

Neural systems involved in delay and risk assessment in the rat

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

Rudolf Nicholas Cardinal, MA PhD MB BChir
St John's College, Cambridge

May 2006

Department of Experimental Psychology
University of Cambridge
Downing Street
Cambridge CB2 3EB
United Kingdom

To Hannah

Contents

| | |
|--|----------|
| <i>Preface</i> | vii |
| <i>Abstract</i> | viii |
| <i>Acknowledgements</i> | x |
| <i>Abbreviations</i> | xi |
| <i>Publications</i> | xiv |
| <i>List of figures</i> | xvii |
| <i>List of tables</i> | xviii |
| CHAPTER 1: INTRODUCTION | 1 |
| 1.1 OVERVIEW | 1 |
| 1.2 NORMATIVE AND BEHAVIOURAL ECONOMIC APPROACHES TO DECISION MAKING | 1 |
| 1.3 BASIC PSYCHOLOGY OF REINFORCEMENT LEARNING | 2 |
| 1.4 DELAYED AND UNCERTAIN REINFORCEMENT: THE PROBLEMS OF LEARNING AND CHOICE..... | 4 |
| 1.5 INDIVIDUAL DIFFERENCES: RISK TAKING AND IMPULSIVITY | 5 |
| 1.6 LEARNING WITH DELAYED REINFORCEMENT IN NORMAL ANIMALS | 6 |
| 1.6.1 <i>Basic phenomena</i> | 6 |
| 1.6.2 <i>Cues and context</i> | 8 |
| 1.7 CHOICE WITH DELAYED AND UNCERTAIN REINFORCEMENT IN NORMAL ANIMALS | 9 |
| 1.7.1 <i>Delayed and probabilistic reinforcement: equivalent or distinct processes?</i> | 9 |
| 1.7.2 <i>Temporal or delay discounting</i> | 9 |
| 1.7.3 <i>Uncertainty discounting</i> | 12 |
| 1.8 SYSTEMIC PHARMACOLOGICAL STUDIES OF DELAYED OR UNCERTAIN REINFORCEMENT | 13 |
| 1.8.1 <i>Serotonin (5-HT)</i> | 13 |
| 1.8.2 <i>Noradrenaline (NA)</i> | 15 |
| 1.8.3 <i>Dopamine (DA)</i> | 15 |
| 1.8.4 <i>Relationship between addictive drugs and impulsivity</i> | 18 |
| 1.9 ANATOMY AND CONNECTIONS OF KEY LIMBIC STRUCTURES..... | 19 |
| 1.9.1 <i>Anatomy of the limbic corticostriatal “loop”</i> | 19 |
| 1.9.2 <i>Basic anatomy of the nucleus accumbens</i> | 26 |
| 1.9.3 <i>Basic anatomy of the hippocampus</i> | 27 |
| 1.9.4 <i>A note on the interpretation of excitotoxic lesion methods</i> | 30 |
| 1.10 BASIC NEUROBIOLOGY OF REINFORCEMENT LEARNING | 31 |
| 1.10.1 <i>Mesolimbic dopamine and the nucleus accumbens</i> | 31 |
| 1.10.2 <i>Habits and the dorsal striatum</i> | 33 |
| 1.10.3 <i>Action–outcome contingency knowledge, planning and value: the PFC and amygdala</i> | 33 |
| 1.10.4 <i>Hedonic assessment</i> | 34 |
| 1.10.5 <i>The hippocampus and the representation of context</i> | 34 |
| 1.11 NEUROANATOMICALLY SPECIFIC STUDIES OF DELAYED OR UNCERTAIN REINFORCEMENT..... | 36 |
| 1.11.1 <i>Nucleus accumbens core (AcbC)</i> | 36 |
| 1.11.2 <i>Nucleus accumbens shell (AcbSh)</i> | 44 |
| 1.11.3 <i>Anterior cingulate cortex (ACC)</i> | 44 |
| 1.11.4 <i>Prelimbic (PrL) and infralimbic (IL) cortex</i> | 45 |

