Neural systems involved in delay and risk assessment in the rat

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Doctor of Medicine

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To Hannah

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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 ($p = 1, 0.5, 0.25, 0.125$, 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

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Abbreviations

$\tilde{\varepsilon}$	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 $a \le x < b$.
$[a, b]$	a range a–b that includes both a and b, i.e. a range $a \le x \le b$.
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.	*confer* (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.	*exempli gratia* (for example)
et al.	and others (*et alii*, masculine plural; *et aliae*, feminine plural; *et alia*, neutral plural)
etc.	*et cetera* (and the rest)
FI	fixed interval
fMRI	functional magnetic resonance imaging
FR	fixed ratio
h	hour
H	hippocampus
i.e.	*id est* (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	*N*-methyl-D-aspartate
NS	not significant
OCD	obsessive–compulsive disorder
OFC	orbitofrontal cortex
p	probability
$P(\mathrm{A})$	probability of event A occurring
$P(\mathrm{A} \mid \mathrm{B})$	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)
$p_{\mathrm{reinforcer}}$	probability of delivery of a reinforcer after it has been chosen
$p_{\mathrm{statistical}}$	statistical *p* value (probability of obtaining the observed data, or results more extreme, were the null hypothesis to be true)
q.v.	*quod vide* (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 $^{1}/_{100}$ 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>.

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