Insights into understanding the placebo response

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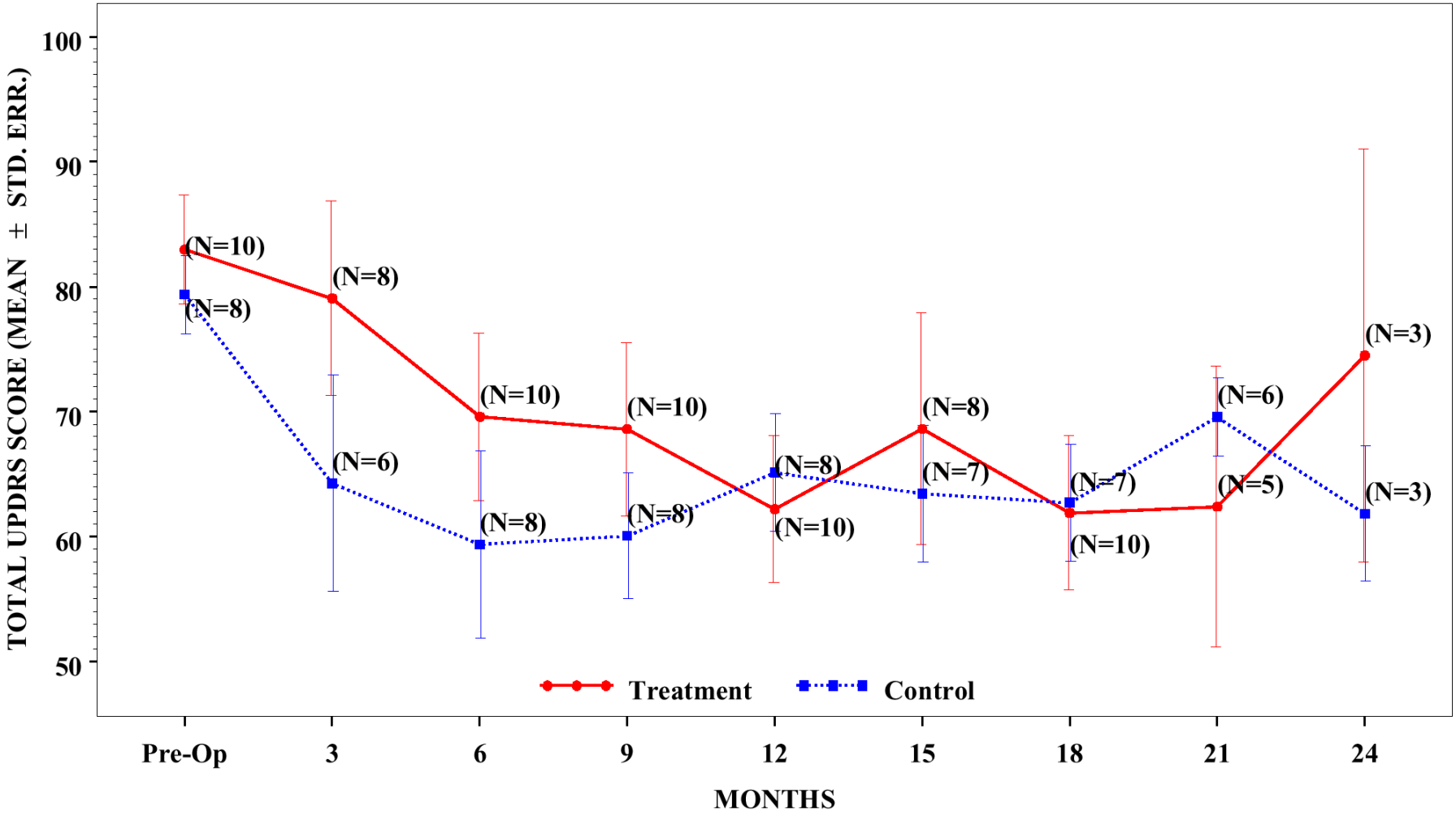
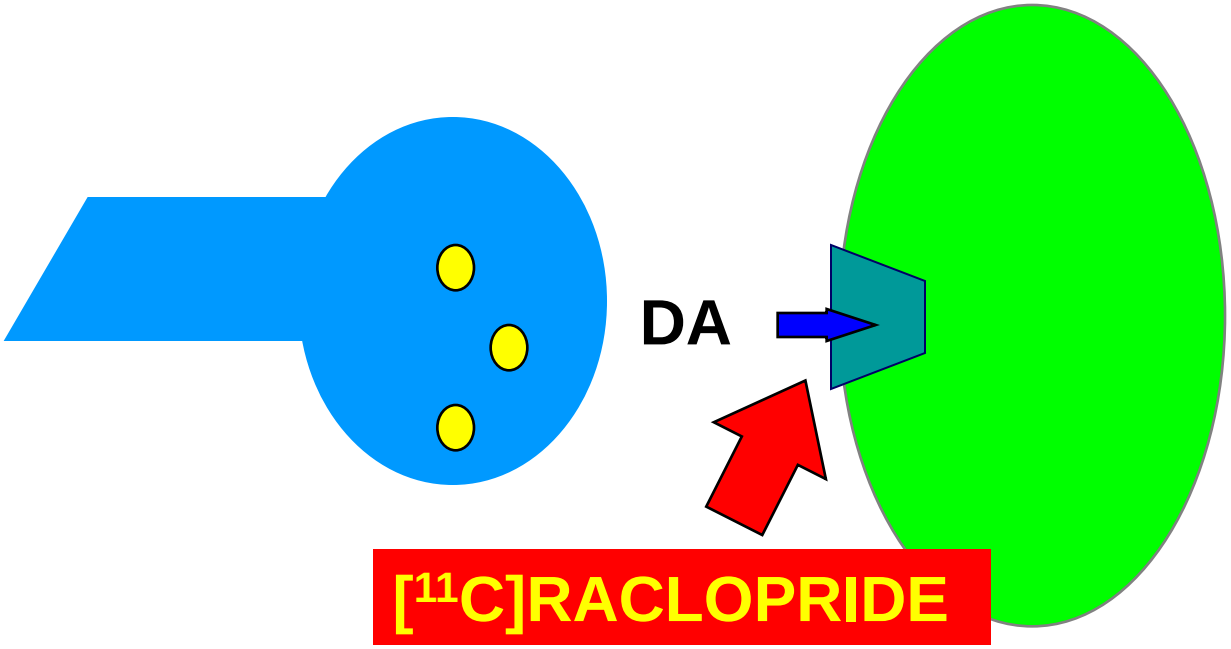
Healthier lives through discovery