| | |
|---|-----------|
| 1.11.5 Orbitofrontal cortex (OFC) | 45 |
| 1.11.6 Insula | 48 |
| 1.11.7 Basolateral amygdala (BLA) | 48 |
| 1.11.8 Subthalamic nucleus (STN)..... | 49 |
| 1.11.9 Hippocampus (H)..... | 49 |
| 1.12 OUTLINE OF EXPERIMENTAL WORK IN THIS THESIS | 50 |
| CHAPTER 2: NUCLEUS ACCUMBENS CORE LESIONS RETARD INSTRUMENTAL LEARNING AND PERFORMANCE WITH DELAYED REINFORCEMENT IN THE RAT, BUT DO NOT IMPAIR REINFORCER MAGNITUDE DISCRIMINATION..... | 51 |
| 2.1 ABSTRACT | 51 |
| 2.2 BACKGROUND..... | 51 |
| 2.3 METHODS | 53 |
| 2.3.1 Overview of experiments..... | 53 |
| 2.3.2 Subjects and housing conditions..... | 54 |
| 2.3.3 Excitotoxic lesions of the nucleus accumbens core | 54 |
| 2.3.4 Behavioural apparatus | 55 |
| 2.3.5 Overview of the Whisker control system..... | 55 |
| 2.3.6 Instrumental conditioning with delayed reinforcement | 55 |
| 2.3.7 Locomotor activity in a novel environment | 57 |
| 2.3.8 Matching of response distribution to reinforcer magnitude distribution on a concurrent schedule | 57 |
| 2.3.9 Histology..... | 58 |
| 2.3.10 Data analysis | 58 |
| 2.4 RESULTS | 59 |
| 2.4.1 Histology..... | 59 |
| 2.4.2 Acquisition of instrumental responding (Experiment 1A)..... | 62 |
| 2.4.3 Experienced response–delivery and response–collection delays (Experiment 1A) | 65 |
| 2.4.4 Effect of delays on learning (Experiment 1A)..... | 67 |
| 2.4.5 Experienced delays and learning on the inactive lever (Experiment 1A) | 67 |
| 2.4.6 Discrimination of relative reinforcer magnitude (Experiment 1B)..... | 68 |
| 2.4.7 Switching behaviour during concurrent schedule performance (Experiment 1B)..... | 69 |
| 2.4.8 Effects of <i>AcbC</i> lesions on performance of a previously learned instrumental response for delayed reinforcement (Experiment 2)..... | 69 |
| 2.4.9 Experienced response–delivery and response–collection delays (Experiment 2)..... | 73 |
| 2.4.10 Relationship between experienced delays and performance (Experiment 2)..... | 73 |
| 2.4.11 Locomotor activity and body mass | 74 |
| 2.5 DISCUSSION | 75 |
| 2.5.1 Effect of delays on instrumental learning in normal animals | 76 |
| 2.5.2 Effect of <i>AcbC</i> lesions on instrumental learning and performance with or without delays..... | 76 |
| 2.5.3 Discrimination of reinforcer magnitude in <i>AcbC</i> -lesioned rats..... | 78 |
| 2.5.4 Contribution of the <i>AcbC</i> to reinforcement learning..... | 79 |
| 2.6 CONCLUSIONS..... | 80 |
| CHAPTER 3: HIPPOCAMPAL LESIONS FACILITATE INSTRUMENTAL LEARNING WITH DELAYED REINFORCEMENT BUT INDUCE IMPULSIVE CHOICE IN RATS | 81 |

| | | |
|--------|--|-----|
| 3.1 | ABSTRACT | 81 |
| 3.2 | BACKGROUND..... | 81 |
| 3.3 | METHODS | 83 |
| 3.3.1 | <i>Overview of experiments</i> | 83 |
| 3.3.2 | <i>Subjects and housing conditions</i> | 83 |
| 3.3.3 | <i>Excitotoxic lesions of the hippocampus</i> | 84 |
| 3.3.4 | <i>Behavioural apparatus</i> | 84 |
| 3.3.5 | <i>Instrumental conditioning with delayed reinforcement (Experiment 1)</i> | 85 |
| 3.3.6 | <i>Lever and nosepoke training prior to the delayed reinforcement choice task (Experiment 2)</i> | 85 |
| 3.3.7 | <i>Choice between small, immediate and large, delayed rewards (Experiment 2)</i> | 85 |
| 3.3.8 | <i>Locomotor activity in a novel environment</i> | 86 |
| 3.3.9 | <i>Food consumption tests</i> | 86 |
| 3.3.10 | <i>Histology</i> | 86 |
| 3.3.11 | <i>Data analysis</i> | 87 |
| 3.4 | RESULTS | 87 |
| 3.4.1 | <i>Histology</i> | 87 |
| 3.4.2 | <i>Acquisition of instrumental responding (Experiment 1)</i> | 89 |
| 3.4.3 | <i>Experienced response–delivery and response–collection delays (Experiment 1)</i> | 93 |
| 3.4.4 | <i>Effect of delays on learning (Experiment 1)</i> | 95 |
| 3.4.5 | <i>Experienced delays and learning on the inactive lever (Experiment 1)</i> | 95 |
| 3.4.6 | <i>Choice between an immediate, small reward and a large, delayed reward (Experiment 2)</i> | 96 |
| 3.4.7 | <i>Effects of removing and reintroducing delays to the large reinforcer (Experiment 2)</i> | 97 |
| 3.4.8 | <i>Locomotor activity, body mass, and food consumption</i> | 98 |
| 3.5 | DISCUSSION | 100 |
| 3.5.1 | <i>Pavlovian and instrumental conditioning with delayed reinforcement</i> | 100 |
| 3.5.2 | <i>Contribution of the hippocampus to instrumental conditioning in the absence of response–reinforcer delays</i> | 102 |
| 3.5.3 | <i>Contribution of the hippocampus to instrumental conditioning in the presence of response–reinforcer delays</i> | 102 |
| 3.5.4 | <i>Contrasting the effects of hippocampal lesions on instrumental and Pavlovian conditioning involving delayed reinforcement</i> | 103 |
| 3.5.5 | <i>Effect of hippocampal lesions on choice involving delayed reinforcement</i> | 105 |
| 3.6 | CONCLUSIONS..... | 107 |

