Tuesday April 26th 2011

CNTRICS
Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

University of St Andrews

Executive control

Verity Brown & Trevor Robbins

Supported by a joint award from the Medical Research Council and the Wellcome Trust

UNIVERSITY OF CAMBRIDGE

wellcome trust

MRC Medical Research Council

The University of Cambridge Behavioural and Clinical Neurosciences Institute

Not All Executive Functions Are Related to Intelligence

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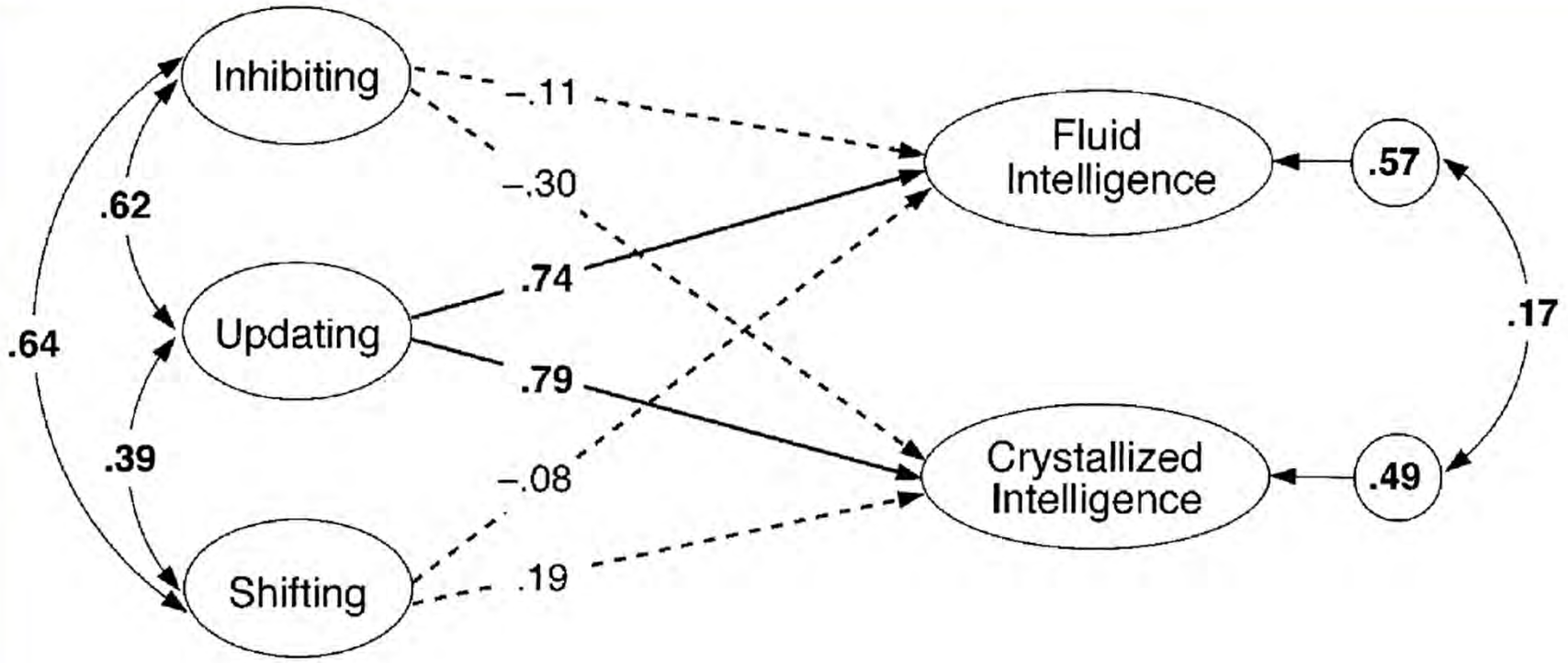
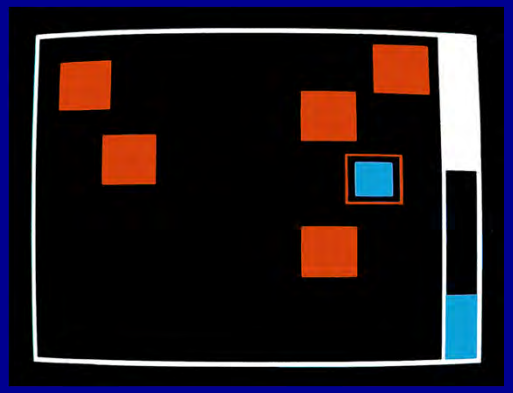
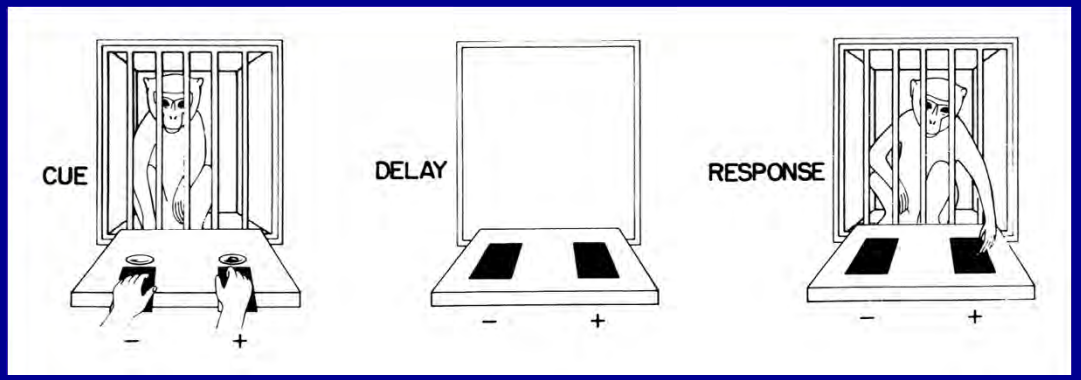
[1]Institute for Behavioral Genetics, University of Colorado at Boulder, and [2]Department of Psychology, University of Colorado at Boulder

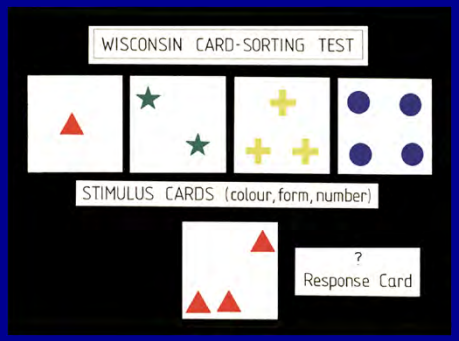


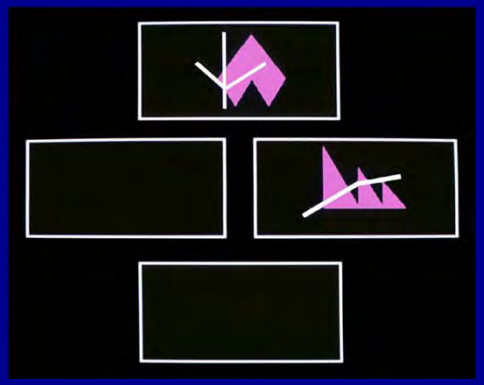
Psychological Science 17, 172-179.

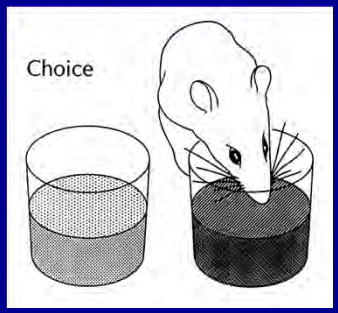
Tests of executive function in monkeys, rodents & humans

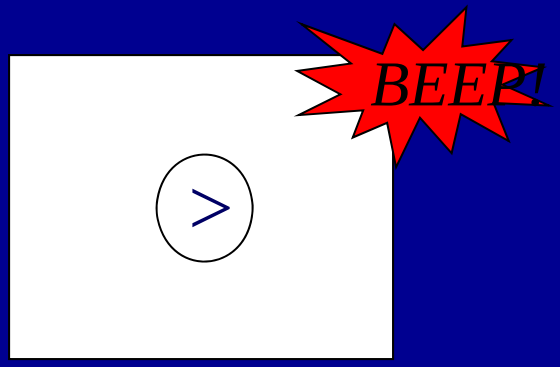


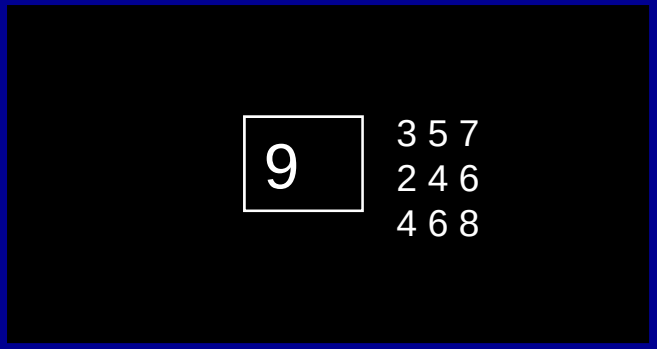


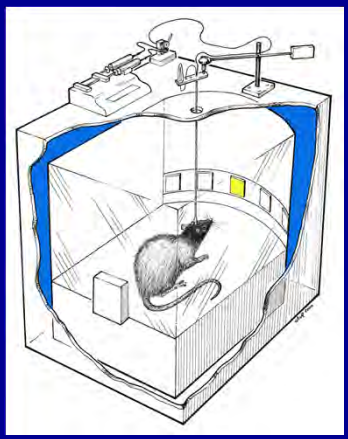










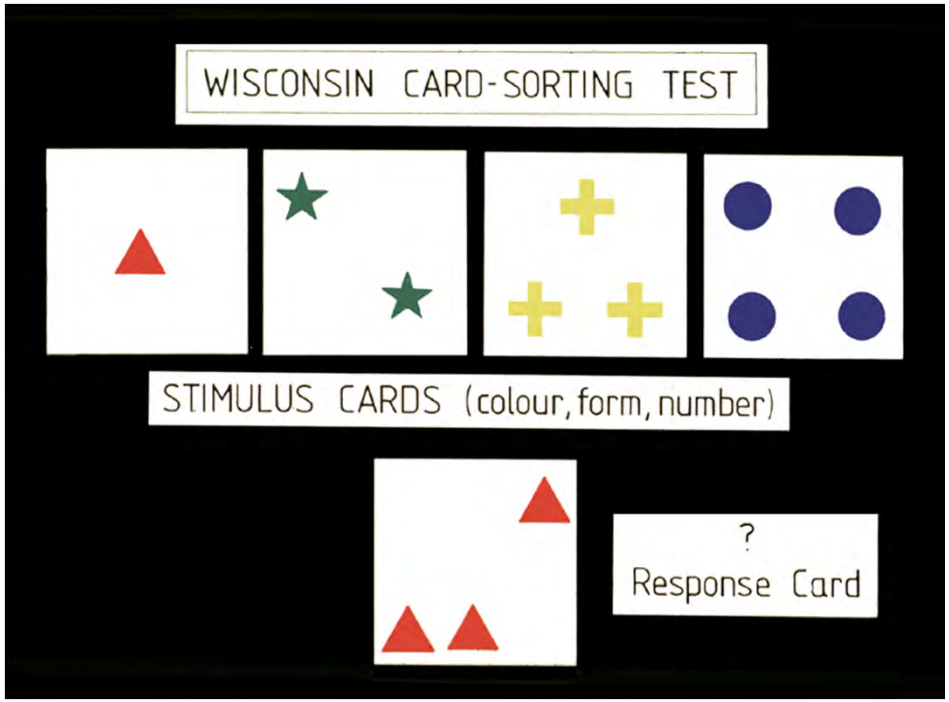


Executive Control

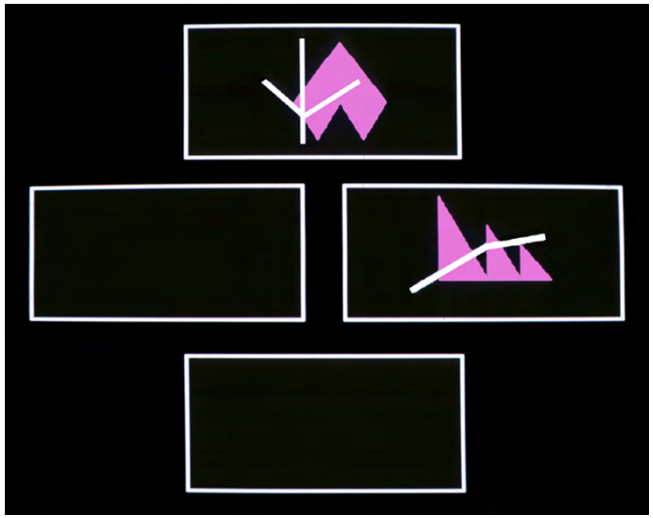
- Rule Generation and Selection: **The processes involved in activating task related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection.**
  - Nominated Tasks:
    - ***1-2 AX-CPT***
    - ***ID-ED Task***
    - ***Groton Maze Learning Test (GMLT) [Construct Unclear]***
    - ***Switching Stroop (task switching asymmetric or symmetric)***
- Dynamic Adjustments of Control: **The processes involved in detecting the occurrence of conflict or errors in ongoing processing, identifying the type of control adjustments needed, and recruiting additional control processes.**
  - Nominated Tasks:
    - *Stroop Task*
    - *Stop Signal Task*
    - ***Simon Task [Interesting, but in need of more development]***
    - ***Attention Networks Task [Different Construct]***

CNTRICS
Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

Classical and modern tests of attentional set-shifting



CANTAB ID-ED



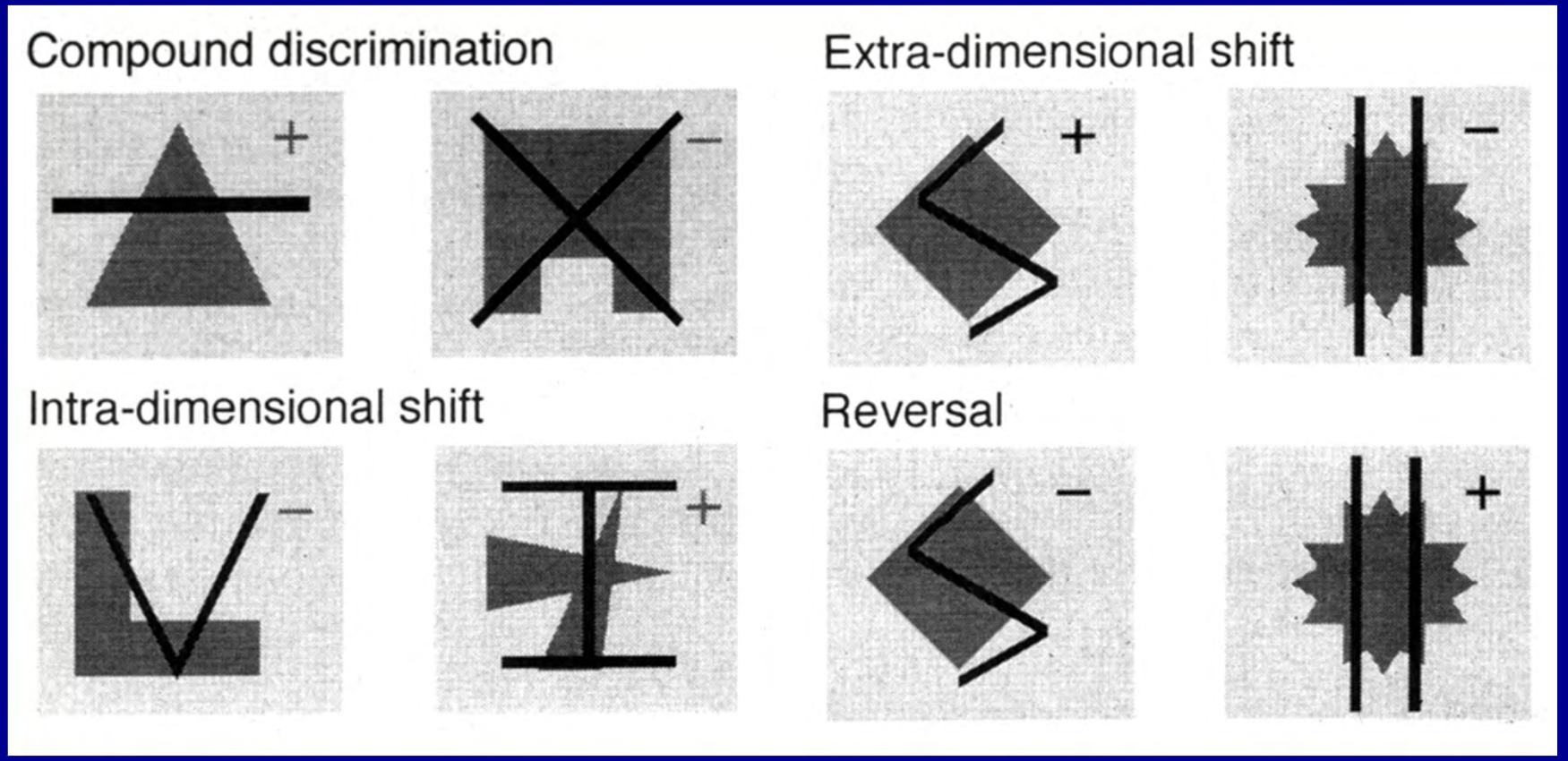
Sensitive to frontal lobe damage
in humans (B. Milner)