Michael Smith Foundation for Health Research

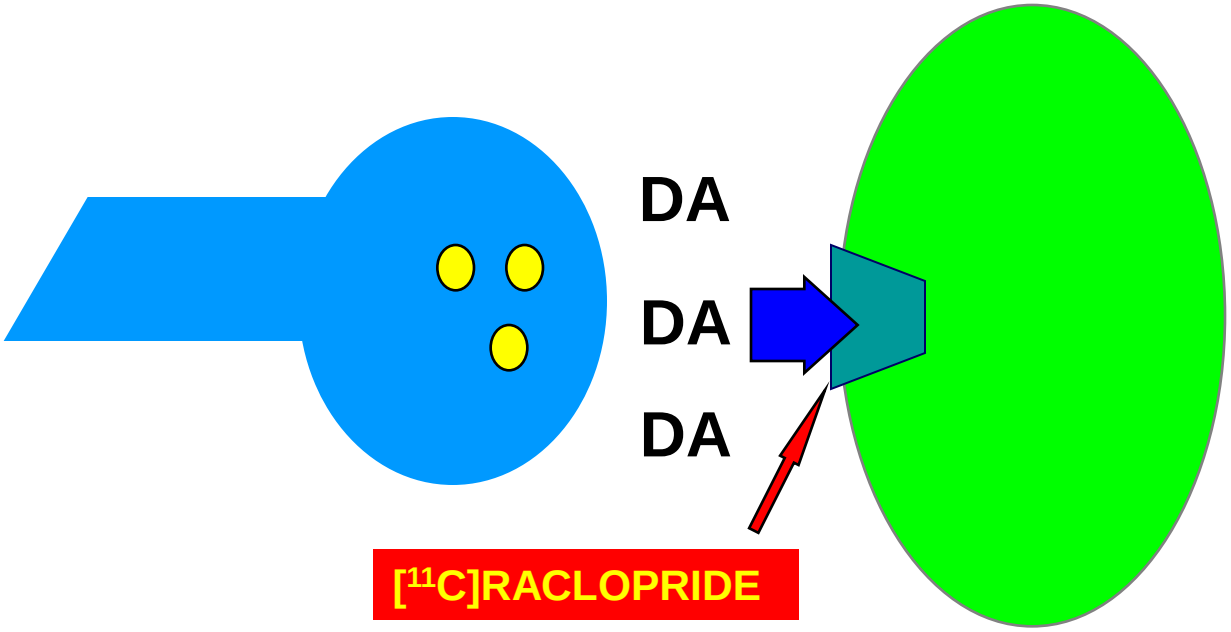
Porcine Transplants: Total UPDRS Score “OFF”