CHAPTER 4: EFFECTS OF LESIONS OF THE NUCLEUS ACCUMBENS CORE ON CHOICE

BETWEEN SMALL CERTAIN REWARDS AND LARGE UNCERTAIN REWARDS IN RATS 108

| | | |
|-------|---|-----|
| 4.1 | ABSTRACT | 108 |
| 4.2 | BACKGROUND..... | 108 |
| 4.3 | METHODS | 110 |
| 4.3.1 | <i>Subjects and housing conditions</i> | 110 |
| 4.3.2 | <i>Behavioural apparatus</i> | 110 |
| 4.3.3 | <i>Initial training</i> | 111 |
| 4.3.4 | <i>Probabilistic choice task</i> | 111 |
| 4.3.5 | <i>Excitotoxic lesions of the <i>AcbC</i></i> | 112 |

| | |
|--|------------|
| 4.3.6 Postoperative testing | 112 |
| 4.3.7 Locomotor activity in a novel environment | 113 |
| 4.3.8 Histology..... | 113 |
| 4.3.9 Data analysis | 113 |
| 4.4 RESULTS | 114 |
| 4.4.1 Histology..... | 114 |
| 4.4.2 Preoperative choice..... | 115 |
| 4.4.3 Early postoperative choice | 116 |
| 4.4.4 Final postoperative choice | 116 |
| 4.4.5 Choice when both reinforcers were certain, or both uncertain | 116 |
| 4.4.6 Choice with ascending probabilities..... | 116 |
| 4.4.7 Postoperative choice: analysis by experienced probability..... | 117 |
| 4.4.8 Indifference probabilities..... | 118 |
| 4.4.9 Omissions and latencies | 120 |
| 4.4.10 Amount of food obtained..... | 120 |
| 4.4.11 Effects of hunger and satiety on choice | 121 |
| 4.4.12 Locomotor activity and body mass | 122 |
| 4.5 DISCUSSION | 122 |
| 4.5.1 Choice in normal subjects..... | 123 |
| 4.5.2 Effects of <i>AcbC</i> lesions in terms of conditioning processes | 123 |
| 4.5.3 Effects of <i>AcbC</i> lesions in terms of probability discounting and reinforcer magnitude sensitivity..... | 124 |
| 4.5.4 Probability versus delay discounting..... | 125 |
| 4.5.5 Implications for <i>AcbC</i> function and impulsivity | 126 |
| 4.5.6 Relationship to structures and neuromodulator systems innervating the <i>AcbC</i> | 126 |
| 4.6 CONCLUSIONS..... | 127 |
| CHAPTER 5: GENERAL DISCUSSION | 129 |
| 5.1 OVERVIEW | 129 |
| 5.2 SUMMARY OF RESULTS | 129 |
| 5.2.1 Role of the <i>AcbC</i> in learning with delayed reward..... | 129 |
| 5.2.2 Role of the <i>AcbC</i> in assessing reward magnitude..... | 130 |
| 5.2.3 Role of the hippocampus in learning with and choosing delayed reward | 130 |
| 5.2.4 Role of the <i>AcbC</i> in choosing uncertain reward..... | 131 |
| 5.3 WIDER IMPLICATIONS | 131 |
| 5.3.1 The hippocampus and time-limited memory storage | 132 |
| 5.3.2 ADHD | 135 |
| 5.3.3 Adolescent impulsivity | 136 |
| 5.3.4 Integration of <i>AcbC</i> functions with respect to impulsivity..... | 137 |
| 5.3.5 Addiction..... | 138 |
| 5.4 CONCLUSIONS: NEURAL SYSTEMS INVOLVED IN DELAY AND RISK ASSESSMENT | 149 |
| REFERENCES | 152 |
| INDEX OF FIRST AUTHORS | 185 |

Preface

The following work was carried out at the Department of Experimental Psychology, University of Cambridge, during the years of 2002–2005.