…. And schizophrenia (D. Weinberger et al)

Three forms of cognitive shifting/plasticity

basic discrimination task

shape to line
line to shape



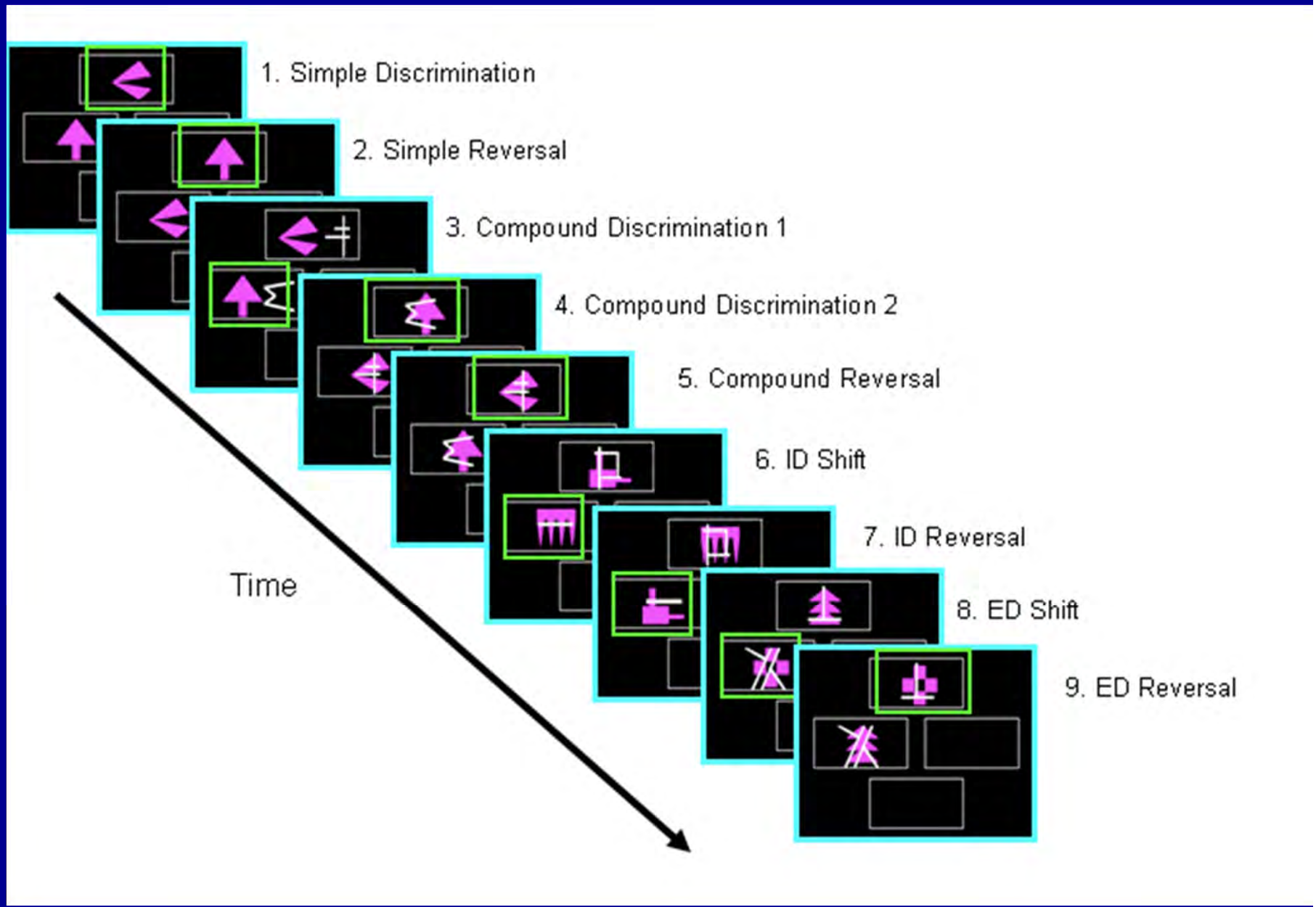
shape to shape
line to line

stimuli stay the same;
reward shifts

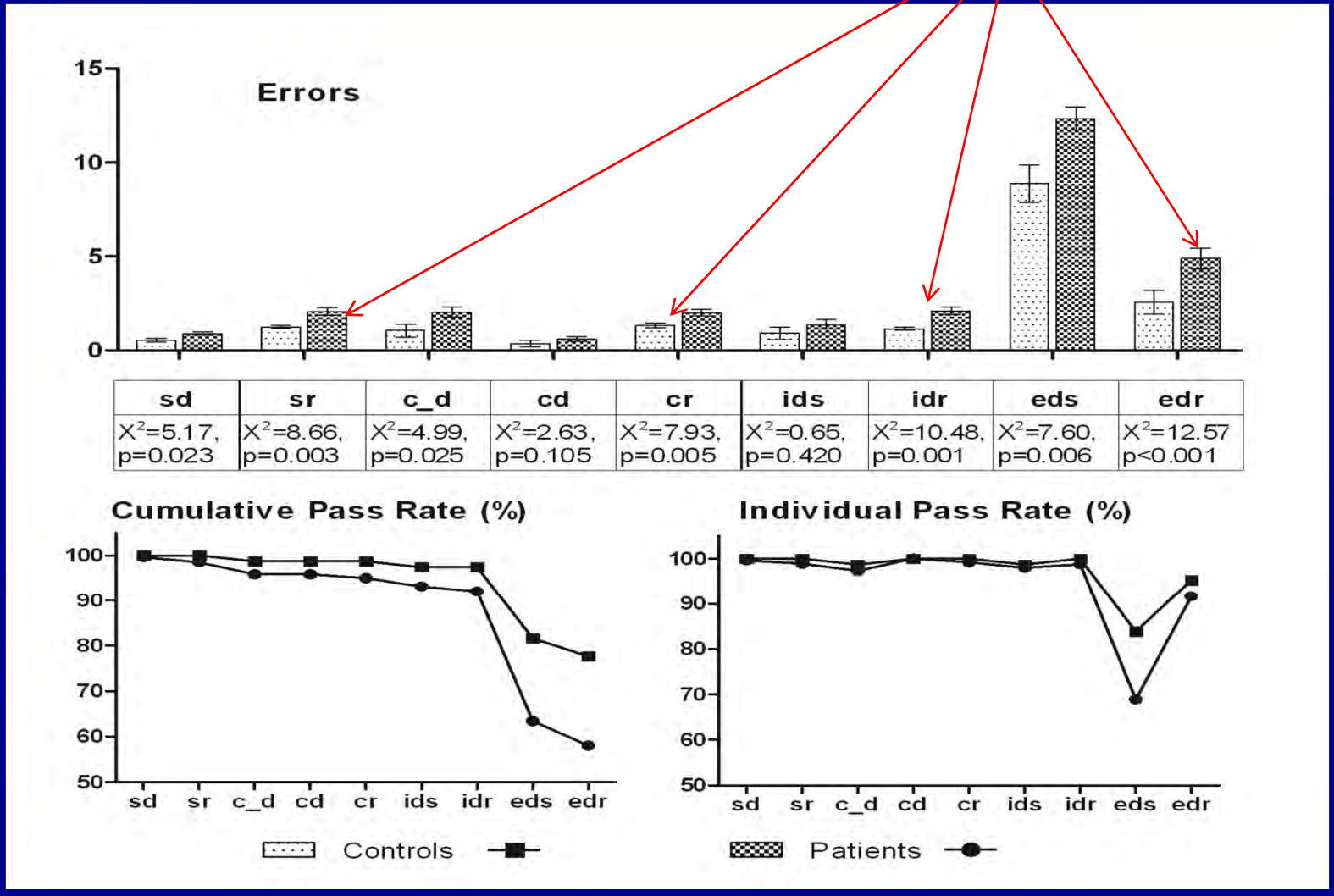
Reversal learning;Theory

- ‘Executive control’ versus new learning and extinction: 3 stimulus reversal tasks
- Effects of ‘over-training reversal shift’ on attentional control
- Effects of reversal learning on dimensional control (i.e. formation of ‘set’)
- Serial reversal learning; influence of higher-order rule learning (e.g. win stay, lose shift)’
- ‘Probabilistic (reversal) learning’

CANTAB: Attentional set-shifting (and reversal)

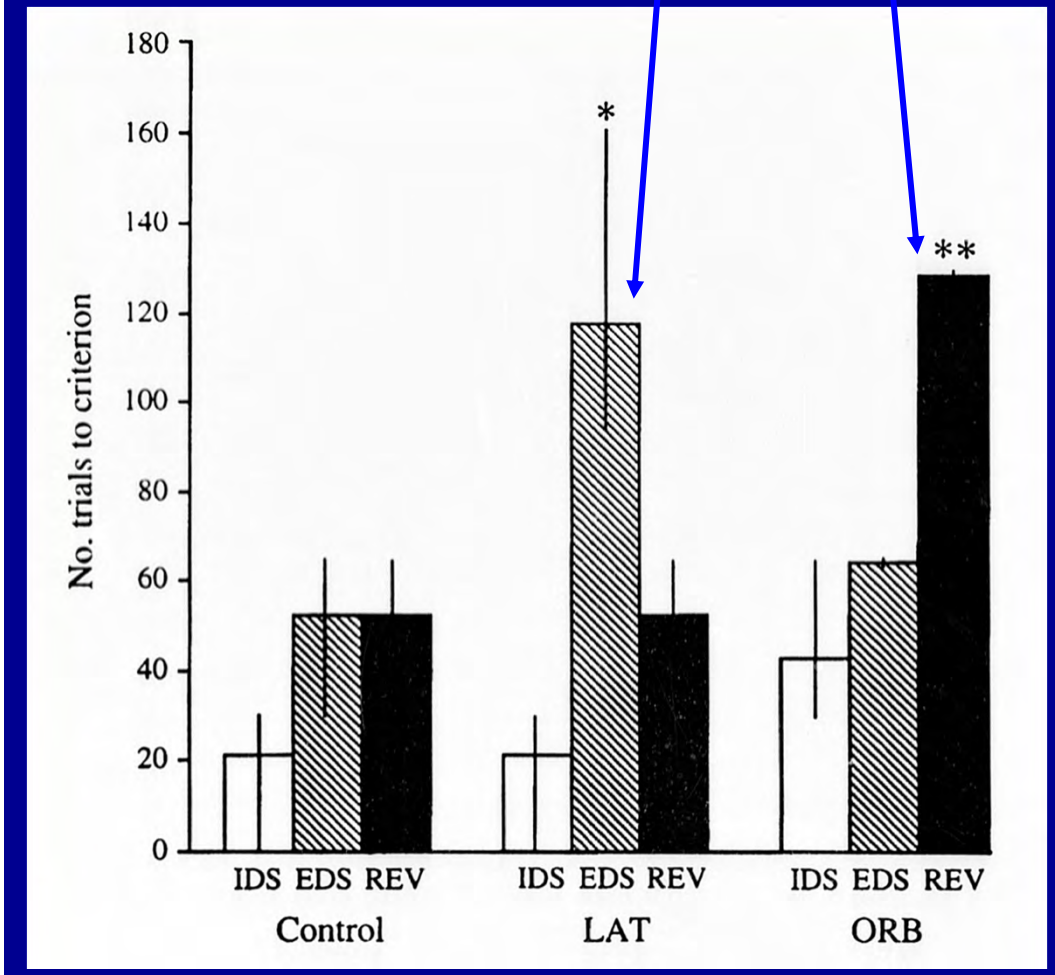


Detailed error analysis in first episode schizophrenia reveals consistent deficits on reversal

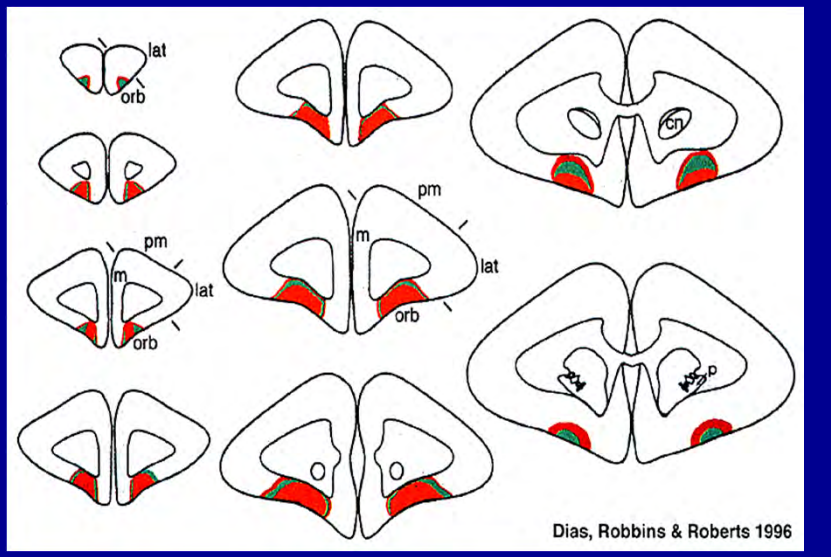


Leeson et al 2009 Biol. Psychiat

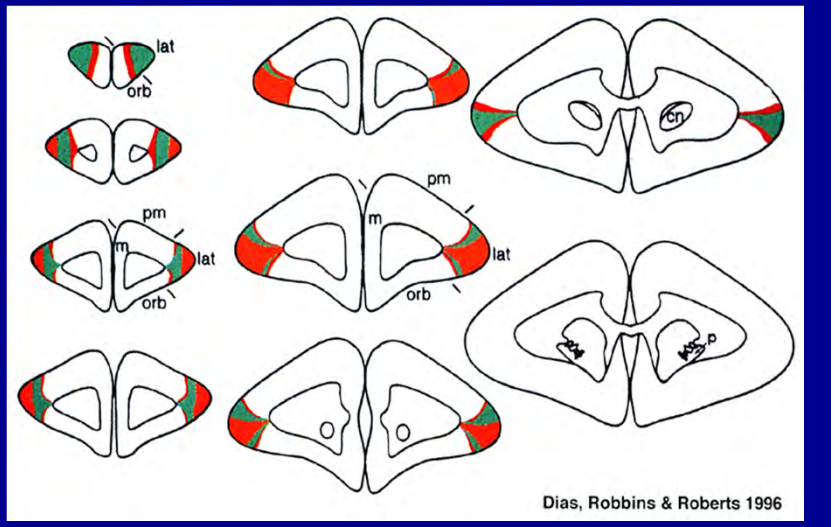
Double dissociation of EDS and reversal learning after frontal lesions



