Schizophrenia, Dopamine, and the Prefrontal Cortex: Theory and Computational Models

Alastair Gilmour Reid

PhD
The University of Edinburgh
1999
I declare that all the work in this thesis is original and my own except where otherwise specified.

Alastair G Reid
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I would like to dedicate this work to the memory of grandmother Freda Reid (1901-1996).
Abstract

The study of schizophrenia over the past decades has generated a sea of data. This is not entirely surprising in view of the vast size of the subject and the fact that it covers so many disciplines. Unfortunately, all this data has not led us to a single set of conclusions regarding the origin and pathophysiology of schizophrenia. Consequently we have seen a number of theories attempting to describe the underlying biological and psychological processes which are dysfunctional in schizophrenics. This thesis attempts to reconcile some of these theories through the use of computational models which allow us to investigate the links between biological and psychological processes.

Existing artificial neural network models of schizophrenia generally have poor biological validity (chapter 4). They also rely on the interpretation of mental states as binary patterns of activity, making it difficult to realistically represent complex mental phenomena such as those that occur in schizophrenia. To try and overcome these problems I have focussed on the information processing properties of certain brain structures implicated in schizophrenia, namely the prefrontal cortex (PfCx) and nucleus accumbens (NAcc), and I have used models which operate at several different levels. Much work has been done on the structure and function of the PfCx and its involvement in schizophrenia. However, an understanding of the role of dopamine (DA) in the PfCx is still lacking. I have suggested a possible mechanism for the action of DA in the PfCx and illustrated this with biologically plausible models which can be interpreted at cellular and pharmacological levels. I have then related this to schizophrenia. Dysfunctions between brain regions are also suggested to underly the symptoms of schizophrenia. This is the other theme of the thesis, where I have used a reinforcement learning based model to examine interactions between brain regions and the effects of variations in DA transmission on these interactions.

More specifically, I will show how oscillations between pyramidal cells and GABA cells in the PfCx may arise (chapter 5), and how disruption of this information processing capacity can occur through multiple different pathologies. The existence of oscillations is shown through simulations and theoretically by modelling neurotransmitter interactions within the mesocortical and mesolimbic dopamine (DA) systems (chapter 6). This work reveals the conditions under which oscillations will occur, and shows how DA can act as a control parameter in initiating oscillations. I have modelled a high level cognitive process, the Tower of London task, using a rule-based model to represent PfCx function (chapter 7). Finally, a reinforcement learning model is presented to illustrate putative NAcc function (chapter 8). The interaction between the two models is investigated and illustrations of the possible origins of the positive symptoms of schizophrenia are given. In all of these models, the role of DA has been crucial. One conclusion from this work is that the symptoms of schizophrenia may arise through inappropriate fluctuations in DA levels in the NAcc and the PfCx. The work is based on a large amount of neurobiological data and follows theories presented by Friston (1998) and Goldman-Rakic and Selemon (1997) amongst others.
Contents

1 Introduction  
1.0.1 Modeling issues ........................................... 3  
1.1 Introduction .................................................. 3  

2 Schizophrenia and neuropsychology  
2.1 What is Schizophrenia? ........................................ 6  
2.1.1 Symptoms and diagnosis .................................... 6  
2.1.2 Epidemiology and aetiology ................................. 7  
2.1.3 The subsyndromes of schizophrenia ........................ 10  
2.2 The cognitive neuropsychology of schizophrenia .......... 13  
2.2.1 Performance of schizophrenics on neuropsychological tasks .......... 18  
2.3 Working memory ............................................... 19  
2.3.1 The PfCx and working memory ............................. 20  
2.3.2 Working memory, the PfCx, and schizophrenia ............ 21  
2.4 Summary ...................................................... 21  

3 Neurobiological issues ........................................... 23  
3.1 Introduction .................................................. 23  
3.1.1 The disconnection hypothesis ............................. 24  
3.1.2 The interneuron hypothesis ................................ 25  
3.2 The Nucleus Accumbens ....................................... 26
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1</td>
<td>Neuroanatomy</td>
<td>26</td>
</tr>
<tr>
<td>3.2.2</td>
<td>Theories of function</td>
<td>31</td>
</tr>
<tr>
<td>3.2.3</td>
<td>The role of the NAcc in reward-based learning</td>
<td>36</td>
</tr>
<tr>
<td>3.2.4</td>
<td>Possible role of the NAcc in schizophrenia</td>
<td>38</td>
</tr>
<tr>
<td>3.3</td>
<td>The hippocampus</td>
<td>41</td>
</tr>
<tr>
<td>3.3.1</td>
<td>The hippocampus in schizophrenia</td>
<td>43</td>
</tr>
<tr>
<td>3.4</td>
<td>Dopamine</td>
<td>46</td>
</tr>
<tr>
<td>3.4.1</td>
<td>Some basic pharmacology</td>
<td>46</td>
</tr>
<tr>
<td>3.4.2</td>
<td>Dopamine in the prefrontal cortex</td>
<td>48</td>
</tr>
<tr>
<td>3.4.3</td>
<td>Dopamine in schizophrenia</td>
<td>48</td>
</tr>
<tr>
<td>3.5</td>
<td>The Prefrontal Cortex</td>
<td>49</td>
</tr>
<tr>
<td>3.5.1</td>
<td>Biology of the PfCx</td>
<td>50</td>
</tr>
<tr>
<td>3.5.2</td>
<td>Difference between rat and human prefrontal cortex</td>
<td>55</td>
</tr>
<tr>
<td>3.5.3</td>
<td>PfCx function</td>
<td>55</td>
</tr>
<tr>
<td>3.5.4</td>
<td>Multiple domains of processing in the PfCx</td>
<td>59</td>
</tr>
<tr>
<td>3.6</td>
<td>PfCx, NAcc and hippocampal interactions</td>
<td>61</td>
</tr>
<tr>
<td>3.6.1</td>
<td>Frontal-subcortical disharmony: hypotheses for schizophrenia</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>Review of computational models</td>
<td>68</td>
</tr>
<tr>
<td>4.1</td>
<td>Modelling issues</td>
<td>68</td>
</tr>
<tr>
<td>4.2</td>
<td>Over-pruning of attractor networks</td>
<td>70</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Results</td>
<td>72</td>
</tr>
<tr>
<td>4.2.2</td>
<td>Analysis</td>
<td>75</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Conclusions</td>
<td>77</td>
</tr>
<tr>
<td>4.3</td>
<td>Modelling cognitive tasks</td>
<td>79</td>
</tr>
<tr>
<td>4.4</td>
<td>Horn and Ruppin</td>
<td>86</td>
</tr>
<tr>
<td>4.5</td>
<td>Summary</td>
<td>88</td>
</tr>
</tbody>
</table>
### 5 Modelling the prefrontal cortex

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>90</td>
</tr>
<tr>
<td>5.2</td>
<td>The spike response neuron</td>
<td>91</td>
</tr>
<tr>
<td>5.3</td>
<td>Stability of the model</td>
<td>95</td>
</tr>
<tr>
<td>5.4</td>
<td>Model of PfCx delay cells</td>
<td>96</td>
</tr>
<tr>
<td>5.5</td>
<td>The effect of DA on PfCx delay cells</td>
<td>100</td>
</tr>
<tr>
<td>5.6</td>
<td>Information processing in the PfCx</td>
<td>103</td>
</tr>
<tr>
<td>5.7</td>
<td>Schizophrenia: multiple pathologies lead to the same outcome</td>
<td>106</td>
</tr>
<tr>
<td>5.8</td>
<td>Summary</td>
<td>110</td>
</tr>
</tbody>
</table>

### 6 Modelling Dopamine Dynamics

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Introduction</td>
<td>111</td>
</tr>
<tr>
<td>6.2</td>
<td>Some dopamine neurobiology</td>
<td>112</td>
</tr>
<tr>
<td>6.2.1</td>
<td>Assumptions and justifications</td>
<td>116</td>
</tr>
<tr>
<td>6.2.2</td>
<td>The equations</td>
<td>118</td>
</tr>
<tr>
<td>6.2.3</td>
<td>Selection of rate constants</td>
<td>120</td>
</tr>
<tr>
<td>6.3</td>
<td>Results</td>
<td>120</td>
</tr>
<tr>
<td>6.3.1</td>
<td>Experiment 1: The action of DA in NAcc</td>
<td>121</td>
</tr>
<tr>
<td>6.3.2</td>
<td>Experiment 2: Somatodendritic dopamine</td>
<td>126</td>
</tr>
<tr>
<td>6.3.3</td>
<td>Experiment 3: Excitation of mesocortical VTA cells</td>
<td>127</td>
</tr>
<tr>
<td>6.4</td>
<td>Focussing on PfCx dynamics</td>
<td>128</td>
</tr>
<tr>
<td>6.4.1</td>
<td>The simplified model</td>
<td>128</td>
</tr>
<tr>
<td>6.4.2</td>
<td>Analysis of the simplified model</td>
<td>130</td>
</tr>
<tr>
<td>6.4.3</td>
<td>Bifurcations</td>
<td>133</td>
</tr>
<tr>
<td>6.4.4</td>
<td>Results: DA as a control parameter</td>
<td>135</td>
</tr>
<tr>
<td>6.5</td>
<td>Criticism of the model</td>
<td>137</td>
</tr>
<tr>
<td>6.6</td>
<td>Interpretation of the results</td>
<td>141</td>
</tr>
</tbody>
</table>
7 Modelling the Tower of London task 144
7.1 Preface to chapters 7 and 8 ................................. 144
7.2 Introduction ............................................. 145
7.3 The Tower of London planning task ......................... 145
7.4 Review of Dehaene’s model ................................ 148
7.5 Basic components of the model ............................. 149
7.6 The PfCx model .......................................... 150
7.7 Lesions of the PfCx Tower of London model ............... 155
  7.7.1 Relevance to schizophrenia: Summary ................. 159

8 Modelling the function of the Nucleus Accumbens with reinforcement learning 160
8.1 Introduction ............................................. 160
8.2 The reinforcement learning model .......................... 161
  8.2.1 Problems with the reinforcement learning analogy ...... 164
  8.2.2 Results of the NAcc model ........................... 165
8.3 NAcc lesions ........................................... 166
8.4 Relevance to schizophrenia ................................. 169
  8.4.1 Conclusion ........................................... 172

9 Discussion 173
9.1 Some dilemmas and hypotheses ............................ 173
  9.1.1 Neurodevelopmental Hypotheses ........................ 179
  9.1.2 The mechanism of action of neuroleptics ................ 183
9.2 Summary of findings ..................................... 184
9.3 Concluding remarks ...................................... 186

10 Dopamine dynamics: 12 equation model 206
10.1 Rate constant values ...................................... 206
Abbreviations

ACh = acetyl choline
AHP = after-hyperpolarising potential
AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid
CNS = central nervous system
DA = dopamine
DAP = depolarising after-potential
DRT = delayed response task
EPSP = excitatory post-synaptic potential
GABA = γ - aminobutyric acid
Glu = glutamate
IPSP = inhibitory post-synaptic potential
LI = latent inhibition
LTP = long-term potentiation
NAcc = nucleus accumbens
NMDA = N methyl-D-aspartate
ODE = ordinary differential equation
PCP = phencyclidine ('Angel Dust')
PET = positron emission tomography
PiCx = prefrontal cortex
PKU = phenylketonuria
PSP = post-synaptic potential
SNpc = substantia nigra pars compacta
SNpr = substantia nigra pars reticulata
STN = subthalamic nucleus
VP = ventral pallidum
VTA = ventral tegmental area (A.10)
5-HT = 5-hydroxytryptamine / serotonin
6-OHDA = 6-hydroxydopamine
Chapter 1

Introduction

The problem with schizophrenia is that it is such a large subject.

The aim of this thesis is to investigate some of the information processing properties of brain structures implicated in schizophrenia, namely the prefrontal cortex (PfCx) and nucleus accumbens (NAcc). I will show the information processing properties of oscillations between pyramidal cells and GABA cells in the PfCx (chapter 5) and how disruption of this information processing capacity can occur through multiple different pathologies. The existence of oscillations is shown through simulations and theoretically by modeling neurotransmitter interactions within the mesocortical and mesolimbic DA systems (chapter 6. A complex model using 12 ODE’s is used to show how DA can effect switching in the NAcc and a role for somatodendritic DA in the VTA. A simplified 2 equation model representing the PfCx is used to show, through simulations, the occurrence of oscillations in the PfCx. This model can be analysed mathematically to show the precise conditions under which oscillations will occur, and in particular, how DA can act as a control parameter in initiating oscillations. Finally, I have modeled a high level cognitive process, the Tower of London task, using a rule-based model to represent PfCx function and a reinforcement learning model to represent NAcc function (7. The interaction between the two models is investigated and illustrations of the possible origins of the positive symptoms of schizophrenia are
given. In all of these models, the role of DA has been crucial. Thus I have investigated at several different levels the role of DA in the PfCx, the role of the PfCx and NAcc in schizophrenia, and the role of DA in schizophrenia. This leads to several conclusions. One, in particular, is that the symptoms of schizophrenia may arise through inappropriate fluctuations in DA levels in NAcc and PfCx. The work is based on a large amount of neurobiological data and follows theories presented by Friston (1998) and Goldman-Rakic and Selemon (1997) amongst others.

1.0.1 Modeling issues

Complex dynamics, such as those described above, cannot be, at the time of writing, investigated in vivo and so modeling is a useful tool in uncovering potentially relevant control paths, and in testing the viability of hypotheses before proceeding to detailed experimental work. No one part, or set of parts, of the brain can really be considered to be a closed system, thus any model which focuses on a subset of the variables which may be considered to operate in the whole brain is inevitably excluding important interactions. However, this is one, of the many, assumptions made in modeling and in science in general, that our observations in a local system pertain only to that system.

**From the book chapter...**

1.1 Introduction

Many strands of evidence indicate that aberrant functioning of the prefrontal cortex (PfCx) is a key part of the pathogenesis of schizophrenia. In particular the idea that the PfCx is underactive in schizophrenics (the hypofrontality hypothesis) is widely accepted (Bachneff, 1991; Wolkin et al., 1992; Berman et al., 1992). Recent research has revealed more information regarding the physiology and morphology of PfCx pyramidal cells (Yang et al., 1996), and the action of D<sub>1</sub> receptors on the firing properties
of these cells has also been investigated (Yang and Seamans, 1996). In this chapter we provide a simple model of PfCx delay cells which is used to illustrate and investigate the actions of the D₁ dopamine receptor on these cells. Activity in the delay cells has also been shown to be modulated by D₁ receptor effects (Williams and Goldman-Rakic, 1995). We suggest a PfCx architecture, in accordance with biological evidence, which accounts for the information processing properties of the delay cells, following the work of Lewis and Anderson (1995). From this architecture we can explore the hypotheses that a reduction in the levels of dopamine in the PfCx effectively isolates the delay cells and also destabilises the firing patterns of these cells. We can also show how other defects in the architecture of the PfCx can also lead to disruption of PfCx function. This enables us to illustrate how multiple pathologies can lead to PfCx dysfunction and so to schizophrenia. This relates to the ideas and work of others (Cohen et al., 1996).

We have used the spike response neuron (Gerstner and van Hemmen, 1994; Gerstner, 1998b,a) as a model for PfCx pyramidal cells. The advantage of this type of model is that it allows us to construct a more biologically realistic model of the PfCx in terms of spiking activity of individual neurons. However the spike response model is simple enough that it can also be investigated at the network level.

The PfCx is considered to be the locus of executive functioning in working memory tasks and as such holds information ‘online’ while other processing occurs. As an illustration of the cognitive deficits which may arise, we have also summarised the results of two models which perform the Tower of London task. One model follows a heuristic derived from studying real subjects performing the task (Ward and Allport, 1997), this a rule-based PfCx model. The other model solves Tower of London task using reinforcement learning and is loosely considered to be a model of the Nucleus Accumbens (NAcc). The NAcc is implicated in schizophrenia because it is the locus of action of traditional neuroleptic drugs. These are D₂ antagonists or mixed D₂ and D₁ antagonists. There is good evidence that the hippocampus and parahippocampal region are also involved in schizophrenia (Friston et al., 1992). Other modeling work has been aimed at investigating the interaction between frontal cortex and hippocampus.
in schizophrenia (Horn and Ruppin, 1995). Recent neuroscience research (Heckers et al., 1998) goes some way to support claims that frontal-hippocampal dysfunction is a key part of schizophrenia. Our two models of the Tower of London task then allow us to investigate potential dysfunctions of these two models and show how either alone or together, or in conjunction with the hippocampus, the symptomatology of schizophrenia can arise through aberrant function of these brain regions.
Chapter 2

Schizophrenia and neuropsychology

2.1 What is Schizophrenia?

2.1.1 Symptoms and diagnosis

Schizophrenia is diagnosed according to the presence or absence of certain behavioural traits over a period of time. The most widely used diagnostic criteria are contained in the DSM-IV (USA) and ICD-10 (WHO) manuals. These have in common stipulations that there must be clear evidence of psychosis including specific hallucinatory experience or delusional ideation. They also state that affective symptoms must not be predominant. It should be stated here that the distinction between symptoms and signs (in psychiatry) is that symptoms are abnormal sensations which are perceived (and complained of) by the patient, whereas signs are abnormal behaviours or mental phenomena which the clinician elicits but which the patient may not be aware of. In the literature on schizophrenia the term symptoms is, unfortunately, often used to refer to signs. In this thesis the phenomena which are considered are generally
signs of schizophrenia rather than symptoms. In terms of diagnosis ICD-10 requires symptoms and signs to be present for a minimum period of 1 month whereas DSM-IV requires a minimum 6 month duration. The symptoms and signs of schizophrenia can be divided into positive, where abnormal behaviours are actively expressed, and negative, where there is a loss of expression of normal behaviour (Crow, 1980). More recently, three subsyndromes of schizophrenia have been described (Liddle et al., 1992) (see below). The positive and negative symptoms and signs are listed in Tables 2.1 and 2.2 (Goldberg et al., 1987).

The most common age of onset is late adolescence and early adulthood, although it can occur between the ages of 7 and 70. Typically, the onset is insidious, with a gradual deviation of the affected person away from their normal patterns of behaviour towards behaviours displaying some of the positive symptoms and signs of schizophrenia. The acute phase of the illness is characterised by florid psychosis with predominantly positive symptoms. It is common for the hallucinations and delusions of the acute illness to gradually disappear over time, to be replaced by the negative symptoms and signs. This represents the chronic stage of the illness and is sometimes known as a ‘defect state’. Before reaching the chronic stage of the illness a sufferer may experience several periods of recovery from the acute illness, but the ‘normal state’ that is returned to during each remission gradually worsens until the illness effectively enters the chronic stage (Johnstone, 1998).

2.1.2 Epidemiology and aetiology

The lifetime risk of schizophrenia, in the industrialised countries where studies have been carried out, is just under 1%, and the incidence is approximately 15 new cases per 100 000 population per annum (Johnstone, 1998). The incidence throughout the world is fairly similar to this figure. Here is a brief summary of some of the other main epidemiological points regarding schizophrenia:
Positive Symptoms/Signs

<table>
<thead>
<tr>
<th>Reduced Contact With Reality:</th>
<th>Disorders of thought possession (thought insertion/broadcasting/withdrawal). The conviction that one’s thoughts are not one’s own or are known to others, or are caused by others.</th>
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<td>Passivity phenomena:</td>
<td>the belief that movements, feelings, impulses are generated or controlled by other people or forces.</td>
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</table>

**Hallucinations:**

- **Thought echo:**
  The experience of one’s own thoughts as being spoken aloud from the outside world.
- **Auditory hallucination:**
  Characteristically the patient hears him/herself referred to in the third person.