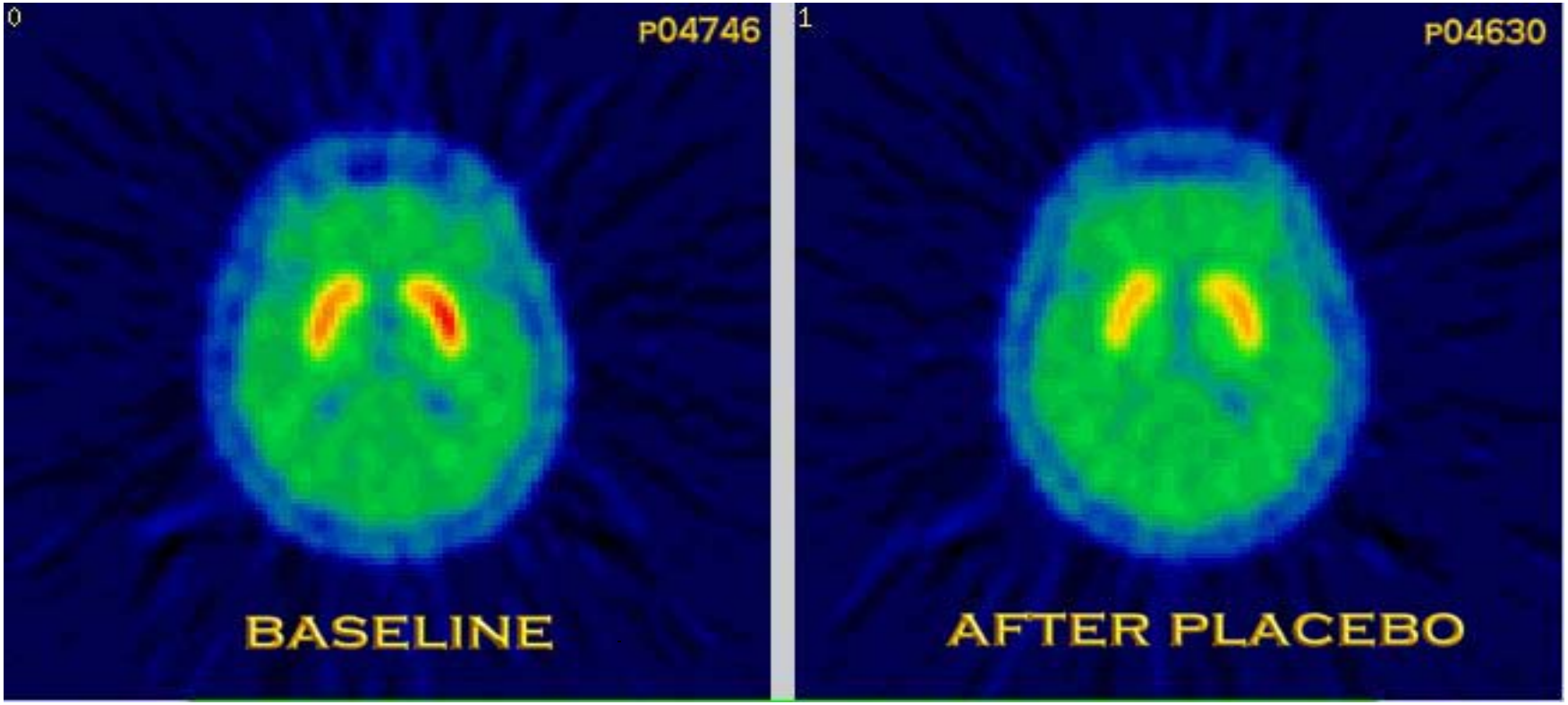


Neurobiology: *In vivo* assessment of endogenous DA concentration



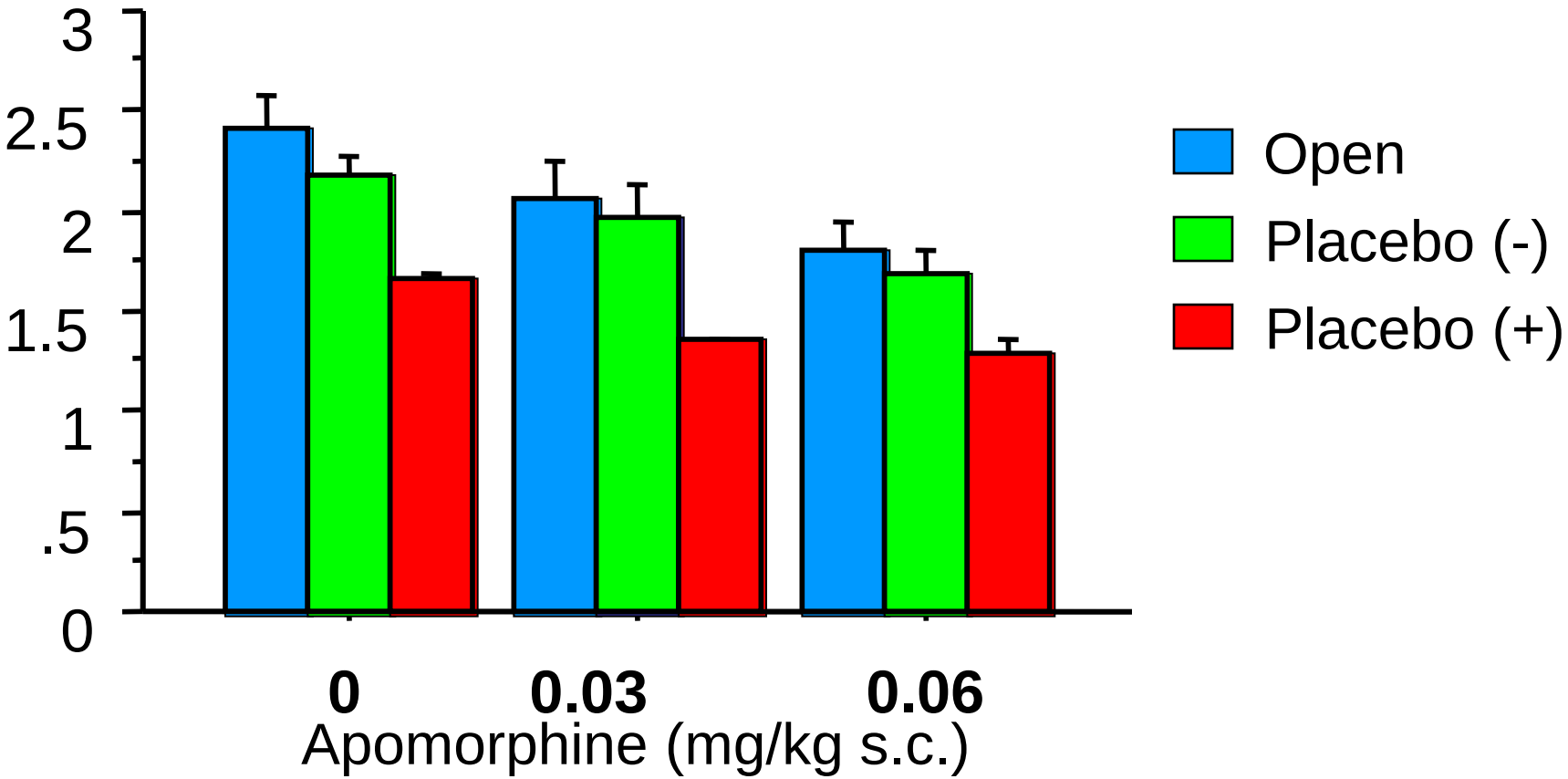
Neurobiology: *In vivo* assessment of endogenous DA concentration





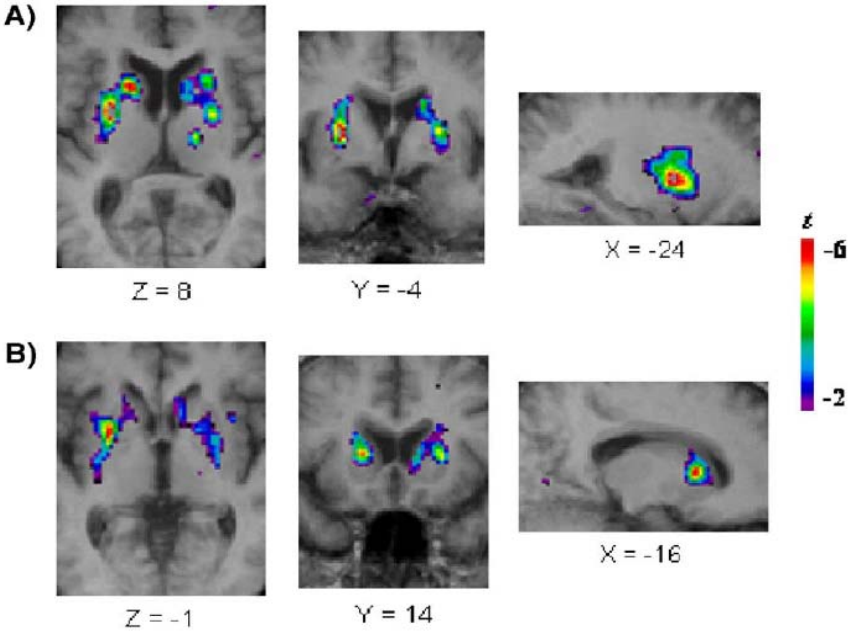
de la Fuente-Fernandez et al., Science 2001

Apomorphine-induced changes in RAC binding (putamen)

