

# *Neuropsychology of reinforcement processes in the rat*

*A dissertation submitted for the degree of  
Doctor of Philosophy*

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To Ann & John

*'How the purer Spirit is united to this clod, is a knot too hard for fallen Humanity to untie.'*

Joseph Glanvill (1661), *The Vanity of Dogmatizing*.

*'It ain't necessarily so.'*

Ira Gershwin and DuBose Heyward (1935), *Porgy and Bess*.

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**Preface**

The following work was carried out at the Department of Experimental Psychology, University of Cambridge, during the years of 1997–2000, under the supervision of Professor Barry J. Everitt.

I hereby declare that this dissertation has not been submitted, in whole or in part, for any other degree, diploma or qualification at any other University. This dissertation is the result of my own work and includes nothing that is the outcome of work done in collaboration. I have attempted to reference appropriately any idea or finding that is not my own.

This dissertation does not exceed the limit of length specified by the Degree Committee for Biology, as stated in the Memorandum to Graduate Students.

## Abstract

This thesis investigated the role played by regions of the prefrontal cortex and ventral striatum in the control of rats' behaviour by Pavlovian conditioned stimuli, and in their capacity to choose delayed reinforcement.

First, the function of the anterior cingulate cortex (ACC) in simple Pavlovian conditioning tasks was addressed. The ACC is a subdivision of prefrontal cortex that has previously been suggested to be critical for the formation of stimulus–reward associations. It was found that lesions of the ACC did not prevent rats from learning a simple conditioned approach response to a conditioned stimulus (CS) predictive of food reward, or from utilizing that CS as a conditioned reinforcer subsequently. Additionally, these subjects successfully acquired a conditioned freezing response to a CS predicting footshock. However, the same animals were impaired at the acquisition of autoshaped behaviour, an impairment that has been demonstrated previously. An autoshaping deficit was also observed when lesions were made following training. The phenomenon of Pavlovian–instrumental transfer was intact in these subjects. The hypothesis was developed that the ACC is not critical for the formation of stimulus–reward associations *per se*, but is critical when multiple stimuli must be discriminated on the basis of their differential association with reward. In support of this hypothesis, animals with lesions of the ACC were impaired on a version of the conditioned approach task in which a second, neutral stimulus, perceptually similar to the CS, was added; the lesioned subjects exhibited reduced discrimination.

Second, the role of the nucleus accumbens (Acb) in Pavlovian–instrumental transfer was investigated. The nucleus accumbens core, together with a larger amygdalar–striatal network of which it is a component, has previously been shown to be necessary for the expression of 'simple' Pavlovian–instrumental transfer. Rats with lesions of the nucleus accumbens core (AcbC) and shell (AcbSh) were tested on a 'response-specific' Pavlovian–instrumental transfer task, in which a Pavlovian CS selectively enhances instrumental responding for the outcome with which the CS was originally paired. AcbC lesions impaired the response specificity of this effect, while AcbSh lesions abolished Pavlovian–instrumental transfer entirely. These results are consistent with some — but not all — previous results in suggesting that the shell provides 'vigour' and the core provides 'direction' for the potentiation of behaviour by Pavlovian CSs.

Third, an attempt was made to train rats on a task for assessing preference for delayed reinforcement, using the 'adjusting-delay' paradigm. It was not immediately apparent that the rats reacted to the contingencies operative in this task, and mathematical analysis of their behaviour was conducted to establish whether their behaviour was sensitive to the delay, and what 'molar' features of performance on this task could be explained by delay-independent processes.

Fourth, a different delayed reinforcement choice task was developed, modifying a previously published task in which the subject is repeatedly offered a choice, in discrete trials, of a small reward delivered immediately, and a large reward delivered after a delay, with the delays systematically varied by the experimenter. Rats were trained on versions of this task in which the large, delayed reinforcer was or was not explicitly signalled by a cue present during the delay. The behavioural basis of performance on this task was examined, and *d*-amphetamine, chlordiazepoxide, and  $\alpha$ -flupenthixol were administered systemically. It was found that the effects of *d*-amphetamine depended on whether the delayed reinforcer was signalled or unsignalled, increasing preference for signalled delayed reinforcement at some doses, but decreasing preference for unsignalled delayed reinforcement. These results may resolve contradictions in the literature, and are suggested to reflect the known effect of amphetamine to potentiate responding for conditioned reinforcers.