**Disturbed Thinking:**

- **Knight’s move/Derailment:**
  A loosening of associations in speech causing disjointed nonsensical speech—essentially semantic errors.
- **Neologisms:**
  Frequent use of invented words.

**Delusions:**

- **Primary delusions:**
  Persistently held abnormal or bizarre beliefs held outside the context of normal societal values.
- **Delusional perception (very characteristic of schizophrenia):**
  Delusions occurring secondary to some other morbid process such as hearing voices. The perceptions are normal but are given delusional significance. This contrasts with secondary delusions, which occur in a variety of psychiatric conditions, and are an attempt by the patient to reconcile his/her strange experiences with the real world e.g. ascribing the cause of hallucinations to computers.

**Emotional Disturbance:**

- **Incongruous affect:**
  Inappropriate outbursts of laughter or anger, sometimes in response to internal morbid experiences.

Table 2.1: The positive symptoms and signs of schizophrenia
# Negative Symptoms/Signs

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</thead>
<tbody>
<tr>
<td>Poverty of Speech:</td>
<td>The patient speaks little and shows reduced complexity of speech.</td>
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<tr>
<td>Psychomotor Slowness</td>
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<tr>
<td>Emotional Flatness:</td>
<td>An absence of normal modulation of mood with a lack of facial expressiveness and emotional responsiveness.</td>
</tr>
<tr>
<td>Loss of Volition:</td>
<td>Poor motivation to work, or to care for oneself in severe cases. This leads to a general underactivity and <strong>social withdrawal</strong>. This is worsened if living in an <strong>under-stimulating environment</strong>.</td>
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Table 2.2: The negative symptoms and signs of schizophrenia

- It is equally common between men and women.

- It is more prevalent in lower socioeconomic groups and city-dwellers. This is probably due to a downward drift phenomenon i.e. having schizophrenia **causes** lower socioeconomic status and migration to the city.

- Schizophrenics are less fertile.

- Schizophrenics have a raised mortality.

- People born in January to March in the northern hemisphere, and July to September in the southern hemisphere are more likely to have schizophrenia.

The aetiology of schizophrenia remains largely unknown, other than 'it has something to do with the brain'. There are certain consistently significant factors however:
• A family history of schizophrenia increases the likelihood of developing it. This implies there is a genetic component to it.

• DA D₂ receptor antagonists (neuroleptics) give relief from the positive symptoms and signs of schizophrenia in many instances. This implicates DA in the pathogenesis of schizophrenia.

• There is some evidence that birth complications increase the chances of developing schizophrenia.

• Patients in a ‘high expressed emotion’ (EE) environment have a highly increased chance of relapse.

Johnstone (1998) concludes that the most plausible synthesis of the various strands of evidence is that schizophrenia is a neurodevelopmental disorder, as suggested by (Weinberger, 1995). This concept is related to the models and ideas presented in this thesis in chapter 9.

2.1.3 The subsyndromes of schizophrenia

The advent of neuroimaging techniques has advanced our knowledge of the functional anatomy of the brain. In particular it has allowed us to observe activity in various brain regions while certain cognitive tasks are being undertaken. This helps to make the elusive link between brain activity and mental activity. Applying these techniques to schizophrenia has revealed some very useful information regarding the brain regions which may be involved. The most widely reported finding is functional hypofrontality, where the PfCx is underactive compared to normal controls during the performance of a cognitive task which is known to tap the PfCx (Andreasen et al.,
Schizophrenia and neuropsychology

<table>
<thead>
<tr>
<th>Subsyndrome</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor poverty</td>
<td>Poverty of speech</td>
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<td></td>
<td>Flattened affect</td>
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<td></td>
<td>Decreased movement</td>
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<tr>
<td>Disorganisation</td>
<td>Inappropriate affect</td>
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<td></td>
<td>Positive formal thought disorder</td>
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<td></td>
<td>Poverty of speech content</td>
</tr>
<tr>
<td>Reality distortion</td>
<td>Delusions</td>
</tr>
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<td></td>
<td>Hallucinations</td>
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</table>

Table 2.3: The subsyndromes of schizophrenia (Liddle et al, 1992).

1992; Berman et al., 1992; Buchsbaum et al., 1992; Wolkin et al., 1992). Another influential piece of work, by Liddle et al. (1992), has shown that there is a correlation between changes in activity in specific brain regions of schizophrenics compared with normals, and that there are particular areas of the brain which relate to particular groupings of symptoms and signs. A factor analysis on eight symptoms and signs scored on the Manchester scale revealed that there were three factors which accounted for 75.9% of the variance in symptom scores. These factors are described in Table 2.3. In addition to this, there were correlations (positive and negative) between changes in activity in various brain regions and the three factors, or subsyndromes, previously characterised (Table 2.4). The finding of three subsyndromes has been replicated and extended (Friston et al., 1992; Kaplan et al., 1993). Friston et al. (1992) found that there is an overlap between the disorganisation and psychomotor poverty syndromes, and between the disorganisation and reality distortion syndromes. They also found that increased activity in the left parahippocampal region and globus pallidus is common to both of these overlaps.

This is very interesting as it lends more weight to the involvement of the PfCx and the hippocampus in much of the symptomatology of schizophrenia. These two brain regions and the NAcc form the anatomical substrate for the modelling investigations
Schizophrenia and neuropsychology

<table>
<thead>
<tr>
<th>Subsyndrome</th>
<th>Brain region</th>
<th>Change in activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor poverty</td>
<td>left &amp; right caudate</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>left DLPfCx</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>left sup. parietal ass. ctx.</td>
<td>−</td>
</tr>
<tr>
<td>Disorganisation</td>
<td>right ant. cingulate</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MD thalamus</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>right VLPfCx</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>left &amp; right angular gyrus</td>
<td>−</td>
</tr>
<tr>
<td>Reality Distortion</td>
<td>left parahippocampal gyrus</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>left ventral striatum</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>right post. cingulate</td>
<td>−</td>
</tr>
</tbody>
</table>

Table 2.4: Changes in regional blood flow in schizophrenics and the subsyndromes they correlate with (from Liddle et al. (1992)). DLPfCx = dorsolateral PfCx; VLPfCx = ventrolateral PfCx; sup. parietal ass. ctx. = superior parietal association cortex.

carried out in the rest of this thesis.

There are problems in the interpretation of scanning studies, however, which mean it would be foolish to try and interpret the alterations in activity in all the brain regions listed in a global theory of schizophrenia. It is interesting to consider the range of potentially confounding variables that may affect imaging study results. At a fundamental level, the mechanism relating change in neural activity to change in regional blood flow (the observed variable) is not known. Nitric oxide and adenosine are released by active neurons and are vasodilators, but their action is not adequate to account for the rapidity of change in cerebral blood flow (Iadecola, 1998). In addition, Krimer et al. (1998) have shown that DA acts as a potent vasoconstrictor of cerebral microvessels. This has potential consequences for the hypofrontality hypothesis (see below) which posits that reduced PfCx activity is due to reduced DA input to the PfCx. This also relates to another problem, which concerns the origin of the change in activity. The question here is, does synaptic activity per se increase regional cerebral blood flow, or is it only changes in neuronal firing rate which are reflected in the measurement...
of blood flow? If synaptic activity affects blood flow then an increase in the firing of GABA interneurons would reduce the firing of the post-synaptic neuron but may increase blood flow. In answer to this, Akgoren et al. (1996) have shown that blood flow does not change in response to blocking GABA activity, but it does increase with the induction of action potentials. From the above it can be said that although scanning studies may give a qualitative indication that a particular brain region is involved in a particular task, the quantitative information is more suspect. In other words, it is still not clear what an increase or a decrease in cerebral blood flow mean in terms of underlying neural activity; particularly if DA is suspected of being involved in the cognitive task being assessed. A final problem with the use of scanning studies to assess brain function in psychiatric patients is that such studies are limited to a subset of patients who can tolerate the scanning protocol. The process of lying still in an fMRI scanner or having a radial artery cannula inserted will not be well tolerated by floridly psychotic patients. Thus the data which is obtained is not necessarily derived from a representative sample of the schizophrenic population.

2.2 The cognitive neuropsychology of schizophrenia

Metarepresentation

Frith (1992) provides a good account, based on many neuropsychological and some early brain imaging studies, of the cognitive changes which may generate the symptoms and signs of schizophrenia. He believes that there are three key disorders at work: 1. disorder of willed action; 2. disorder of self-monitoring; and 3. disorders in monitoring the interactions of others. All three of these disorders represent a loss of awareness. In the first category there is a loss of awareness of goals; in the second category there is a loss of awareness of one's own intentions; and in the third category there is a loss of awareness of the intentions of others. Beneath all of these disorders Frith proposes that there is a more fundamental deficiency in what he calls metarepresentation. This is the representation of facts about facts about the world, as opposed to
Schizophrenia and neuropsychology

<table>
<thead>
<tr>
<th>Primary disorder</th>
<th>Description</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willed action</td>
<td>An inability to produce spontaneous behaviour in the absence of external cues</td>
<td>No ability to respond in novel situations; routine actions not terminated when inappropriate (perseveration); distractibility; eventual burn-out of novelty system leading to negative symptoms and signs</td>
</tr>
<tr>
<td>Self-monitoring</td>
<td>A dissociation between the intention to perform an act and the actual performance of it</td>
<td>Actions not perceived as being performed by self, leading to strong feelings of alienation; this accounts for many of the positive symptoms and signs</td>
</tr>
<tr>
<td>Monitoring intentions of others</td>
<td>loss of awareness of intentions of others</td>
<td>Paranoid delusions, delusions of reference, inappropriate beliefs, 3rd person auditory hallucinations</td>
</tr>
</tbody>
</table>

Table 2.5: The three key disorders in schizophrenia according to Frith (1992).

A straightforward representation of facts about the world. For example, the proposition that 'trees are green' is a fact about the world, but the proposition that 'John believes trees are green' is a fact about a fact about the world i.e. a metarepresentation. Frith proposes that metarepresentations are relationships between the world and self, and as such help to define the self. Schizophrenia is inherently a failure of the relationship with self. Table 2.5 illustrates the symptom sets that may correlate with the 3 disorders described above. A link between metarepresentation and the role of the adaptive critic is suggested in chapter 9.

Another interesting point that Frith makes is that he needs to account for the similarity between some schizophrenic traits, such as attentional deficits and the set of negative symptoms and signs, and autism. It seems clear that one of the key features of autism is also a failure of metarepresentation, yet autism shares only a subset of the symptoms
and signs of schizophrenia. Frith’s answer to this dilemma is that people with autism have always had certain difficulties in cognitive processing, and so their model of the world, although distorted, has always been that way. In contrast, schizophrenia has an onset in late adolescence and early adulthood and prior to this time cognitive deficiencies are generally absent. Thus schizophrenics are used to a model of the world which makes sense. Frith suggests that the psychotic symptoms and signs which autistic people do not possess, are compensatory moves by the schizophrenic mind to try and make sense of their perceptions of the world which used to be coherent but are now disintegrated and alien. This relates to the idea of cognitive compensation discussed below.

Automatic and controlled processing

At the level of information processing, it is useful to consider the distinction between controlled processing and automatic processing. Controlled processing occurs where there is a need to actively control behaviour rather than rely on automatic learned responses. Situations where controlled processing is required are those in which there is no learnt response, for example when planning or problem-solving skills are needed or in novel situations. Controlled processing also comes into play when the automatic responses are incorrect or need to be over-ridden. It can be suggested that controlled processing requires the ability to hold information online for various purposes. For example the action of inhibiting automatic responses occurs through holding online an alternative response. Controlled processing is implicitly an attentional process and is highly dependent on frontal lobe function. In schizophrenia there is known to be a failure of selective attention, which can also be described as an inability to filter out irrelevant stimuli. The anterior cingulate region, which is effectively part of the PfCx, is implicated in selective attention (Liddle, 1992), and changes in the activity of this region are seen in schizophrenia. It has also been shown that DA agonists can modulate activity in the anterior cingulate of schizophrenics during a verbal fluency task (Dolan et al., 1995). One example of a cognitive task which requires selective attention is the Stroop Task, which will be discussed with respect to neural network modelling in chapter 4.
Automatic processing is essentially the use of learnt responses. One way in which responses may be learnt is through reward-based learning, essentially a form of operant conditioning. A computational analogy to this learning process is reinforcement learning, where behaviours are learned based solely on a feedback signal from the environment which indicates how successful a behaviour is in achieving a particular goal. I will investigate further in chapter 8 the possibility that a disruption to reinforcement learning in the NAcc can produce some of the symptoms and signs of schizophrenia.

This suggests that both automatic and controlled processing are altered in schizophrenia. As will become apparent in later parts of the thesis, the one factor that combines working memory function in the PfCx and reward-based learning in the NAcc is DA. The consequences of changes in DA levels in the PfCx and NAcc are investigated in chapters 5, 6, 7 and 8.

**Cognitive compensation**

Another suggestion accounting for the disruption of both controlled and automatic processing is that the primary deficit is a failure of automatic processing and as a compensatory move there is an overuse of controlled processing (van den Bosch, 1994). Van den Bosch uses excerpts from first-person accounts of schizophrenia which describe the fragmentation of consciousness and the failure of linguistic function very vividly. Although the account is short on mechanistic details one valuable idea is presented. That is the concept that the mental phenomena experienced in schizophrenia are a form of *cognitive compensation* for underlying information processing deficits. He suggests that a failure in schema-controlled automatic mechanisms leads to compensation by conscious processes to prevent a cognitive overload. When this happens, analytical and sequential procedures end up replacing holistic processes. A consequence of this is that subjective experience is intensified and the meaning of ‘trivialities’ is altered. The normal attribution of significance to the whole picture, or gestalt, cannot occur because the gestalt is itself fragmented. This leads to the disordered or unbound components of the gestalt being inappropriately focused upon. He says:
Hyperconscious relationship with the world provokes unjustified experiences of significance:

and he quotes:

"In such acute states the senses are extraordinarily intensely concentrated - not a normal concentration, which everybody is familiar with in intensive, responsible en[sic] dangerous work - but much more, I would say, 'beastly instinctive'. I discovered that I had a talent which until now has been dormant, a talent which enabled me to understand the real nature, the character of people immediately and much better" (Matussek, 1953).

"What I do want to explain, if I can, is the exaggerated state of awareness in which I lived before, during, and after my acute illness. At first it was as if parts of my brain 'awoke' which had been dormant, and I became interested in a wide assortment of people, events, places and ideas which normally would make no impression on me. Not knowing that I was ill, I made no attempt to understand what was happening, but I felt that there was some overwhelming significance in all this" (MacDonald, 1960)."

The quoted passages above give an idea of how delusional states are perceived and tie in with the formulation of cognitive fragmentation given above.

While the foregoing provides us with some insight into the genesis of schizophrenic symptoms and signs at a cognitive level, the underlying mechanisms behind this are not really touched on. The idea is raised and built upon in this thesis, that automatic processing fails as a consequence of a failure in reward-based learning, and reward-based learning can fail for many reasons, including: PfCx dysfunction, hippocampal
dysfunction and changes in DA transmission. In addition, these three modes of failure may well be inter-dependent.

Some cognitive accounts of schizophrenia have focused on the inability of schizophrenics to use stored regularities from past experiences to guide current behaviour; this is incorporated into the model of (Gray et al., 1991).

2.2.1 Performance of schizophrenics on neuropsychological tasks

The performance of schizophrenic patients on a variety of neuropsychological tasks which are known to correlate with specific brain lesions can give us information regarding brain regions which may be dysfunctional in schizophrenia. Prior to the introduction of accurate brain imaging techniques this process was the only means of assessing disturbance of specific brain regions. It still provides us with useful information by allowing us to compare cognitive abilities with brain regional activation on scanning, and also to compare cognitive abilities between patients with specific brain lesions and schizophrenia.

Kolb and Whishaw (1983) produced a very influential study which investigated the performance of schizophrenic patients on tasks specific to the PfCx, the temporal lobe, and the parietal lobe. They found decreased performance by schizophrenics on all of the temporal lobe tests and most of the frontal lobe tests, but normal performance on parietal lobe tests. Tasks on which schizophrenics perform poorly are those requiring planning, such as the Tower of London task (Owen, 1997) (see chapter 7) and the Wisconsin Card Sort Test; attentional tasks, e.g. Stroop; verbal fluency and design fluency tests; and tasks involving spatial working memory. These all utilise the frontal lobes. Verbal fluency probably taps temporal lobe function in addition. Spatial span and digit span tasks, which are also localised to the frontal lobes, are performed normally. Thus it is not a failure of frontal lobes per se which occurs in schizophrenia, but a failure of specific functions of the frontal lobes. Morice and Delahunty (1996) provide an updated version of Kolb and Whishaw’s original study. The form of failure on these tasks
was often similar to that of patients with frontal lobe syndrome (Levin et al., 1991), in particular they frequently exhibit perseveration and impulsiveness. The performance on certain of these tasks leads to an important paradigm in assessing PfCx function and a route for investigating the nature of frontal lobe involvement in schizophrenia. This is the concept of working memory

2.3 Working memory

The distinction between long-term and short-term memory has been with us for over 30 years. The original conception of short-term memory as simply a short-term store was revised in the 1970's to account for the fact that certain short-term memory functions, e.g. a reasoning task and a digit span task, could be carried out simultaneously with only mildly reduced performance rather than the catastrophic failure that was predicted. The new model introduced by Baddeley (1992, for a summary) was termed working memory and has a tripartite organisation. There is a central executive which has an attentional function and oversees the operation of the two slave systems: the visuospatial scratchpad and the phonological loop. The latter system is assumed to be responsible for maintaining speech-based information, including digits and digit-span, while the former system performs a similar function for visuospatial data. Working memory is particularly involved in situations where there are no learnt responses e.g. in language acquisition, planning, problem-solving and novel situations. This makes it an excellent example of controlled processing. A more parsimonious definition of working memory is that it is a form of memory which holds information online in the short-term and allows concurrent manipulation of that information. This definition places more emphasis on measuring properties of the central executive, but does not reveal much about the component processes. One experimental paradigm to come out of this is the delayed response task (DRT). The essential feature of these tasks is that a stimulus or cue is presented and then removed without a response being made. The response is requested at some short time after the stimulus has been removed. Clearly, a vital constituent in performing this task accurately is the ability to the hold
the stimulus information online until the response is requested. Goldman-Rakic has done extensive work in this area and has shown that the dorsolateral PfCx is the locus for holding information online during DRTs (Fuster, 1989; Goldman-Rakic, 1990, 1995).

2.3.1 The PfCx and working memory

Recent work has shown that the PfCx is implicated in working memory tasks (using the shorter definition of working memory), and it has been suggested that it is the seat of the central executive (Funahashi and Kubota, 1994, for example). Many brain imaging studies have shown increased blood flow in the PfCx during working memory tasks (Jonides et al., 1993; Raichle, 1993; Rezai et al., 1993; Cohen et al., 1997; Courtney et al., 1997). Changes in other brain regions also occurred but were dependent on the specific nature of the working memory task. However, the dorsolateral PfCx has been singled out as the locus of active maintenance during a continuous performance task (Barch et al., 1997). As discussed above, it is not clear exactly what an increase in blood flow in the PfCx indicates in terms of the underlying neural activity, and some workers have shown a reduction in PfCx activity during working memory tasks (Kimberg et al., 1998). This may be related to the involvement of DA in working memory, which is discussed in chapters 3 and 9.

It is interesting to note that the vast majority of working memory studies have used visuospatial tasks, whereas a large amount of the symptomatology of schizophrenia arises from linguistic dysfunction which relates to auditory processing. Most auditory processing does not require PfCx, but does utilise temporal lobe areas. There are, however, reciprocal connections between the PfCx and auditory association areas (see chapter 3), and auditory processing is inherently dependent on temporal sequencing and integration, functions which are classically performed by the PfCx. In a rare study examining auditory short-term memory in schizophrenics, Strous et al. (1995) have shown a severe impairment in schizophrenics in the ability to match two tones separated by 300msec, but not for tones with no delay. This result is not particularly
surprising, but it does indicate that brain regions other than the PfCx are involved in working memory and are dysfunctional in schizophrenia.

