INTENSITY AND DURATION IN BRAIN-STIMULATION REWARD

By Ian Robert Price

> Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy, University of New England, Armidale, New South Wales, Australia. October, 1987.

DECLARATION

I declare that no part of this thesis has been accepted or presented for the award of any degree or diploma by any University, and that to the best of my knowledge, the thesis contains no material previously published or written by any other person, except where due reference is given to that author by direct credit in the text or bibliography.

Acknowledgements

I wish to express appreciation to Associate Professor W. Noble for reviewing the final drafts of this thesis and to Mr. D. K. Tegart for comments and suggestions throughout the earlier preparation.

Thanks also go to several of the staff at the Psychology Department for assistance and moral support over the past few years. In particular, Dr. B. Byrne for help in obtaining equipment and Professor R. A. M. Gregson for assistance in unravelling some of the mysteries of time series analysis¹. Particular thanks also go to the Professional Officer, Mr. David Heap for development of computer control of stimulus presentation and on-line recording of data. Mr. Gavin Mascord and the Physics Department, particularly Mr. Dick Jenkins, also made contributions to the construction of equipment. Thanks are also due to Mr. Frank Niebling for the time-consuming, and not so enviable, task of caring for experimental animals for many months. Staff of the Computer Centre, especially Julian Creedy and Michelle Horne, for cooperation and assistance on numerous occasions and Mr. Wayne Higgins from the Zoology Department for help and advice with histology are also sincerely thanked.

Finally, many thanks go to my wife, Janet. for several years of patient cooperation and understanding. Without her forbearance this work may never have been completed. Her practical assistance with typing. referencing, and histology is also gratefully acknowledged.

The study was made possible by a Commonwealth Postgraduate Award provided by the Australian Government.

¹Part of the time series analysis reported in Chapter 9. was funded by a research grant held by Professor Gregson

Abstract

Electrical stimulation of certain regions of the vertebrate brain produces behaviour analogous to a powerful motivational state. The electrical stimulation that produces this behaviour is described as rewarding brain stimulation. When an animal is placed in a situation in which it can control both the initiation and termination of rewarding brain stimulation, an alternation often occurs between periods of stimulation and periods of no stimulation which has been termed shuttling behaviour. The research program reported here examined the relationship between shuttling behaviour and the intensity and duration of rewarding brain stimulation.

Shuttling behaviour has been argued as capable of yielding valid measures of the rewarding effect produced by this type of stimulation. As a result, measures that are available from a consideration of the self-regulation of stimulation have found an increasing use in pharmacological studies. However, some of the assumptions and theoretical interpretations on which such arguments rest have not been adequately examined. In particular, the assumption that the two durations are independent and may be consistently interpreted in terms of reward and aversion have not received sufficient attention. The series of experiments reported here examined in detail the relationship between the selected durations and the intensity of stimulation, and also evaluated hypotheses concerning the termination response in terms of how well the observed relationships may be explained.

The literature review shows that the selected durations of stimulation (ON time) and the selected durations of no stimulation (OFF time) are both decreasing functions of the intensity of stimulation. Evidence also indicates that there is no significant correlation between these two durations. However, for several reasons, existing evidence could not be accepted with confidence: including, a considerable range in the reported correlation (-0.47 to +0.79), considerable differences in how the correlation was calculated, and a failure to consider the possible effect of intensity on the correlation.

In the present study, the correlation between ON and OFF time was examined in several ways, including the correlation between mean ON and OFF time, the correlation between within-trial ON time and the immediately preceding OFF time, the correlation between within-trial ON time and the immediately following OFF time. Within-trial correlations were also calculated after differencing and after time series methods had been used.

The decrease in OFF time that occurs as intensity is increased may be caused directly by the increase in intensity, or may occur indirectly as a result of the concurrent decrease in the duration of stimulation. Three experiments are reported which attempt to dissociate the effects of intensity of stimulation from the effects of duration of stimulation on OFF time under continuous reinforcement. The statistical relationship between ON and OFF time was examined throughout all experiments.

The results indicated that the intensity of stimulation was the major determinant of OFF time. An increase in the intensity of stimulation produces highly significant decreases in both ON and OFF time, whereas an increase in the duration of stimulation produces small, but significant. increases in OFF time.