Fifth, rats that had been trained on this task (with no explicit signals present during the delay) were given lesions of the ACC, AcbC, or medial prefrontal cortex (mPFC). ACC-lesioned rats were no different from sham-operated controls in their ability to choose a large, delayed reinforcer. Lesions of mPFC reduced the tendency of subjects to shift from one lever to the other during the course of a session, but mPFC-lesioned subjects responded normally to removal of the delays, suggesting a loss of stimulus control. However, rats with lesions of the AcbC were severely impaired on this task, preferring the small, immediate reward, even though they discriminated the reinforcers. Additionally, the effects of intra-Acb amphetamine were assessed using a different version of the delayed reinforcement choice task, and found to have slight but inconsistent effects to reduce preference for the delayed reinforcer, though this effect did not depend on whether the delayed reward was signalled or unsignalled. These results suggest that the AcbC contributes significantly to the rat's ability to choose a delayed reward, a finding that has important implications for the understanding of Acb function. It is suggested that dysfunction of the AcbC may be a key element in the pathology of impulsivity.

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## Publications

To date, the following publications have arisen in whole or in part from this thesis:

### Abstracts

1. **Cardinal RN, Everitt BJ, Robbins TW** (1999). Amphetamine interacts with cue stimuli to affect preference for delayed reinforcement. *Behavioural Pharmacology* **10** (supplement 1): S15–S16. (First Congress of the Behavioral Pharmacology Society and European Behavioural Pharmacology Society, 1–4 September 1999, Boston, Massachusetts, USA.)
2. **Cardinal RN, Lachenal G, Parkinson JA, Robbins TW, Everitt BJ** (2000). Effects of anterior cingulate cortex lesions on responding for conditioned reinforcement, discrete fear conditioning, autoshaping performance and Pavlovian–instrumental transfer. *European Journal of Neuroscience* **12** (supplement 11): 88 (abstract 44.8). (Federation of European Neuroscience Societies Second Forum Meeting, 24–28 June 2000, Brighton, UK.)
3. **Cardinal RN, Parkinson JA, Robbins TW, Dickinson A, Everitt BJ** (2000). Effects of lesions of the nucleus accumbens core and shell on response-specific Pavlovian–instrumental transfer. *Journal of Psychopharmacology* **14**(3) (supplement): A68 (abstract PH20). (British Association for Psychopharmacology Summer Meeting, 16–19 July 2000, Cambridge, UK.)
4. **Cardinal RN, Parkinson JA, Djafari Marbini H, Toner AJ, Robbins TW, Everitt BJ** (2000). Role of the anterior cingulate cortex in the control over behaviour by Pavlovian conditioned stimuli in rats. *Society for Neuroscience Abstracts* **26**: 980. (Society for Neuroscience 30th Annual Meeting, 4–9 November 2000, New Orleans, Louisiana, USA; abstract #366.13.)
5. **Everitt BJ, Parkinson JA, Lachenal G, Halkerston KM, Rudarakanchana N, Cardinal RN, Hall J, Morrison CH, Dalley JW, Howes SR, Robbins TW** (2000). Effects of limbic corticostriatal lesions on autoshaping performance in rats. *Society for Neuroscience Abstracts* **26**: 979. (SFN New Orleans; abstract #366.12.)

### Papers and book chapters

1. **Everitt BJ, Cardinal RN, Hall J, Parkinson JA, Robbins TW** (2000). Differential involvement of amygdala subsystems in appetitive conditioning and drug addiction. In Aggleton JP (ed.), *The amygdala: a functional analysis* (second edition). Oxford University Press, New York (ISBN 0198505019), pp. 353–390.
2. **Parkinson JA, Cardinal RN, Everitt BJ** (2000). Limbic cortical-ventral striatal systems underlying appetitive conditioning. *Progress in Brain Research* **126**: 263–285. Chapter 17 of Uylings HBM, van Eden CG, de Bruin JPC, Feenstra MGP, Pennartz CMA (eds), *Cognition, emotion and autonomic responses: The integrative role of prefrontal cortex and limbic structures*. Elsevier, Amsterdam (ISBN 0444503323).
3. **Cardinal RN, Robbins TW, Everitt BJ** (2000). The effects of *d*-amphetamine, chlordiazepoxide, alpha-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology* **152**: 362–375. (Available online via digital object identifier at <<http://dx.doi.org/10.1007/s002130000536>> or at <<http://link.springer.de/>>.)