2.3.2 Working memory, the PfCx, and schizophrenia

From the work mentioned above and in earlier sections, the PfCx is implicated in working memory, schizophrenics perform more poorly on working memory tasks, and PfCx blood flow is reduced in schizophrenics while they perform working memory tasks (Park and Holzman, 1992). An intact DA innervation of PfCx is also required for proper PfCx function, as will be discussed in chapter 3. The final piece in the jigsaw relating PfCx, working memory, DA, and schizophrenia is that there is good evidence that in schizophrenia there is a reduction in PfCx dopamine activity (Dolan et al., 1995; Svensson et al., 1995; Okubo et al., 1997). Some workers have found, however, that although there seem to be changes in DLPfCx activity in people with schizophrenia, these do not necessarily correlate with reduced working memory performance (Fletcher et al., 1998; Rubinsztein et al., 1997). This follows from earlier work by McKenna (e.g. McKenna et al., 1994) which emphasises the deficits in semantic memory, rather than working memory, in people with schizophrenia. The issue of semantic memory and schizophrenia will be touched on in some more detail in chapter 3.

2.4 Summary

In this chapter I have looked at what schizophrenia is in terms of symptoms and signs, diagnosis and epidemiology, and where it comes from in terms of aetiology. I have also looked at the brain regions involve in schizophrenia through brain-imaging studies and some of the problems which arise in the interpretation of these studies. Following this I have discussed some of the theories relating to the cognitive dysfunction in schizophrenia and how this can give rise to specific symptoms and signs. The ideas of
failure of automatic processing, cognitive compensation and cognitive fragmentation are considered to be fundamental to understanding the origins of the various symptoms and signs. In terms of brain regions involved in schizophrenia, most evidence seems to point to the PfCx and the temporal lobes, including the hippocampus, being key structures. These regions interact both directly and, in the case of the PfCx via the ventral tegmental area (VTA), indirectly with the NAcc. Finally, working memory is discussed as a useful paradigm linking PfCx, DA and schizophrenia. The idea that schizophrenia can be understood as a disorder of reward-based learning in the NAcc is also introduced. One area of study which I have not mentioned and which is not addressed in this thesis is that of hemispheric functional asymmetry occurring in the brains of schizophrenics. This is discussed by Cutting (1994). Some more recent work points to changes in structural and functional asymmetry in certain brain regions of schizophrenics who suffer from auditory hallucinations (Rossell et al., 1999; Shapleske et al., 1997). The neurobiology, normal functions, and dysfunction of these brain regions are examined in the next chapter.
Chapter 3

Neurobiological issues

3.1 Introduction

The nature of the underlying physical deficit in schizophrenia, whether it is psychologically induced or occurs due to genetic and environmental influences, remains unknown. From many post-mortem and neuroimaging studies we do know that there are some changes in brain function and structure, however there is no consistent picture. There is no evidence that schizophrenia is a neurodegenerative disease and no evidence either that it arises from gross physical changes in just one brain structure or neurotransmitter pathway. In this chapter I will describe the normal structure and function of the PfCx, hippocampus and NAcc, and then describe why they are implicated in schizophrenia and how individual dysfunctions may combine to give an overall loss of integration in certain cognitive domains which gives rise to the symptoms of schizophrenia. In order to do this I will need to introduce some hypotheses regarding the normal function of these structures and the normal interactions between them. A key concept throughout the chapter is that the symptoms of schizophrenia can be divided into the three subsyndromes of Liddle et al. (1992). By this account the blend of symptoms seen in any one patient with schizophrenia results from the relative imbalance in processing between brain regions. From this, it is possible to
suggest that multiple different pathologies can lead to subsets of schizophrenic symptoms. Models in chapters 5 and 8 will illustrate potential cellular mechanisms which may be involved in PfCx and NAcc function and show how irregular interactions between the three brain regions may affect information processing.

3.1.1 The disconnection hypothesis

The idea that schizophrenia arises due to a dysfunctional integration between neuronal systems has been termed the disconnection hypothesis (Friston, 1996, 1998). It is worth discussing it in some detail here as some of the work in this thesis (chapter 8) serves to illustrate and expand upon this idea. The basic concept is that alterations in the process of synaptic modification (learning) will lead to a disruption of the reinforcement of adaptive behaviour, and this in turn will underly the disintegrative nature of schizophrenia.

The term disconnection refers to a functional disconnection rather than a physical disruption of neural tracts. Normal function depends on the appropriate interactions between brain regions, and these interactions crucially depend on the correct setting of synaptic strengths between these regions. It is postulated that in schizophrenia the neurotransmitters which modulate the synaptic strengths operate at altered levels and/or are released inappropriately. This leads to the incorrect setting of synaptic strengths and so to abnormal interactions between certain brain regions. Synapses which are more plastic (i.e. more modifiable) will be more at risk of disruption in this way. Thus behaviours relying heavily on high synaptic plasticity will be the most likely to be disrupted. The processes which are implicated are those which are expressed post-natally e.g. both short- and long-term learning and memory processes. An experimental model of this situation is operant conditioning, which can be modelled computationally using reinforcement learning. The models in chapter 8 illustrate the consequences of fluctuations in the level of DA on the learning of sequences of
patterns. The disconnection hypothesis is discussed further in chapter 9, where developmental theories such as the constructivist approach (Quartz and Sejnowski, 1997) are also brought to bear on the issue of aberrant connectivity.

3.1.2 The interneuron hypothesis

The other main theme in this thesis is that some alteration in numbers or dysfunction of interneurons in prefrontal and limbic-temporal areas can account for much of the pathology of schizophrenia. Bachneff (1991) provides an extensive review of PET and MRI scanning studies and concludes that slight atrophy of PfCx and temporal lobes seems to be the most consistent finding in schizophrenia. Since these brain regions have the highest levels of DA receptors then this also implicates DA in schizophrenia. Bachneff believes that changes in DA-GABA interactions are the key to generating schizophrenic symptomatology. In particular, a loss of GABAergic damping by interneurons on DA post-synaptic sites could effectively lead to excessive DA action. GABA interneurons are more at risk from developmental damage, he says, because the shape and connectivity of interneurons "may be much less constrained genetically and much more modifiable...by their cellular and biochemical environment" (pg 875). The result of reduced GABA activity may be an undamped DA system which could interact with environmental stress, which is likely to be increased during adolescence and which increases DA release, to cause hyperdopaminergic states. These states would cause the positive symptoms of schizophrenia through various, loosely specified, means. The negative symptoms would arise through chronic neuroleptic usage which may induce depolarisation block in VTA DA neurons. Bachneff admits that his hypothesis is speculative, and more recent work suggests that the details of the mechanism he proposes are incorrect. For example, DA increases GABA levels in the PfCx (Grobin and Deutch, 1998) but there is no evidence that GABA presynaptically modulates DA release. Nonetheless, the hypothesis that changes to interneuron function underlies the pathogenesis of schizophrenia remains intriguing, and in this
chapter and chapter 5 I will show mechanisms for how disruption to interneuron function in the hippocampus and the PfCx could generate dysfunction in those structures which could lead to schizophrenia.

3.2 The Nucleus Accumbens

The first brain structure I will discuss is the Nucleus Accumbens (NAcc).

3.2.1 Neuroanatomy

The NAcc is not homogeneous and is divided into two regions: the core and the shell. The NAcc (and certain parts of the olfactory tubercle, caudate and putamen) is referred to as the ventral striatum (Nolte, 1998), which is morphologically similar to the dorsal striatum, itself composed of the caudate and putamen (CPu). The dorsal and ventral striata are part of a larger collection of nuclei known as the basal ganglia (Kandel et al., 1991). The basal ganglia comprise globus pallidus (internal and external segments), the subthalamic nucleus, the substantia nigra, and the neostriatum. The neostriatum and dorsal striatum are standardly considered to be synonymous, although there seems some confusion over whether the NAcc should also be included in the neostriatum. Figure 3.1 illustrates the basic circuit that connects these structures.

The NAcc forms circuits analogously with the other components of the striatum, but involving different structures. Thus the NAcc projects to the ventral pallidum as opposed to the globus pallidus. Some of these circuits are illustrated further (Figure 3.2), but it is instructive to consider the general functioning of the basal ganglia before specific discussion of the NAcc.
The basal ganglia in general

The basal ganglia are generally thought to be involved in the coordination of motor activity, although more recently it has been suggested that they play a role in cognition. The connections between the various components of the basal ganglia, and between the basal ganglia and certain other brain structures form a set of parallel...
Neurobiological issues

It has become apparent that these loops constitute functionally distinct circuits (Alexander and Crutcher, 1990). Thus there are thought to be two prefrontal circuits, a limbic circuit (involving anterior cingulate), a motor circuit and an oculomotor circuit. The basic mode of operation of any particular circuit is as follows: cortical structures project to the striatum, which is seen as the input stage of the basal ganglia. The output stage of the basal ganglia (globus pallidus internal segment (GPI), substantia nigra pars reticulata (SNr), and ventral pallidum (VP)) exert tonic GABAergic inhibition on the relevant thalamic nuclei. This output is modulated by two opposing but parallel pathways from the striatum to the output nuclei. One pathway is the direct path, which goes straight from the striatum to GPI and SNr and is inhibitory. This has the effect of disinhibiting the thalamic nuclei and so allowing activity in reciprocal thalamocortical loops which leads to action. The other pathway is the indirect pathway which goes from striatum to GPe, then to the subthalamic nucleus (STN), and then to GPI and SNr. This path is inhibitory-inhibitory-excitatory, and so has the net effect of exciting the GPI and SNr cells, which inhibit the thalamic nuclei and preclude action. Thus cortically selected actions can be reinforced by the direct pathway, with the indirect pathway applying some sort of inhibitory braking or smoothing to the selected action if the two pathways project to the same GPI and SNr neurons (Alexander and Crutcher, 1990). Another possibility is that the indirect pathway may project to different neurons in the GPI and SNr, and co-activation of the two pathways has the effect of reinforcing one action and inhibiting other different, and possibly competing actions. Thus the indirect path may serve to focus neural activity. The role of DA in this process is unclear, but one theory is that it facilitates the direct path via D_1 receptors and inhibits the indirect path via D_2 receptors (Strange, 1993). In the braking theory this would have the effect of enhancing the selected action through both pathways. In the focusing theory the effects of DA would be contradictory in that facilitating the direct path enhances the selected action, but inhibiting the indirect path effectively disinhibits the competing unselected actions. This latter scenario may have the effect of promoting competition between different possible actions, and may be a means of switching between actions. It has been suggested that one of the roles of DA in the NAcc is to allow switching between neural ensembles (Pennartz et al., 1994), and this
Neurobiological issues

Figure 3.2: Connectivity of the NAcc core and shell regions. Green (lighter) connections are excitatory and red (darker) connections are inhibitory. Blue (dashed) connections are dopaminergic. Thalamic nuclei: pv = paraventricular nucleus; im = intermediodorsal midline nucleus; cmi = central medial intralaminar nucleus; MD = mediodorsal nucleus. vmVP = ventromedial ventral pallidum; dlVP = dorsolateral ventral pallidum; STN = subthalamic nucleus; mSNr = medial substantia nigra pars reticulata; (m)VTA = (medial) ventral tegmental area.

will be discussed below and investigated further in chapter 6. DA is also implicated in “the initiation and sequencing of conditioned or learned motor acts” (Amalric and Koob, 1993, pg. 214). This role as a sequencer will also be investigated further in chapter 8.

The circuits involving the NAcc specifically have been worked out more recently (see Deutch (1993), Montaron et al. (1996) and Maurice et al. (1998) for some details and further references), and are illustrated in Figure 3.2.

In a similar fashion to the dorsal striatum, the NAcc is composed of three main cell-
types. Medium spiny neurons are the most prevalent. These are GABAergic and are the source of the NAcc efferent projections. The other two cell-types are large aspiny interneurons, which release ACh, and GABAergic interneurons. Both types of interneuron are inhibitory. There are extensive axon collaterals from the medium spiny and GABA interneuron which may be important in the formation of functionally distinct ensembles, to be discussed below. As well as different afferent and efferent connections, the core and shell regions have a different morphology. The shell medium spiny neurons have fewer dendrites, with fewer branches and fewer spines. The core projection neurons have 50% more surface area for synaptic contacts (Meredith et al., 1993). It is thought that the shell regions is more involved with autonomic and visceral type functions, whereas the more heterogeneous core region may be involved in complex association and motor functions.

The excitatory inputs to the NAcc act via Glu on both NMDA and AMPA/kainate receptors. The former have slow excitatory actions but are also implicated in learning via LTP. The latter receptor types have fast excitatory effects. All other neurotransmitters (ACh, DA, GABA) seem to have a net inhibitory effect on the medium spiny neurons (Calabresi et al., 1993). This makes sense in view of the fact that excessive levels of Glu can cause excitotoxic damage, making it important to keep Glu levels down. However the action of DA is not as straightforward as this since the D1 and D2 receptor types have different modes of action.

A final word on the general functioning of the basal ganglia. It has been proposed that the family of circuits described above have the common role of modulating frontal lobe behaviour in a parallel fashion. Reinforcement and switching of behavioural sets may occur through prefrontal and limbic circuits, and planning and execution of limb and eye movements may act via motor and oculomotor circuits. With this general conception of basal ganglia function in mind, it will now be possible to discuss the function of the NAcc in more detail.
3.2.2 Theories of function

Locomotion

From rat studies, the NAcc is known to be involved in the initiation of locomotor action (Amalric and Koob, 1993). This effect is strongly linked to the function of DA in the NAcc. Both direct applications of DA, such as injecting DA and DA agonists into the NAcc and local application of D-amphetamine (which directly causes release of DA from presynaptic terminals) in the NAcc; and indirect applications of DA, such as stimulating the VTA (the site of origin of the NAcc DA innervation), disinhibiting the VTA with GABA antagonists, dosing with systemic D-amphetamine, and stress, cause an increase in varied patterns of locomotor and exploratory behaviour in the rat. High doses of amphetamine and high levels of stress cause repetition of invariant sequences, that is, stereotyped behaviour. In addition, loss of DA through 6-OHDA (a terminal neurotoxin) lesions causes reduced locomotion, distraction, switching, spontaneous alternation, disturbed acquisition of spatial habits and difficulty in reversing learned habits (Amalric and Koob, 1993). The mechanism by which DA induces locomotion is thought to involve the core region more than the shell (Deutch, 1993). If “the primary effect of DA is to inhibit the firing of accumbal neurons” (Meredith et al., 1993, pg. 14), then increased DA acting on the indirect path will disinhibit the thalamic projection neurons and allow cortical motor activation. This is supported by the fact that increasing the level of GABA in the VP (effectively increasing NAcc output) reduces DA-induced locomotion. This also supports the idea that the NAcc core is more involved in motor type functions. It appears then that the NAcc core is aligned functionally with the dorsal striatum and the NAcc shell is related to limbic/motivational processes. What is not clear from this, however, is what an increase in locomotion in the rat means in cognitive and human terms.

It is hard to reconcile the fact that NAcc medium spiny neurons have little spontaneous activity with the paradoxical facts that: 1. excitation of spiny neurons generally increases locomotion; 2. DA has an overall inhibitory effect on spiny neurons; and
3. increases in intra-accumbal DA increase locomotion. The application of Glu in the NAcc, however, is neither necessary nor sufficient to induce locomotion (Dalia et al., 1998). Also, the ultimate projection sites from the VP are not necessarily motor cortex, but more like PfCx. Thus it is difficult to see exactly how the NAcc initiates motor behaviour. If we assume that the VP projections do project to motor cortex via the appropriate thalamic neurons, and we assume that DA has different effects on the direct and indirect paths as in the dorsal striatum, then it is possible to see how DA can initiate motor action. Essentially this is by disinhibiting the tonically active VP neurons. A clearer way to view this is by looking at the circuit described in (Gray et al., 1991) and illustrated in Figure 3.3. The dual actions of DA can be demonstrated quite nicely. If there is no activity in loop I then a pulse of DA in the NAcc (triggered by an external agent) will cause inhibition of the tonically active VP and allow reverberatory activity to commence in loop I. The switching action of DA can also be envisaged: if loop I is active, then loop II will also be active, allowing activity to continue by keeping the VP inhibited. A pulse of DA in this situation will switch off loop II, causing the tonic activity in VP to re-assert itself and inhibit activity in loop I. This will allow alternative excitatory patterns to be selected. The action of DA here can be likened to dipping the clutch in a car in order to select a different gear, or different excitatory patterns in this context.

The meaning of the locomotor activity in a rodent caused by increasing DA in the NAcc is not clear (Robbins and Everitt, 1996). A ‘normal’ increase in DA may be seen as appetitive behaviour and represents approach responses and exploration in anticipation of a reinforcer of reward. This is in distinction to consummatory behaviour such as eating and sexual mounting which occur in the presence of the reinforcer (Robbins and Everitt, 1996). However ‘abnormal’ increases in DA in NAcc by amphetamine, for example, cause locomotor hyperactivity which does not fit a particular behavioural pattern. From Figure 3.3 we can see that sustained increases in DA can lead to permanent disinhibition of the VP and so to locomotion. In the next section the mechanisms underlying these behaviours and their reliance on the NAcc and DA will be discussed.
Pennartz et al.

Pennartz et al. (1994) have provided a very thorough analysis of the physiological, neuroanatomical and behavioural data regarding the NAcc, and have proposed a new theory regarding NAcc function. This theory will be utilised in some of the modelling work in chapters 6 and 8. They conclude that the two possible theories of NAcc function, namely that strong firing in NAcc neurons projecting to VP causes inhibition of locomotion or facilitation of locomotion, are inadequate to describe all the facts. In particular, the following facts do not fit in:

1. hippocampal afferents and amygdalar afferents both cause the same response in medium spiny neurons (a fast EPSP-IPSP sequence), but amygdalar input reduces locomotion while hippocampal input facilitates it.
2. The effect of DA is not always to stimulate or inhibit locomotion, but depends on the presence of hippocampal and other inputs.

3. Destruction of NAcc projection neurons does not lead to decreased locomotion.

4. Injection of GABA agonists into NAcc have equivocal effects. At low doses they stimulate locomotion and high doses they inhibit it.

From this they propose that (pg 726):

"behaviourally meaningful information in the nucleus accumbens is represented by fine-grained spatiotemporal firing patterns in spiny projection neurons"

They suggest that the NAcc is composed of distinct associative networks (ensembles) of spiny neurons which can encode different patterns. These patterns would represent learned actions, and a particular pattern is selected depending upon the configuration of inputs. Inputs come from hippocampus, PfCx and amygdala. Thus the NAcc acts to integrate these different inputs and produce, in parallel, a set of appropriate output actions. The way in which appropriate actions are learned is thought to be via reward-based reinforcement (see below). There are at least five different compartments in the NAcc, based on afferent/efferent and neurochemical similarities, which are suggested to be the basis for the ensembles. I will mention briefly the salient circuitry which is proposed to underly these ensembles.