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

Abstract

This thesis investigated the contribution of the nucleus accumbens core (AcbC) and the hippocampus (H) to choice and learning involving reinforcement that was delayed or unlikely. Animals must frequently act to influence the world even when the reinforcing outcomes of their actions are delayed. Learning with action–outcome delays is a complex problem, and little is known of the neural mechanisms that bridge such delays. Impulsive choice, one aspect of impulsivity, is characterized by an abnormally high preference for small, immediate rewards over larger delayed rewards, and is a feature of attention-deficit/hyperactivity disorder (ADHD), addiction, mania, and certain personality disorders. Furthermore, when animals choose between alternative courses of action, seeking to maximize the benefit obtained, they must also evaluate the likelihood of the available outcomes. Little is known of the neural basis of this process, or what might predispose individuals to be overly conservative or to take risks excessively (avoiding or preferring uncertainty, respectively), but risk taking is another aspect of the personality trait of impulsivity and is a feature of a number of psychiatric disorders, including pathological gambling and some personality disorders.

The AcbC, part of the ventral striatum, is required for normal preference for a large, delayed reward over a small, immediate reward (self-controlled choice) in rats, but the reason for this is unclear. Chapter 3 investigated the role of the AcbC in learning a free-operant instrumental response using delayed reinforcement, performance of a previously learned response for delayed reinforcement, and assessment of the relative magnitudes of two different rewards. Groups of rats with excitotoxic or sham lesions of the AcbC acquired an instrumental response with different delays (0, 10, or 20 s) between the lever-press response and reinforcer delivery. A second (inactive) lever was also present, but responding on it was never reinforced. The delays retarded learning in normal rats. AcbC lesions did not hinder learning in the absence of delays, but AcbC-lesioned rats were impaired in learning when there was a delay, relative to sham-operated controls. Rats were subsequently trained to discriminate reinforcers of different magnitudes. AcbC-lesioned rats were more sensitive to differences in reinforcer magnitude than sham-operated controls, suggesting that the deficit in self-controlled choice previously observed in such rats was a consequence of reduced preference for delayed rewards relative to immediate rewards, not of reduced preference for large rewards relative to small rewards. AcbC lesions also impaired the performance of a previously learned instrumental response in a delay-dependent fashion. These results demonstrate that the AcbC contributes to instrumental learning and performance by bridging delays between subjects' actions and the ensuing outcomes that reinforce behaviour.

When outcomes are delayed, they may be attributed to the action that caused them, or mistakenly attributed to other stimuli, such as the environmental context. Consequently, animals that are poor at forming context–outcome associations might learn action–outcome associations better with delayed reinforcement than normal animals. The hippocampus contributes to the representation of environmental context, being required for aspects of contextual conditioning. It was therefore hypothesized that animals with H lesions would be better than normal animals at learning to act on the basis of delayed reinforcement. Chapter 4 tested the ability of H-lesioned rats to learn a free-operant instrumental response using delayed reinforcement, and their ability to exhibit self-controlled choice. Rats with sham or excitotoxic H lesions acquired an instrumental response with different delays (0, 10, or 20 s) between the response and reinforcer delivery. H-lesioned rats responded slightly less than sham-operated controls in the absence of delays, but they became better at learning (relative to shams) as the delays increased; delays impaired learning less in H-lesioned rats than in shams. In contrast, lesioned rats exhibited impulsive choice, pre-

ferring an immediate, small reward to a delayed, larger reward, even though they preferred the large reward when it was not delayed. These results support the view that the H hinders action–outcome learning with delayed outcomes, perhaps because it promotes the formation of context–outcome associations instead. However, although lesioned rats were better at learning with delayed reinforcement, they were worse at choosing it, suggesting that self-controlled choice and learning with delayed reinforcement tax different psychological processes.

Chapter 5 examined the effects of excitotoxic lesions of the AcbC on probabilistic choice in rats. Rats chose between a single food pellet delivered with certainty (probability $p = 1$) and four food pellets delivered with varying degrees of uncertainty ($p = 1, 0.5, 0.25, 0.125, \text{ and } 0.0625$) in a discrete-trial task, with the large-reinforcer probability decreasing or increasing across the session. Subjects were trained on this task and then received excitotoxic or sham lesions of the AcbC before being retested. After a transient period during which AcbC-lesioned rats exhibited relative indifference between the two alternatives compared to controls, AcbC-lesioned rats came to exhibit risk-averse choice, choosing the large reinforcer less often than controls when it was uncertain, to the extent that they obtained less food as a result. Rats behaved as if indifferent between a single certain pellet and four pellets at $p = 0.32$ (sham-operated) or at $p = 0.70$ (AcbC-lesioned) by the end of testing. When the probabilities did not vary across the session, AcbC-lesioned rats and controls strongly preferred the large reinforcer when it was certain, and strongly preferred the small reinforcer when the large reinforcer was very unlikely ($p = 0.0625$), with no differences between AcbC-lesioned and sham-operated groups. These results suggest that the AcbC contributes to action selection by promoting the choice of uncertain, as well as delayed, reward.