## Abbreviations used in this thesis

### 1. Pharmacology and chemistry

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine (serotonin)
6-OHDA	6-hydroxydopamine
CCK	cholecystokinin
DA	dopamine
GABA	$\gamma$ -aminobutyric acid
LiCl	lithium chloride
NMDA	<i>N</i> -methyl-D-aspartate
PB	phosphate buffer
PBS	phosphate-buffered saline

### 2. Psychology

CPP	conditioned place preference
CR	conditioned response
CRf	conditioned reinforcer
CS	conditioned stimulus
CS-	negative conditioned stimulus (i.e. predicts absence of stimulus)
CS+	positive, or predictive conditioned stimulus (be it appetitive or aversive)
CS <sub>0</sub>	neutral conditioned stimulus (strictly uncorrelated with stimulus)
CVD	conditional visual discrimination
ext	extinction
FI	fixed interval
FR	fixed ratio
IRI	interreinforcement interval
IRT	interresponse time
ISI	interstimulus interval
ITI	intertrial interval
NCRf	not-conditioned-reinforcer (e.g. a lever that produces no response; a control)
NS	not significant
OR	orienting response
PIT	Pavlovian to instrumental transfer
RI	random interval
RT	random time
S	subject (in analysis of variance notation); stimulus
UR	unconditioned response
US	unconditioned stimulus
VI	variable interval
VR	variable ratio



### 3. *Neurobiology and medicine*

ADHD	attention deficit/hyperactivity disorder
APCR	amphetamine potentiation of conditioned reinforcement
fMRI	functional magnetic resonance imaging
i.c.v.	intracerebroventricular
i.p.	intraperitoneal
i.v.	intravenous
IVSA	intravenous self-administration
MRI	magnetic resonance imaging (= nuclear magnetic resonance, NMR)
NMR	nictitating membrane reflex (eye-blink), typically in the rabbit
OCD	obsessive–compulsive disorder
PET	positron emission tomography
EEG	electroencephalogram
ERN	error-related negativity

### 4. *Neuroanatomy*

Abbreviations are those used by Paxinos & Watson (1996), except for those marked (\*).

Acb	nucleus accumbens
AcbC	nucleus accumbens, core
AcbSh	nucleus accumbens, shell
ACC	anterior cingulate cortex (*)
AV	anteroventral nucleus of the thalamus
BLA	basolateral amygdala (BL) (*)
CeA	central amygdaloid nucleus (Ce) (*)
Cg1	cingulate cortex, area 1
Cg2	cingulate cortex, area 2
CPu	caudate putamen (striatum)
DLPFC	dorsolateral prefrontal cortex (*)
DS	dorsal striatum (*)
LC	locus coeruleus
LH	lateral hypothalamic area
MD	mediodorsal nucleus of the thalamus
NBM	nucleus basalis magnocellularis (nucleus of Meynert) (*)
OFC	orbitofrontal cortex (*)
OMPFC	orbitomedial prefrontal cortex (*)
PAG	periaqueductal grey
PCC	posterior cingulate cortex (*)
PFC	prefrontal cortex (*)
PRh	perirhinal cortex
SN	substantia nigra
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
Sub	subiculum (S) (*)
VP	ventral pallidum
VS	ventral striatum (comprising Acb, ventromedial portions of caudate/putamen, olfactory tubercle) (*)

VSub	ventral subiculum (*)
VTA	ventral tegmental area

### 5. Physical units

These may be prefixed with k (kilo-,  $10^3$ ); c (centi-,  $10^{-2}$ ); m (milli-,  $10^{-3}$ );  $\mu$  (micro-,  $10^{-6}$ ).

A	amp ( $C s^{-1}$ )
C	coulomb
cd	candela
g	gram
h	hour (3600 s)
Hz	Hertz ( $s^{-1}$ )
l	litre ( $10^{-3} m^3$ )
m	metre
M	molar ( $mol l^{-1}$ )
min	minute (60 s)
mol	mole ( $\approx 6.022 \times 10^{23}$ )
N	Newton ( $kg m s^{-2}$ )
s	second
W	watt ( $kg m^2 s^{-3}$ )

### 6. Statistics and probability

*	significant at $\alpha = 0.05$
**	significant at $\alpha = 0.01$
***	significant at $\alpha = 0.001$
ANOVA	analysis of variance
$F$	$F$ statistic: the ratio of $MS_{\text{treatment}}$ to $MS_{\text{error}}$
MS	mean square
$P(X / Y)$	the probability of X, given that Y is true
$P, p$	probability
SD	standard deviation
SE	standard error
SED	standard error of the difference (between means)
SEM	standard error of the mean
$\alpha$	threshold for determining statistical significance
$\tilde{\epsilon}$	Huynh–Feldt epsilon
$\mu$	mean

### 7. General

$\varnothing$	diameter
$\sqrt{\quad}$	square root
W, D, H	(when referring to dimensions) width, depth, height
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