orbitofrontal

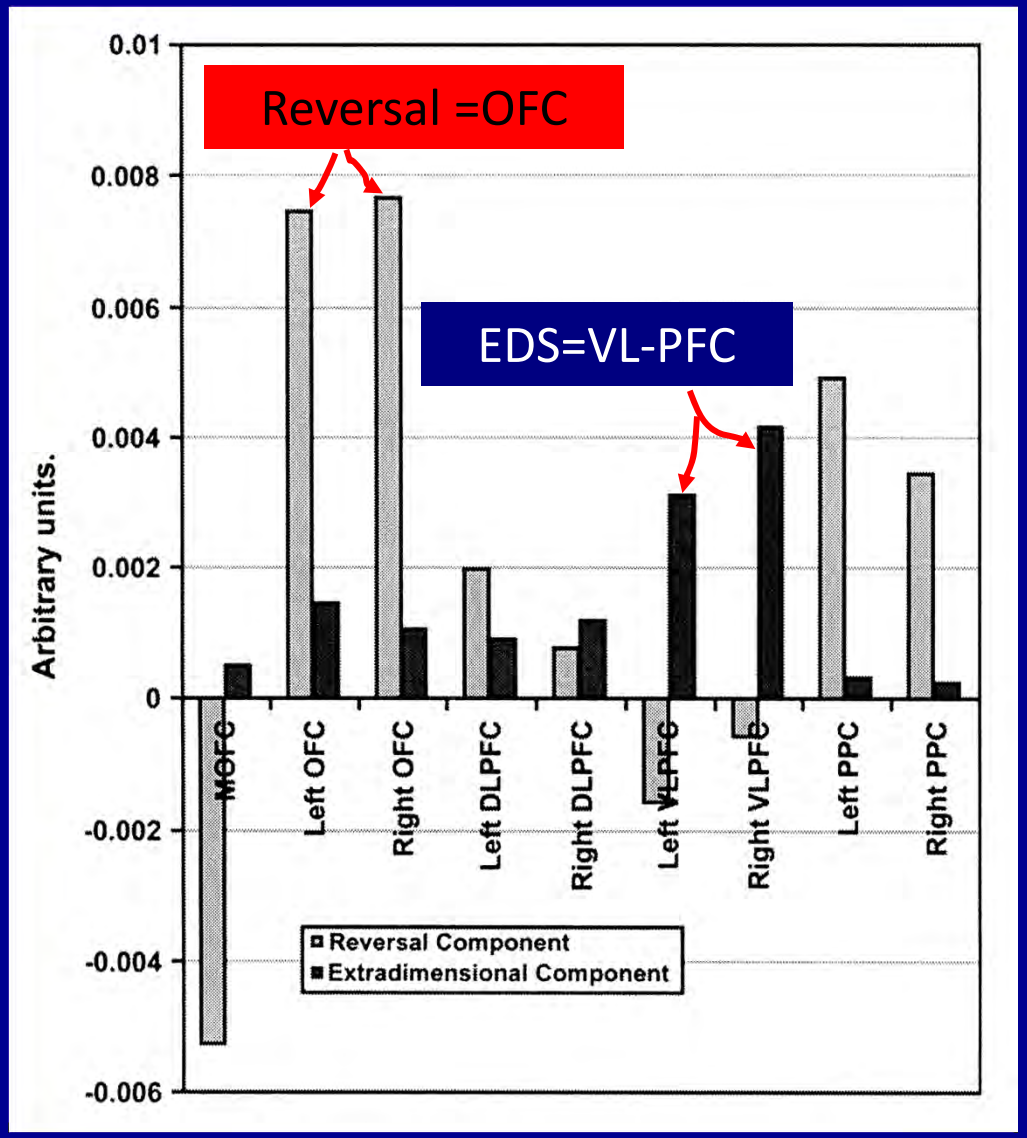


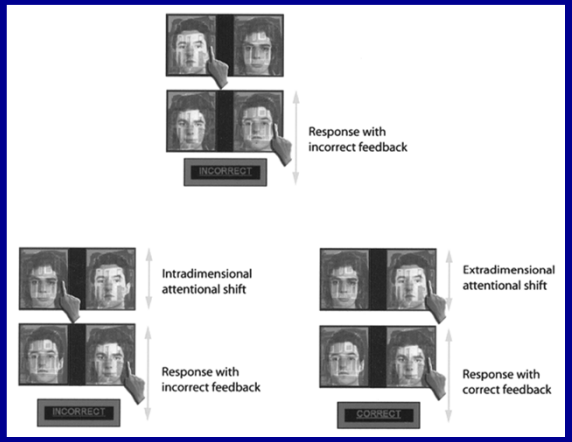
lateral

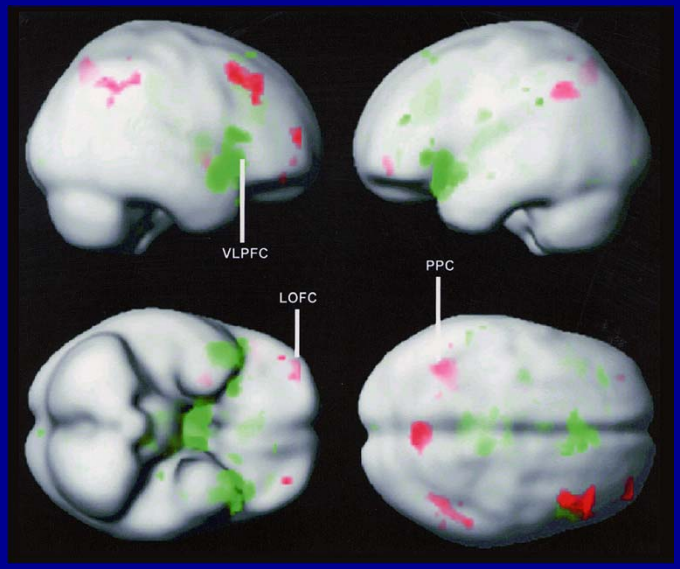


Dias , Robbins & Roberts Nature 1996

Extra-dimensional set shifting and reversal learning involve different PFC circuitry: Evidence from human fMRI



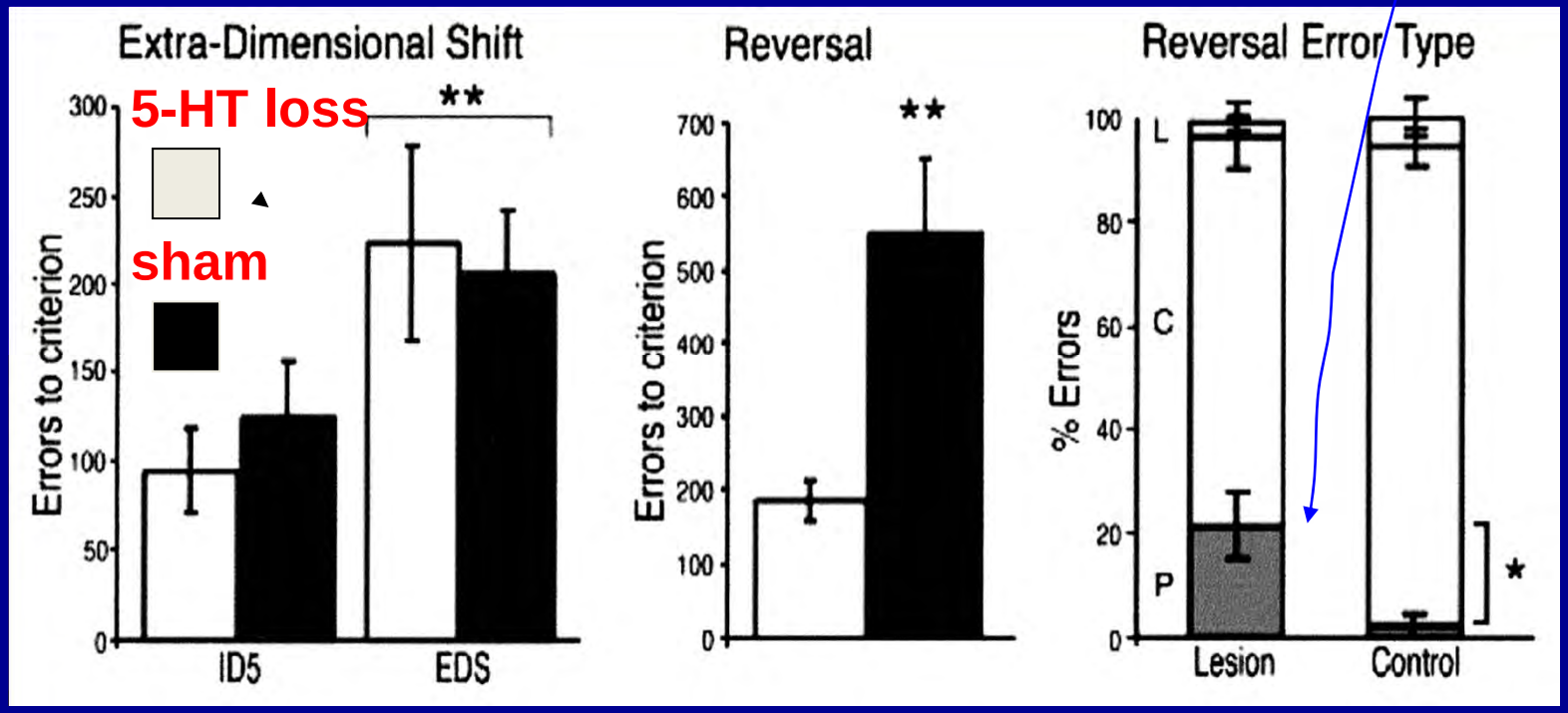


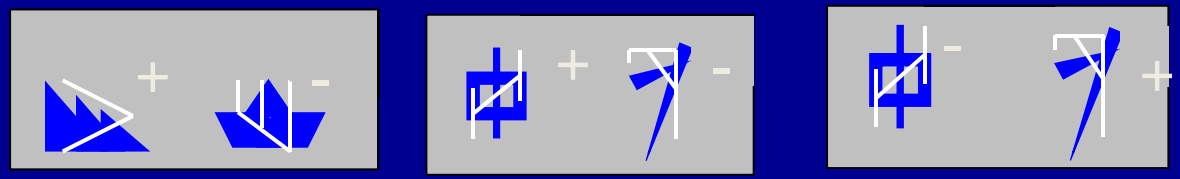


Hampshire & Owen Cerebral Cortex, 2006

Orbitofrontal 5-HT depletion impairs reversal but spares attentional set-shifting in monkeys

Nb increased perseveration following 5-HT loss

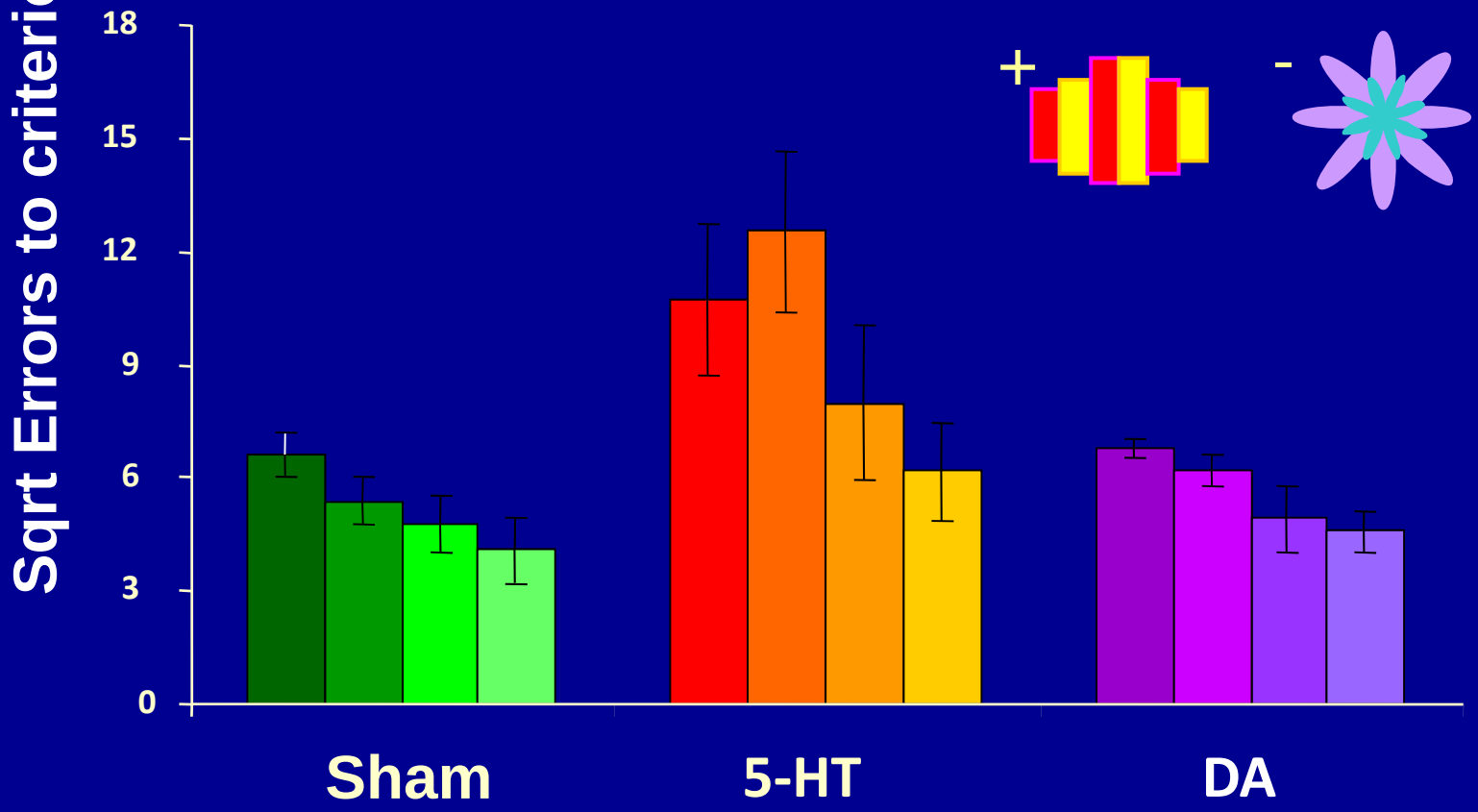




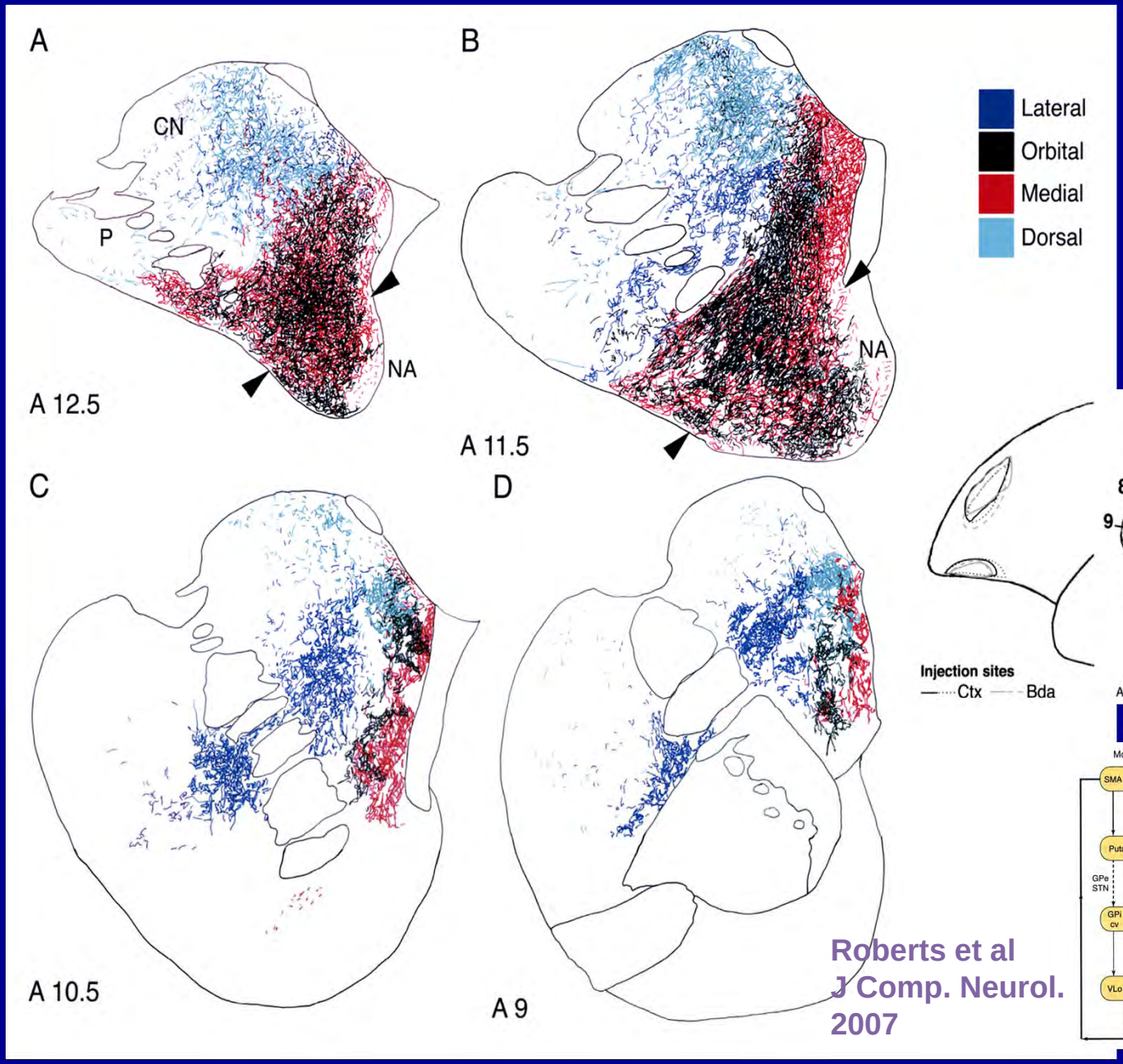
Clarke et al 2005 J. Neuroscience

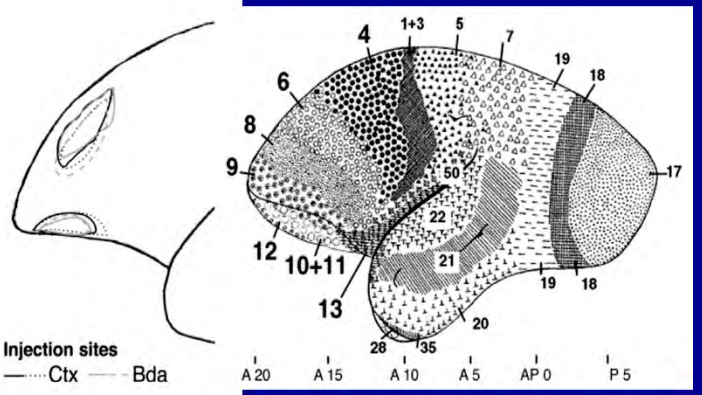
5-HT (but not DA) depletion in OFC impairs serial reversal learning in marmosets