Key words:

delay
uncertainty
impulsivity
addiction
nucleus accumbens
hippocampus

Acknowledgements

First and foremost, I thank Tim Cheung and Nathan Howes for their contributions to this project. Tim performed much of the behavioural testing and a substantial part of the surgery and histological processing for the experiments reported in Chapters 2 and 3, under my tutelage. Nathan performed much of the behavioural testing for the experiments reported in Chapter 4 under my supervision. Both contributed to the ensuing discussion about the results, and both were a pleasure to work with; it is my privilege to have done so.

I thank Anthony Dickinson, Nick Mackintosh, Trevor Robbins, John Parkinson, Barry Everitt, Ann Kelley, Ron Dahl, Rudy Vuchinich, Nick Heather, Suzanne Mitchell, Olav Gjelsvik, Robert MacCoun, and George Ainslie for helpful discussions; Trevor, also, for making available the facilities of his department; Caroline Parkinson, Mercedes Arroyo, Jeff Dalley, and Rutsuko Ito for skilled technical assistance; and all those who looked after the animals so well. I also thank Barry Everitt, Trevor Robbins, Warren Bickel, Martin Ince, Anthony Phillips, Elliot Stein, and nine anonymous referees for their helpful comments on portions of this text.

This research was supported by a Wellcome Trust programme grant (to Trevor W. Robbins, Barry J. Everitt, Angela C. Roberts, and Barbara J. Sahakian), and was conducted within the UK Medical Research Council (MRC) Behavioural and Clinical Neuroscience Centre at Cambridge (now the University of Cambridge Behavioural and Clinical Neurosciences Institute, supported by the MRC and the Wellcome Trust). I thank these funding bodies and investigators for their support.

Thanks to Hannah, Ann, and John for all their love and support, and to Puzzle, a veteran of neuroscience, for providing insistent distractions. Thanks also to Mike, Meredith, Tanya, Nicola, Luke, Phyllis, Ulrich, Henry, and Andrew for providing such a pleasant and entertaining working environment!

Abbreviations

| | |
|---------------------|---|
| $\bar{\varepsilon}$ | Huynh–Feldt epsilon |
| ε | price elasticity |
| (a, b) | a range a – b that includes neither a nor b , i.e. a range $a < x < b$. |
| $[a, b)$ | a range a – b that includes a but not b , i.e. a range $a \leq x < b$. |
| $[a, b]$ | a range a – b that includes both a and b , i.e. a range $a \leq x \leq b$. |
| 5-HIAA | 5-hydroxyindoleacetic acid |
| 5-HT | 5-hydroxytryptamine (serotonin) |
| Acb | nucleus accumbens |
| AcbC | nucleus accumbens core |
| AcbSh | nucleus accumbens shell |
| ADHD | attention-deficit/hyperactivity disorder |
| AMPA | α -amino-3-hydroxy-5-methyl-4-isoxazolpropionate |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| AP-5 | D-(–)-2-amino-5-phosphonopentanoic acid |
| BLA | basolateral amygdala |
| BOLD | blood oxygen level dependent (of an fMRI signal) |
| CA | cornu ammonis (Ammon’s horn) |
| cf. | <i>confer</i> (compare) |
| ch. | chapter |
| COD | changeover delay |
| CPP | 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid |
| CR | conditioned response |
| CRH | corticotrophin-releasing hormone (also known as corticotrophin-releasing factor, CRF) |
| CS | conditioned stimulus |
| CSF | cerebrospinal fluid |
| DA | dopamine |
| df | degrees of freedom |
| DRL | differential reinforcement of low rates |
| DRO | differential reinforcement of other behaviour |
| ECS | electroconvulsive shock (synonym for ECT) |
| ECT | electroconvulsive therapy (synonym for ECS) |
| e.g. | <i>exempli gratia</i> (for example) |
| <i>et al.</i> | and others (<i>et alii</i> , masculine plural; <i>et aliae</i> , feminine plural; <i>et alia</i> , neutral plural) |
| etc. | <i>et cetera</i> (and the rest) |
| FI | fixed interval |
| fMRI | functional magnetic resonance imaging |
| FR | fixed ratio |
| h | hour |
| H | hippocampus |
| i.e. | <i>id est</i> (that is to say) |
| i.m. | intramuscular |