Recurrent axon collaterals have been postulated (Groves, 1983) to be highly relevant to striatal function. Pennartz et al. (1994) cite evidence for short-range and long-range collaterals and suggest that these form the basis for short-range and long-range lateral inhibition. Short-range lateral inhibition is limited to the neurochemical compartment in which the particular ensemble resides and is hypothesised to have a focussing and
synchronising effect on the extra-accumbal inputs. Long-range lateral inhibition is postulated to provide competitive interaction between ensembles. Another form of inhibition is feed-forward inhibition, which may be provided by GABA interneurons (Kita, 1993). Feed-forward inhibition is thought to enhance the effects of short-range lateral inhibition, and may also help to remove temporal irregularities in the excitatory inputs. Figure 6.2 illustrates the connectivity within an ensemble. There is contradictory evidence for a functional inhibitory action by the collaterals (Jaeger and Wilson, 1994) in the dorsal striatum. However, Kötter and Wickens (1998) have suggested that this functional inhibition does occur, but not in in vitro conditions, rather in a high DA environment. This would imply that DA is necessary for the integrity of patterns triggered by excitatory inputs to the striatum/NAcc.

Glu inputs provide excitation of all NAcc cell-types and GABA actions are described above. This leaves DA as the other major neurotransmitter in the NAcc to be discussed. In general, DA seems to have an arousing or amplifying function on behaviour, and it is also involved in switching between behaviours. There is no direct evidence for DA to be involved in modulating lateral inhibition. DA, acting on D₁ receptors, appears to attenuate both EPSP's and IPSP's (Pennartz et al., 1992), which would give it an inhibitory action on spiny neurons, but also an indirect disinhibitory action by inhibiting feed-forward GABA interneurons. Pennartz et al. (1994) suggest that whether DA is inhibitory or disinhibitory to NAcc projection neurons depends on the balance of inhibitory and excitatory loads on the network. In chapter 6 I will investigate this issue further and show that the overall effect of DA appears to be inhibition, but only in the presence of excitatory input.

We can speculate further on the core-shell distinction. As mentioned above, the core appears to be more aligned with motor-type functions and the shell seems to be more aligned with emotional and motivational functions by dint of its hippocampal, entorhinal, and amygdalar afferents, and its hypothalamic and extended amygdalar (amongst others) efferents. If the ensembles envisaged by Pennartz et al. (1994) incorporate cells from both shell and core, then the patterns which can be selected for by
excitatory afferents will have both motor and limbic components. Thus there is integration of the two modalities. This supports the idea that the NAcc is involved in the integration of actions and motivational states in goal-driven reward-based situations. I will now discuss the NAcc's role in reward-based learning.

3.2.3 The role of the NAcc in reward-based learning

The other important, and possibly related, function of the NAcc is its role in reward-based learning. DA appears to play a key part in this process (Schultz, 1997). Reward-based or goal-based learning are types of learning which aim to modify behaviour in order to achieve a particular goal given a particular situation. This form of learning links input states (the situation) and motivational states, with desirable outcomes (the goal), via a sequence of actions or behavioural steps. As mentioned above, there is good evidence that the NAcc would be involved in such processes since it links brain regions associated with motivational and emotional states (e.g. amygdala and hypothalamus), with motor processes (e.g. thalamic projections to cortex).

The two main types of learning that can be examined in the rat are classical (or Pavlovian) conditioning and instrumental (or operant) conditioning. Both of these types of conditioning can affect appetitive behaviour. In classical conditioning, an unconditioned stimulus (UCS) such as food elicits a response (e.g. salivation). If the UCS is presented frequently with a conditioned stimulus (CS), such as a bell, then the presentation of the CS on its own will initiate the response. However, if the motivational state of the animal is taken into account we find that presenting the CS to a hungry animal can induce increases in appetitive behaviour. Instrumental conditioning is slightly more complex but it essentially entails learning to associate different voluntary actions with a reinforcing outcome, such as pulling the correct lever to obtain food. In this case behaviour is modified by past experience as well as motivational state.
DA in the NAcc

In their review, Robbins and Everitt (1996) cite evidence that the NAcc is a positively reinforcing site in the brain. From this spring the ideas that naturally occurring reinforcers of reward alter behaviour through increasing DA release in the NAcc, and that certain DA-release inducing drugs such as amphetamine and cocaine mimic natural reinforcers and can directly affect behaviour through the NAcc, forming a vicious circle of acquisition and use i.e. addiction.

The consequence of mesolimbic DA neurons firing has been investigated extensively by Schultz and colleagues (Schultz et al., 1993; Schultz, 1997). They have found that the DA neurons fire in response to stimuli which are either predictive of reward, or unexpected rewards themselves. Once a reward, or reinforcer, becomes predictable it no longer causes firing of DA cells. The cells can be activated by stimuli from different modalities, including food and liquid rewards, and auditory and visual reinforcers of appetitive reward. Inputs to the DA neurons in the VTA come from many sources but according to Schultz (1997) the three most likely to give rise to the activating (and depressing) responses are those from the pedunculopontine nucleus (ACh and Glu), the striatum (GABAergic in nature) and the STN (Glu). The fact that DA neurons only fire in response to unpredicted stimuli means that once learning of the implications of a particular reinforcer is complete the DA neurons will stop firing. It has been suggested that this gives DA the property of being an error signal in a reinforcement learning system (Montague et al., 1996), signifying in a scalar fashion the degree of improbability that a particular stimulus leads to reward and indicating how much learning is required before a reward is predictable.

Kelley et al. (1997) have shown that NMDA receptors in the NAcc core are significantly more important than those in the shell region for learning an appetitive response. In addition, there is some evidence that D1 receptors modulate the effects of reinforcement. Wickens et al. (1996) have shown that phasically applied DA can facilitate LTP of cortical inputs to the NAcc. This is compatible with a three-factor Hebbian
learning rule which requires activation of presynaptic excitatory input (from cortex or hippocampus), postsynaptic NAcc cells, and a DA input all occurring within a brief time window and all at the same dendritic spine. The original formulation of Hebb's learning rule (Hebb, 1949) required only two factors, co-activation of pre- and postsynaptic neurons, for the synaptic strength to be increased. The three-factor formulation requires, in addition to these two factors, a third factor which arises following reward, and it has been suggested that DA mediates this reward. The details of such a mechanism are explored by Wickens and Kötter (1995), who focus on D₁ dopaminergic actions. So far I have only mentioned reinforcement of rewarding or pleasurable stimuli, but there is likely to be a similar but opposite response to aversive stimuli. It has been found (Mirenowicz and Schultz, 1996) that the mesolimbic DA neurons fire mostly in response to positively rewarding stimuli, however. In relation to this (Arbuthnott and Wickens, 1996) have suggested that tonic DA in the neostriatum may induce LTD and cause extinction of unrewarded behaviour.

3.2.4 Possible role of the NAcc in schizophrenia

A crucial implication for NAcc being involved in schizophrenia is that there is evidence that it is the locus of action for neuroleptic drugs. However, it is not clear that this is the only site of action of neuroleptics, nor is their mode of action fully understood. This will be touched on again in chapter 9.

Gray et al. (1991) have suggested a complex theoretical model for the origins of schizophrenic symptoms. They speculate with their model that the fundamental lesion in schizophrenia may lie in the link between the subiculum and the NAcc. This link is purported to mediate the application of previous experience (from the septo-hippocampal system) to the selection of new environmental stimuli to attend to. They also focus on latent inhibition (LI) as a potential model for selective attention. Latent inhibition is the phenomenon whereby pre-exposure to a conditioning stimulus in the absence of any reinforcer actually impairs the subsequent learning of association between the same conditioning stimulus and a reinforcer. This suggests that
pre-exposure to the conditioning stimulus makes it predictable and therefore does not require attention. Several interesting features regarding LI are noted (Gray et al., 1997, for summary):

- Firstly, it is reduced with the administration of DA agonists to normal subjects during the conditioning phase.

- Secondly, it is enhanced by damage to DA terminals in the NAcc and by the administration of neuroleptics at the time of conditioning.

- Thirdly, it is generally dependent on intact input from the hippocampus.

If the NAcc is the site of reward-based learning, can the facts pertaining to LI be accommodated into this conception of NAcc function? LI uses a much simpler learning paradigm than is represented by reinforcement learning, so intuitively it seems likely that the latter can subsume the former. If the pre-exposed stimulus comes to be associated with no reward then subsequent exposure to it will not initially trigger firing of VTA DA cells. That is, the adaptive critic (described in chapter 8) has learnt that the pre-exposed stimulus does not lead to reward. Subsequent pairing with a reinforcer means that the adaptive critic has to re-learn the implications of the pre-exposed stimulus. Initially DA release will be low, but as the critic’s predictions continue to be erroneous the level of DA (acting as an error signal) will increase. Gradually the new association will be learnt and DA release will subside. It seems quite clear that applying exogenous DA at the time of conditioning will reduce the time taken for DA levels to build up, and thus remove the inhibition effect. Similarly, DA antagonists and loss of DA neurons would slow the time taken for DA levels to rise in the NAcc and thus increase the degree of LI. It is less clear what role the hippocampal input plays, although it can be suggested that if the hippocampus relays contextual information to the NAcc (see below) then the absence of context may make it easier to make simple
associations where there is little need for disambiguation. Thus it seems that LI can be explained in terms of temporal and DA manipulations within the reinforcement learning paradigm. The modelling in chapter 8 does not address this issue but for future work this would be an interesting topic to study. In relation to schizophrenia, patients with acute, but not chronic, schizophrenia are found to be impaired on tasks involving latent inhibition. Most scanning studies indicate cortical regions, such as the anterior cingulate mentioned above, are the loci for selective attention. Also, there is evidence that lesioning PfCx does not impair LI. This makes the analogy between LI and selective attention doubtful.

A Hypothesis: the consequences of the failure of reinforcement learning in the NAcc

A pathological situation can be imagined: if the DA neurons fire inappropriately then associations between a stimulus and reward will be made inappropriately. Thus stimuli which do not predict reward may acquire reinforcer status, while genuine predictors of reward may not become reinforcing. There would be three immediate consequences of this:

1. the animal would respond inappropriately much of the time, often initiating reward-seeking behaviours when there is no chance of a reward, and also failing to claim rewards which are imminent.

2. most rewards would remain unpredictable, thus keeping the DA neurons in a much higher state of firing than they would normally be.

3. under normal learning conditions, chains of reinforcement could be learnt. Only the first stimulus in the chain would trigger firing of the DA neurons. In the abnormal situation such reinforcement sequences would never properly form.
Such a disturbance in the acquisition of an appropriate reinforcement landscape may underly some of the symptoms of schizophrenia, and is one of the main concepts in the disconnection hypothesis. In effect it is a more physiologically specific version of the ideas presented in the ‘Abnormal modulation in schizophrenia’ section in Friston (1998). A model in chapter 8 investigates some of the consequences of a disturbance in reward-based learning, and this is related back to the disconnection hypothesis in chapter 9. The reliance on hippocampal input via the subiculum to the NAcc to provide context information, as suggested by Gray et al. (1991), will be utilised to extend the above hypothesis on the NAcc involvement in schizophrenia.

3.3 The hippocampus

Since the hippocampus is implicated in schizophrenia and also has strong functional connections with the NAcc and PfCx it is necessary to discuss some aspects of it. The basic configuration of the hippocampal formation and the intimately related structures the subiculum, entorhinal cortex and dentate gyrus are illustrated in Figure 3.4. A useful review of normal anatomy and physiology is given in Knowles (1992).

While the structure of the hippocampus has been studied for many decades and is relatively well delineated, there is still no consensus regarding its function, or the neurophysiology that might be involved. There are two main theories regarding the function of the hippocampus. One is that it is involved in the consolidation of declarative memories. This branch of investigation stems from original findings that lesions to the hippocampal formation can cause anterograde and retrograde amnesia. The other theory is that it is involved in spatial navigation and learning. These two theories are not entirely incompatible if we consider that most of the navigational research has been done in rats, and rats have a very large hippocampus relative to the size of the neocortex. It is quite conceivable that navigational issues, such as learning optimal routes to food, constitute a much larger part of a rat’s cognitive landscape than a human’s. This being the case it can be argued that the hippocampus is involved more
Figure 3.4: Basic circuitry of the hippocampus and associated structures. The output projections include afferents to the NAcc and the PfCx. Inputs to the entorhinal cortex include afferents from the orbitofrontal cortex. SUB = subiculum; Dent Gyrus = dentate gyrus; Ento Ctx = entorhinal cortex; DLPFC = dorsolateral prefrontal cortex

generally in 'map-making'. In the rat this involves learning to recognise geographical and navigation-related cues; in the human this involves learning to recognise cues in a wide variety of cognitive domains which relate to a particular goal. These cues could be stored as memories. This depends crucially on the hippocampal pyramidal cells being able to code for both spatial and non-spatial information, and there is some evidence for this (see Redish and Touretzky (1997)). In this vein these authors have suggested that rodents represent their position within reference frames that are goal or task dependent. These reference frames are then linked with appropriate actions aimed at achieving a goal, and with current motivational/emotional states, by
the NAcc. An alternative name for reference frames might be contexts. I will assume that the function of the hippocampus is to provide contextual information, as part of its memory retrieval activities, which can be used by other brain structures for various cognitive tasks.

3.3.1 The hippocampus in schizophrenia

The hippocampus has been shown to be involved in schizophrenia from several different perspectives. Overactivity of the hippocampal region has been demonstrated during acute psychosis using scanning studies (Busatto et al., 1995; Heckers et al., 1998) and linked with all three symptom subsyndromes (Friston et al., 1992). Also it has been linked more specifically with the generation of auditory hallucinations (Silbersweig et al., 1995). Other studies have shown reduced hippocampal volume is a correlate for schizophrenia (Bachneff, 1991, for review).

As well as auditory hallucination, there is another specific auditory deficit in schizophrenia, which appears to be hereditary. This is a loss of inhibition of auditory response. In the normal brain it is possible to observe a reduction in the amplitude of the response (measured as an evoked potential) to the second of a pair of auditory stimuli presented 500ms apart (Freedman et al., 1987). Thus there is an inhibition of the auditory response, with the ratio of second response to first response being approximately 0.4 or less. This response attenuation has been suggested to underly a general process of sensory gating to prevent 'information overload', and a defect in this process occurs in schizophrenia. To tie this in to the hippocampus, it has been shown that certain strains of inbred mice have this sensory gating deficit and it is correlated with reduced numbers of α7 nicotinic receptor subtypes in the hippocampus (Stevens et al., 1998). In addition, Freedman et al. (1997) have shown linkage of a defect on chromosome 15 at the site of the α7 nicotinic receptor to the sensory inhibition deficit in certain familial cases of schizophrenia. Thus a reduction in the action of the α7-nicotinic receptor subtype in the hippocampus may be involved in the genesis of auditory-based symptoms in schizophrenia, such as hallucinations.
Neurobiological issues

Work by Barkai and Hasselmo (Barkai and Hasselmo, 1994; Barkai et al., 1994) may shed some light on the precise mechanisms at play here. They have modelled the effects of ACh on rat piriform (olfactory) cortex acting as an associative memory. This has subsequently been extended to the hippocampus (Hasselmo et al., 1995). A problem in storing multiple patterns which have even a small degree of overlap in a recurrent associative memory is that the recurrent connections become activated by any similarities between the pattern to be stored and patterns already stored in the network. Thus a pattern being input (i.e. learnt) can trigger activation of stored patterns which can then activate yet other patterns (through recurrency) until, in a worst case scenario, all the cells in the network are activated. If Hebbian learning is taking place during this process, then two things will happen: 1. memories will not be stored effectively; and 2. synapses will become over-stimulated. This last process has been termed runaway synaptic modification (Barkai et al., 1994). However, if the recurrent connections are inhibited during learning then there is no triggering of pre-existing memories and learning can proceed smoothly. Crucially, it has been shown (Hasselmo and Bower, 1992) that ACh increases transmission at the excitatory input synapses but impairs transmission at the excitatory recurrent (intrinsic) synapses. Associative memory function is improved massively by inhibiting the recurrent connections during learning, i.e. high ACh levels, and allowing normal synaptic transmission during recall. It can be hypothesised that pathologically reduced ACh action at the recurrent synapses during learning can induce schizophrenic-type deficits in hippocampal function. Reduced function of α7-nicotinic receptors could potentially lead to the impairments in laying down of declarative memories, and there is some evidence for disruption of memory function in schizophrenics (Heckers et al., 1998). However, it is not clear how such a memory impairment would form part of the genesis of the symptoms of schizophrenia. Clearly there is intrusion of stored memories into memory patterns to be laid down, but whether this underlies delusional thinking or is purely a dysfunction of memory processes remains unknown. Another problem with suggesting reduced inhibition of synaptic transmission at the recurrent synapses is instrumental in the genesis of the positive symptoms of schizophrenia is that the majority of hippocampal α-bungarotoxin-sensitive receptors (which contain the α7 nicotinic subunit)
Neurobiological issues

are found on interneurons.

Adler et al. (1998) have expanded upon the effects of nicotine on sensory gating and have developed a more general theory regarding schizophrenia. My suggestion for the nature of the dysfunction in the hippocampus is presented in the following section.

**Hippocampal inhibitory interneurons in schizophrenia**

Inhibitory interneurons are included in Barkai et al. (1994)'s model of piriform cortex. Interestingly, these neurons are necessary to provide the correct timing between excitatory cycles of the network during recall. Without the inhibition overlapping patterns will begin to activate one another and exponential growth in excitatory activity (runaway synaptic modification) in the network would result, leading to an epileptic seizure type of activity. If we assume that the interneurons rely on activity at nicotinic receptors to perform their inhibitory role optimally, then reduction in \( \alpha_7 \) subtype numbers may reduce inhibition to the point where the recall of memory patterns causes a slow intrusion of overlapping patterns without inducing the extreme overactivity seen in epilepsy. This seems a more likely candidate for the mechanism underlying the pathogenesis of some of the positive symptoms of schizophrenia. We would expect to see impairments of recall with insertion of extraneous material into recalled items while learning remains largely intact. The uncontrolled intrusion of memory fragments into consciousness could possibly underly the symptoms of the reality distortion subsyndrome. In addition, the ability of the hippocampus to provide contextual information would be impaired, potentially leading to derangements of reward-based learning in the NAcc and the sequelae described above. In physical terms, the ultimate effect of reduced ACh action on the interneurons could be chronically reduced inhibition leading to overactivity and excitotoxic damage to hippocampal pyramidal cells. This in turn may be the mechanism underlying the loss of hippocampal volume observed in schizophrenia. In addition, this explanation may help explain the links which are seen between epilepsy and schizophrenia which are (Sachdev, 1998).
The inclusion of interneurons in the simulation, necessary because of the biophysical nature of the model, also precludes the network behaving as an attractor with longer-term settling dynamics. A discussion of the use of attractor neural networks in modelling schizophrenia can be found in chapter 4.

3.4 Dopamine

Dopamine has long been implicated in the pathogenesis of schizophrenia and will be discussed in this section. Details of the pharmacology and control of DA release are covered in chapter 6.

3.4.1 Some basic pharmacology

DA is a member of the catecholamine class of neurotransmitter and is closely related to norepinephrine and epinephrine. The synthetic pathway through which DA is generated is as follows:

\[
\text{Tyrosine} \rightarrow L - \text{DOPA} \rightarrow \text{Dopamine} \rightarrow \text{Norepinephrine} \rightarrow \text{Epinephrine}
\]

DA is found widely throughout the CNS and the cell bodies of the DA neurons are located in the midbrain. The two main sources are the VTA, with major projections to the PfCx (mesocortical projection) and NAcc (mesolimbic projection), and the substantia nigra pars compacta (SNpc) which projects mainly to the striatum. The latter projection is implicated in Parkinson's Disease, in which there is massive loss of DA cells. The other projections are thought to be involved in schizophrenia as will be described in subsequent sections.
Although DA has been known as a neurotransmitter for decades now, its precise actions in the CNS are still not fully understood. It is generally considered to be a neuromodulator of pre-existing synaptic activity. The synapses it forms are symmetric in nature which implies it has an inhibitory action, however the picture is not as straightforward as that. For instance, there are two main types of DA receptor: D₁ and D₂. There are, in fact, known to be at least five DA receptors but they all fall into the two basic categories (D₃ and D₄ receptors are functionally similar to D₂, and D₅ receptors are similar to D₁). Table 3.1 summarises some of the properties of the D₁ and D₂ receptors (Jaber et al., 1996).