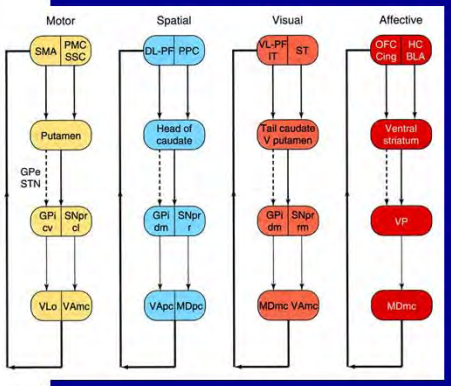
Clarke et al 2007 Cerebral Cortex



Mapping the cortico-striatal loops in the marmoset brain

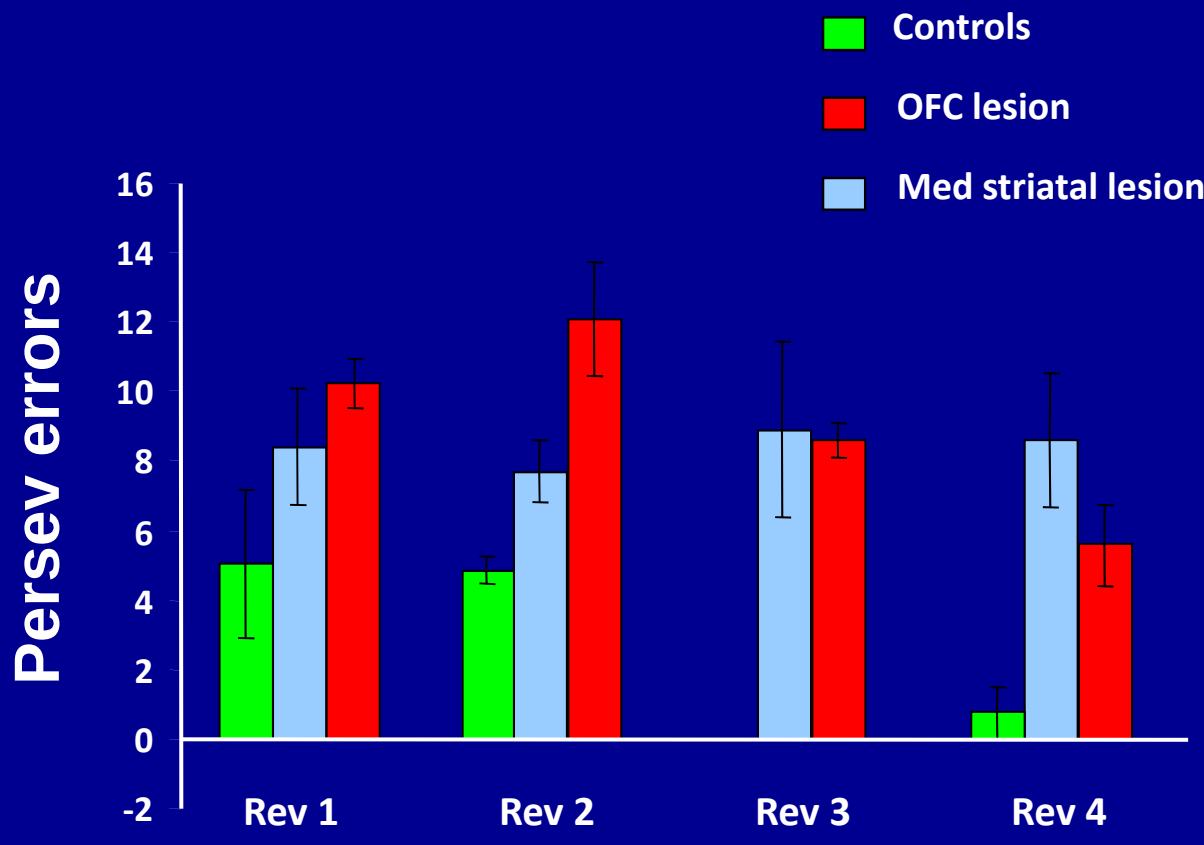






Roberts et al
J Comp. Neurol.
2007

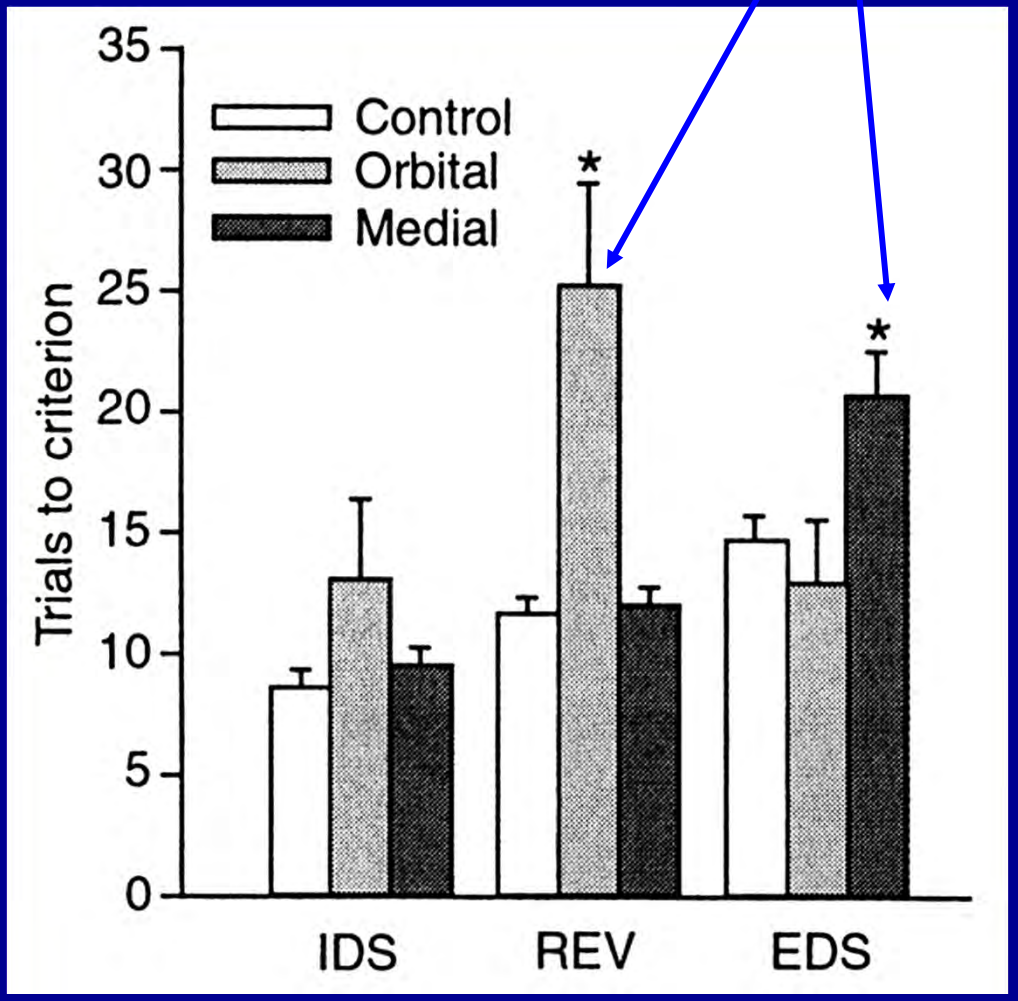
Excitotoxic medial striatal lesions also cause perseveration

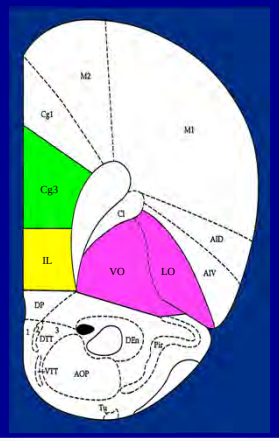


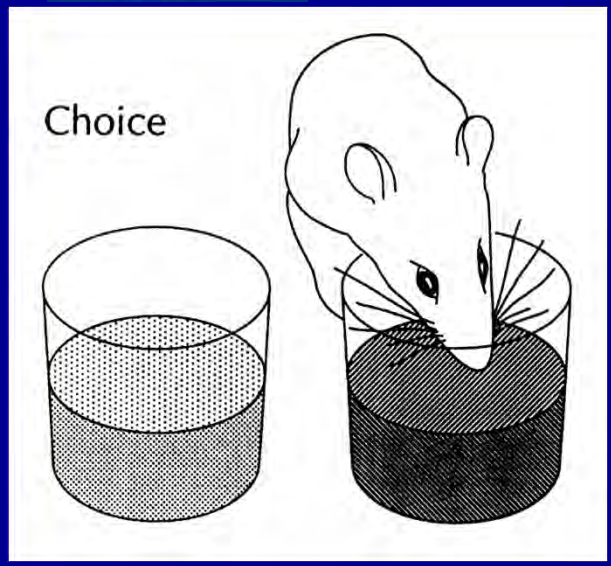
Controls vs MS/OFC, $P < 0.005$

Clarke et al., 2008 J. Neurosci

Double dissociation of reversal learning and extra-dimensional set-shifting in rats

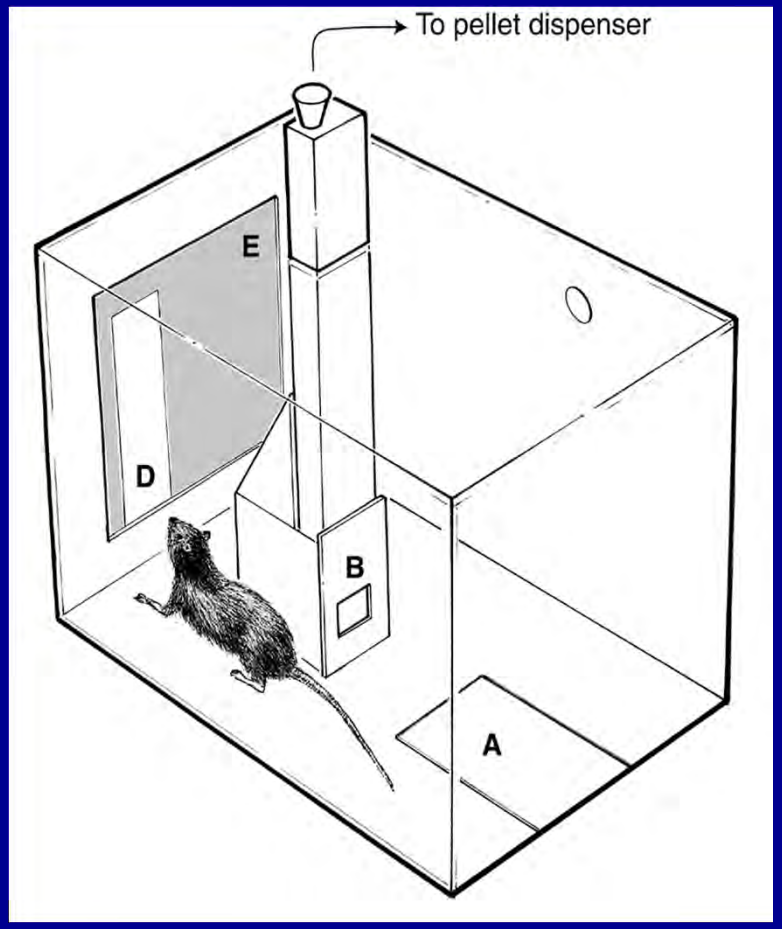


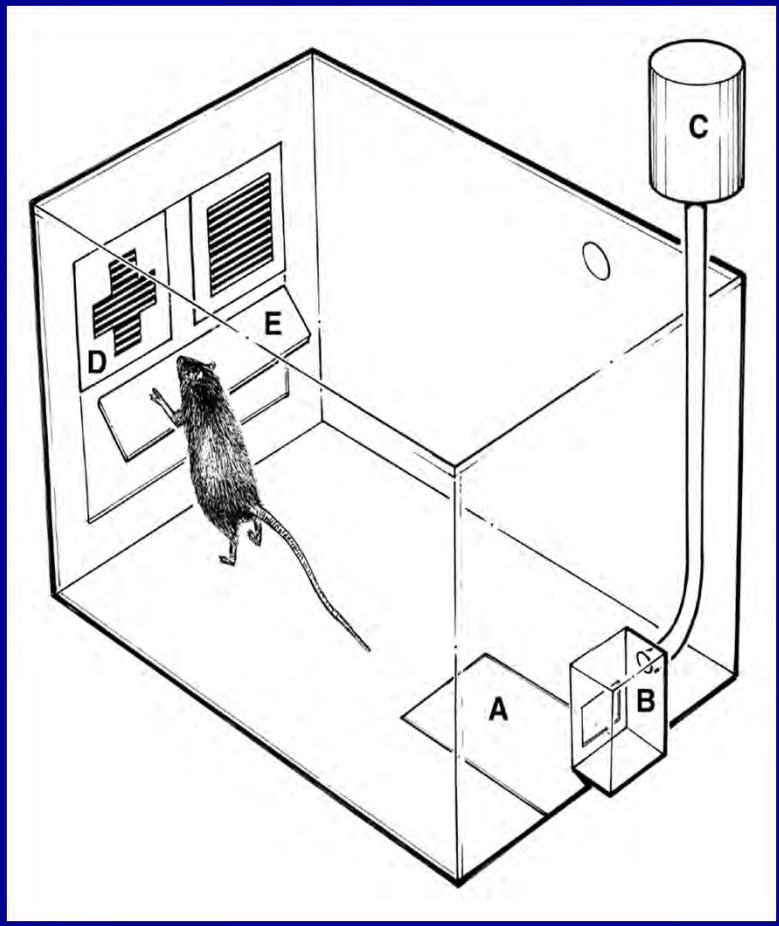




; Birrell and Brown 2000;Brown & Bowman 2002 ; McAlonan & Brown 2003

Automated touchscreen apparatus

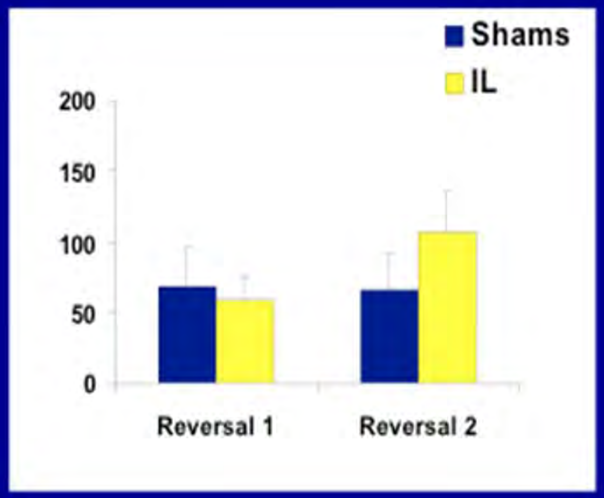




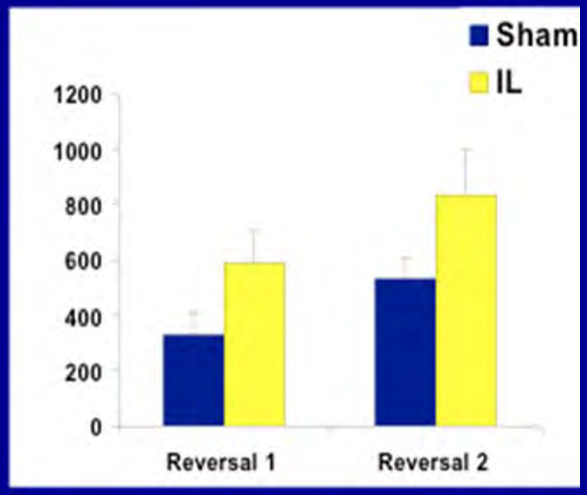
Bussey et al

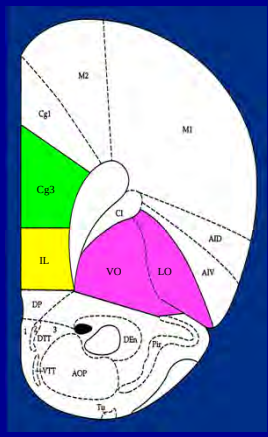
Stage of reversal learning analysis: Dissociable effects of IL and PFC lesions