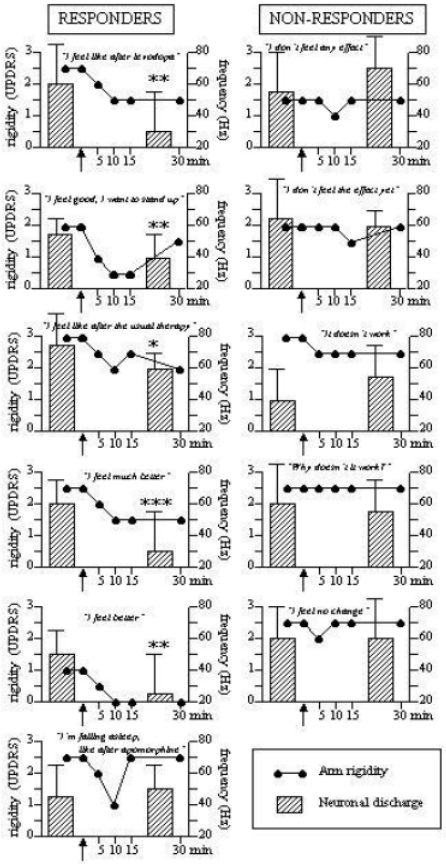


de la Fuente-Fernandez et al., Science 2001

More evidence for placebo-induced DA release in PD

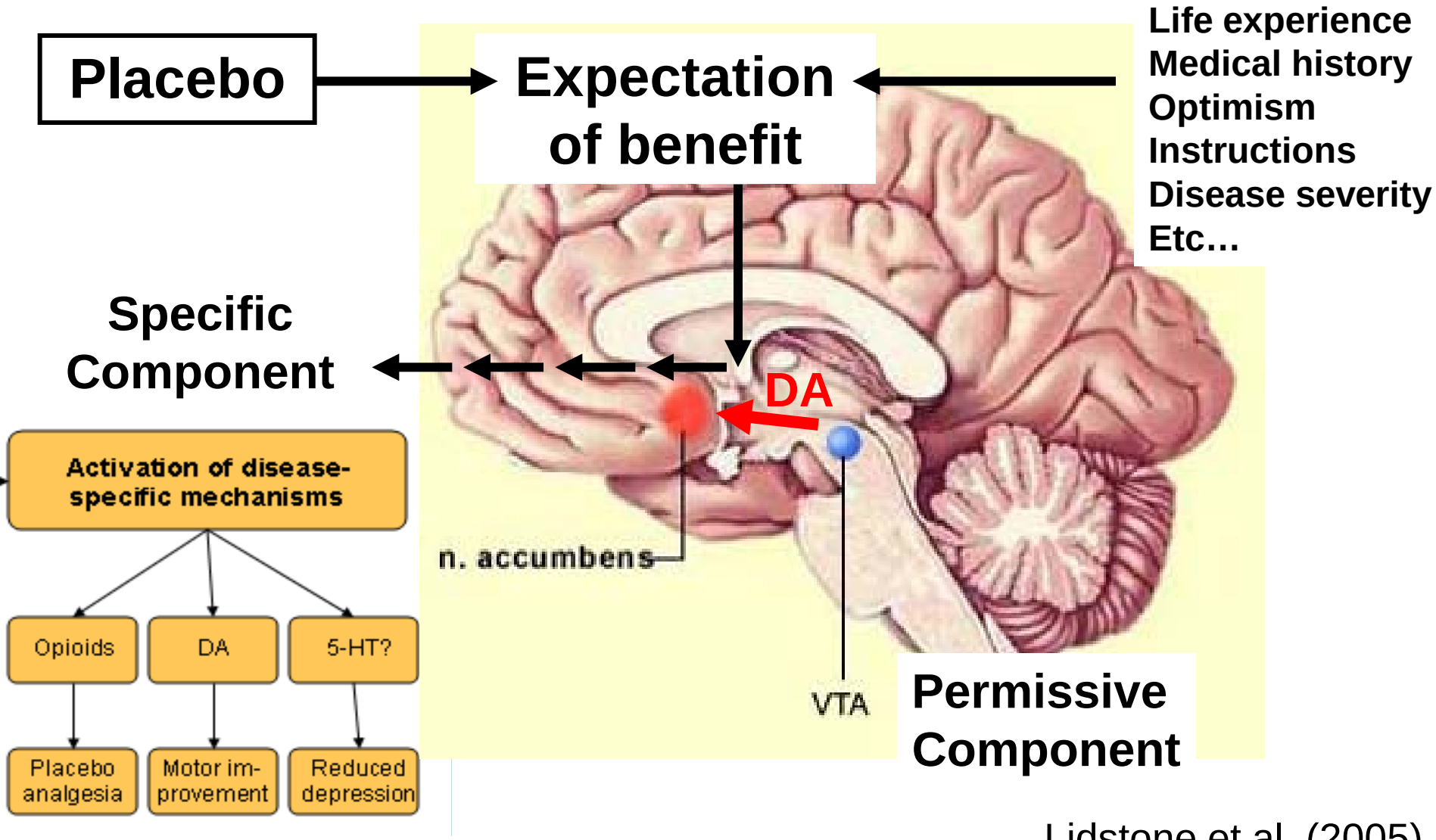


Strafella *et al.*, Neuroimage 2006



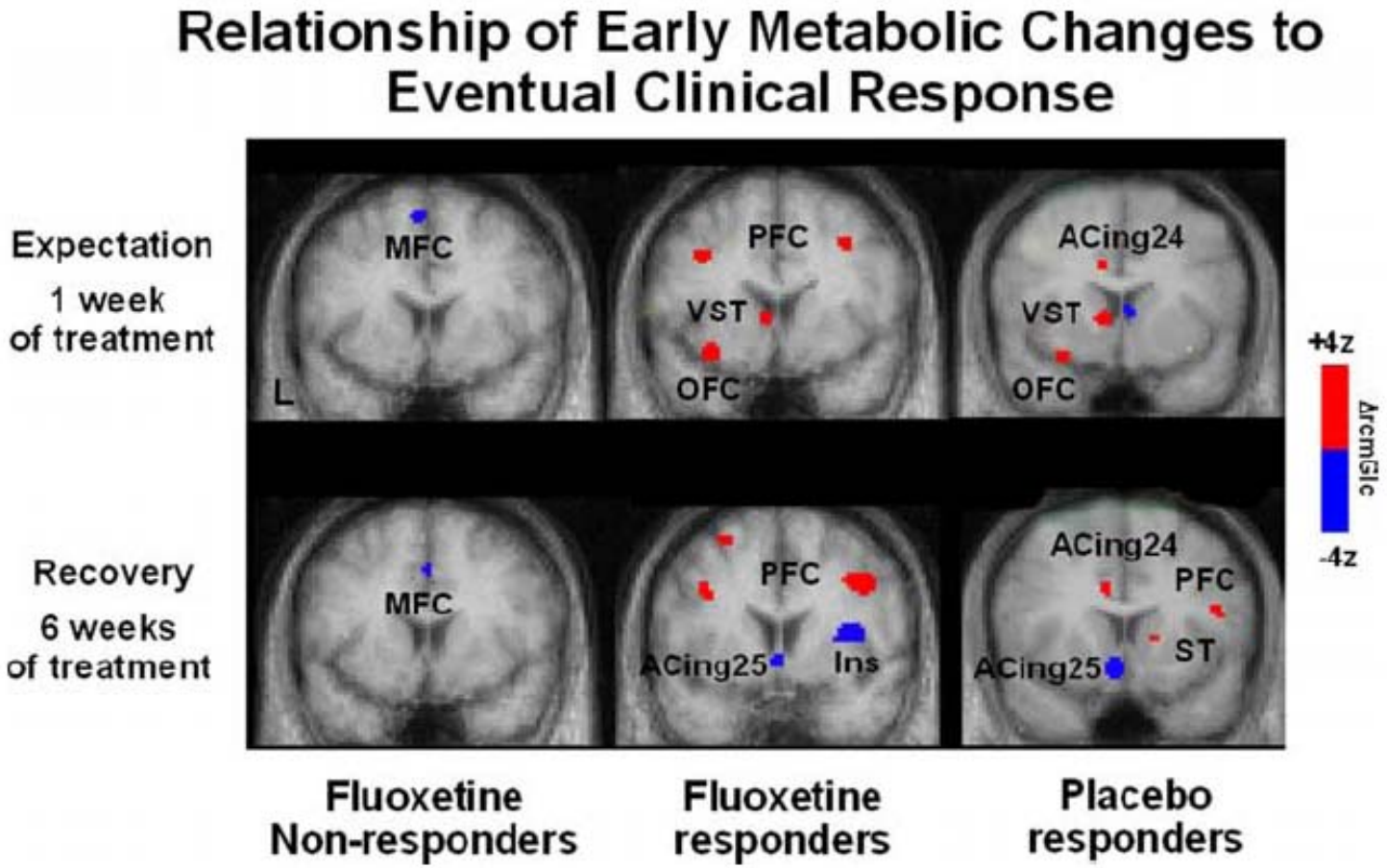
Benedetti et al., Nat. Neurosci. 2004

Reward Expectation Hypothesis



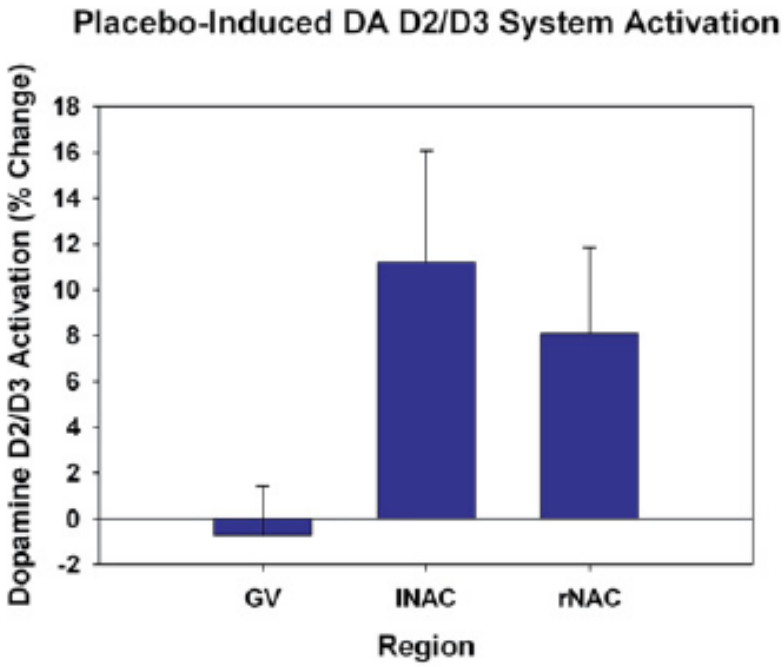
Lidstone et al. (2005)

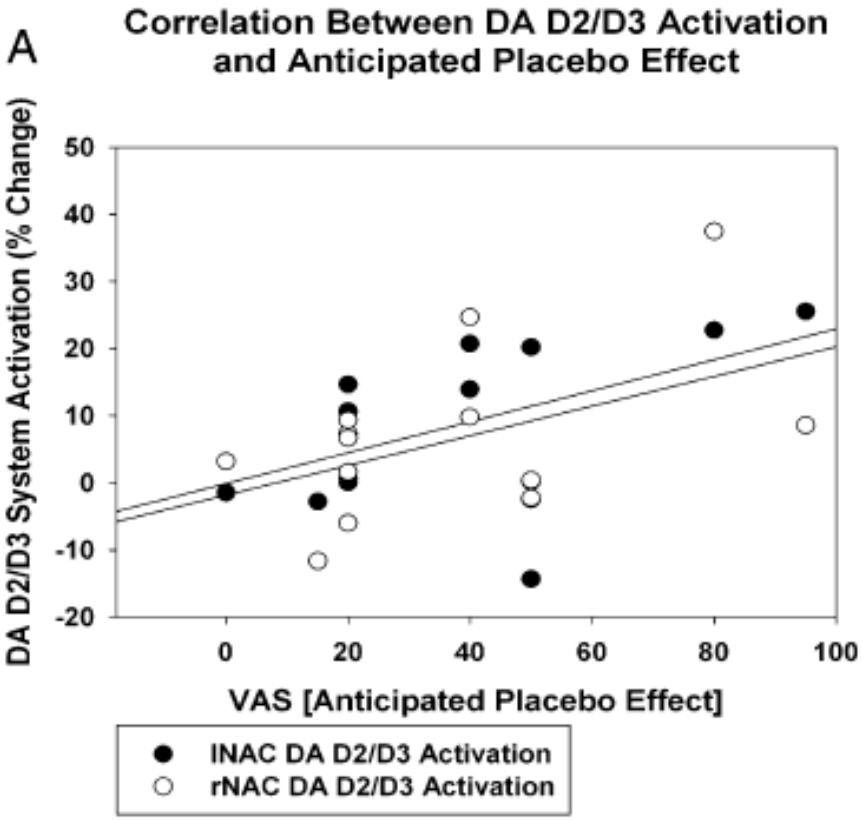
Early *vs.* Late Changes - Depression



Mayberg, in Benedetti *et al.*, J. Neurosci. 2005

Placebo analgesia: Ventral Striatal DA release





Scott *et al.*, Neuron 2007

Effects of Perceived Treatment on Quality of Life and Medical Outcomes in a Double-blind Placebo Surgery Trial

Cynthia McRae, PhD; Eva Cherin, MA; T. Gayle Yamazaki, PhD; Gretchen Diem, PhD; Alexander H. Vo, PhD; Dan Russell, PhD; J. Heiner Ellgring, PhD; Stanley Fahn, MD; Paul Greene, MD; Sandra Dillon, RN; Hal Winfield, RN; Kimberly B. Bjugstad, PhD; Curt R. Freed, MD