The correlation between ON and OFF time varied markedly depending on whether mean values were correlated (across animals or trials), or whether the within-trial ON and OFF times were correlated. Correlation between mean values at low to moderate intensities were significantly positive, but at higher intensities, nonsignificant, near-zero correlation were found. Within-trial correlations were not significant at any intensity level once a tendency for linear trend in the data was accounted for. Particular animals in particular trials can show significant correlations between ON and OFF time but correlation across animals or across trials was not consistent.

An analysis from a time series perspective indicated that except for the tendency for linear trend, each ON time and each OFF time is generated independently and stochastically; past durations of stimulation have little or no effect on the determination of the immediate duration of stimulation.

Two models that satisfactorily accommodate the main features of shuttling behaviour are discussed in relation to how the behaviour might be produced. The results supported a two system substrate for brain stimulation reward, which. in turn, could support either a reward/aversion or a reciprocal inhibition model. From a neurophysiological point of view, the interaction of the two systems and the timing of the termination response might be best interpreted in terms of adaptation and the arousal of an inhibitory system. The timing of the initiation response appears to depend on several factors including the presence of various stimulus contingencies.

Contents

\mathbf{A}	Acknowledgements iii			
\mathbf{A}	bstra	ict		iv
1	Bac	kgrou	nd, definitions and the VTM	2
	1.1	Introd	uction	2
	1.2	Backg	round and definitions	3
		1.2.1	Response measures	4
		1.2.2	Modelling of behaviour	7
	1.3	Anato	my and the ventral tegmental area	8
		1.3.1	The ventral tegmental area	8
	1.4	Organ	isation of chapters	12
2	Inp	ut and	output factors	14
	2.1	Stimu	lus factors	14
		2.1.1	Intensity	15
		2.1.2	Intensity and response rate	17
	2.2	Intens	sity and shuttling behaviour	21
		2.2.1	The independence of ON/OFF times	$\overline{23}$
	2.3	Outpu	1t factors	25
		2.3.1	The interpretation of shuttling behaviour	25
3	The	eoretic	al perspectives	30
	3.1	The r	eward/aversion model	31
		3.1.1	Source of the aversion	36
		3.1.2	Conclusions	. 39
	3.2	Adap	tation	40
		3.2.1	The reciprocal inhibition model	. 44

		3.2.2	ICSS and inhibition	48
		3.2.3	Conclusions	49
	3.3	Other	hypotheses	50
	3.4	Single	or dual system substrates	51
	3.5	Conclu	usions and current research	54
4	Ger	neral m	nethod	57
	4.1	Subjec	cts	57
		4.1.1	Care and housing	57
		4.1.2	Surgery	58
		4.1.3	Electrodes	59
		4.1.4	Coordinates	59
	4.2	Appar	atus	59
		4.2.1	Standard shuttlebox	60
		4.2.2	Definition of dependent variables	60
		4.2.3	T-maze/shuttlebox	61
	4.3	Comp	uter control of stimulus parameters	65
		4.3.1	Modes of operation	65
		4.3.2	Stimulus waveform	67
		4.3.3	Contingency of stimulation	68
		4.3.4	Stimulus control files	70
	4.4	Behav	vioural testing	70
		4.4.1	Training and pre-screening	70
		4.4.2	Definition of self-stimulation	71
		4.4.3	Testing procedure	72
	4.5	Histol	ogy	73
5	\mathbf{Exp}	perime	nt I: Intensity and shuttling behaviour	75
	5.1	Exper	iment Ia: Mapping of response measures	75
		5.1.1	Introduction	75
		5.1.2	Subjects and apparatus	79
		5.1.3	Method	79
		5.1.4	Definitions of variables and statistics	80
		5.1.5	Results	82
		5.1.6	Discussion	96

	5.2	Exper	iment Ib: Stability of measures
		5.2.1	Introduction
		5.2.2	Subjects and apparatus
		5.2.3	Method
		5.2.4	Results
		5.2.5	Discussion
	5.3	Conclu	usions from Experiment I
6	Exp	erime	nt II: Fixed durations 116
	6.1	Exper	iment IIa: Fixed ON time
		6.1.1	Introduction
		6.1.2	Subjects and apparatus
		6.1.3	Method
		6.1.4	Results
		6.1.5	Discussion
	6.2	Exper	iment IIb: Fixed OFF time
		6.2.1	Introduction
		6.2.2	Subjects and apparatus
		6.2.3	Method
		6.2.4	Results
		6.2.5	Discussion
	6.3	Concl	usions from Experiment II
7	Exp	perime	nt III: Within-trial stimulus changes 142
	7.1	Exper	iment IIIa: Within-trial changes in duration
		7.1.1	Introduction
		7.1.2	Subjects and apparatus
		7.1.3	Method
		7.1.4	Results
		7.1.5	Discussion
	7.2	Exper	riment IIIb: Within-trial changes in intensity
		7.2.1	Introduction $\dots \dots \dots$
		7.2.2	Subjects and apparatus
		7.2.3	Method
		7.2.4	Results

