A

**ChA**: AMPH Challenge (0.5 mg/kg) in Context A
**ChB**: AMPH Challenge (0.5 mg/kg) in Context B

# Experiment 3: Compound context-dependent sensitization