Arch Gen Psychiatry. 2004;61:412-420

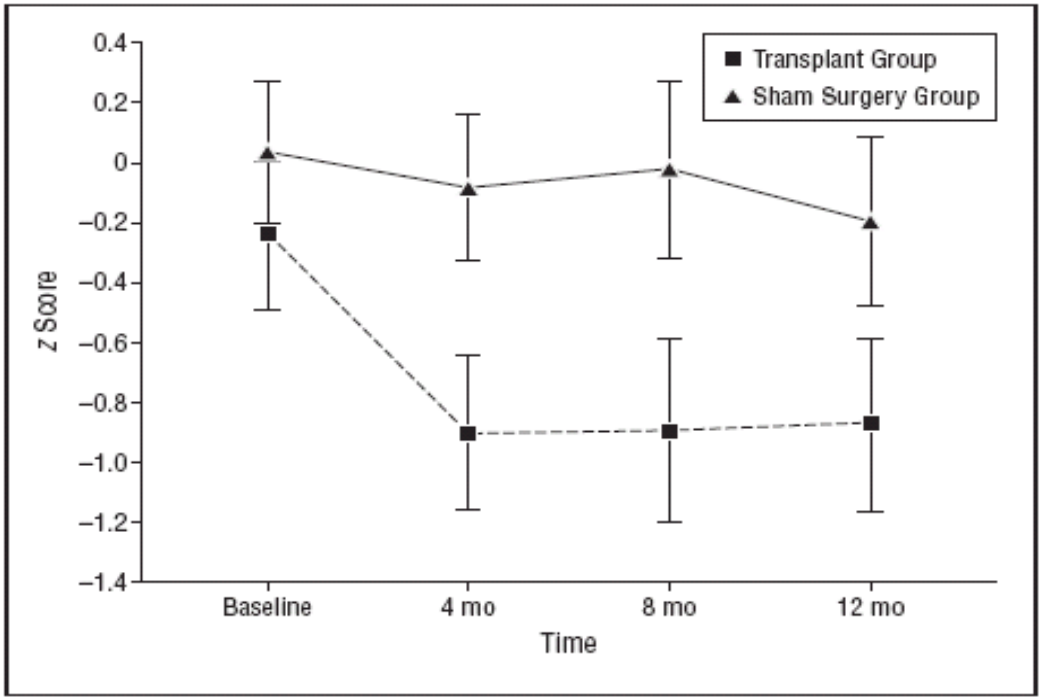
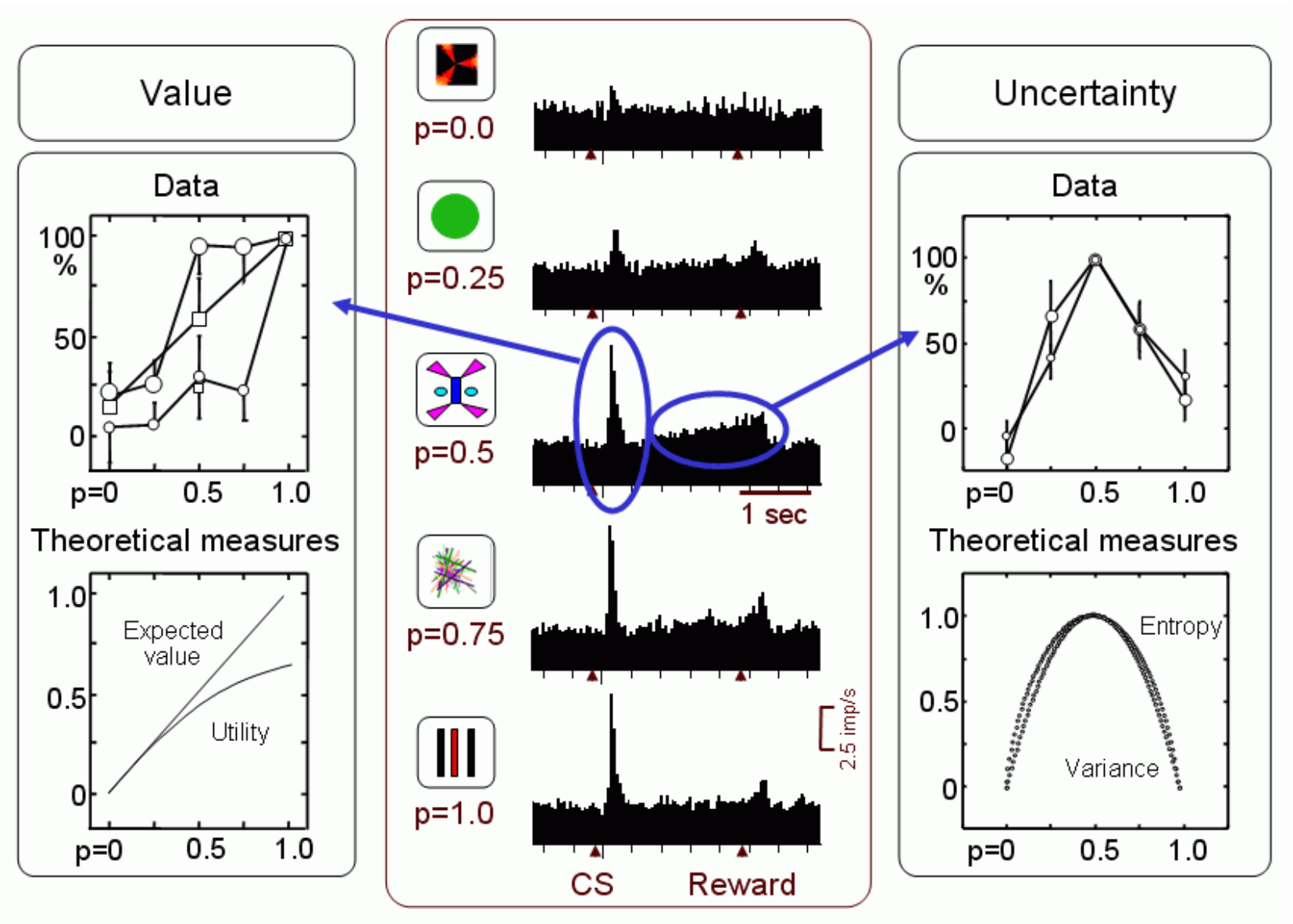


Figure 2. Mean changes in Physical functioning quality of life from baseline to 12 months: perceived surgery. Decreased scores indicate improvement. Error bars represent SEM.

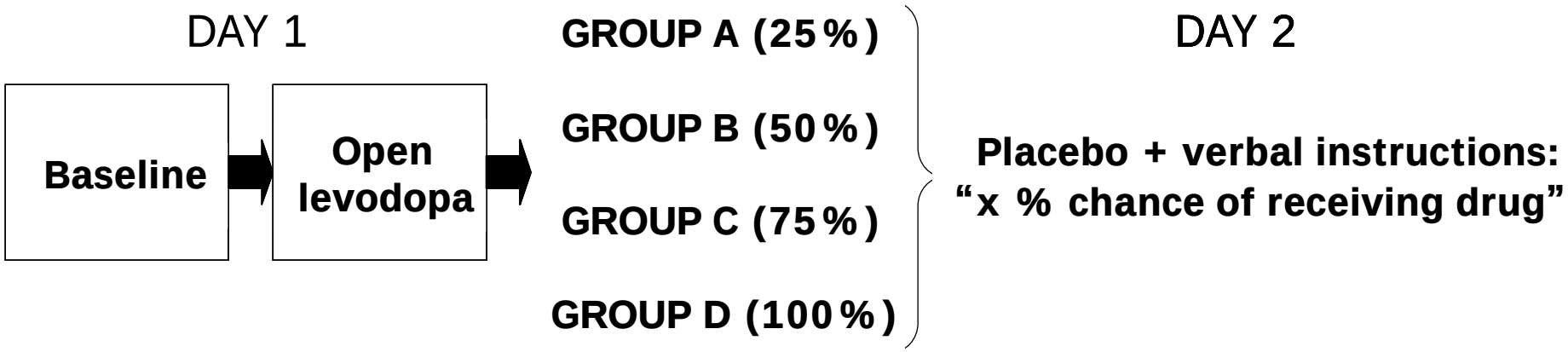
Table 5. Changes From Baseline to 12 Months: Perceived Groups