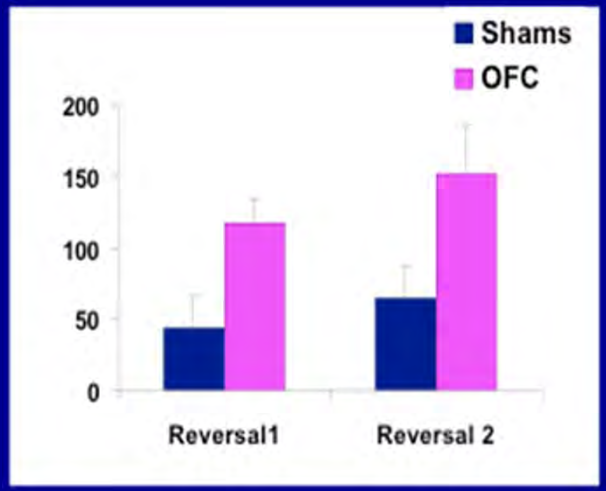
Perseverative errors

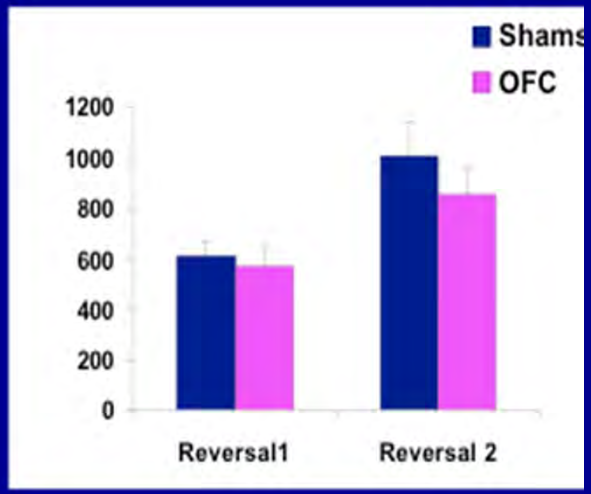


Learning errors



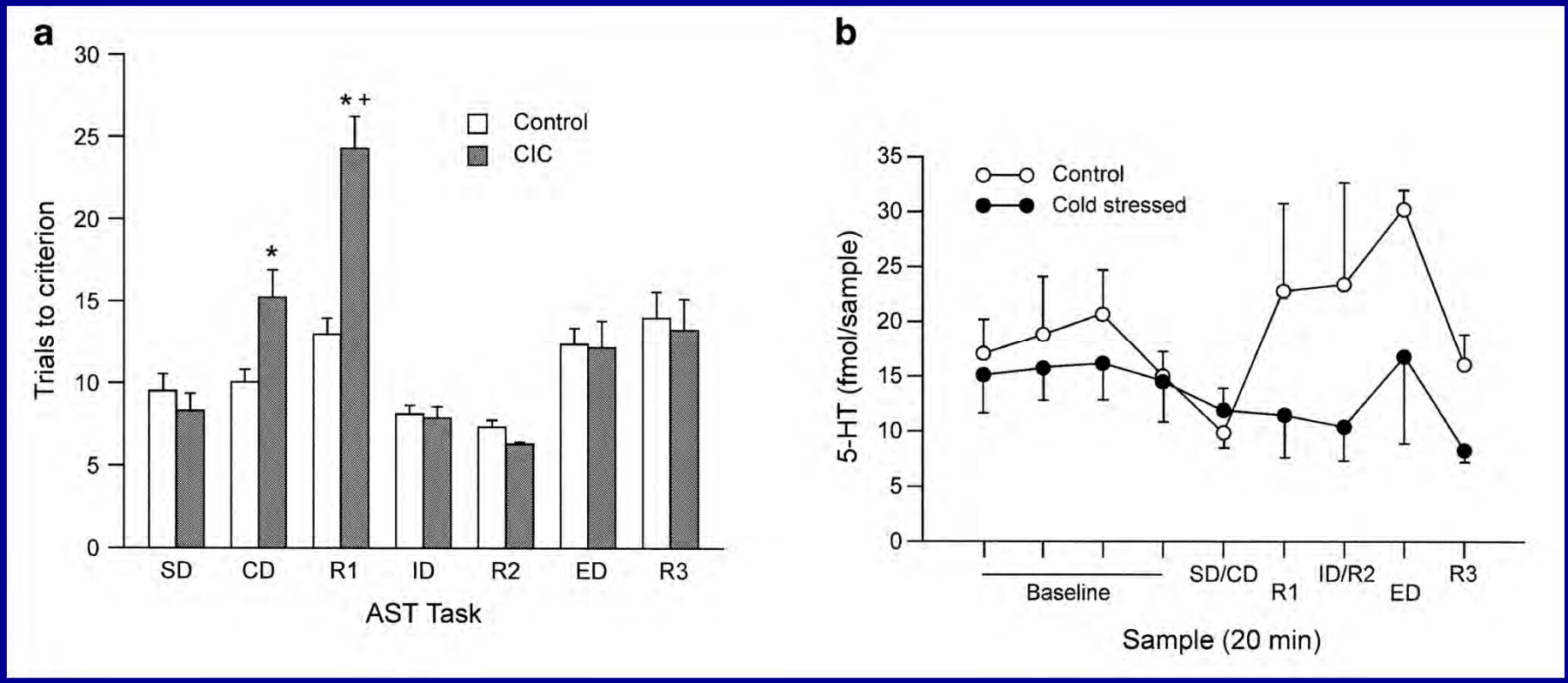






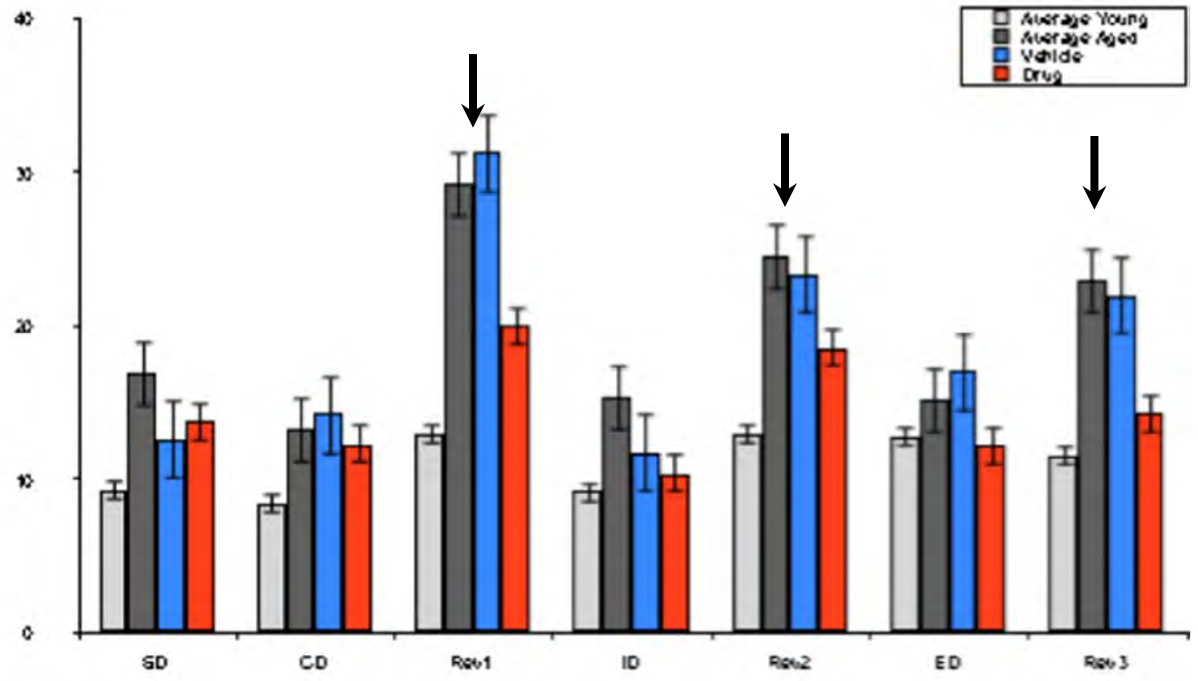
Chudasama & Robbins

Chronic (cold) stress impairs reversal learning and prevents recruitment of 5-HT system in OFC in rats



Lapiz-Bluhm et al Psychopharm 2009

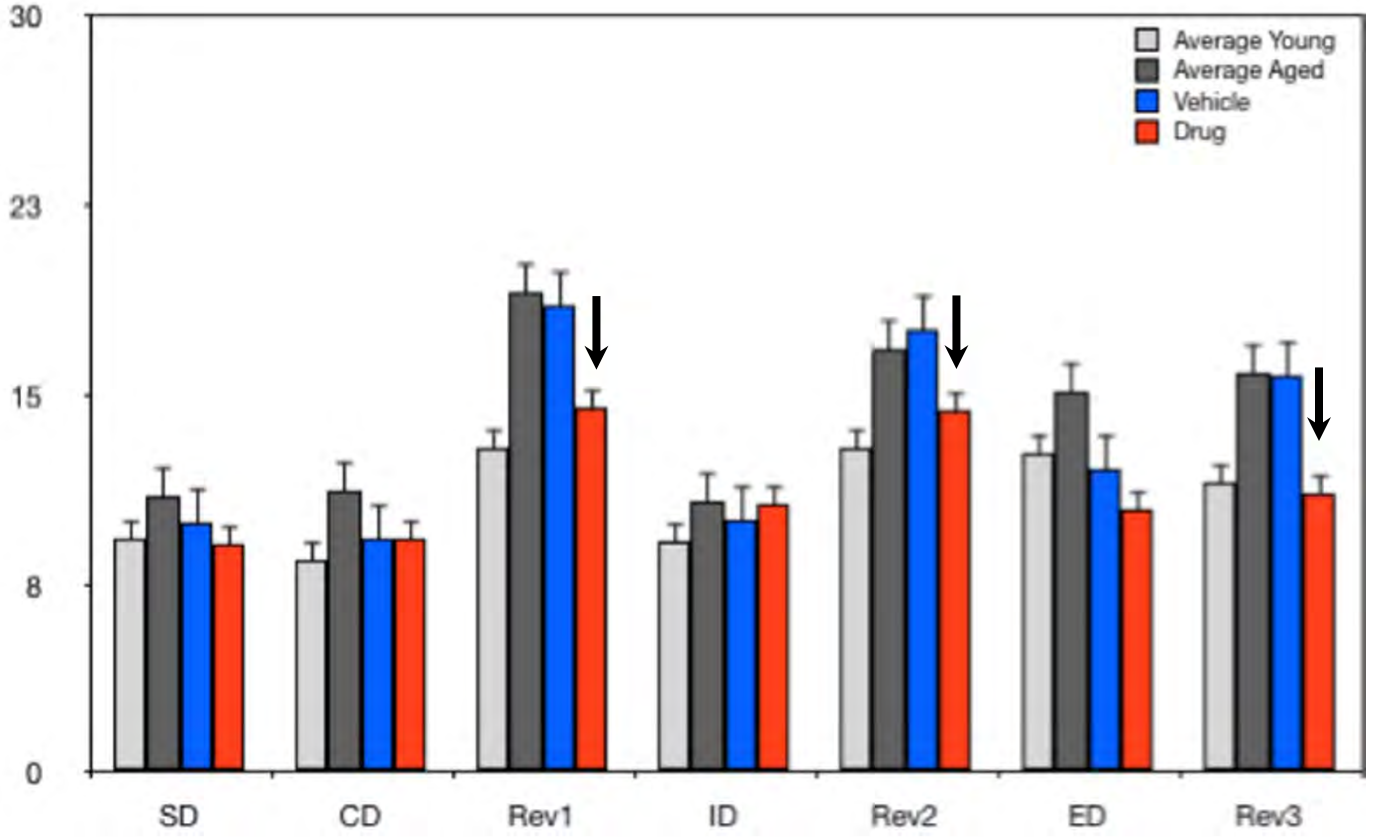
Aged rats and the ID/ED task



- Modulation of NMDA attenuates the reversal deficit, but drug-treated rats still aren't as good as young rats (Chase et al 2010)

Chase, Tait & Brown unpublished observations 2011

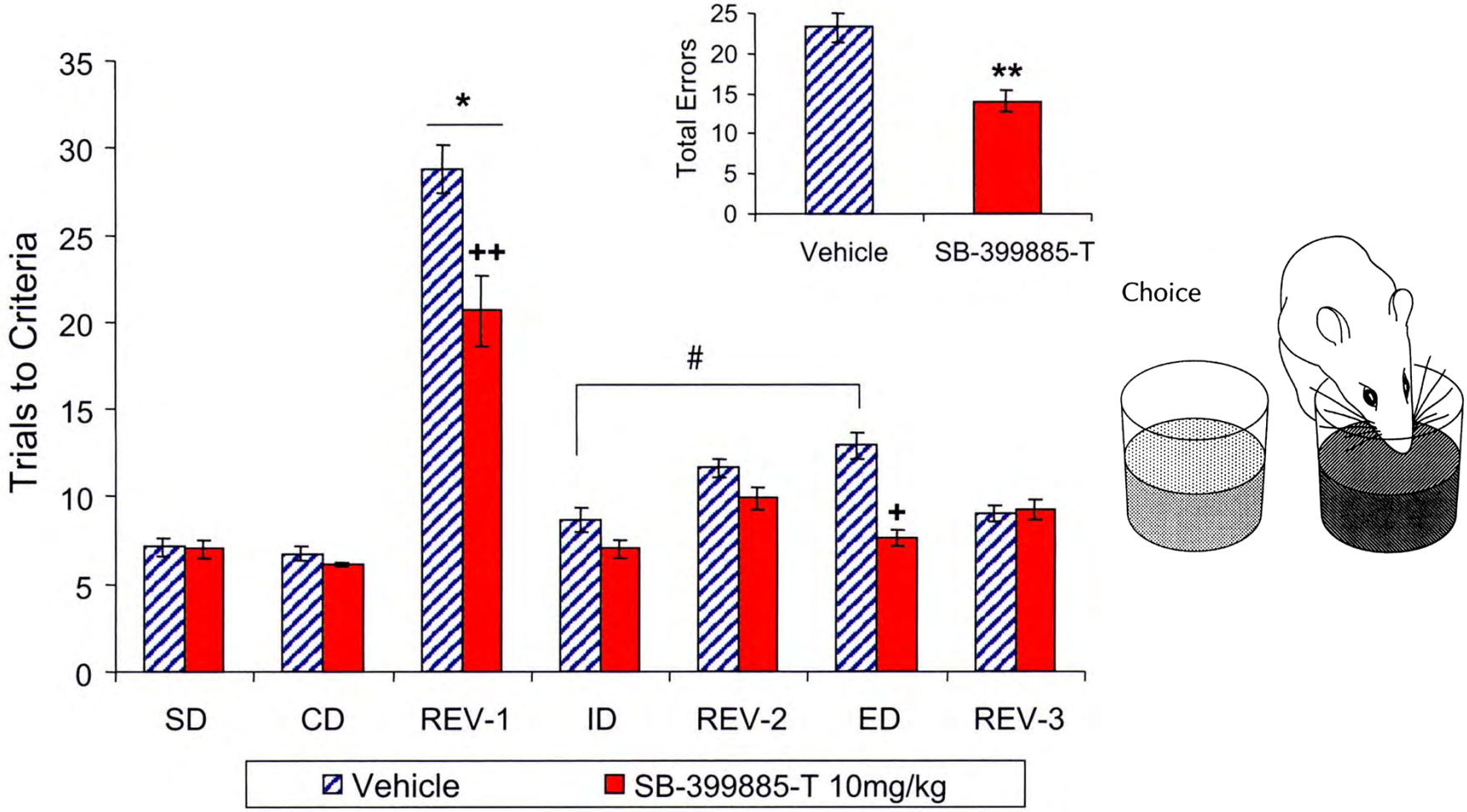
Improved reversal learning with cholinergic agents



Rats treated with the anti-cholinesterase inhibitor donepezil (Tacrine) are more flexible on reversal stages