| | |
|--------------------------|--|
| i.p. | intraperitoneal |
| ICSS | intracranial self-stimulation |
| ISI | interstimulus interval |
| ITI | intertrial interval |
| L. | Latin for |
| LL | larger, later (in the context of rewards) |
| LTP | long-term potentiation |
| LTD | long-term depression |
| min | minute |
| mPFC | medial prefrontal cortex |
| MRI | magnetic resonance imaging |
| n | number of subjects or observations |
| NA | noradrenaline |
| NMDA | <i>N</i> -methyl-D-aspartate |
| NS | not significant |
| OCD | obsessive–compulsive disorder |
| OFC | orbitofrontal cortex |
| p | probability |
| $P(A)$ | probability of event A occurring |
| $P(A B)$ | probability of A occurring, given that B has occurred |
| p., pp. | page, pages |
| PBS | phosphate-buffered saline |
| PFC | prefrontal cortex |
| PIT | Pavlovian–instrumental transfer |
| PKA | protein kinase A (cyclic-adenosine-monophosphate-dependent protein kinase) |
| $p_{\text{reinforcer}}$ | probability of delivery of a reinforcer after it has been chosen |
| $p_{\text{statistical}}$ | statistical p value (probability of obtaining the observed data, or results more extreme, were the null hypothesis to be true) |
| <i>q.v.</i> | <i>quod vide</i> (which see) |
| r^2 | proportion of variance explained |
| RI | random interval |
| RR | random ratio |
| SED | standard error of the difference between means |
| SEM | standard error of the mean |
| SHR | spontaneously hypertensive rat |
| SNc | substantia nigra pars compacta |
| S–R | stimulus–response |
| SS | sum of squares (sum of squared deviations from a mean) (in the context of statistics) |
| SS | smaller, sooner (in the context of rewards) |
| STN | subthalamic nucleus |
| TCP/IP | transmission control protocol/internet protocol |
| US | unconditioned stimulus |
| v. | versus |

| | |
|-----|-------------------------------------|
| v/v | volume per unit volume ¹ |
| VR | variable ratio |
| VTA | ventral tegmental area |
| w/v | weight per unit volume |

¹ Concentrations given as percentages are calculated as follows. A 1% solution, volume per unit volume (v/v), is a solution in which $\frac{1}{100}$ of the total volume is solute. A 1% solution, weight by unit weight (w/w), is one in which 1% of the total weight of the solution is solute; thus, a 1% solution implies 1 g of solute dissolved in 99 g of solvent. A 1% solution, weight by unit volume (w/v), is a solution of 1 g in a total volume of 100 ml (10 g l^{-1}); "100%" denotes 1 kg l^{-1} . Similarly, the notation "1:1000" denotes 1 g l^{-1} (1 mg ml^{-1}).

Publications

The publications listed below are submitted in support of this dissertation, under Regulation 7 of the Ordinances of the University of Cambridge concerning the degree of Doctor of Medicine (Ordinances, Chapter 7, at http://www.admin.cam.ac.uk/univ/so/so_ch07.pdf). These publications do not form part of work I have submitted for any other degree, diploma or qualification at any University. Those marked (*) are central to the material presented in this thesis.

Articles indexed by digital object identifier (DOI) can be retrieved electronically from the publisher: if the DOI is xxx, the URL is <http://dx.doi.org/xxx>. An up-to-date publication list, with electronic copies, is at <http://pobox.com/~rudolf/publications>.

2001

1. **Rahman S, Sahakian BJ, Cardinal RN, Rogers RD, Robbins TW** (2001). Decision-making and neuropsychiatry. *Trends in Cognitive Sciences* **5**: 271–277. DOI 10.1016/S1364-6613(00)01650-8.
2. **Dalley JW, McGaughy J, O’Connell MT, Cardinal RN, Levita L, Robbins TW** (2001). Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and non-contingent performance of a visual attentional task. *Journal of Neuroscience* **21**: 4908–4914.
3. **Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ** (2001). Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of Pavlovian approach. *Journal of Neuroscience* **21**: 9471–9477.
4. **Cardinal RN, Aitken MRF** (2001). *Whisker*, version 2, computer software. Described in detail at <http://www.whiskercontrol.com>.

2002

5. **Cardinal RN, Parkinson JA, Lachenal G, Halkerston KM, Rudarakanchana N, Hall J, Morrison CH, Howes SR, Robbins TW, Everitt BJ** (2002). Effects of selective excitotoxic lesions of the nucleus accumbens core, anterior cingulate cortex, and central nucleus of the amygdala on autoshaping performance in rats. *Behavioral Neuroscience* **116**: 553–567. DOI 10.1037//0735-7044.116.4.553.
6. **Parkinson JA, Dalley JW, Cardinal RN, Bamford A, Fenhert B, Lachenal G, Rudarakanchana N, Halkerston KM, Robbins TW, Everitt BJ** (2002). Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behavioural Brain Research* **137**: 149–163. DOI 10.1016/S0166-4328(02)00291-7.

2003

7. **Cardinal RN, Robbins TW, Everitt BJ** (2003). Choosing delayed rewards: perspectives from learning theory, neurochemistry, and neuroanatomy. Chapter 6 (and reply to commentary) of Vuchinich RE, Heather N (eds), *Choice, Behavioral Economics and Addiction* (proceedings of a conference in Birmingham, Alabama, USA; 15–17 March 2002). Elsevier, Amsterdam (ISBN 0080440568), pp. 183–213 and 217–218. (*)

8. **Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW** (2003). Appetitive behavior: the impact of amygdala-dependent mechanisms of emotional learning. *Annals of the New York Academy of Sciences* **985**: 233–250.