D₁ receptors are much more prevalent than D₂ receptors. It has been suggested that D₁ receptors facilitate activity and D₂ receptors attenuate activity in the basal ganglia (Strange, 1993), although others have found D₁ receptors to attenuate activity in NAcc (Pennartz et al., 1992).

A more recent suggestion regarding the neuromodulatory function of catecholamines is that they improve the signal-to-noise ratio in synaptic transmission (Servan-Schreiber et al., 1990). It is not clear whether this function applies to all catecholamines, for example there is some evidence suggesting it applies only to norepinephrine and not DA (Woodward et al., 1979). It is possible that norepinephrine increases the signal-to-noise ratio while DA decreases it. Alternatively, D₁ receptors may enhance and D₂...
receptors attenuate the signal-to-noise ratio. In chapter 4 I will discuss models which use this conception of DA function. The role of DA in the NAcc and reward-based learning have already been covered.

3.4.2 Dopamine in the prefrontal cortex

It has been shown that stimulation of DA cells in the VTA causes a reduction in the firing of PfCx pyramidal neurons. (Thierry et al., 1990; Gulledge and Jaffe, 1998) and that this occurs via D₂ receptors. This action could well be via GABA interneurons (Pirot et al., 1992), although there is also evidence that there is a direct reduction in excitability (Gulledge and Jaffe, 1998). The inhibitory effect reduces both spontaneous and evoked firing. Conversely, Yang and Seamans (1996) have shown that activation of D₁ receptors, which are 10 times more prevalent than D₂ receptors in the PfCx, have an excitatory effect on evoked firing of rat pyramidal neurons. In addition, D₁ receptors have been implicated in the working memory functions that the PfCx subserves (Williams and Goldman-Rakic, 1995). In chapter 6 I will show how it is possible to reconcile these facts using computer simulations. Essentially, I will show that DA induces reciprocal activity in the pyramidal cells and GABA interneurons, which has been shown to occur by (Wilson et al., 1994). The PfCx has a significant input to the VTA and can control burst firing of DA neurons located there in experimental situations (Murase et al., 1993). In addition, reduction of PfCx output by DA can reduce the release of DA in the NAcc and removes the hyperlocomotion that raised DA in the NAcc can induce (Kolachana et al., 1995; Karler et al., 1998). There is more on this in chapter 9.

3.4.3 Dopamine in schizophrenia

The standard theory regarding the role of DA in schizophrenia is that the mesolimbic DA system is over-active. This is based on two main findings. One is that typical neuroleptics (e.g. haloperidol) are DA antagonists, generally acting on D₂ receptors. The
other fact is that drugs which stimulate DA release (e.g. amphetamine and cocaine) can also produce psychosis that mimics the positive symptoms of schizophrenia. Also, giving amphetamine to people with schizophrenia can worsen their symptoms.

There has been recent interest in D₄ receptors (Jaber et al., 1996) due to the higher affinity for these receptors by the atypical neuroleptics (e.g. clozapine) and its distribution which includes the frontal cortex. It appears that the facilitating action of DA on GABA cells in the PfCx may be mediated by D₄ receptors (Goldman-Rakic and Selemon, 1997), although in the rest of this thesis it is assumed that these are D₂ receptors. In any event, there is no direct evidence that the D₄ receptor plays a predominant role in the pathogenesis of schizophrenia.

The standard picture is not quite so clear now, however, as several researchers have proposed more sophisticated theories based on a greater understanding of the DA system. These will be discussed at the end of the chapter as they involve interactions between different PfCx, NAcc and other brain regions.

3.5 The Prefrontal Cortex

One of the aims of this thesis is to investigate the function of the PfCx and the mechanisms through which it operates. In the next section I will discuss the neurobiology of the PfCx in some detail. It should be stated at the outset, however, that the prefrontal cortex accounts for approximately one third of the neocortex. Although the heterogeneity of the prefrontal cortex is taken into consideration through this thesis, the region of the prefrontal cortex to which the models in chapters 4 and 5 refer is the Principal Sulcus of the Dorsolateral Prefrontal Cortex (Brodmann areas 9 and 46).
3.5.1 Biology of the PfCx

Gross anatomy

The PfCx is traditionally defined in terms of its reciprocal connections with the mediodorsal nucleus (MD) of the thalamus. Layer III of the PfCx projects and receives fibres predominantly from other neocortical regions, while layer V has mostly cortico-fugal projections, although it sends some recurrent collaterals back to layer III. In general the PfCx has reciprocal connections with all structures except the basal ganglia, to which it projects but does not receive connections from. Passingham (1993) describes the connectivity of the PfCx in some detail. He explains that the ventral and orbitofrontal regions project to more limbic regions and autonomic areas, especially the reciprocal connections with amygdala and afferents to lateral hypothalamus. The latter structure projects to the nucleus tractus solitarius and dorsal motor vagus (autonomic centres), and to the pituitary gland. The dorsal regions of the PfCx have reciprocal connections with the cingulate cortex, entorhinal cortex and subiculum, and sends afferents to the NAcc, VTA and SN. In summary, the four main regions receiving PfCx efferents are: thalamus, cortical/subcortical limbic structures, neocortical sensory regions, and the basal ganglia and other subcortical motor control areas.

In terms of evolution, the PfCx has developed in a dual fashion, with there being two distinct trends distinguishable by architectonic differences. The archicortical (or hippocampal) trend has a more dorsal distribution, while the paleocortical (or olfactory) trend has a more ventral distribution (Pandya and Yeterian, 1990). The two trends can be classified: the ventral trend comprising Brodmann’s areas: 13, 12, 14, 11, 10, 46, 8; and the dorsal trend comprising Brodmann’s areas: 24, 25, 32, 9, 10, 46, 8. The dorsal trend can be split into dorsolateral (areas: 9, 10, 46 and 8, 46) and medial (areas: 24, 25, 32 and 9, 10, 14). While the ventral trend can be split into orbitofrontal (areas 12 and 13) and ventrolateral (areas: 10, 12, 46 and 8, 46). Regions 23 and 24 constitute the cingulate gyrus, while regions 23, 24, 25, 32 constitute the cingulate region. The paralimbic association areas include caudate orbitofrontal (13) and the cingulate region. Auditory association areas project to the dorsal trend:
Neurobiological issues

AA₁ → Area 8
AA₂ → Dorsolateral (9, 46) reciprocally
AA₃ → Orbitofrontal (12, 13) + medial (25, 32) reciprocally

Peripheral vision projects to the dorsal trend and central vision projects to the ventral trend. The cingulate region is more closely associated with the dorsal / hippocampal trend, whereas the temporal pole more associated with the ventral trend. Pandya and Yeterian (1990) tentatively suggest that the ventral trend deals with questions of "what" and the dorsal trend deals with questions of "where". It appears that both divisions of PfCx are faulty in schizophrenia (Pantelis et al., 1997). Although the dorsal trend may be implicated more strongly through its connections with the hippocampus, cingulate cortex and auditory association areas — all regions which have been shown to be involved in schizophrenia.

Microanatomy

The PfCx has a basic six layered structure with a well-developed internal granular layer (layer IV) which distinguishes it from the rest of the frontal cortex (Fuster, 1989). Pyramidal cells are found in layers III and V (with a few in layers II and VI also), those in layer III being larger. The layer III cells project within the cortex to cortical association regions and the contralateral cortex. Layer V cells project to subcortex, including the ventral tegmental area (VTA), amygdala, hippocampus and NAcc, and also back to layer III via recurrent collaterals, where there are a series of stripe-like bands composed of pyramidal neuron axon arbors (Lund and Lewis, 1993; Lewis and Anderson, 1995). The PfCx has reciprocal connections with most of its efferents apart from those in the striatum and NAcc. In addition there are reciprocal connections with the mediadorsal thalamus. The PfCx also contains many GABA interneurons, in particular wide-arbor and chandelier types.

The three most important aspects of the PfCx, at least in terms of information processing, are:
The electrophysiological and morphological properties of pyramidal cells in layers V-VI of the PFC have been characterised recently (Yang et al., 1996). Although this study was in vitro and used rats it is still a useful starting point for modelling. It is, anyway,
Neurobiological issues

the only study to date looking in detail at the firing characteristics of PFC cells. Yang et al. (1996) have found three distinctive types of cell. The cell types are (percentage of total cell population in brackets):

- Regular Spiking (19%). No bursting.
- Intrinsic Bursting (64%). A burst is a doublet of spikes (100-200Hz), which is dependent on Ca2+. There is evidence of adaptation. Morphology: thick ascending apical dendritic trunk with bifurcations and arborisations into layers I-II. Proximal dendrites from soma bifurcate profusely, with many spines. Collaterals are observed.
- Repetitive Oscillatory Bursting (13%). Only in layer VI. Fired spontaneously with sustained rhythmicity in response to a sustained depolarising current.

In a companion paper to this Yang and Seamans (1996) discuss the role of DA with respect to the above cell types. The following information is very relevant to the model in 5. The functional architecture is illustrated in Figure 5.1.

Layer III pyramidal neurons appear to act as input cells to layer V pyramidal neurons. The presence of D1 receptors on dendritic spines indicates a working memory role for those cells (Williams and Goldman-Rakic, 1995). The majority of dopaminergic inputs to the PfCx go to layer III so this would seem to be the most likely site for the delay cells. In addition, this layer is noted to be more active during the delayed response task (Friedman and Goldman-Rakic, 1994). I propose that the stripes observed in layer III of PfCx are composed of a network of delay cells which are fully interconnected with each other via lateral dendrites and axons. This network is known as a delay ensemble and is responsible for maintaining information during the delay phase of a delayed response task. The delay ensemble has several interesting properties which will be explored in chapter 5. Crucially, these ensembles are isolated and stabilised by dopamine.
The action of dopamine at the apical of layer III cells is to reduce noise and prevent spurious inputs from disturbing activity in the delay cells (Yang and Seamans, 1996). The dopamine projection to the PFCx from the VTA innervates predominantly layers III and V, mostly synapsing on apical dendrites in layer III. This projection is not topographic and D₁ receptors are found mostly at extra-synaptic sites (Smiley et al., 1994) which suggests a diffuse action. It is important to note that the PFCx sends glutamatergic inputs back to the VTA which can induce burst-firing in dopaminergic neurons. Thus there is a potent mechanism for the PFCx to auto-regulate its own dopamine levels.

There is further evidence that single pyramidal neurons of the rat frontal cortex receive dual input from both GABA and catecholamine terminals (Cowan et al., 1994), which is supported by (Sesack et al., 1995) who find that DA afferents provide direct synaptic inputs to GABA local circuit neurons across cortical regions.

The role of GABA interneurons is also crucial. These generally have roughly spherical dendritic and axonal arbors and have fast-spiking firing action. This would make them ideal for the role of providing global inhibition. It has been documented that pyramidal cells receive both inhibitory and dopaminergic inputs (forming synaptic triads) (Cowan et al., 1994) and also that GABA interneurons receive excitatory and dopaminergic inputs. The dopaminergic input to GABA interneurons increases GABA levels in the PFCx and is thought to act via D₂ receptors (Grobin and Deutch, 1998). It is highly plausible that these neurons provide feedback inhibition to pyramidal cells, assisted by dopaminergic activity. In support of this is the observation of reciprocal firing between pyramidal and GABA interneurons in the PFCx (Wilson et al., 1994). In addition, GABA interneurons are implicated in the pathogenesis of schizophrenia. Benes (1993) shows that there are reduced numbers of these cells in layer II/III of anterior cingulate cortex, a brain region closely related to the PFCx and involved in attentional processes.
3.5.2 Difference between rat and human prefrontal cortex

Much of the data used in this thesis is taken from experiments on rat brains so it is important to consider the differences between rat and primate PfCx. Uylings and van Eden (1990) have done such a comparison and conclude that the existence of a PfCx in the rat cannot be based solely on reciprocal connections with MD thalamus. However, based on a comparison of thalamic connections and cortico-cortical and cortico-subcortical connections they conclude that there is a rat PfCx with a particular homology to primate PfCx. They believe that the rat PfCx is a less evolved version of the primate PfCx, with homologies as follows: rat Fr2 (or medial precentral area, or medial agranular cortex) and some of rat anterior cingulate corresponds to primate areas 9, 46, 8, 6, and 10. The cingulate characteristics of the rat anterior cingulate correspond to primate area 24. The rat prelimbic and infralimbic regions possibly correspond to primate orbitofrontal areas (12, 13) and cingulate areas 25 and 32. Finally, the rat agranular insular cortex may also correspond to orbitofrontal areas. From this it would appear that rat medial PfCx corresponds most strongly to the dorsal trend in primate PfCx, and rat infralimbic and prelimbic cortex corresponds to the ventral trend. There is homology between some parts of rat anterior cingulate and primate anterior cingulate. In terms of PfCx function, Kolb (1990) claims that there is an “apparent general similarity in prefrontal function across mammals” (pg 516), and that function is to temporally organise behaviours. The more complex and plastic the behaviours, the more organisation is required and hence the size of PfCx increases as we progress up the evolutionary tree.

3.5.3 PfCx function

The PfCx, as a whole, is attributed with the general cognitive functions of planning, integrating information, temporal sequencing, motivation and inhibition of ‘primitive drives’ (Fuster, 1989).

Knight (1991) cites a list of syndromes of PfCx damage (see table 3.2).
Neurobiological issues

<table>
<thead>
<tr>
<th>Area damaged</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>11, 12 (Orbitofrontal)</td>
<td>Emotional lability</td>
</tr>
<tr>
<td></td>
<td>Reduced control of impulses and anger</td>
</tr>
<tr>
<td></td>
<td>Inappropriate laughing/crying/sexual behaviour</td>
</tr>
<tr>
<td></td>
<td>Attention is preserved</td>
</tr>
<tr>
<td></td>
<td>Insight is preserved</td>
</tr>
<tr>
<td>24, 25, 32, 33, 6, 8, 9</td>
<td>Reduced motivation, akinetic, apraxic (motor)</td>
</tr>
<tr>
<td>(Supplementary motor +</td>
<td>disturbances</td>
</tr>
<tr>
<td>cingulate cortex)</td>
<td></td>
</tr>
<tr>
<td>9, 10, 44, 45, 46 (dorsolateral)</td>
<td>(early) subtle changes in creativity and mental</td>
</tr>
<tr>
<td></td>
<td>flexibility</td>
</tr>
<tr>
<td></td>
<td>(late) problems with planning, goal-directed</td>
</tr>
<tr>
<td></td>
<td>behaviour, judgement, insight, temporal organisation</td>
</tr>
<tr>
<td></td>
<td>of events</td>
</tr>
</tbody>
</table>

Table 3.2: Syndromes of damage to PfCx.

Damasio et al. (1991) suggests that in order to function appropriately in a social situation we need to be able to hold online, for periods of seconds, heterogeneous sets of cognitive information for social decision-making. The PfCx has a large role to play in social behaviour. It seems to make sense that while such online processes are occurring it is beneficial for automatic subcortical processes to be inactive. Thus suppression of automatic responses ought to occur simultaneously with online processing.

Petrides (1991) shows that frontal lobe patients can learn a perform responses and can discriminate between stimuli but cannot choose an appropriate response to a cue when there are several to choose from. This could be a failure to be able to store temporarily a context from the hippocampus. It would be interesting to see if the same thing
Neurobiological issues

happens with hippocampal lesions.

Delayed response tasks

One of the key features of PfCx function is its ability to hold information online. This forms the basis of working memory, as discussed in chapter 2. Much work has been done on the role of the dorsolateral PfCx in holding information online using delayed response tasks (DRT). Research by Goldman-Rakic, Fuster (Fuster, 1989) and others has shown that certain cells in the dorsolateral PfCx fire in response to a stimulus while others fire as part of the response (i.e. motoric activity). It has also been shown that there are individual cells in the PfCx which respond during the delay period of a DRT, and that DA modulates (attenuates) the activity of these cells via D$_1$ receptors (Williams and Goldman-Rakic, 1995). In chapter 5 I have attempted to model the activity of these so-called delay cells.

Memory retrieval

The PfCx also plays a role in declarative memory retrieval. This is of interest because it highlights the different functional roles within the PfCx. Scanning studies (Buckner and Petersen, 1996; Buckner and Koutsaaal, 1998) show that the left inferior PfCx is activated during storage of semantic and episodic memories, while the right anterior PfCx, in the vicinity of Brodmann area 10, is activated during retrieval of episodic memories, including auditory sentences. However, some other areas are also activated during episodic memory retrieval, including posterior prefrontal areas, sometimes bilaterally. Precisely which areas are activated depends on the nature of the task, for example purely verbal retrieval has activated left posterior and right anterior prefrontal areas whereas pictorial (face) retrieval has exclusively activated right prefrontal areas. Buckner and Petersen (1996) suggest that episodic memory retrieval requires “multiple, distinct prefrontal areas to access the specific kind of information being retrieved” (pp 53-54), with activation of the right anterior PfCx being required for all retrieval
tasks. They state that it could be involved in relating information to a specific context, or recruited to guide searching processes as an item is explicitly retrieved from long term memory. These processes could be performed partly by holding information online, thus uniting the two types of memory process.

The following is a hypothesis connecting the hippocampus and the PfCx in the function of memory retrieval. It can be suggested that PfCx areas hold online contextual representations which are input from the hippocampus. This representation then dictates the retrieval of a long-term memory through some sort of partial pattern matching associative process. The presentation of the stimulus or cue to the hippocampus could be transformed by the hippocampus into a pattern representing a set of contexts related to the cue. These contexts are then held in area 10 and the hippocampus, possibly by reverberatory reciprocal connections, while the PfCx representation associatively triggers patterns in other areas of neocortex and binds together the results of the associative process. It is not clear how this binding process might work although it may be through a process of temporal synchronisation. According to this scheme of things, the hippocampus is required to make the connections between cue and subcomponents of the memory which together form the context. The PfCx is required for explicit retrieval. If this hypothesis were true then this would imply that the hippocampus is involved in retrieval of long-term declarative memories, and also in the retrieval of more complex memories where contexts are required. There is certainly evidence that hippocampus and PfCx interact in memory retrieval (Heckers et al., 1998), and also that it is required for memory tasks which are more complex and have longer delays (Berman et al., 1994).

Both of these studies imply a dysfunction of this interaction in schizophrenia. Heckers et al. (1998) show that hippocampal activity is reduced and dorsolateral PfCx activity is increased during explicit memory retrieval, while Berman et al. (1994) show the opposite effect but for a working memory task (the Wisconsin Card Sort Test) which does not have a heavy memory requirement. It is difficult to interpret these results, but, as mentioned in chapter 2, there are problems in assessing the results of scanning studies, particularly if DA is involved. It could be the increase in PfCx DA in the
working memory tasks which is causing the difference in these two studies. It would be interesting to know what the effect of DA is on memory retrieval processes. Although the effects of DA on working memory have been studied extensively there have been no attempts, to my knowledge, to study the effects of DA agonists and antagonists on long-term memory retrieval, particularly in humans. Such a study would be enhanced if fMRI or other scanning was used during the retrieval process.

3.5.4 Multiple domains of processing in the PfCx

Having seen the anatomical heterogeneity of the PfCx it is not surprising that there is good evidence for functional heterogeneity within the PfCx. Wilson et al. (1993) have shown that the dorsolateral PfCx seems to be specific for spatial information while object identity (pattern-based) information is encoded in ventrolateral aspects of the PfCx.