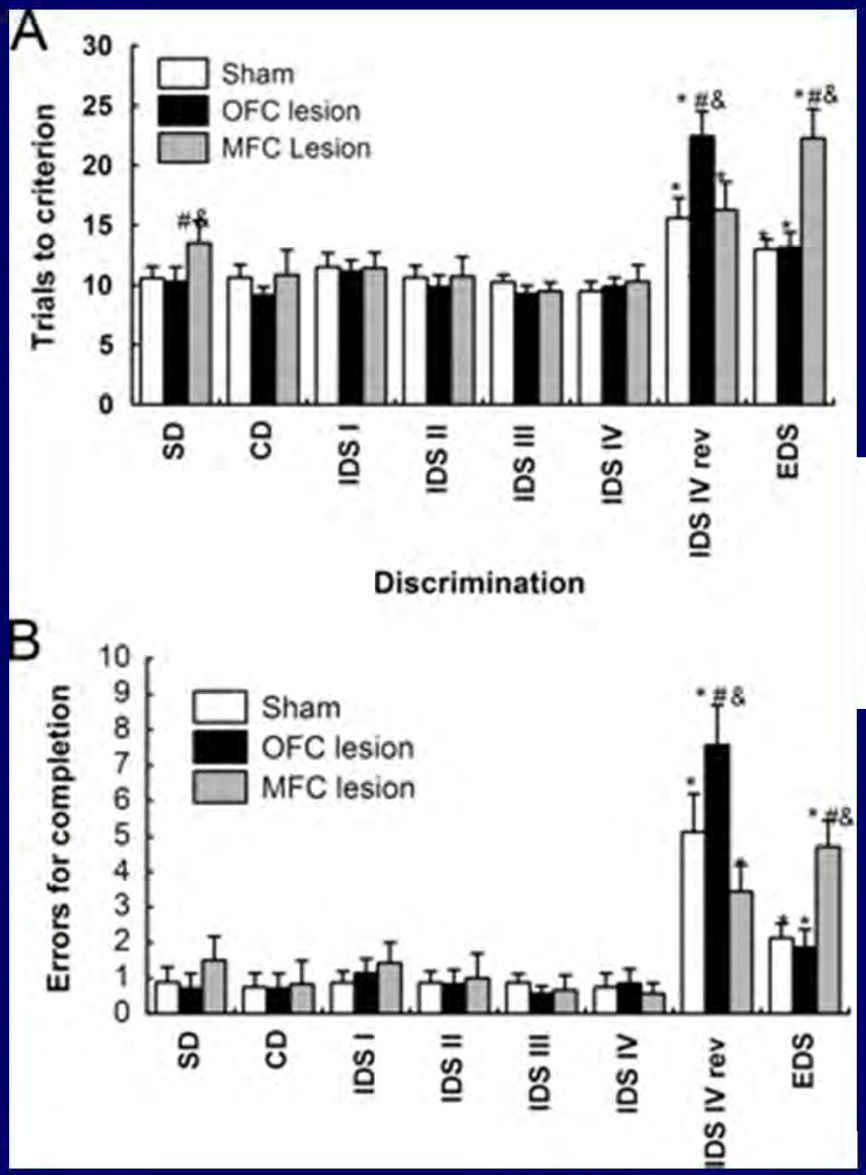
Chase, Tait & Brown unpublished observations 2011

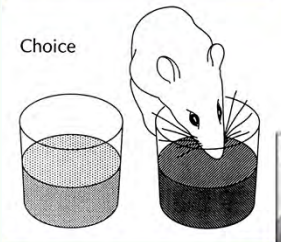
5-HT6 antagonists improve reversal learning AND attentional set-shifting performance in rats

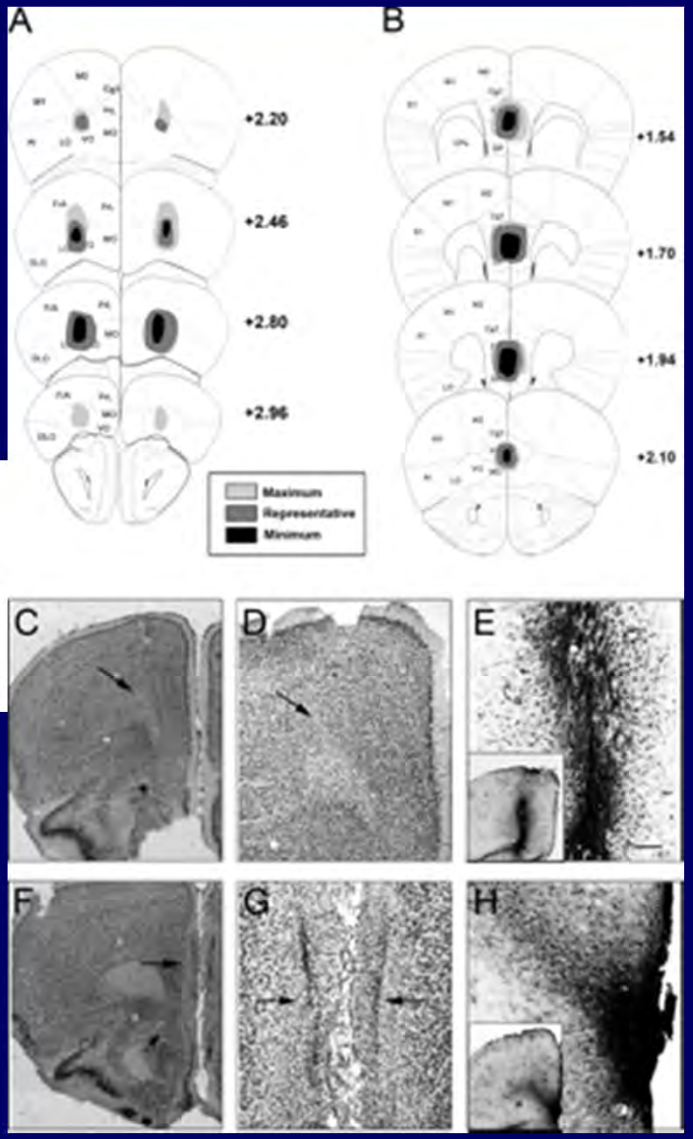


Hatcher et al 2005

Double dissociation of effects of PFC lesions performance on reversal and set-shifting tasks in mice



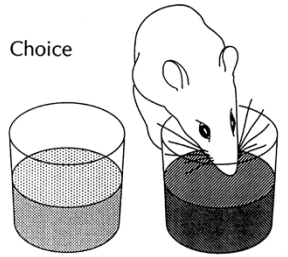




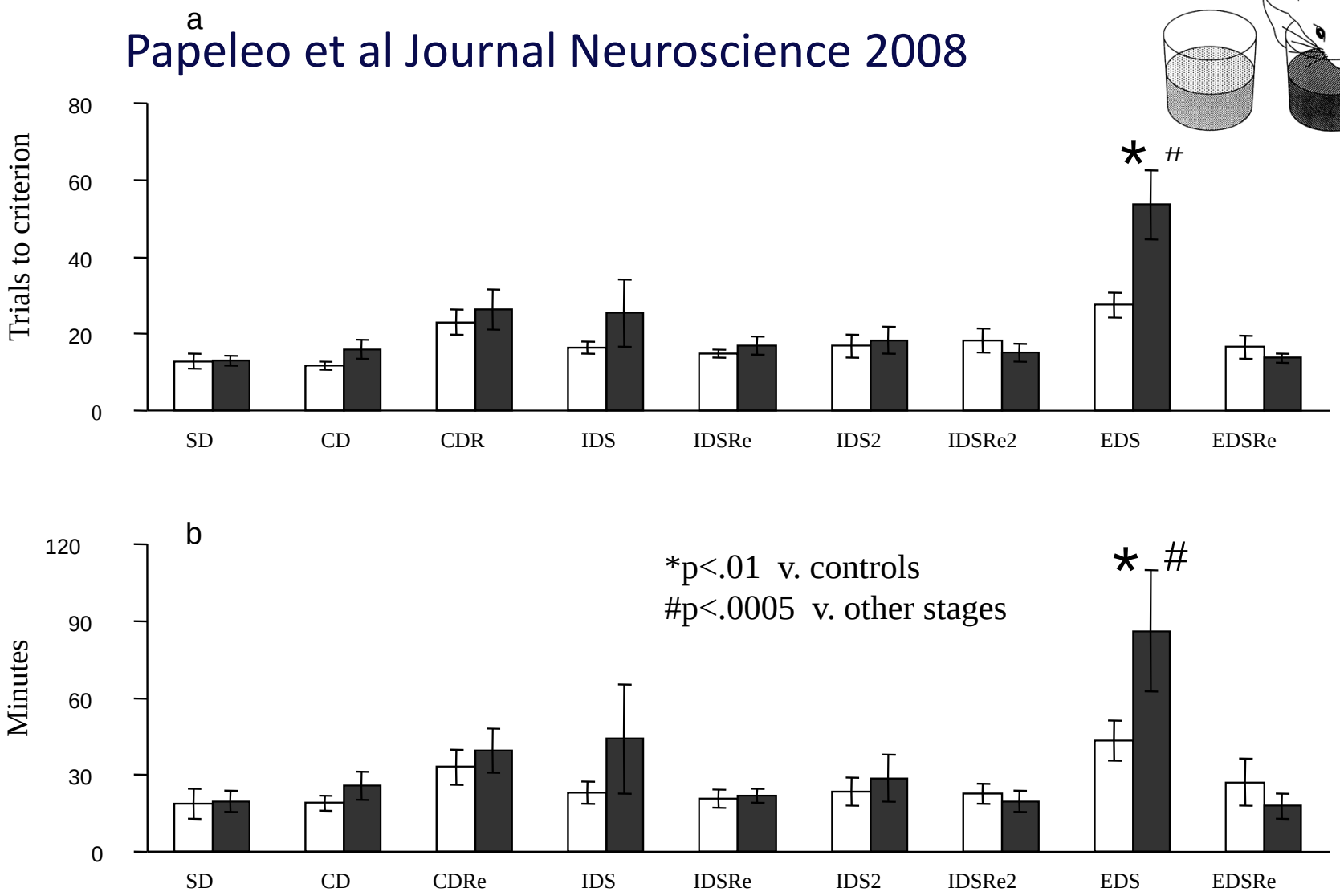
Copyright ©2008 Society for Neuroscience

Bissonette, G. B. et al. J. Neurosci. 2008;28:11124-11130

Over-expression of human COMT-Val impairs attention shift task in mice



Papeleo et al Journal Neuroscience 2008



Task development (pragmatic & theoretical)

- Touchscreen 3-stimulus discrimination and reversal learning (Mar et al, NEWMEDS)

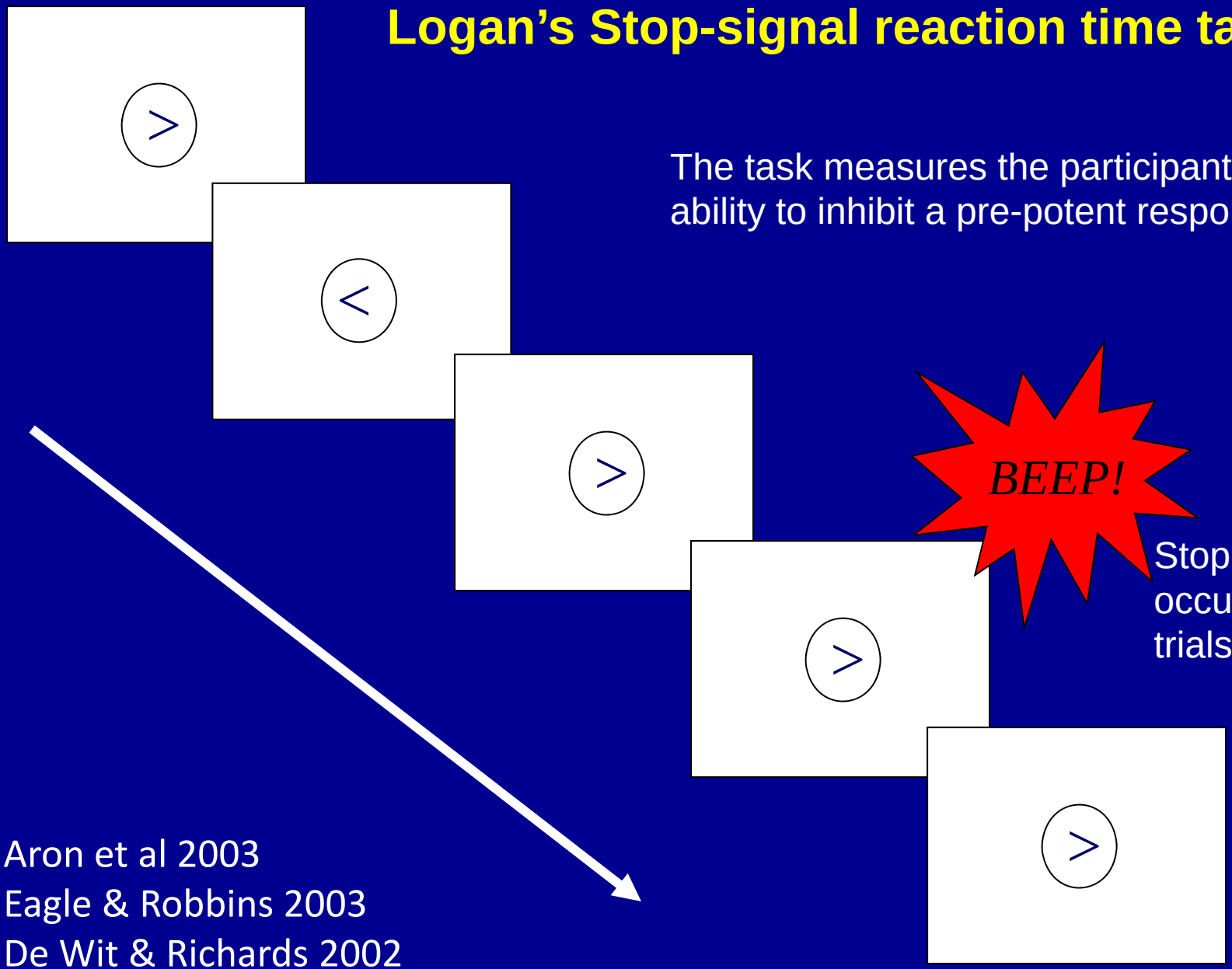
- **Within-session** reversal learring (bowl-digging paradigms) Brown et al

- Probabilistic reversal learning (e.g., Bari et al., 2009 for touchscreen)

- Serial reversal learning as bridge/intermediate to more complex ED shifting (e.g. Rygula et al 2010)

Logan's Stop-signal reaction time task

The task measures the participant's ability to inhibit a pre-potent response.



Stop-signal occurs on 25% trials.