2004

9. **Cardinal RN, Winstanley CA, Robbins TW, Everitt BJ** (2004). Limbic corticostriatal systems and delayed reinforcement. *Annals of the New York Academy of Sciences* **1021**: 33–50. DOI 10.1196/annals.1308.004. (*)
10. **Cardinal RN, Everitt BJ** (2004). Neural and psychological mechanisms underlying appetitive learning: links to drug addiction. *Current Opinion in Neurobiology* **14**(2): 156–162. DOI 10.1016/j.conb.2004.03.004.
11. **Dalley JW, Cardinal RN, Robbins TW** (2004). Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. *Neuroscience and Biobehavioral Reviews* **28**: 771–784. DOI 10.1016/j.neubiorev.2004.09.006.
12. **Cardinal RN** (2004). Waiting for better things. *The Psychologist* **17**: 684–687.
13. **Winstanley CA, Theobald DEH, Cardinal RN, Robbins TW** (2004). Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. *Journal of Neuroscience* **24**: 4718–4722. DOI 10.1523/JNEUROSCI.5606-03.2004.
14. **Dalley JW, Theobald DE, Bouger P, Chudasama Y, Cardinal RN, Robbins TW** (2004). Cortical cholinergic function and deficits in visual attentional performance in rats following 192 IgG-saporin-induced lesions of the medial prefrontal cortex. *Cerebral Cortex* **14**: 922–932. DOI 10.1093/cercor/bhh052.

2005

15. **Cardinal RN, Cheung THC** (2005). Nucleus accumbens core lesions retard instrumental learning and performance with delayed reinforcement in the rat. *BMC Neuroscience* **6**: 9. DOI 10.1186/1471-2202-6-9. (*)
16. **Winstanley CA, Theobald DEH, Dalley JW, Cardinal RN, Robbins TW** (2005). Double dissociation between serotonergic and dopaminergic modulation of medial prefrontal and orbitofrontal cortex during a test of impulsive choice. *Cerebral Cortex* **16**: 106–114 (advance access 13 April 2005). DOI 10.1093/cercor/bhi088.
17. **Cheung THC, Cardinal RN** (2005). Hippocampal lesions facilitate instrumental learning with delayed reinforcement but induce impulsive choice in rats. *BMC Neuroscience* **6**: 36. DOI 10.1186/1471-2202-6-36. (*)
18. **Cardinal RN, Howes NJ** (2005). Effects of lesions of the nucleus accumbens core on choice between small certain rewards and large uncertain rewards in rats. *BMC Neuroscience* **6**: 37. DOI 10.1186/1471-2202-6-37. (*)
19. **Robbins TW, Cardinal RN, Di Ciano P, Halligan PWG, Hellemans KGC, Lee JCL, Everitt BJ** (2005). Neuroscience of drugs and addiction. UK Office of Science and Technology *Foresight: Brain Science, Addiction and Drugs* project, 13 July 2005; <<http://www.foresight.gov.uk>>. [The OST is part of the Department of Trade and Industry; the project was also supported by the Home Office and the Department of Health.] (*)

2006

20. **Cardinal RN, Aitken MRF** (2006). *ANOVA for the behavioural sciences researcher*. Lawrence Erlbaum Associates, New Jersey (ISBN 0805855858 hardback or 0805855866 paperback). Supporting Web site at <<http://www.psychol.cam.ac.uk/statistics>>.
21. **Cardinal RN** (2006, in press). Neural systems implicated in delayed and probabilistic reinforcement. *Neural Networks*. (*)