Variable	Transplant Group (n = 10)	Sham Surgery Group (n = 20)	*P* Value
	Medical Staff Ratings*		
UPDRS score			
Tremor "off"	−1.0	−1.0	.02†
Total "off"	−10.5	2.1	.006‡
Motor "off"	−6.2	1.8	.008‡
Bradykinesia "off"	−3.7	1.6	.001‡
Gait "off"	−1.3	1.2	.004‡
Pull test "off"	-0.5	0.3	.02‡
Hoehn and Yahr "off" score	−0.2	0.3	.04‡
Schwab and England "off" score	11.4	−4.8	.004‡
	Patient Ratings*		
Global Rating Scale score	1.9	−0.7	<.001‡

Dopamine, Reward & Expectation

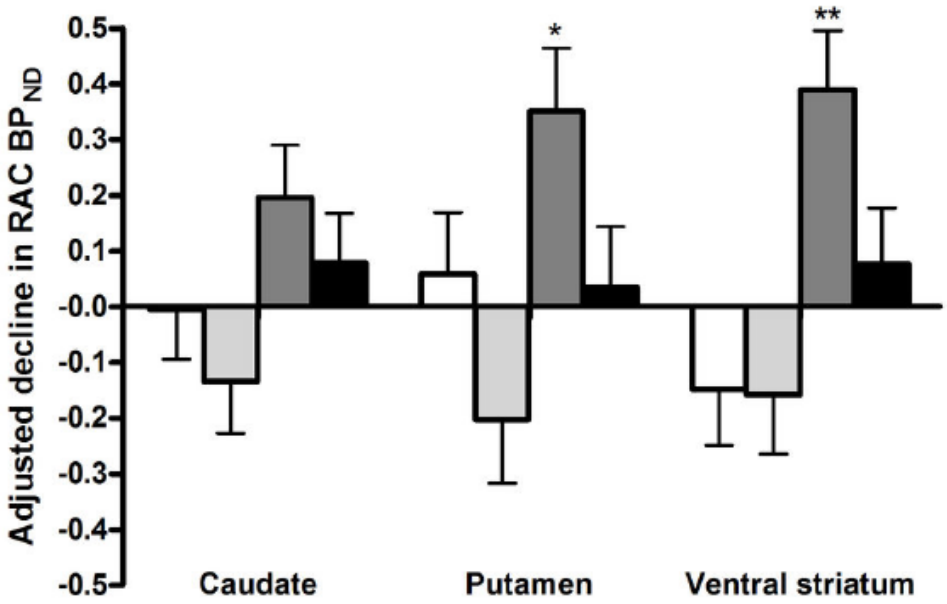


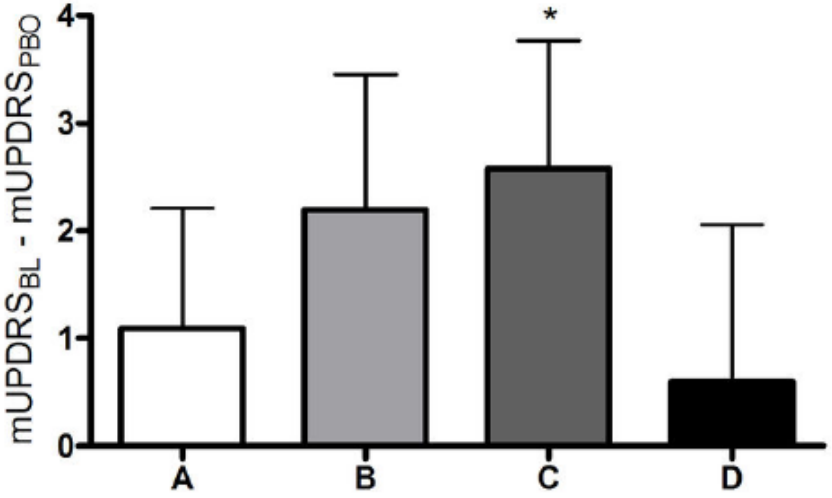
Manipulation of Expectation: Study design



1. Objective placebo effect
   – Unified Parkinson’s disease Rating Scale (UPDRS III)
2. Subjective placebo effect
3. Biochemical placebo effect
   – Changes in RAC BP

Expectation modifies DA release and clinical response to Placebo





Lidstone et al., Arch Gen Psych, in press

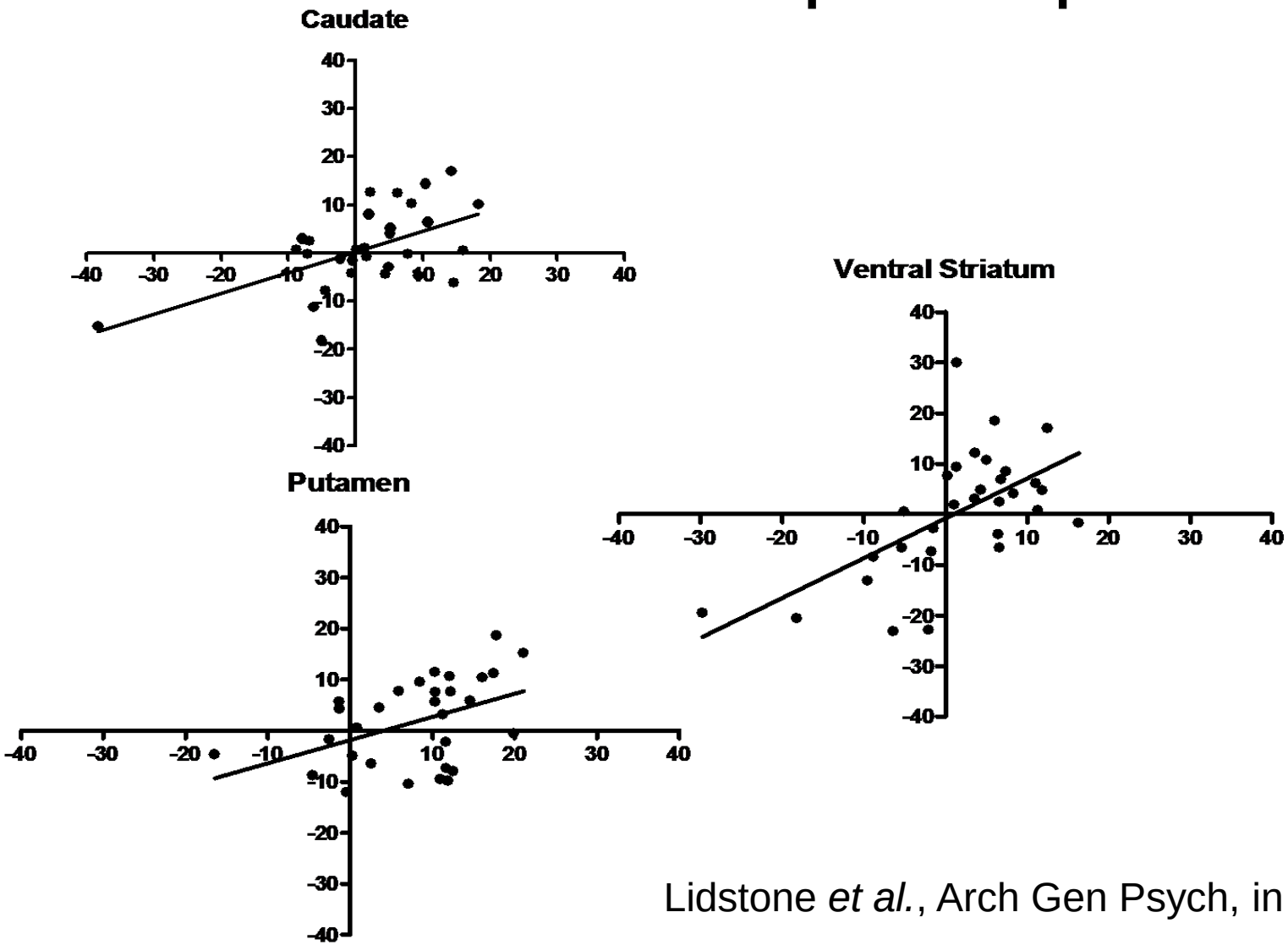
Why 75%?