Aron et al 2003
Eagle & Robbins 2003
De Wit & Richards 2002

Impaired stop-signal inhibition in schizophrenia

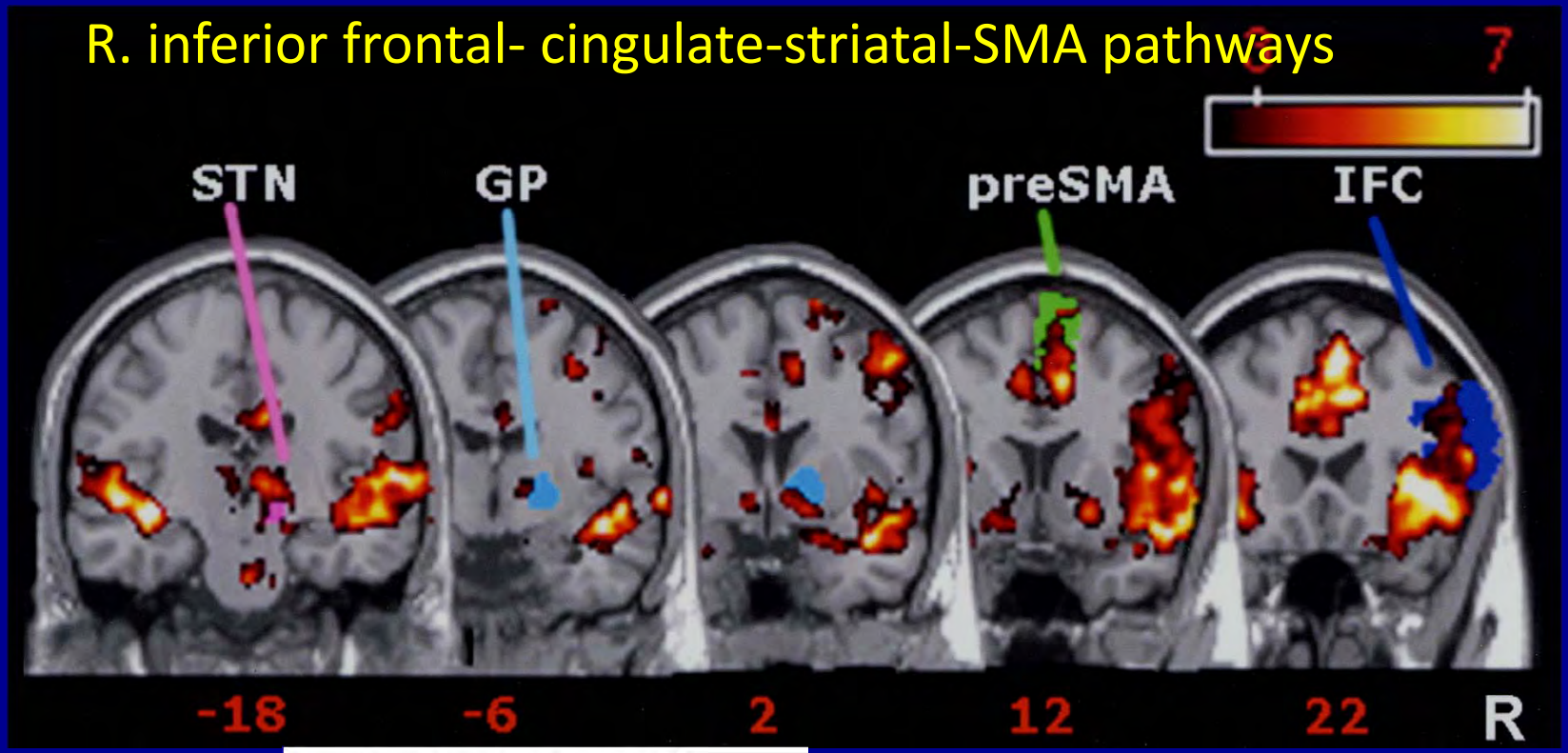
Performance characteristics of the patient and control groups on the stop-signal task. Differences in performance are shown with pre-morbid IQ (WTAR) as a covariate. Median scores for SSRT are given in square brackets

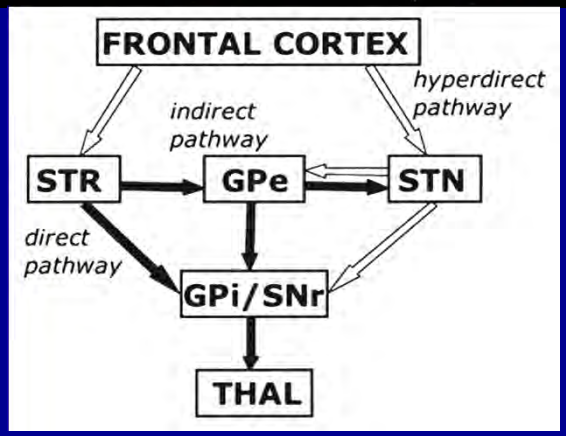
	Patients Mean (S.D.)	Controls Mean (S.D.)	Statistics	df	*p*
GO RT (ms)	531 (125)	471 (82)	Group $F=3.4$	55	0.070
			WTAR $F=0.0$		N.S.
SSRT (ms)	234 (93)	158 (39)	Group $F=9.2$	55	0.002
	[227]	[161]	WTAR $F=1.9$		N.S.
Probability of inhibition (%)	50.0 (8.9)	51.0 (4.6)	Group $F=0.0$	55	N.S.
			WTAR $F=1.4$		N.S.
GO task errors (%)	2.3 (1.9)	0.8 (1.0)	Group $F=7.3$	55	0.009
			WTAR $F=3.6$		N.S.

WTAR, Wechsler Test of Adult Reading; RT, reaction time; SSRT, stop-signal reaction time; S.D., standard deviation; df, degrees of freedom; N.S., not significant.

Huddy et al 2009. Psych Med.

R. inferior frontal- cingulate-striatal-SMA pathways

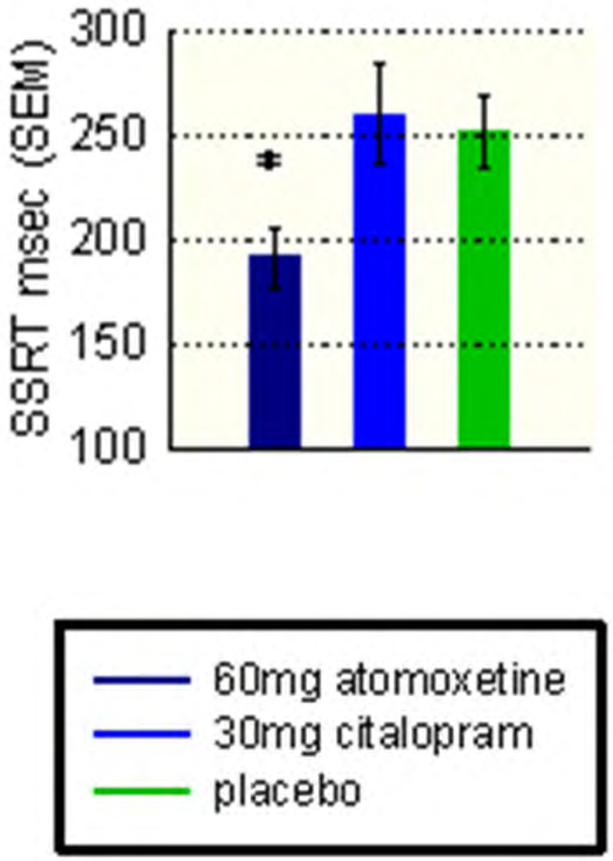




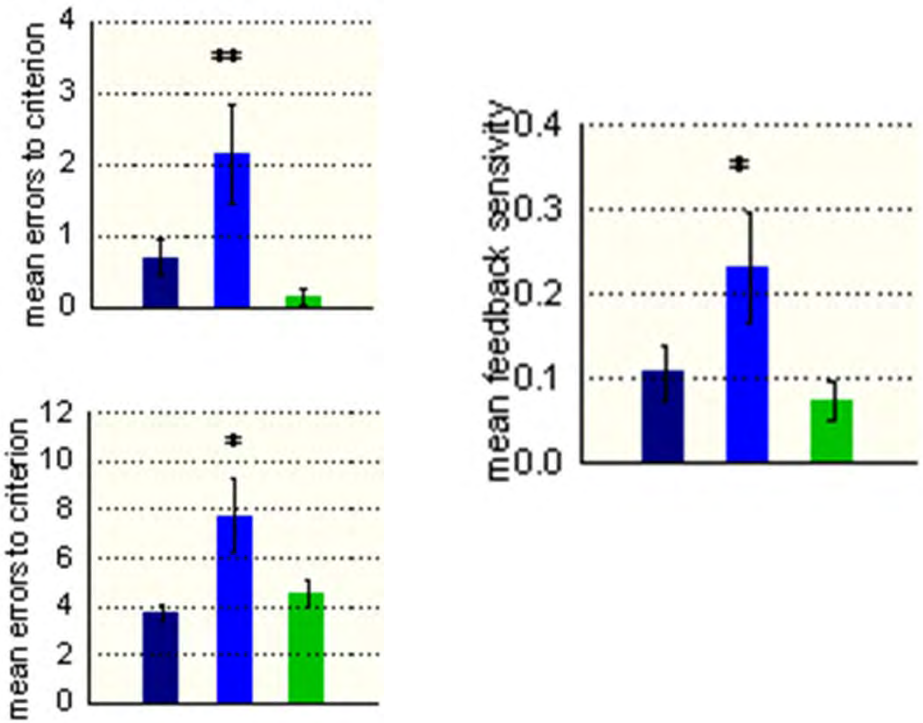
Aron and Poldrack 2006

Double-dissociation in the involvement of noradrenaline and serotonin in human cognition:response inhibition and probabilistic learning

Stop-signal task



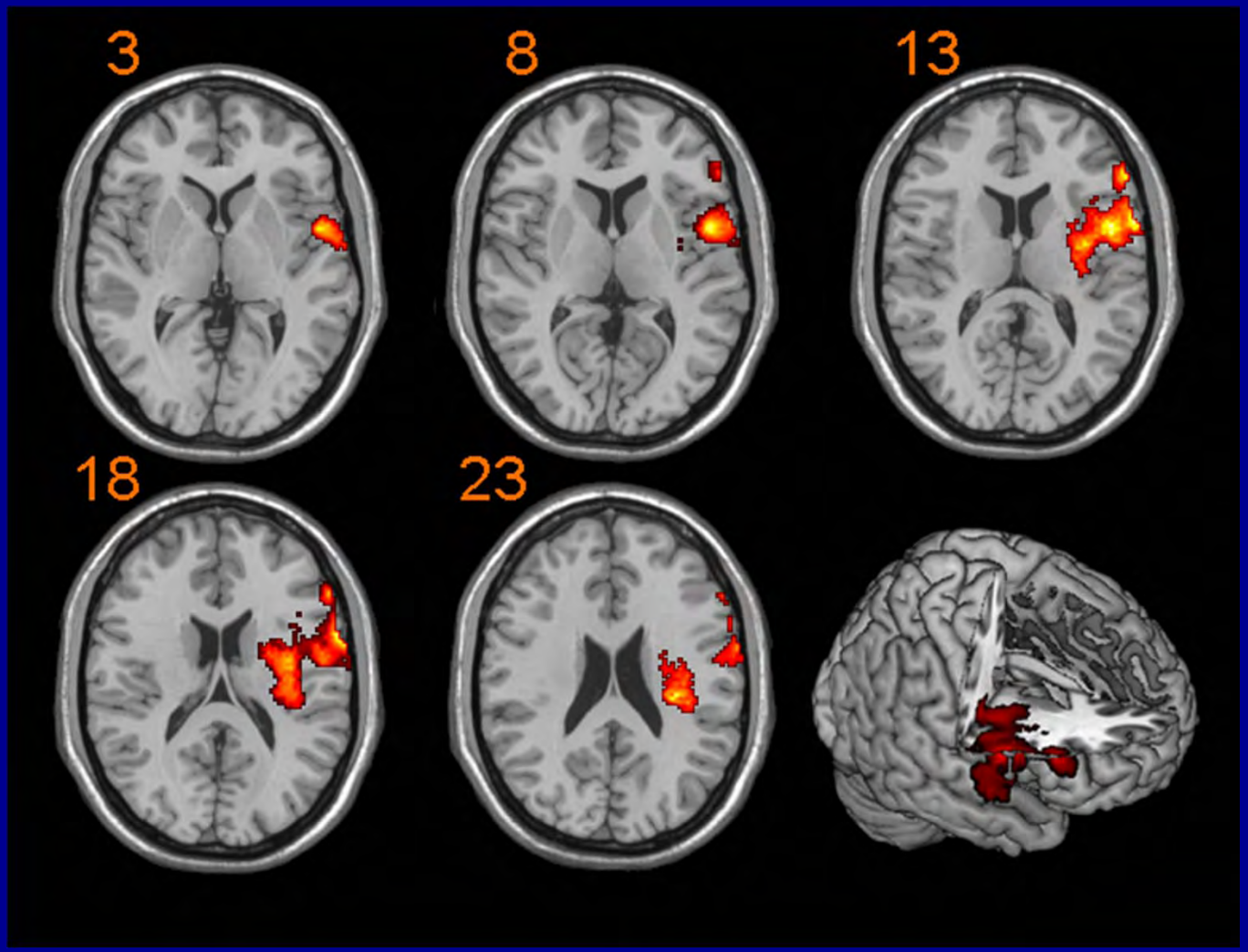
Probabilistic learning task



* p<0.05, ** p<0.01 difference v controls

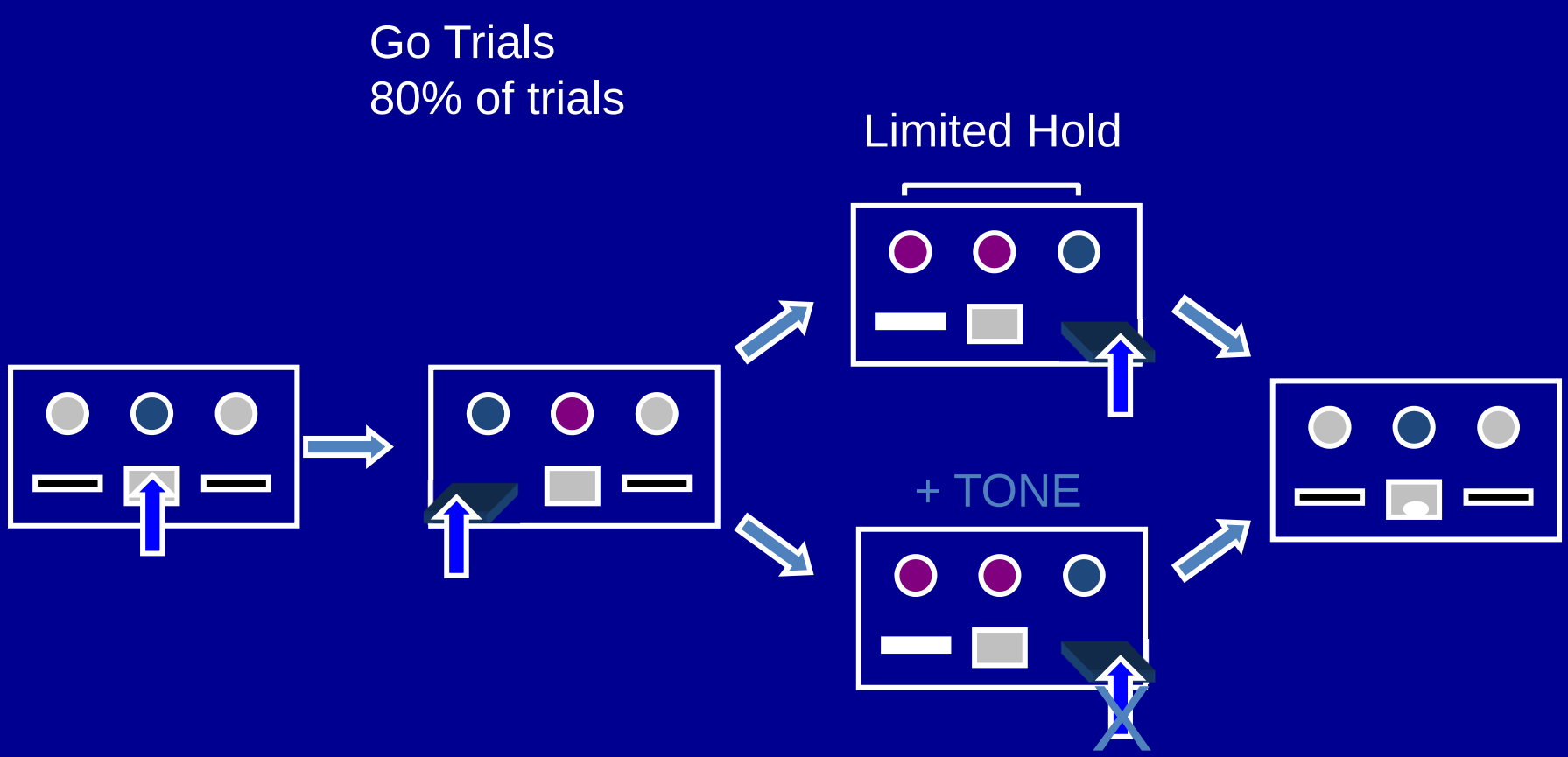
SR Chamberlain, U Muller, AD Blackwell, L Clark, TW Robbins, BJ Sahakian. Science 2006

The SNRI atomoxetine enhances task-dependent SSRT activity in right inferior frontal gyrus



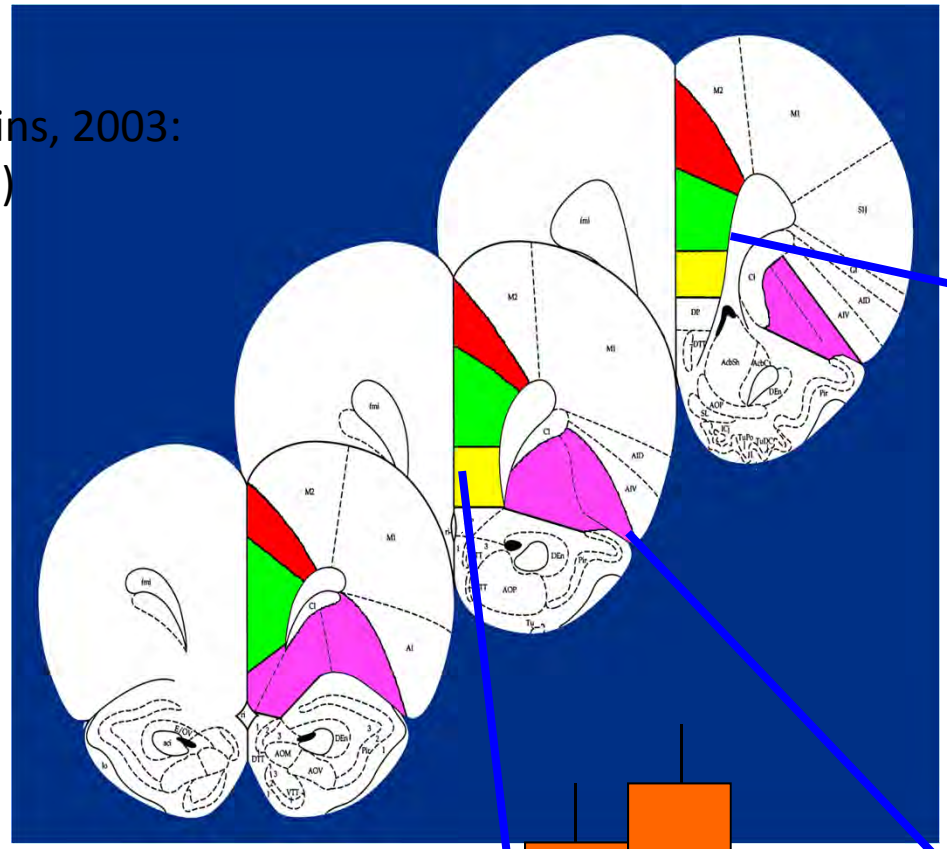
Chamberlain et al 2009 Biological Psychiatry.