		7.2.5 Discussion	166
	7.3	Conclusions from Experiment III	168
8	Hist	tological results 1	172
	8.1	Histology	172
	8.2	Electrode orientation	183
	8.3	Threshold changes	184
		8.3.1 Electrode materials	186
9	\mathbf{T} im	ne series analysis 1	87
	9.1	Introduction	187
	9.2	ARMA models	188
		9.2.1 Univariate output series	189
		9.2.2 Input-output analysis	191
	9.3	Conclusions	208
10 General discussion and conclusions 209			
	10.1	Main results	209
		10.1.1 ON and OFF times	209
		10.1.2 Correlation data	211
		10.1.3 Models of ICSS shuttling behaviour	214
	10.2	Conclusions and further research	218

References

221

Volume 2: Raw data

List of Figures

1	The reciprocal inhibition model
2	T-maze/shuttlebox
3	Rate-intensity functions 83
4	Number of crosses
5	Mean ON and OFF time
6	Proportion of time ON
7	Total time ON
8	Mean charge accepted
9	Total charge accepted
10	Regression line slope
11	Correlation — original series 95
12	Correlation — differenced series
13	Stability of number of crosses
14	Stability of ON and OFF time measures
15	Stability of proportion of time ON
16	Stability of mean charge accepted
17	Stability of total charge accepted
18	Stability of regression line slope
19	Stability of correlation measures
20	OFF time as a function of ON time
21	ON time as a function of OFF time
22	ON time changes — Subject R12
23	Corr (X, Y_{-1}) for Fixed OFF group
24	Corr (X, Y) for Fixed OFF group
25	Duration \times Group

26	Mean OFF time at two levels of ON time
27	Corr $D(X,Y)$ — Group × Trials interaction
28	Subject R23 — ON time (2:1)
29	Subject R49 — ON time (2:1)
30	Mean ON and OFF time changes across conditions
31	Subject R12 — Intensity (2:1)
32	Subject R18 — Intensity (2:1)
33	Subject R49 — Intensity (2:1)
34	Subject R58 — Intensity (2:1)
35	Change in distribution for LH animal
36	M-Series electrode locations
37	R-Series electrode locations R01–R35
38	R-Series electrode locations R36–R70
39	Plate 1
40	Plate 2
41	Plate 3
42	Plate 4
43	Plate 5
44	CROSS time and first differences for M01. M12, and M16 194
45	ACFs and PACFs for CROSS time data
46	CROSS time and first differences for R09, R24, and R49
47	ACFs and PACFs for CROSS time data
48	Input \Rightarrow output relationship for M01 and M12
49	Input \Rightarrow output relationship for M16 and R09
50	Input \Rightarrow output relationship for R24 and R49
51	Input =output relationship for R48 at two intensities $\dots \dots \dots$
52	Remaining cross-correlation functions
53	Smoothed ON time emphasising low frequency components $\ldots \ldots 207$

List of Tables

1	Experimental design 1
2	Current intensities used for each subject (μa)
3	Summary data for dependent variables at successive intensity levels 87
4	Results of trend analysis
5	Results of ANOVA for intensity main effects — correlation data 96
6	Calculation of fixed durations
ī	Experimental design II
8	Summary of analysis of variance on OFF time data
9	Summary of analysis of variance on ON time data
10	F-values calculated for ON time 2:1 trials
11	OFF time (secs) — ON time presented in 2:1 format
12	Comparison among within-trial correlation variables
13	Experimental design III
14	Results of orthogonal comparisons
15	F-values calculated for intensity 2:1 trials
16	ON time (secs) — intensity 2:1 trials
17	OFF time (secs) — intensity 2:1 trials
18	Comparison among within-trial correlation variables
19	ICSS success rate
20	Subject electrode orientation
21	ARMA models
22	Relationship between CCF and correlation variables