- Abnormal reward processing in PD (loss of DA)
  - “Off” patients underestimate the value of expected rewards (Frank *et al.* 2004,Schott *et al.* 2007)
  - PD patients impaired on probabilistic learning tasks (Knowlton *et al.* 1996)
- Success of expectancy manipulation?
  - Impossible to measure subjective probability
- Not uncertainty *per se*, rather salience of the placebo
  - Conditioned learning does not take place if outcome deemed certain (Rescorla & Wagner)

Faith & uncertainty – Sir Francis Galton & STEP

- Father of biostatistics, cousin of Darwin
- 1872: Study of intercessory prayer; rigorous endpoint (death)
- Members of royal houses mean life expectancy 64.0 – *vs.* 67.3 for other aristocrats
- Study of Therapeutic Effects of Intercessory Prayer (Am. Ht. J. 2007): no improvement in outcome if one is the subject of prayer
- ***Certainty*** of prayer on ones behalf is associated with increased risk (59%) of complications compared to uncertain possibility (52%)

Placebo-induced DA release is strongly related to the levodopa response



Lidstone *et al.*, Arch Gen Psych, in press

Deception and ethical considerations

- Consent form
  - “The purpose of this study is to examine the different factors that contribute to a person’s response to the treatment of their Parkinson’s disease. The study requires the use of some deception, and as a result the full purpose of the study cannot be revealed to you at this time.”
- Debriefing
- Secrecy

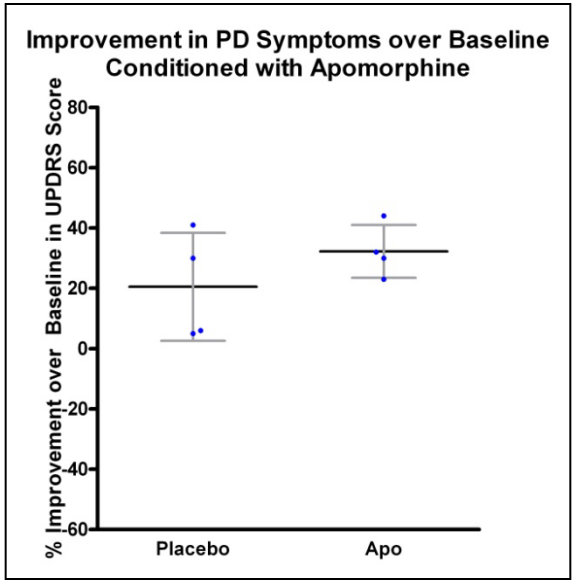
Acknowledgements

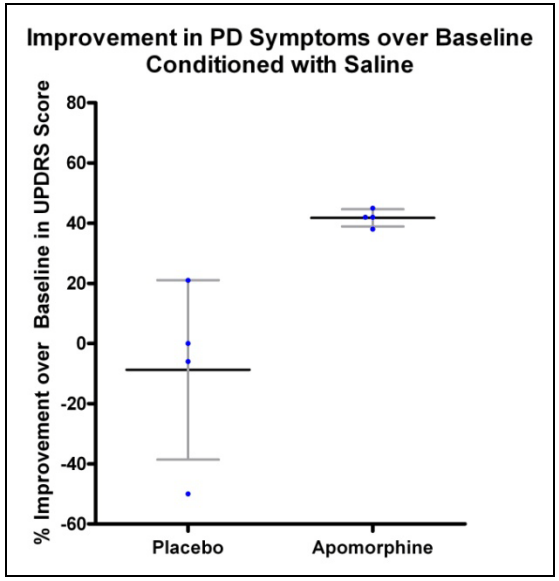
- Sarah Lidstone
- Michael Schulzer, Edwin Mak
- Katie Dinelle, Tom Ruth, Vesna Sossi, TRIUMF, Jess McKenzie, Raul de la Fuente-Fernandez, Tony Phillips

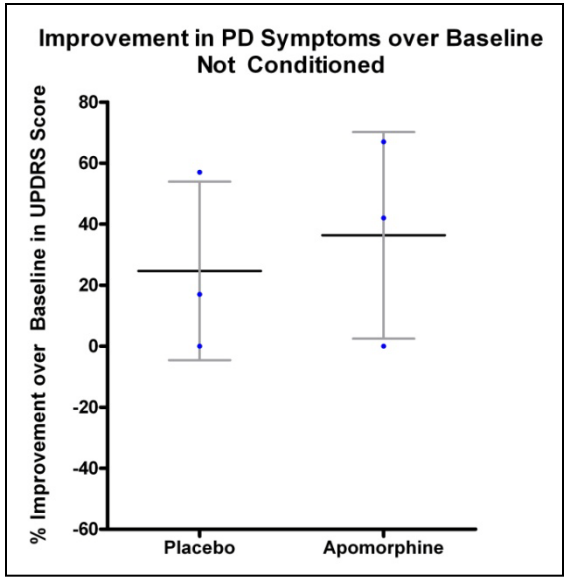
CIHR IRSC

Michael Smith Foundation for Health Research

Preliminary Data: Conditioning







- Protocol:
  - 5 days apomorphine in highly ritualized environment *vs.* saline control; injection of active drug or placebo on Day 6
  - Control condition: 5 days self-administration of apomorphine at home

Manipulation of reward probability: Healthy controls

- Computerized card task
  - 0, 25, 50, 75% winning hands per game
  - Subjects tested on 4 occasions
  - Cards displayed, pick one, new hand dealt
- Preliminary data
  - Significant DA release in bilateral putamen (but not VS) at P=0.5.