Dias et al. (1996) have suggested that damage to the lateral PfCx in marmosets (Brodmann's area 9) causes loss of inhibitory control in attentional selection while damage to the orbitofrontal cortex causes a loss of inhibitory control in affective processing. Inhibition in these studies takes the form of inhibiting a previously acquired visual discrimination response. Subsequently, they (Dias et al., 1997) claim to have shown that the ability to hold information online in the PfCx is independent of the response inhibition function. Thus lateral lesions of the marmoset PfCx impaired the ability to switch response between two different stimuli (lines and shapes) which are forming a compound stimulus (extra-dimensional shift = EDS), and orbital lesions impair the ability to switch response from one whole compound stimulus to another (compound reversal = CR). Another task was to continue responding to the same stimulus within a compound as the compound changed (intra-dimensional shift = IDS). There was no deterioration in performance on the last task with either of the lesions. In addition, the impaired performance only occurred on the first trial requiring a change in response i.e. when the response-switching was still novel. The main conclusion from these experiments is that different regions of PfCx perform different functions.
Dias et al. (1997) suggest that their results imply that there is a distinction between online processing and response inhibition, however it is not clear to what extent online processing is required in these tasks. It can certainly be envisaged that the monkey has to hold the previous ‘rule’ online in order to inhibit this response, however it is not necessarily the case that the rule needs to be held online when it does not change (IDS). If this is true then the study does not show dissociation between response inhibition and online processing. Further studies investigating the neural substrate of the IDS task are required, possibly making more extensive lesions to the PfCx to see if it is utilised at all in this task. The fact that impairment of response inhibition only occurred in a novel situation is also interesting. This implies that the PfCx is only required in novel situations where there are no learned (or automatic) responses. It is known that DA levels in the PfCx rise in novel situations (Feenstra et al., 1995), and DA is involved in working memory (as discussed in chapter 2). In addition DA neurons are known to respond only when reward is unpredictable, thus we would not expect the IDS task to be dependent on DA/working memory processes since there is no element of switching rewards and thus no unpredictability in reward provision. I conclude that although different regions of the PfCx may be involved in different functions, response inhibition and online processing may be performed by the same working memory mechanism in the PfCx, contrary to the claims of Dias et al. (1997).

Summary

The PfCx has been measurably implicated in at least three cognitive paradigms:

1. holding information online (delay response tasks).

2. retrieval of long-term memories.

3. response inhibition and switching.
Inhibition of previous responses and holding information online may be two aspects of the same underlying mechanism.

3.6 PfCx, NAcc and hippocampal interactions

The PfCx, NAcc and hippocampus are all implicated in the pathogenesis of schizophrenia. I have discussed how each of these structures may individually involved in schizophrenia. In this section I will discuss how it is the interactions between these regions which are potentially more important in schizophrenia.

There are potentially complex interactions between various of the inputs to the NAcc. While DA input may provide a scalar error signal, other vector information is required to improve the learning process. Incoming stimuli are put into a particular context in order to be able to select an appropriate action and to indicate specifically which reward or reinforcer has occurred (Schultz, 1997). This context information is likely to be conveyed by hippocampal input. Disruption of the DA input to the NAcc is explored in chapter 8. A hypothesis relating hippocampal dysfunction and fluctuations in the level of DA in the NAcc is also presented in that chapter.

The role of the PfCx input to the NAcc is less clear. In terms of locomotor activation by DA in the NAcc, Glu is neither necessary nor sufficient to induce activity (Dalia et al., 1998), but does seem to enhance the DA effect. This suggests that PfCx input to the NAcc may act to facilitate DA actions. Conversely, if PfCx output is reduced, as it appears to be during a working memory task, then this would have the effect of attenuating the locomotor action of DA. It would also reduce the amount of firing of the DA VTA cells, thus reducing locomotor effects further. This may represent the inhibitory function of the PfCx. Further evidence is supplied by Karler et al. (1998) who have shown that increases in PfCx DA can reduce the locomotor effect produced by increased DA in the NAcc. Kolachana et al. (1995) have shown a similar effect
whereby increasing PfCx DA reduces basal DA levels in the caudate nucleus of the rhesus monkey.

Some recent studies have looked at PfCx, NAcc and hippocampal interactions in rats and mice. It has been shown (Burns et al., 1996) that in response to novelty the PfCx seems to mediate the initial choice between exploring a novel food item or approaching a familiar one. This work has implications for the role of the PfCx in controlled behaviour rather than automatic behaviour. Another study (Floresco et al., 1997) has shown that in learning a radial-arm maze task the subiculum is necessary for both straightforward learning, and performance after a 30 minute delay once the maze has been learnt. If the subiculum and NAcc are disconnected then the rat fails on the simple task but not the delayed task, and if the PfCx and subiculum are disconnected the rat fails on the delayed task but not the simple task. In a related study Seamans et al. (1998) have shown that activity at D1 receptors is necessary for the PfCx input to be able to guide behaviour in the delay condition. These studies underline the PfCx role in delayed response tasks and working memory and the role of DA in this process.

Carr and Sesack (1996) discuss relations between the hippocampus and PfCx. They claim that hippocampal terminals in the PfCx form asymmetric (excitatory) synapses. While spines receiving contact from DA terminals (symmetric) usually receive asymmetric synapses from an unknown source there were no examples of convergence of DA and hippocampal terminals on common post-synaptic targets.

3.6.1 Frontal-subcortical disharmony: hypotheses for schizophrenia

Grace's theory

Grace (Grace, 1991, 1993) introduces a two tier concept to account for the dynamics of DA release in the striatum and NAcc. This system is composed of a tonic and a phasic component to DA release. According to Grace, the tonic release of DA occurs in
response to Glu from PfCx afferents acting presynaptically on NMDA receptors and is spike-independent. DA released in this manner is thought to underlie the basal ECF DA in subcortical structures. Changes in this background level should trigger homeostatic mechanisms to restore the correct balance and so by regulating this background level corticostriatal afferents will modulate the sensitivity of the tonic DA receptors. This in turn will bring about homeostatic changes that will alter the responsivity of the whole DA system and thus modulate the amplitude of the phasic DA response. The phasic response is a transient DA release produced by the burst firing of DA neurons. It is a brief but large amplitude pulse that activates postsynaptic receptors and is rapidly removed from the synaptic cleft by the fast high-capacity reuptake systems before any homeostatic mechanisms are initiated.

The way in which the tonic DA modulates phasic DA must be via D_2 autoreceptors. The theory states that a decrease in the activation of these autoreceptors would potentiate impulse-dependent phasic DA release. If the decrease in tonic DA is maintained then the ultimate outcome would be: 1. an increase in DA synthesis (as a homeostatic response); 2. an increase in the number of D_2 receptors; and 3. sprouting of DA axons. These changes would maintain a stable level of tonic DA but would cause an up-regulation of the phasic DA response. It is suggested (Grace, 1993) that in the NAcc. the prefrontal cortical afferents synapse on the same dendritic spines as the dopaminergic VTA afferents, and also the glutamatergic afferents from the hippocampus. It has also been shown that DA inhibits Glu release from Glu terminals in the NAcc (Kalivas and Duffy, 1997). If there was a sustained reduction in the excitatory prefrontal input then this could produce the scenario envisaged above—an up-regulated phasic DA system that responds to environmental stressors with increased frequency and amplitude of burst firing. Grace considers the dynamic range of the phasic DA system to be extended at both ends in the schizophrenic, with positive symptoms being generated by a low tonic-high phasic combination.

There are serious problems with this theory however. The main one is that most phasic DA release in the NAcc and striatum is due to firing of VTA cells, and thus it is the control of these cells which is more important than the direct effects of Glu in the
Neurobiological issues

NAcc. The interactions between Glu and DA are complex (see chapter 6). In addition, it is not clear that an increased phasic DA response is enough to cause schizophrenic symptoms. In chapter 8 I will investigate this and suggest that fluctuations in the level of DA are more likely to be the cause of schizophrenic symptoms. Another very important point is that it seems as though one of the normal PfCx functions is to have a reduced output to NAcc in certain situations e.g. novelty, stress, utilisation of working memory. Clearly PfCx dysfunction could mean that there is a chronically reduced subcortical projection. Two possibilities apply for this to be the case. There could be a reduction in excitatory input from other cortical regions but there is no evidence to suggest this; or there could be increased DA and/or GABA interneuron activity in the PfCx, which could be the case but would contradict the hypofrontality hypothesis. In fact there is evidence that the PfCx of schizophrenics is over-active in some situations (Heckers et al., 1998). Another point is that the source of DA, in the VTA, will still be functioning normally since there is no phasic DA activity there. Also, there is debate over whether there are DA autoreceptors in the VTA (Cragg and Greenfield, 1997), implying that alterations in tonic levels of DA in the VTA are unlikely to affect DA transmission. Finally, there is some evidence that Glu in the NAcc reduces basal DA levels (Taber et al., 1996), although most evidence points the other way. In summary, although there may be a chronic down-regulation in the level of tonic DA in the NAcc which could lead to an increased phasic response, the ideas that this is a) pathological and b) a potential cause of schizophrenic symptomatology are not totally tenable.

Grace’s hypothesis is used as the basis for a recent and more extensive theory of schizophrenia (O’Donnell and Grace, 1998), which is more complete but still suffers from the flaws mentioned above.

Deutch’s theory

Deutch (1993) believes that there are two parallel but functionally different circuits involving the PfCx, NAcc, VTA and ventral pallidum. This is based on findings that mild stress preferentially activates the mesocortical DA system, whereas more severe
and/or prolonged stress activates the mesolimbic system in addition. He describes a 'mild stressor' circuit and a 'prolonged stressor' circuit both of which are affected in schizophrenia—the former is more associated with the limbic system and the latter with the dorsal striatum. He finds that lesions to the PfCx DA innervation cause an increased responsiveness in subcortical DA projections to the NAcc, in line with work described above. This is in contrast to Grace's hypothesis, where he considers reduced PfCx output to be the significant lesion, leading to a reduction in subcortical DA tone. Deutch considers the cause of hypofrontality to be reduced DA innervation or a reduction in the numbers of GABA interneurons in the PfCx.

Again, it is not clear how the symptoms of schizophrenia arise from this hypothesis. It predicts increased subcortical DA responsiveness with an over-driving of the mild stress circuit leading to activation of the prolonged stress circuit. This may account for the agitation often seen in schizophrenia, but does not say anything more specific. Nevertheless, the basis of this hypothesis seems sound and can be extended in other theories of schizophrenia such as I am attempting to present. The idea that hyper-responsiveness to stress underlies schizophrenia has been translated into an animal model for schizophrenia which allows for investigation of hypotheses that schizophrenia arises due to neonatal brain damage. (Lipska et al., 1993) have shown that neonatal excitotoxic damage to the rat hippocampus produces an increased sensitivity of the mesolimbic DA system. This is expressed as an increase in motor responsiveness to stress and can be prevented by pre-treatment with haloperidol. The sensitivity only appears in early adulthood and appears more akin to adult lesions of the medial PfCx than to adult lesions of the ventral hippocampus. This provides some support for the hypothesis that neonatal damage to the hippocampus can induce developmental abnormalities in the PfCx.

Other fronto-subcortical theories

Pantelis et al. (1997) have used a battery of psychological tests on patients with schizophrenia and patients with Parkinson's Disease and medial temporal lobe dam-
Neurobiological issues

Neurobiological issues

age (including amygdalo-hippocampectomy). Their aim was to see whether the neuropsychological deficits in schizophrenia resemble more closely deficits in fronto-striatal loops or in frontal-hippocampal loops. Fronto-striatal loops are taken to be parallel pathways, as described earlier with respect to the NAcc, which incorporate dorsolateral PfCx, orbitofrontal cortex, and anterior cingulate cortex. The frontal-hippocampal hypothesis implicates dorsolateral PfCx explicitly. The two main tasks they use are spatial span and spatial working memory. The former requires the ability to hold information online, and the latter requires this ability and also the ability to use or manipulate this information. They find that ventrolateral PfCx is implicated in spatial span and dorsolateral PfCx is implicated in spatial working memory, and deficits in both of these processes occur in schizophrenia. By comparing the performances of the different groups on the Tower of London Task, a spatial working memory and planning task (see chapter 7 for more details of this task) they conclude that the schizophrenic deficits resemble more closely those seen in frontal lobe and Parkinsonian patients than in those with medial temporal lobe lesions. They point out that the lack of deficits in executive functions in medial temporal lobe lesioned patients implies that the working memory deficits in schizophrenia cannot be solely due to dysfunction in the connectivity between PfCx and medial temporal lobe. They suggest that their data indicates a loosening of relationships between different components of cognitive tasks. The binding of these relationships is assumed to occur in frontal lobe. Finally, they concede that the tests used do not test known medial temporal lobe functions such as learning and recall, and schizophrenics may well exhibit some medial-temporal lobe dysfunctions. As a supplement to this Biver et al. (1995) also find altered fronto-striatal metabolism in unmedicated schizophrenic patients at rest.

In contrast to Pantelis et al. (1997), Heckers et al. (1998) find disturbances in dorsolateral PfCx and hippocampal function in schizophrenics undertaking a conscious recall experiment. They used PET scanning to show increased right dorsolateral PfCx activity and reduced hippocampal activity during episodic memory retrieval. This is interesting as, not only does it contradict Pantelis et al. (1997), but it contradicts the hypofrontality hypothesis. However, if we consider that two different tasks are be-
Neurobiological issues

In the two studies then there may be a reconcilable hypothesis. Firstly, hypofrontality may not be a finding in all cases of schizophrenia (Fletcher, 1998). Friston et al. (1992) showed that the one brain region which appears to be implicated in all instances of schizophrenia is the medial temporal lobe. Secondly, the fact that a different task reveals a different dysfunctional pairing, but involves structures which are expected to be involved in the task, indicates that the nature of the task undertaken is highly important. Since schizophrenia is highly heterogeneous in the symptoms exhibited by patients, it is quite possible that the cognitive task used in such studies merely taps into a subset of symptoms which are statistically significant for that population of patients. Between the two studies, however, the three brain regions that appear to be involved are PfCx, NAcc (striatum), and hippocampus. Thus it still seems worthwhile attempting to formulate a theory of the pathogenesis of schizophrenia built around dysfunctional interactions between these regions. This may help reconcile the two competing theories that fronto-striatal versus fronto-hippocampal dysfunction underlies schizophrenia.
Chapter 4

Review of computational models

4.1 Modelling issues

This chapter reviews some of the original work applying the techniques of computational modelling to schizophrenia. A more complete review may be found in Ruppin (1995). The application of computational modelling to schizophrenia was a logical extension of the use of connectionist models of cognition to situations of cognitive dysfunction. All the models described are variations on neural network models (Rumelhart et al., 1986). Such models are characterised by being intrinsically parallel in their architecture and consist of multiple neuron-like elements which perform a simple summation of inputs to generate an output according to some activation function. The sum of the inputs is modified by the relative strengths of the inputs which are known as synaptic weights. Such networks act fundamentally as associative memories. Learning in a network proceeds by modifying the weights according to a learning rule. The most commonly used form of learning is that suggested by Hebb (Hebb, 1949; Hertz et al., 1991), which states that the synaptic weight is increased if there is activity in both presynaptic and postsynaptic neurons.
The main value of using neural network models to investigate complex cognitive dysfunctions, such as schizophrenia, is that they can join several levels of description in one model. For example, it is possible to address issues of connectivity and architecture, neurotransmitter action, and behaviour by setting up appropriate learning situations in the neural network and then manipulating various parameters of the model. This sounds very attractive, however there are two major drawbacks in using these models which limit their usefulness, particularly in modelling complex phenomena such as schizophrenia. The first and most significant problem is that of biological validity and specificity. By this I mean that neural networks are probably over-simplified models of the brain which do not adequately capture the range of neural mechanisms, interactions and dynamics which occur in real brains. The level of biological detail is not there to test specific brain-related hypotheses and get meaningful results. As our knowledge of neuroscience continues to increase this becomes a major flaw for models which purport to link brain events with cognitive events. The second problem is more general to the whole of science, and that is the question of interpretation of results. Following from the first problem, if the level of representation in the model is not really adequate for the investigation being carried out, then interpretation of results becomes even more fraught. A more useful paradigm for investigating brain mechanisms might be computational neuroscience. Neural networks still remain useful for investigating large scale effects in the brain and cognitive processes due to the fact that these models are computationally simple and can simulate either long periods of activity and/or statistical effects distributed over a very large number of elements. They also have value in generating new hypotheses to be tested with either psychological or neuroscientific methods. The three main models presented later in this thesis operate at different levels but the aim is to link quite low-level biological processes such as neurotransmitter interactions and neuronal spiking, with higher level processes such as working memory. It is hoped that the level of detail across the three models allows for a useful interpretation of the results.
4.2 Over-pruning of attractor networks

Hoffman and Dobscha (1989) used an attractor (Hopfield) neural network to model the effects of over-pruning in the human cerebral cortex in an attempt to demonstrate an underlying brain mechanism for schizophrenia (Keshavan et al., 1994). One of their main findings is the emergence of autonomous regions of activity in the network unrelated to input—they call these ‘parasitic foci’. In a later paper (Hoffman and McGlashan, 1993), they relate the occurrence of parasitic foci to the symptoms of schizophrenia. I will discuss their model in some detail to illustrate some of the pitfalls of this type of modelling.

Hoffman and Dobscha used a 100-unit stochastic Hopfield-type network organised as a 10x10 grid and pruned according to the following rule:

Prune connection from unit $i$ to unit $j$ if:

$$w_{ij} < (p \times \text{distance between unit } i \text{ and unit } j)$$ (4.1)

where $p$ is the pruning coefficient with values from 0.6 to 1.0 and $w_{ij}$ is the synaptic weight between units $i$ and $j$. In a stochastic attractor network $S_t$, the state of unit $i$, is set by:

$$\text{Prob}(S_t = 1) = \frac{1}{1 + e^{-(\frac{1}{T_{\text{off}}} h_i)}}$$ (4.2)

where $T_{\text{off}}$ is the ‘pseudo-temperature’ and $h_i$ the net input to unit $i$. All simulations use the value $T = 4$.

The network was set up to store 9 memories. Inputs to the networks consisted of the stored memory patterns with either every fifth or every third bit flipped. This gave two sets of input patterns with respectively Hamming distances of 20 (HD20)
and 33 (HD33) from the stored memories. These inputs were intended to represent two different levels of ambiguity for the memory model to cope with. Over-pruned networks showed the following three 'pathological' output states:

- **generalisations**: An amalgamation of memory fragments

- **loose associations**: Output with more than 10 bits different from input and not a generalisation

- **parasitic foci**: Certain populations of neurons converging on the same non-memory output regardless of input. These are determined by comparing all the loose association outputs for one run of a network. An area of overlap which is at least a block of 12 units in size (either 3x4 or 2x6 units) occurring between all the output states examined is said to be a parasitic focus. Figure 4.1 represents three loose association end-states of a network for three different inputs. The white dots represent units with the same activation across all three output patterns, black dots are units with different activations.

It was claimed (Hoffman and McGlashan, 1993) that the occurrence of similar parasitic foci in different brain regions, though principally the frontal lobes, could underly
the positive symptoms of schizophrenia. The main idea was that the parasitic focus represents an irrelevant thought or linguistic construction which is converged upon inappropriately and regardless of input stimuli.