Stop-Signal Reaction Time Task for Rats



Stop-signal RT performance is impaired by orbitofrontal but not prelimbic or infra-limbic PFC lesions in the rat

Eagle and Robbins, 2003:
Eagle et al 2008)



CG1

PL

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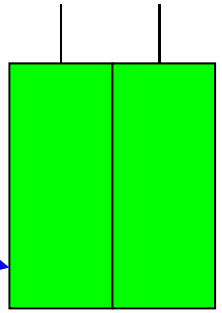
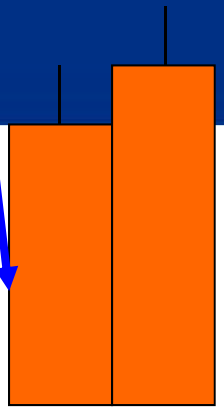


PL

PRE- POST-OP



IL

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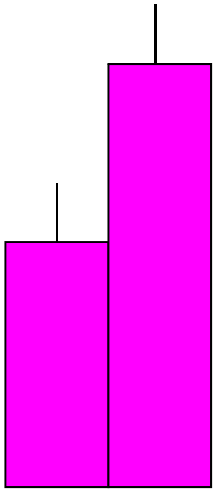
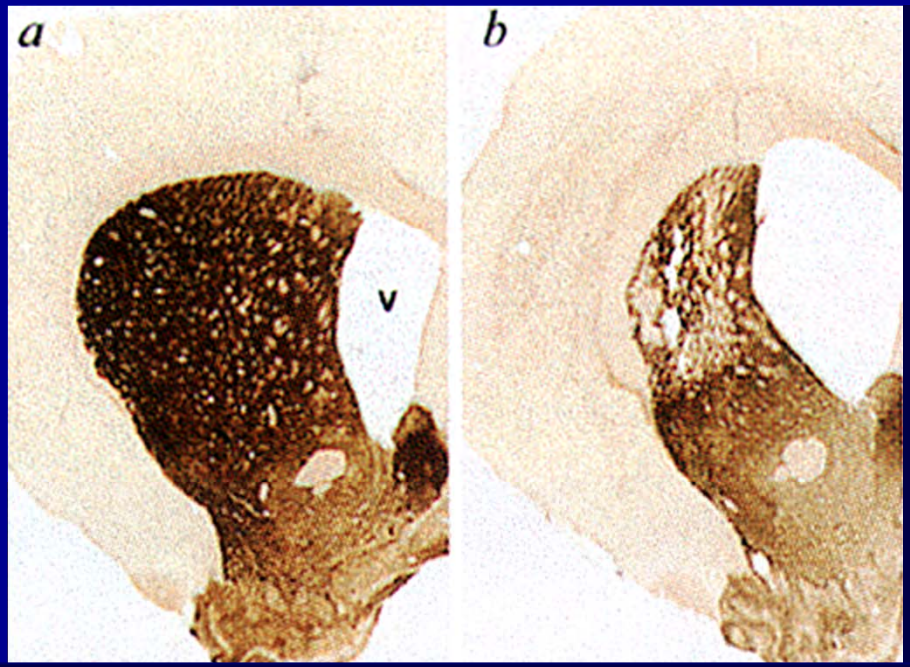


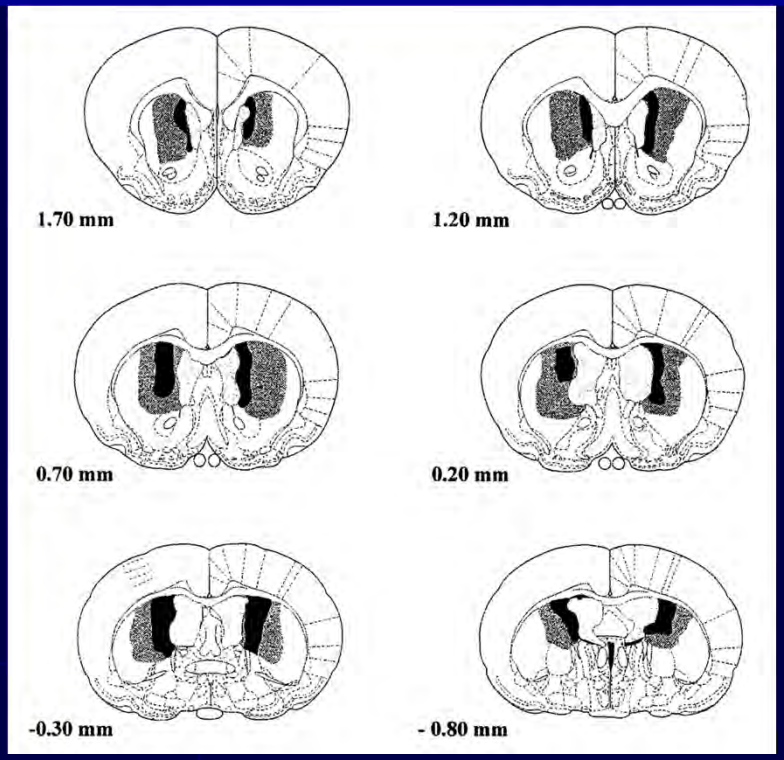
OFC

PRE- POST-OP

Excitotoxic lesions of rat medial striatum (caudate nucleus)

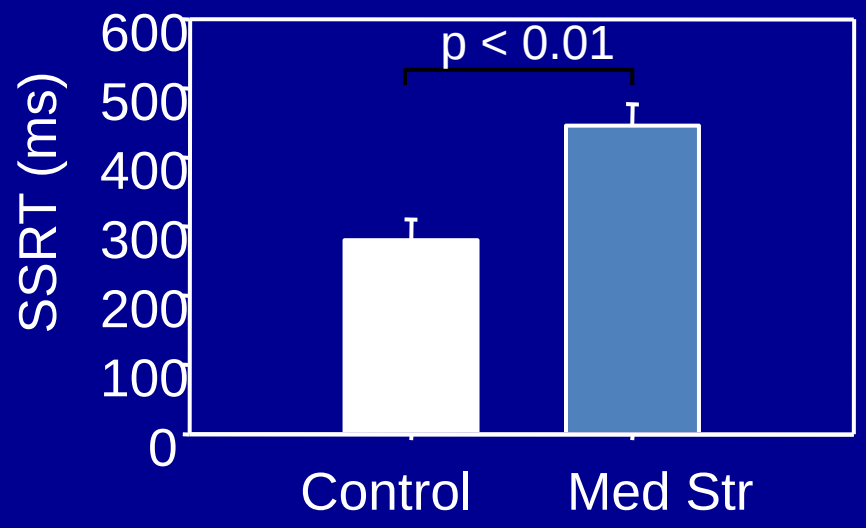
Control Quinolinate

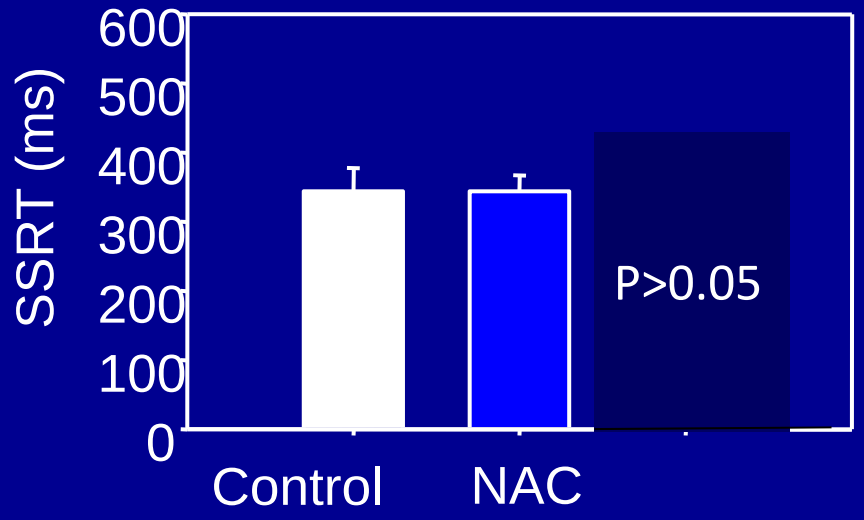




Eagle and Robbins 2003

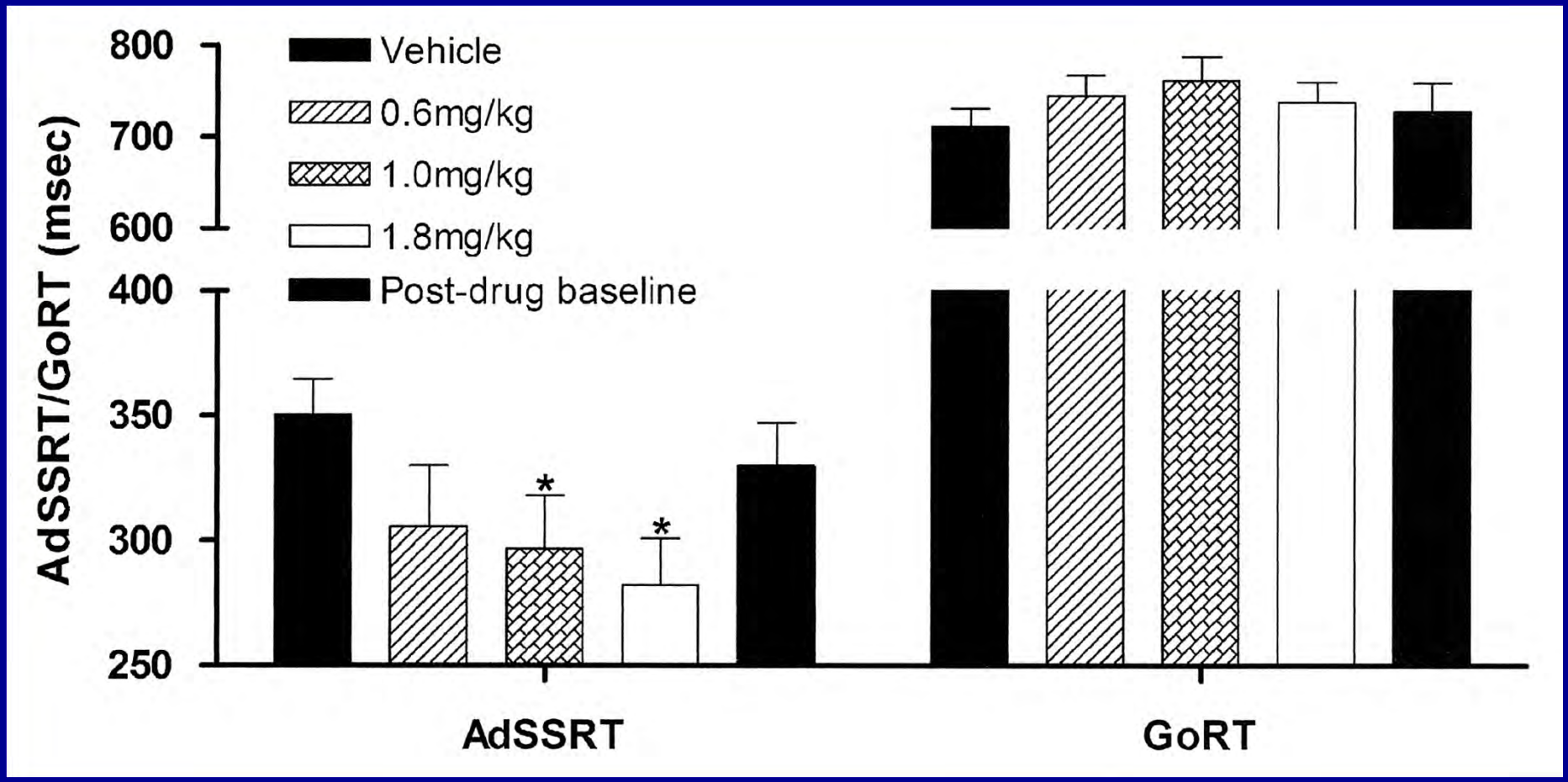
Medial Striatal Lesions but not nucleus accumbens core lesions slow SSRT





Eagle & Robbins (2003a, b,
Behav. Neurosci. Behav. Brain Res.)

Atomoxetine dose-dependently improves SSRT in the rat, while not affecting Go-RT



Robinson et al Neuropsychopharmacology 2008

Bari et al 2011

SST variables

Drug	Dose(s)	SSRT	mRT	% Stop accuracy	% Go accuracy	SDGoRT	PES	NP/TO	RCL
Atomoxetine (SNARI)	1 mg/kg	⇩	⇧	—	⇧	—	na	⇩	na
Guanfacine (α2 ago)	0.3 mg/kg	⇧	⇧	⇩	⇩	—	na	⇩	na
Atipamezole (α2 ant)	0.3 mg/kg	⇩	—	—	—	⇩	—	—	—
Prazosin (α1 ant)	0.5 mg/kg	—	⇧	—	⇩	⇧*	—	—	—
Propranolol (β1/2 ant)	3 mg/kg	—	—	—	—	⇧	—	—	—
GBR 12909 (DARI)	5 mg/kg	—	⇩	⇩	—	—	—	—	—
	10 mg/kg	—	—	⇩	⇩	—	—	—	—
Sulpiride (D2 ant)	10 mg/kg	—	—	—	—	—	—	—	—
SCH 23390 (D1 ant)	10 µg/kg	—	—	—	—	—	—	—	—
Nafadotride (D3 ant)	3 mg/kg	⇧	⇧	—	⇩	—	⇧	⇩	—
7-OH-PIPAT (D3 ago)	1mg/kg	—	⇧	—	⇩	—	⇧	—	⇧
L-745,870 (D4 ant)	5 mg/kg	—	—	—	⇩	—	—	—	—
PD 168,077 (D4 ago)	5 mg/kg	—	—	—	—	—	—	—	—
Citalopram (SSRI)	1 mg/kg	—	⇧	—	⇩	—	na	—	na
Ciproxifan (H3 ant)	3.2 mg/kg	—	⇩	—	⇩	—	—	—	—
Cetirizine (H1 ant)	10 mg/kg	—	—	—	—	—	—	—	—

Abbreviations: SSRT, stop-signal reaction time; mRT, mean reaction time; SDGoRT, standard deviation of go reaction time; PES, post-error slowing; NP/TO, nose pokes during time-out periods; RCL, reward collection latency; ⇧ increased, ⇩ decreased and – no change in the specific measure; * only main effect; ACC, anterior cingulate cortex; dmPFC, dorso-medial prefrontal cortex; vmPFC, ventro-medial prefrontal cortex; OFC, orbitofrontal cortex.

Effects of PFC inactivation and atomoxetine intra-PFC on SSRT

SST variables									
AREA	DRUG	SSRT	mRT	% Stop accuracy ZD	% Stop accuracy SSD	% Go accuracy	SDGoRT	PES	NP/TO	RCL
ACC	Musc	⇧	—	—	⇩	—	—	—	⇧	—
	Ato	—	—	—	—	—	—	—	—	—
dmPFCr	Musc	—	—	⇩	—	—	—	—	⇧	⇩
	Ato	—	—	—	—	—	—	⇩	—	—
dmPFCc	Musc	⇧	—	⇩	⇩	—	—	—	⇧	—
	Ato	⇩	—	—	—	—	—	—	—	—
vmPFC	Musc	—	—	—	⇩	⇩	—	—	—	—
	Ato	—	—	—	—	—	⇧	—	⇩	—
OFC	Musc	—	⇧	—	⇧	⇩	—	—	—	—
	Ato	⇩	—	—	⇧	—	—	—	—	—

Bari et al J. Neuroscience 2011