List of figures

| | |
|--|----|
| Figure 1: Discrimination learning with delayed reinforcement..... | 6 |
| Figure 2: Free-operant learning with delayed reinforcement | 7 |
| Figure 3: The speed of free-operant learning with delayed reinforcement in normal rats..... | 8 |
| Figure 4: Temporal discounting | 10 |
| Figure 5: An early example of precommitment..... | 12 |
| Figure 6: Exaggerated temporal discounting in drug addicts | 19 |
| Figure 7: Key elements of the limbic corticostriatal “loop” | 21 |
| Figure 8: Coronal sections of the rat brain, showing selected limbic and related structures..... | 22 |
| Figure 9: Sagittal paramedian views of the rat brain, showing selected limbic and related structures..... | 23 |
| Figure 10: Horizontal views of the rat brain, showing selected limbic and related structures. | 24 |
| Figure 11: “Glass brain” views showing selected limbic and related structures. | 25 |
| Figure 12: Diagram of the rat hippocampus..... | 28 |
| Figure 13: Outline of connections of the hippocampus..... | 29 |
| Figure 14: Cross-sectional structure of the primate hippocampus..... | 30 |
| Figure 15: Task schematic: choice between small, immediate and large, delayed rewards | 38 |
| Figure 16: Schematics of lesions of the nucleus accumbens core (AcbC), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC)..... | 38 |
| Figure 17: Choice between immediate, small and large, delayed rewards in rats with lesions of the AcbC, ACC, or mPFC..... | 39 |
| Figure 18: Further testing of AcbC-lesioned rats in the delayed reinforcement choice task..... | 40 |
| Figure 19: Delay and magnitude discounting applied to choice..... | 41 |
| Figure 20: Choice between immediate, small and large, delayed rewards in rats with lesions of the orbitofrontal cortex (OFC)..... | 46 |
| Figure 21: Choice between immediate, small and large, delayed rewards in rats with lesions of the basolateral amygdala (BLA) or OFC..... | 47 |
| Figure 22: Task schematic: free-operant instrumental responding on an FR-1 schedule with delayed reinforcement..... | 53 |
| Figure 23: Stereotaxic frame | 55 |
| Figure 24: Operant chamber..... | 56 |
| Figure 25: Schematic of lesions of the AcbC..... | 60 |
| Figure 26: Photomicrographs of lesions of the AcbC..... | 61 |
| Figure 27: Effects of delays to reinforcement on acquisition of free-operant responding under an FR-1 schedule..... | 63 |
| Figure 28: Effect of AcbC lesions on acquisition of free-operant responding with delayed reinforcement..... | 64 |
| Figure 29: Programmed and experienced delays to reinforcement in AcbC-lesioned and sham-operated rats..... | 66 |
| Figure 30: Learning as a function of programmed and experienced delays to reinforcement in AcbC-lesioned and sham-operated rats..... | 67 |
| Figure 31: Discrimination of reinforcer magnitude: matching of relative response rate to relative reinforcement rate in AcbC-lesioned and sham-operated rats | 69 |
| Figure 32: Postoperative performance under an FR-1 schedule for delayed reinforcement..... | 71 |
| Figure 33: Effect of AcbC lesions on performance of free-operant responding for delayed reinforcement..... | 72 |
| Figure 34: Programmed and experienced delays to reinforcement following AcbC lesions made after initial training | 73 |

| | |
|---|-----|
| Figure 35: Performance as a function of delays to reinforcement in animals trained preoperatively before sham or AcbC lesions were made | 74 |
| Figure 36: Locomotor activity in a novel environment and body mass in AcbC-lesioned and sham-operated rats.... | 75 |
| Figure 37: Schematic of lesions of the hippocampus | 88 |
| Figure 38: Photomicrographs of lesions of the hippocampus..... | 89 |
| Figure 39: Effects of delays to reinforcement on acquisition of free-operant responding under an FR-1 schedule ... | 91 |
| Figure 40: Effect of hippocampal (H) lesions on acquisition of free-operant responding with delayed reinforcement | 92 |
| Figure 41: Programmed and experienced delays to reinforcement in H-lesioned and sham-operated rats | 94 |
| Figure 42: Learning as a function of programmed and experienced delays to reinforcement in H-lesioned and sham-operated rats..... | 95 |
| Figure 43: Effects of hippocampal lesions on choice between immediate, small rewards and large, delayed rewards | 97 |
| Figure 44: Locomotor activity in a novel environment and body mass in H-lesioned and sham-operated rats | 99 |
| Figure 45: Task schematic: choice between small, certain and large, uncertain rewards..... | 110 |
| Figure 46: Schematic of lesions of the AcbC | 114 |
| Figure 47: Choice with probabilistic reinforcement in AcbC-lesioned and sham-operated rats | 115 |
| Figure 48: Choice, by experienced probability, in AcbC-lesioned and sham-operated rats..... | 118 |
| Figure 49: Indifference probabilities in AcbC-lesioned and sham-operated rats | 119 |
| Figure 50: Amount of food obtained, and effects of satiety on choice, in AcbC-lesioned and sham-operated rats .. | 121 |
| Figure 51: Locomotor activity in a novel environment in AcbC-lesioned and sham-operated rats | 122 |
| Figure 52: A simple mechanism for transient involvement of the hippocampus in memory storage..... | 133 |
| Figure 53: The “primrose path” to addiction..... | 142 |
| Figure 54: Skog’s classification of addiction | 143 |
| Figure 55: Key limbic corticostriatal structures involved in processing delayed reinforcement..... | 150 |

List of tables

| | |
|--|-----|
| Table 1: Some inputs to the nucleus accumbens | 27 |
| Table 2: Some outputs from the nucleus accumbens..... | 27 |
| Table 3: Interpretation of lesion studies | 30 |
| Table 4: Training and testing schedule for reinforcer magnitude matching task..... | 58 |
| Table 5: Parameters for excitotoxic hippocampal lesions | 84 |
| Table 6: Testing schedule for probabilistic choice task..... | 113 |