In order to investigate further the origin of these parasitic foci and the validity of this hypothesis as the basis for psychotic phenomena I have replicated Hoffman and Dob-scha’s original pruning experiments. I have also extended my simulation to include:

1. unpruned networks

2. pruned networks without self-weighted terms (i.e. \( w_{ii} = 0 \))

3. randomly pruned networks

4. unpruned overloaded networks

5. pruned and unpruned networks storing 5 patterns

4.2.1 Results

The performances of pruned and unpruned networks when presented with HD20 and HD30 patterns is shown in Figure 4.2, while Figure 4.3 shows the results of overloading a network. From Figures 4.2 and 4.3 we see a deterioration in memory performance and an increase in the number of loose associations with increased pruning and with overloading of the network. The results are summarised in Table 4.1 and below:

- unpruned 9-pattern networks produced parasitic foci to the same extent as pruned networks.
Review of computational models

<table>
<thead>
<tr>
<th>Type of Network</th>
<th>No of parasitic foci</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-patterns pruned</td>
<td>24</td>
</tr>
<tr>
<td>9-patterns unpruned</td>
<td>31</td>
</tr>
<tr>
<td>Overloaded</td>
<td>13</td>
</tr>
<tr>
<td>5-patterns pruned</td>
<td>33</td>
</tr>
<tr>
<td>5-patterns unpruned</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.1: This table summarises the results. Note that overloaded and unpruned 9-pattern networks both produce parasitic foci, in addition to the pruned 9-pattern network.

Figure 4.2: The upper graphs show the results of pruning a 9-pattern network (left) and a 5-pattern network. Lower graphs show the same networks without pruning. — — = HD33 hits; — — — — = HD20 hits; — — — — = HD33 loose associations; — — — — = HD20 loose associations. Hits refers to either the correct retrieval of a pattern or a generalisation. Results are averaged over 10 simulations and $p$ ranged from 0.6 to 1.05.
Figure 4.3: This Figure shows results for a network overloaded with between 10 and 19 patterns. Key as in Figure 4.2. No pruning occurs here. Results are averaged over 10 simulations and $p$ ranged from 0.6 to 1.05.

- the removal of self-weighted terms produced fewer loose associations but did not affect the number of parasitic foci.

- randomly pruned networks functioned poorly as memories when the number of connections removed was the same as the number lost in the rule-based case (60-85% loss). They did not retrieve successfully any memories and produced no parasitic foci. When the number of connections lost randomly was lower (20-55% loss) the results obtained were similar to the rule-based case.

- overloaded networks showed very similar behaviour to pruned networks but produced fewer parasitic foci.
4.2.2 Analysis

We can consider Hoffman and Dobscha's model in terms of the phase transition diagram for the stable states of the Hopfield network on which it is based. The phase transition diagram (Amit, 1989) shows the stability of the network through time relative to the values of $T$ and $\alpha$ (Figure 4.4), where $T$ is the pseudo-temperature, related to $T_{\text{hoff}}$ in equation 4.2, and $\alpha$ is a measure of the occupancy of the network, given by:

$$\alpha = \frac{\text{Number of patterns stored}}{\text{Number of units in the network}}$$  \hfill (4.3)

The diagram represents phase transitions in terms of the normalised value of $T$ and $\alpha$. Normalised in the sense that it is usual to include a $\frac{1}{N}$ term in the equation for $h_v$, which Hoffman and Dobscha did not do. Also, the stochastic update equation used by Hoffman and Dobscha utilised $\frac{1}{N}$ rather than the usual $\frac{2}{J}$ in the exponential term. If $T_{\text{norm}}$ is the usual (normalised) form of $T$ and $T_{\text{hoff}}$ the form of $T$ used in their simulations then the following equivalence holds:
Thus the value $T = 4$ in Hoffman and Dobscha's model is equivalent to a normalised value of $T = 0.08$. This value is illustrated in Figure 4.4. It can be seen that storing 9 patterns in a 100 unit network will leave the network in region B of the phase diagram. Here the most stable states are spin glass states, not memory states. This implies that Hoffman and Dobscha's model was destined to enter extraneous states by its design.

The analysis can be continued by looking at the mathematical implications of removing connections from the network. In the situation of weak dilution of the number of connections in a Hopfield-type network the relative concentration of connections $c$ is given by:

$$c = 1 - \left( \frac{\text{Number of connections removed}}{\text{Total number of connections}} \right)$$

(4.5)

There is clearly a correspondence here between dilution and pruning since in both cases connections are being removed. In fact we can surmise that pruning the network is equivalent to weak dilution. If we use $c$ as above to represent the number of remaining connections in a pruned network then the input $h_i$ in the pruned case becomes (Hertz et al., 1991):

$$h_i^{\text{pruned}} = c \Sigma w_{ij}^{\text{unpruned}} S_j$$

(4.6)

leading to:

$$h_i^{\text{pruned}} = ch_i^{\text{unpruned}}$$

(4.7)
This is equivalent to increasing $T$ in the state update equation by $\frac{1}{\epsilon}$. The effect of increasing $T$, in terms of phase transitions, is to move the stable states of the system away from region A and into regions B and C where spin glass states predominate. This accounts for the gradual deterioration of a network's performance with pruning. Similarly, however, if a network is overloaded then clearly the size of $\alpha$ is increased and the effect is to move along the x-axis of the phase transition diagram. Again the stable states of the system move from region A to regions B and C.

Thus I can conclude that in analytic terms Hoffman and Dobscha's generalisations are mixture states; their loose associations are spin glass states; and their parasitic foci are parts of spin glass state outputs from a particular network which overlap with each other to a significant degree. Comparing the simulation results with the phase transition analysis above it can be seen that the simulation results are as might be expected. Both pruned 9-pattern networks and networks overloaded with more than 9 patterns never have stable states in region A of the phase transition diagram and so never function well as memories. 5-pattern unpruned networks function as near perfect memories and 9-pattern unpruned networks function as moderate to poor memories, again as predicted by the phase transition diagram.

### 4.2.3 Conclusions

I have looked at the analytical work on attractor networks and shown that parasitic foci are overlaps in spin glass states which automatically exist in the network, and that pruning is equivalent to raising the ‘temperature’ in the stochastic state update equation. In addition I have shown that overloading instead of pruning the network will give the same qualitative results. This analysis is in agreement with the simulation results. The conclusion is that while parasitic foci may form a very weak analogy with brain states occurring in schizophrenia, the pathogenesis of this illness cannot be attributed to one particular process in the model i.e. the model shows that both pruning and overloading can give rise to parasitic foci.
As alluded to above, there are problems with Hoffman and Dobscha's methodology and with their model. These are summarised below:

- it is unusual to include self-weighted terms in a Hopfield net as these increase the number of spurious patterns.

- Hoffman and Dobscha have used 9-pattern networks which have parasitic foci even when unpruned. While 5-pattern networks show genuine transitions to pathological states when pruned, these states can also be obtained by overloading the network rather than pruning it. Thus pruning is not the only cause of parasitic foci. This seriously undermines the use of this model to show a potential brain mechanism for schizophrenia.

- The motivation for the pruning rule is unclear. Pruning and synapse formation are both developmental processes but synapse formation is not included in the model. The pruning rule uses fixed weights which implies that pruning takes place at an instant in time, and after the cognitive processes which the model represents have been formed i.e. in the mature brain. Pruning is neither instantaneous nor a mature process in real brains.

- Allowing connection strengths to be symmetric (i.e. $w_{ij} = w_{ji}$) is also a problem in terms of the biological realism of the model.

- The model lacks biological realism and this arises largely from using a Hopfield net to model biological processes.

While parasitic foci are real phenomena in a Hopfield net it seems unlikely that they actually occur in this way in the brain. However, the idea that alterations in the nature
of the attractors that exist in real brain dynamics could describe the pathogenesis of schizophrenia symptoms remains very interesting. An alternative description for the consequences of over-pruning is provided in chapter 5. There I use models of spiking neurons to simulate PICA function in working memory and show that over-pruning could lead to impairment in the ability to hold information online.

4.3 Modelling cognitive tasks

Cohen and Servan-Schreiber (1992) have elected to focus on the dysfunction of selective attention and language in schizophrenia (see also Cohen et al., 1996). They model three tasks: the Stroop Test, a continuous performance task (CPT), and a lexical disambiguation task. The Stroop Test is an old test designed to show the interference between two modalities of visual sensation. The test uses words written in ink of one colour but spelling out a word of a different colour. For example, RED spells the word "red" but is written in green ink. The task is to respond to one of the modalities e.g. the written word rather than the colour, so responding to red rather than green in the example. Responses are measured as reaction times to give the correct response. This means that the unwanted sensory modality must be ignored i.e. the correct modality is selectively attended to. Control stimuli are either words written in black spelling colours or a row of XXXXX's in a certain colour. Normal subjects have a harder time responding to colours than to words. It is not known exactly why this should be, but a prominent theory is the dual-processing hypothesis which states that words and colours are processed through separate neural pathways (Freyss and Keane, 1995).

The reason for the discrepancy between attending to colours and words is thought to be that we have a greater exposure to words and in general are more often required to interpret stimuli according to their lexical content rather than their colour content. If it is assumed that processing pathways are selected through the frequency of their use, perhaps by some conditioning process, then the word-processing pathway will be preferentially activated over the colour-processing pathway.
There have been five studies (according to Cohen and Servan-Schreiber) applying this test to schizophrenics, and all the studies used chronic patients. Results show that schizophrenics perform significantly worse on this task than normals, in other words they exhibited an overall slowing of response which was most marked when required to respond to colours. This corresponds with the thesis that a major cognitive deficit in schizophrenia is a *failure of selective attention*, thus the schizophrenic has great difficulty in 'switching off' or not responding to the inappropriate modality. The Stroop Test has been shown to activate the anterior cingulate cortex, underlining the role of this region in selective attention. It appears to be less active in schizophrenics performing the Stroop Test, further connecting the anterior cingulate with schizophrenia (Liddle, 1992; Carter et al., 1997).

All three of the tasks used by Cohen and Servan-Schreiber are intended to capture context effects and are also performed poorly by schizophrenics. Their aim in modelling these three tasks is to show that a disturbance in the internal representation of contextual information can account for schizophrenic deficits in selective attention and language, and in addition that a change in one parameter of the model can cause a switch from normal to schizophrenic behaviour. This parameter is deemed to represent the neuromodulatory effect of DA. The models used are based on simple neural networks and have little 'anatomical correctness'. I will look at one of their models, that dealing with the Stroop effect, in slightly more detail. This model has the basic architecture shown in figure 4.5

The original model is described fully in Cohen et al. (1990). It is a feedforward network trained by the standard backpropagation algorithm but with a 'cascade' mechanism (described below) to simulate the time course of psychological processes. This gives the network a temporal domain while it is running, unlike a standard backpropagation network. In this model, then, reaction times are considered to be linearly proportional to the number of cycles it takes for an output unit to reach its threshold. The model has two information processing pathways; one for colour information and the other for word information. These both converge on a common response mechanism (the output units). The model also has two 'task demand units' which are intended to represent
Figure 4.5: The basic architecture of Cohen and Servan-Schreiber's (1992) model of the Stroop Test. The model has two paths, one for colour-naming and one for word-naming.

an attentional mechanism. These are used to allocate attention to one or other set of intermediate units, depending on the nature of the task required. It can be seen (Figure 4.5) that the network is not fully connected. The intermediate units are fully connected to the output units, representing the common final pathway, however the two information processing modalities are segregated. The task demand units are fully connected to the intermediate units, however, thus they form a crucial link between the two modalities.

I will now outline the dynamics of the model. The way in which the cascade mechanism is implemented is as follows. The net input to unit \( j \) at time \( t \) is:

\[
\text{net}_j(t) = \sum_i a_i(t)w_{ij}
\]

(4.8)

where \( a_i(t) \) refers to the activation of unit \( i \) in the preceding layer of the network. The activation of a unit, however, is given, unusually, by a discounted running average of its \textit{net input over time}:

\[
a_j(t) = \tilde{\text{net}}_j(t) = \tau \text{net}_j(t) + (1 - \tau)\tilde{\text{net}}_j(t - 1)
\]

(4.9)
where \( \text{net}_j(t) \) is the time average of the net input to unit \( j \) and \( \tau \) is a constant discount value. Thus for a given (fixed) input set to the network, it will take several iterations or cycles for the activation in all the units to reach an asymptotic value. We are guaranteed that "the network will always reach a stable state in which each unit has achieved a characteristic activation value" (Cohen et al., 1990, pg 337). This is the way in which the time course of psychological processes such as the Stroop task is represented. Cohen et al. (1990) in fact use a nonlinear version of this activation function in order to avoid the computational limitations of a linear network. Thus the activation function becomes:

\[
a_j(t) = \frac{1}{1 + e^{\text{net}_j(t)}}
\]  

The network is trained by the standard backpropagation algorithm, although it should be noted that this takes longer than might be expected because for each iteration of the learning algorithm the units require several cycles to achieve their asymptotic activation values. In order to give the model the behaviour seen in normals performing the Stroop task, the word-naming pathway was given more (tenfold) training examples than the colour-naming pathway. This produced the effect that when one of the colour units and one of the word units were stimulated the word output unit reached its threshold first, simulating a predominant response to the word rather than the colour it is written in. The 'task demand' units had connection strengths fixed, however, such that the net input to the intermediate units in the attended-to pathway was 0, in order to make these units as sensitive as possible to input. Units in the non-attended-to pathway had more negative net inputs.

Having trained the network the testing phase could proceed as follows. The appropriate 'task demand' unit was activated and the activity in all the other units was allowed to reach asymptote values. The intermediate units in the selected pathway and all the output units were found to have resting values of 0.5 while the intermediate units in the competing pathway had resting values of 0.01. The test pattern was then presented and the network allowed to cycle until one of the output units had
reached its threshold value (1.0). The network is found to have the following properties which simulate the Stroop effect in humans: 1. word reading is faster than colour naming; 2. word reading is not affected by ink colour (i.e. the condition where the task demand is word reading, the word is red (green) and the ink colour is green (red)); 3. word reading slows colour naming in the conflict condition (i.e. the task demand is colour naming and the word and ink colour are in conflict). These results are unsurprising given the architecture and dynamics of the model. The word naming pathway is trained with 10 times as many examples as the colour naming pathway thus the weights in the word naming pathway are likely to be much stronger. It is very likely that almost all the output activity is due to the word naming pathway regardless of the task demand. Thus it makes sense that the only condition in which it takes longer to produce an output is when the output is required to be generated by the colour naming pathway, namely the condition where the task demand is colour naming and there is conflict in the inputs so that the word naming path input is not acceptable as the output. Here it takes a little longer for the negative bias of the task demand unit to overcome the strength of the word naming path weights.

The effect of the task demand units is to simulate that intentions are able to override conditioned responses. Cohen and Servan-Schreiber see the task demands as providing “the context necessary to disambiguate the stimulus and choose the appropriate response”. They consider this context information to be localised to the PfCx in adults. This conception of context is very limited and really represents the goal. In a goal-driven learning situation there needs to be a representation of the goal, but there could also be contextual information which acts to guide responses. In later chapters of this thesis I will suggest that context information is generated by the hippocampus and held online in the PfCx during memory retrieval and planning tasks. This is not incompatible with Cohen and Servan-Schreiber’s use of context here but provides an extended account of it.

The next stage is to change the model in some way so as to simulate changes in the schizophrenic brain and at the same time simulating the performance of schizophrenics on the Stroop Test. Cohen and Servan-Schreiber focus on changes in DA trans-
mission postulated to occur in schizophrenia. They assume that DA acts to potentiate post-synaptic potentials (PSPs). This action of DA is by no means certain and is discussed further in chapters 3 and 9. In general DA is thought to be more inhibitory than excitatory and so attenuates PSPs. Cohen and Servan-Schreiber also assume that there is a decrease in dopaminergic activity in the PfCx, in accordance with the hypofrontality hypothesis. Finally they choose the parameter of gain to represent the neuromodulatory effect of DA in their models. The activation function they use is a logarithmic function producing a sigmoidal activation curve, given by:

\[ S(h) = \frac{1}{1 + \exp(-gh + b)} \]  \hspace{1cm} (4.11)

where \( g \) is the gain, \( h \) is the time-averaged net input to a unit (not made explicit in Cohen and Servan-Schreiber (1992)), and \( b \) a bias value. To simulate the effects of a reduction in PfCx DA the gain parameter is reduced in the task demand units only. A value of 0.6 was found to be the most effective. Simulations were run again and two effects were noted: 1. an overall increase in the response time for both tasks (i.e. increase in number of cycles required for output activation to be reached), and 2. a disproportionate increase in response-time in the colour-naming task. These results mimic performance of schizophrenics. Cohen and Servan-Schreiber's explanation for these results is that both tasks rely on context to some extent, but the colour-naming one is more context-dependent and so performance is affected more on this task by a failure to apply contextual regulation. These results are, however, entirely predictable from looking at the dynamics of the model and the effect of manipulating \( g \) on the activation function. Figure 4.6 shows that as \( g \) is reduced the activation function becomes flatter. For positive values of net input the effect of reducing \( g \) is to reduce the activation of the unit. Quite clearly if the input to the intermediate units from the task demand units is reduced then it will take longer for them to achieve certain activation levels, and the knock-on effect on the output units is that it will take them longer to reach their threshold level. In the condition which requires the colour naming task demand unit to overcome the strength of the word naming path weights, this increase will be longer.
because we have effectively reduced the responsiveness of the intermediate units to input in a nonlinear way, thus their activations will be disproportionately slower to change. Cohen and Servan-Schreiber, pg 57 note that if they reduce the cascade rate for all the units then they do not get a disproportionate slowing in the colour naming conflict condition. What they do not suggest is reducing the cascade rate in the task demand units only. It is highly likely that this would give similar results to those obtained from manipulating $g$, thus weakening the explanatory power of their model.

Another point to note is that reducing $g$ in this model is analogous to increasing $T$ in Hoffman and Dobscha’s model. Thus the same manipulation comes to represent both pruning of synapses in an attractor network model of the brain, and a reduction in the level of DA in the PfCx in a back-propagation network model of the brain. This serves to illustrate the point made earlier that while neural network models may be useful in exploring ideas and representing cognitive processes, they are not very good models of brain processes i.e. they lack biological plausibility. From this it becomes clear that in using this modelling paradigm one must be very careful to choose the correct level of correspondence between the structure of the model and established biological facts in order to draw inferences and make predictions.

In conclusion, the motivation and theory behind Cohen and Servan-Schreiber’s model are interesting and provocative, but the results obtained from the model do not add
very much to these ideas.

4.4 Horn and Ruppin

The third model to be discussed is particularly interesting in the light of recent neuroscience data. The model, proposed by Horn and Ruppin (1995), is based on an attractor network, as Hoffman and Dobscha’s was. Horn and Ruppin use a modified version of the standard Hopfield-type attractor network which uses sparse patterns (only 10% of bits in an input pattern are positive) and a version of the unit input rule which separates external input from internal ongoing activity:

\[ h_i(t) = \sum_j W_{ij} S_j(t - 1) + F_i^e \]  \hspace{1cm} (4.12)

In this equation synaptic weights are represented by \( W_{ij} \); the activity of a unit \( j \) at time \( t \) is given by \( S_j = 0, 1 \) and determined by a deterministic sigmoid function similar to equation 4.2; \( F_i^e = e \cdot \xi_i^m \) determines the external input, where \( \xi_i^m \) is input pattern \( m \). \( F_i^e \) crucially depends on \( e \), the strength of external inputs. The activity of the network is measured as a comparison between the current state of the network and the set of stored memories within the network. This comparison takes the form of an overlap between current state and stored memories. Stimulus-dependent retrieval occurs when a cue pattern is presented (as \( F_i^e \)) and the network then evolves until it reaches a stable state, measured as a high overlap. Under normal conditions the network maintains a basal level of activity without converging on any of the stored memories (negligible overlap). Under certain conditions, however, the network may converge on a stored memory in the absence of external input. This condition is called spontaneous retrieval.

The model is intended to represent frontal lobe activity, with the external inputs coming from the temporal lobe. Extra input from other sources is modelled as a change in the noise parameter \( T \) (see Figure 4.7).
Horn and Ruppin refer to Stevens (1992)' hypothesis that the symptoms of schizophrenia arise due to abnormal reinnervation of the frontal cortices following reduced temporal lobe input. From this theory, Horn and Ruppin show that in the face of reduced external input (e.g. \( e = 0.01 \)) then a compensatory increase in the weights by a factor of \( c > 1.0 \) can maintain stimulus-dependent retrieval. However, a side-effect of the increase in weights is that the rate of spontaneous retrieval increases. Horn and Ruppin suggest that an increase in spontaneous retrieval of memories reflects some of the positive symptoms of schizophrenia such as hallucination and delusions. In this model they clearly focus on frontal-temporal interactions and memory retrieval as the
Review of computational models

major deficits in schizophrenia, which are issues discussed in chapter 3 and which the
work in this thesis is in agreement with.

The model that Horn and Ruppin have produced is very interesting and shows some
not entirely predictable behaviour. The theory on which it is based is slightly more
dubious. It is probably unwise to base a model on a single hypothesis. Although
there is evidence that hippocampal volume is reduced, there is also evidence that hip-
 pocampal activity is increased (Liddle et al., 1992; Friston et al., 1992) in schizophrenia.
The most compelling argument linking these facts is that excitotoxic damage to the
hippocampal region through overactivity causes the loss of volume. There is also evi-
dence that neonatal damage to the hippocampus causes compensatory changes in the
PfCx (Lipska et al., 1993, 1998, discussed in chapter 9), but there is also evidence that
dendritic changes in PfCx lead to a loss of dendritic field (Selemon et al., 1995), as
opposed to the increase suggested by Stevens. Finally, Horn and Ruppin are at great
pains to ensure that the pathological states of their network, while occurring unbid-
den, are characterised by genuine memories (i.e. high overlap) and not non-memory
states such as the parasitic foci of Hoffman and Dobscha. This is because they believe
(and cite evidence) that there is no deficit in memory retrieval in schizophrenics, and
that this fact is a fundamental flaw of Hoffman and Dobscha's model. Recent evidence,
however, casts both light and darkness on Horn and Ruppin's model. Heckers et al.
(1998) show increased PfCx activity and reduced hippocampal activity in schizophreni-
ics undertaking a memory retrieval task, however their performance is also impaired
on the task. Thus Horn and Ruppin's insistence that pathological activity involves the
retrieval of real memories may be their downfall.

4.5 Summary

In this chapter I have reviewed three of the most influential computational models
of schizophrenia to date. While they raise interesting issues and can demonstrate a
range of dynamics relating to cognitive activity, they make poor models of the brain
and thus limit the extent to which the levels of behaviour and biology can be linked. In the following chapters I will introduce four different models which operate at different biological and cognitive levels, but which taken together, I hope, will allow for examining the effect of changes in biological function on cognitive function.
Chapter 5

Modelling the prefrontal cortex

5.1 Introduction

The aim of this chapter is to investigate the function of the PfCx and the role of DA in PfCx using a model neuron, the spike response neuron (Gerstner and van Hemmen, 1994; Gerstner, 1998b,a), which characterises the spiking behaviour of individual neurons. Such a model summarises various ionic actions which could have been individually represented as differential equations. The use of a convolution model such as this was chosen for simplicity, it being felt that a model which mimics the dynamics of neuronal firing more closely would not add overly to the principles being illustrated by the spike response neuron.

The first step is to use a single model neuron and replicate some neurophysiological data relating to normal firing. Then I will model firing in the presence of DA acting on D₁ receptors. Having achieved this I will then proceed to connect several of these neurons together into an ensemble and show how the presence of DA allows the ensemble to maintain a particular pattern firing. This is, in effect, a form of weightless short-term memory. Crucial to this process are recurrent connections between different layers in the PfCx and inhibitory GABA interneurons (see Figure 5.1). It is contended that this
Modelling the prefrontal cortex

model represents a neural basis for the core feature of working memory, namely the ability to hold information 'online' in the absence of a stimulus. By considering lesions in different parts of the ensemble system, I am able to suggest a way in which different pathologies can all contribute to PfCx dysfunction and potentially to the symptoms of schizophrenia.

5.2 The spike response neuron

The basic model is composed of an ensemble of interconnected spike response neurons which form a network. The main premise behind the spike response model is that the form of coding used by real neurons may depend upon the timing of individual spikes. Thus neural codes which are based on mean firing rates or the averaging of spatial inputs may not be adequate to capture the full spatio-temporal dynamics of a biological network of neurons. It is argued that in order to investigate the dynamics and information processing properties of a biological neural network we need models which can capture the full range of dynamics of such networks. The spike response model represents a compromise between extreme biological detail exemplified by complex multi-compartmental models which require huge computational resources to generate a single spike, and more standard artificial neural networks which can compute complex functions but do not capture enough biological detail to make them plausible models of real neurons.

I will briefly describe how a spike response model works. The activity of a spike response neuron at time $t$ is given by a single equation (see Gerstner and van Hemmen (1994) for full details):

$$V(t) = P(t) + R(t)$$  \hspace{1cm} (5.1)

Where $V(t)$ represents the membrane potential, $P(t)$ represents the postsynaptic potential (PSP) and $R(t)$ represents the refractory potential of the neuron. If $V(t)$ exceeds
Figure 5.1: This diagram shows the PfCx circuitry captured in my model. Pyramidal cells in Layer III receive excitatory inputs (descending arrows) from other cortical regions and the hippocampus. They also receive DA afferents from the VTA and recurrent inputs from layer V pyramidal cells. The layer III cells form a fully connected ‘delay ensemble’, which is reciprocally connected with an inhibitory GABA interneuron. The layer V cells also play a crucial part in the delay ensemble, as well as projecting subcortically.
Figure 5.2: Figure (a) shows a simulated refractory potential with a very small DAP and a slow AHP. Figure (b) shows the DAP plotted on a much larger scale with $y=0$ plotted in red (dotted). Figure (c) shows a simulated PSP with axonal delay $\Delta^{ax} = 5.0$. This value is used for all the simulations in this chapter.

A threshold value $\Theta$ then the neuron is considered to have spiked and produced an action potential. In the discrete time case the PSP is given by:

$$P(t) = \sum_{t=0}^{\infty} \epsilon(s) S_j(t-s)$$

(5.2)

where $\epsilon(s)$ is the shape of a single PSP arising in neuron $j$ due to a spike from neuron $i$ at time $s$ (Figure 5.2 (c)). It is given by an alpha function:

$$\epsilon(s) = \begin{cases} 
0 & \text{for } 0 \leq s \leq \Delta^{ax} \\
\left((s - \Delta^{ax})/\tau_s^2\right) \exp\left(-(s - \Delta^{ax})/\tau_s\right) & \text{for } s > \Delta^{ax}
\end{cases}$$

(5.3)

$\Delta^{ax}$ represents the axonal conduction delay and $\tau_s$ is the membrane constant. In equation 5.2 the term $S_j(t-s)$ represents the existence of a presynaptic spike in neuron $j$ at time $s$ and accordingly takes values $\{0, 1\}$. 
Figure 5.2 (a) shows the basic shape of the refractory potential $R(t)$. However the shape of this will vary depending upon the exact firing conditions of the neuron, in particular, whether there is burst-firing or not.

The time of firing of a single neuron will depend on the superposition of the two curves, Figures 5.2 (a) and (c), shifted according to the time of firing of the presynaptic input and the value of $\Delta^a x$. The value of $\Delta^a x$ is of great importance in determining the stability states within a spike response model, discussed below.

If a number of spike response neurons are connected together then we have to consider the synaptic weights ($W_{ij}$) between them. These act to modify the PSP and equation 5.2 becomes:

$$P(t) = W_{ij} \sum_{t=0}^{\infty} \epsilon(s) S_j(t-s)$$  \hspace{1cm} (5.4)

In order to make the model more realistic I will incorporate some noise into the system. Thus the firing of a neuron is considered to be probabilistic and to depend upon a noise parameter ($1/\beta$). The equation for the firing of a neuron is:

$$P_f(t) = 1 - \exp (-p^{-1}(V))$$  \hspace{1cm} (5.5)

$$p(V) = p_0 \exp (-\beta(V - \Theta))$$  \hspace{1cm} (5.6)
5.3 Stability of the model

A fully connected network of spike response neurons linked with uniform synapses and with negligible noise can exist in one of two fundamental states: synchronous or asynchronous. The network will show either synchronous or asynchronous behaviour depending on the value of the axonal delay parameter ($\Delta^ax$). This can be explained if we imagine a network which is almost perfectly synchronised. If a particular neuron fires early in this network then the PSPs it induces in other neurons will all arrive early. In order to remove the effect of the rogue early firing neuron we need the temporal advance in firing of postsynaptic neurons to be less than the temporal advance in PSP arrival. In this way the firing time discrepancy in the rogue neuron will be absorbed by the network and it will tend toward perfect synchronisation. The factor which defines whether the advance in firing is greater or less than the advance in PSP arrival is the point of intersection between the PSP and the effective threshold ($R(t) - \Theta$), and this point of intersection is strongly affected by $\Delta^ax$ (Figure 5.3).

If the effective threshold intersects on the rising part of the PSP then the firing advance
will be less than the incoming PSP advance. This will have the effect of gradually reducing the increase in firing times until firing is synchronised. Conversely, if the effective threshold intersects on the falling part of the PSP then the advance in firing time will be greater than the incoming PSP advance and the overall effect is to continue to advance the firing times, thus pulling the system out of synchronisation. Figure 5.4 illustrates this.

Now that we know the importance of the point of intersection between the effective threshold and the PSP curve, we can see, from Figure 5.3 the importance of the value of $\Delta^{az}$. A higher value of $\Delta^{az}$ allows intersection on the rising part of the PSP curve and pushes the network into a synchronised state. Shorter $\Delta^{az}$'s will produce a network that is not able to absorb fluctuations in the timing of individual neurons and, assuming a minimum level of noise, the network will settle into an asynchronous firing state. The relevance of this will become clear when I look at possible lesions to the system. In particular, the effects of excessive synaptic pruning may relate to this.

Synchronous firing states can be harnessed to hold temporal sequences of patterns, although this is not investigated in the context of PfCx delay cells and DA.

### 5.4 Model of PfCx delay cells

In order to model PfCx delay cells we need to be able to reproduce the firing properties of a single PfCx cell. (Yang et al., 1996) show that the most prevalent pyramidal cell type in layer V-VI of rat PfCx has an initial spike doublet which is due to a prominent depolarising after-potential (DAP). They term these cells intrinsic bursting (IB) cells. I make the assumption that these results can be applied to layer III pyramidal neurons since they are morphologically similar although generally larger.

The DAP is dependent on the influx of $Ca^{2+}$ ions to the cell (HajDahmane and Andrade, 1997). IB's also show a marked slow after-hyperpolarisation (AHP) which increases with the number of spikes fired until the cell stops firing. In order to reproduce
Figure 5.4: This Figure demonstrates the consequences of the intersection of the effective threshold with the PSP curve. In both diagrams the dashed lines represent the intended time of firing in a synchronised system and the solid lines the actual time of firing. In both cases the neuron fires earlier than it should, and this is shown with respect to the PSP the neuron receives from the other synchronised neurons in the network. In the upper graph it is clear that T2 is significantly less than T1, thus the subsequent advance in firing is much less than the initial advance in firing. In the lower graph, T2 is greater than T1 and so the advance in firing is augmented. This will pull the system out of synchronisation.

these firing characteristics we need to assume that the shape of the refractory potential changes between the initial spike and subsequent spikes. It is known that slow AHP's are due to Ca\(^{2+}\)-activated potassium channels (Hille, 1992). These channels
are activated by $Ca^{2+}$ influxes occurring during each action potential. The slow AHP is absent when extracellular $Ca^{2+}$ is absent, and is enhanced when $[Ca^{2+}]_e$ is raised or after a series of action potentials. This tells us that the shape of the refractory potential is largely dependent on $Ca^{2+}$ fluxes and so will vary between action potentials. We use the following equations to model the change in refractory potential. The initial refractory potential, as shown in Figure 5.2 (a), is given by:

$$R(t) = 2^{(8-\frac{s}{5})} \left(\frac{k}{35}\right)^3 - 20 \left(\frac{k}{40} - 0.065\right)^2 + 0.001 - e^{-k}$$

(5.7)

$$k = \frac{s - refr_{abs}}{5} + 2$$

(5.8)

This equation was derived by trial-and-error curve-fitting using MATLAB. Subsequent refractory potentials are given by a modified version of equation 5.7:

$$R(t)_{subsequent} = \frac{NumPrevSpikes}{10} R(t)$$

(5.9)

$$k = \frac{s + 50 - refr_{abs}}{5} + 2$$

(5.10)

$refr_{abs}$ refers to the fast AHP or absolute refractory period which can be specified explicitly. In all simulations this was set to $refr_{abs} = 4.0$. Figure 5.5 illustrates the increasing magnitude of refractoriness with increasing number of presynaptic spikes.

The spiking characteristics for firing of a single IB PfCx cell are shown in Figure 5.6.

For a single cell there is no synaptic input therefore there are no PSP's to contribute to the membrane potential $V(t)$. We can see that as a result of the increasing magnitude of the AHP, spike frequency adaptation occurs, as is seen in the IB neurons. My model of the delay cell produces similar firing frequencies to the IB neurons and also shows spike frequency adaptation (Figure 5.6), thus reproducing the firing properties seen in the IB cell of the rat PfCx.
Figure 5.5: Increasing magnitude of refractory potentials with number of presynaptic spikes.

Figure 5.6: Simulation of a single delay cell given a triggering spike to represent initial depolarising current. This technique is used in all subsequent simulations. There is an initial spike doublet followed by spike frequency adaptation. Note that the graph indicates spiking on the y-axis and not membrane potential. Parameters used: $\Theta = 0.0$, $\frac{1}{\tau} = 4.0$. 
Figure 5.7: A single delay cell firing under the influence of DA acting on D₁ receptors in the presence of an initial depolarising current. Parameters used: $\Theta = -4.0$, $\frac{1}{\beta} = 40.0$

5.5 The effect of DA on PfCx delay cells

Yang and Seamans (1996) noted two main effects of DA on the firing properties of IB PfCx cells. There is an increase in firing frequency, and a loss of AHP and spike frequency adaptation. The increase in firing frequency is due to an effective reduction in the firing threshold of the neuron.

To simulate the effects of DA I have used a lower threshold and a refractory potential which does not change with the number of spikes produced. The latter is responsible for the loss of spike frequency adaptation seen in the model. While this gives simulation results which mirror the biological data it is not clear what the ionic basis for the lack of change in the shape of the refractory potential. One possibility may be that the increase in adenyl cyclase caused by activation of D₁ receptors stabilises the $[Ca^{2+}]$ at a higher level than occurs through the generation of action potentials. The equations for this refractory potential are equations 5.7 and 5.10.
Figure 5.7 illustrates the effects of DA on a single neuron. It can be seen that there is an increase in firing frequency and a loss of spike frequency adaptation, in agreement with Yang and Seamans' data. Figure 5.8 shows a comparison of the firing frequencies of neurons with and without DA. The graph compares simulation results with hand-picked data from Yang and Seamans pg. 1925 and shows that the model achieves a good degree of biological realism.

The effects of DA on PfCx pyramidal cells mentioned above are thought to occur at the soma. There is another effect of DA on the delay cells, however, which occurs in the distal dendrites. DA appears to increase the threshold of the $Ca^{2+}$-dependent high-threshold spike (HTS). This has the effect of attenuating distal input to the layer III delay cells. It is only larger, i.e. layer III, pyramidal cells which exhibit HTS spikes. The effect of DA here is to gate inputs to the layer III delay cells and so act to isolate the delay cells during a working memory task.

Having constructed a biologically plausible model of a single delay cell and the action of DA on this cell we now need to consider a network of such neurons. We can compare directly the effects of DA on the ensemble activity of a network with an unmodified system. Results are shown in Figures 5.9 and 5.10.
Figure 5.9: A network of 100 delay cells fully inter-connected with uniform weights, representing a delay ensemble. The network shows asynchronous activity. Parameters: $\Theta = 0.0$, $\beta = 4.0$, $\Delta \Delta = 5.0$, $\tau_\alpha = 4.0W_{ij} = \frac{1}{N}$, where $N$ = number of neurons in an ensemble.

Figure 5.10: The same network as in Figure 5.9 but under the influence of DA. The network shows synchronous activity. Parameters: same as in Figure 5.9, except $\Theta = -4.0$, $\beta = 40.0$. 
We can see that DA gives rise to coherent network activity. By regularising the firing of individual neurons in the network we can see how DA in the PfCx is able to stabilise activity and allow for information processing to take place. I will discuss exactly how the architecture of the PfCx can be utilised for information processing and the role DA has in the next section.

5.6 Information processing in the PfCx

Salient aspects of the architecture of the PfCx are shown in Figure 5.1; now it is time to put this into the context of information processing within the PfCx. We know that at the single cell level the PfCx has delay cells which remain active during the delay period of delayed response tasks. If we consider information to consist of temporospatial firing patterns then we need to consider how an ensemble of pyramidal delay cells can maintain such a pattern.

As mentioned in chapter 3, I propose that the layer III cells form a delay ensemble which is the fundamental unit of activity in working memory or delayed response tasks. Layer III pyramidal cells also act as input cells to the layer V cells which project subcortically, in particular to hippocampus, NAcc, and VTA. Layer III cells receive inputs from association cortex and so can direct processed aspects of sensory input into the delay ensemble (see Figure 5.1).

The crucial role of DA is to isolate and stabilise the delay ensemble. Through its actions, at proximal dendrites and soma, it regularises the firing frequency of individual neurons. Without a concurrent DA input to PfCx the delay ensemble will not enter a coherent firing state. In order for information to be held online the delay ensemble needs to be isolated from further inputs. This is the other role of DA. Acting at D₁ receptors on apical dendrites it increases the HTS threshold and makes it harder for inputs to reach the delay ensemble.
An important requirement is that any pattern may be stored in this delay ensemble without any learning process or structural re-arrangement occurring, that is, it acts as a weightless short-term memory. Without some other mechanism for ensuring that non-firing (off) cells within the pattern are not pushed into a firing state by the activity of other cells in the ensemble, we cannot ensure that the exact input pattern is maintained within the regular firing of the delay ensemble. This other mechanism is supplied by the GABA interneurons which provide reciprocal global inhibition to pyramidal delay cells and the recurrent connections from layer V. GABA interneurons also receive dopaminergic input, which acts via D2 receptors to increase the concentration of GABA in the PfCx. This will be dealt with in more detail in chapter 6, where the dynamics of the interaction between GABA cells and pyramidal cells is explored more fully.

Putting the actions of DA and GABA interneurons on the activity of PfCx delay cells together we get the following sequence of events. Excitatory input from other cortical or subcortical regions arrives at the delay ensemble. If the DA afferents are active then the delay ensemble is able to store information. The delay cells are reciprocally connected to a GABA interneuron which globally inhibits all cells in the ensemble and effectively increases the firing threshold of all cells. GABA synapses are known to be fast acting, so it is entirely plausible that the inhibitory effects will initially override the excitatory input from lateral connections. Those cells which fired initially will activate recurrent connections via layer V pyramidal cells and this excitatory input will re-activate these cells. Cells which do not receive recurrent input will not have enough excitatory input to overcome the increase in threshold due to GABA cell inhibition and so will remain quiet. In this way the spatial resolution of the input firing pattern is maintained over time. It is clear that both these mechanisms must be intact for accurate pattern retention to occur. If there is no interneuron inhibition then the lateral connections between the cells in the ensemble will cause all the cells in the ensemble to become activated over time. If there are no recurrent connections then the interneuron inhibition will prevent all the cells from firing and the ensemble will remain quiescent.

We can illustrate the effects of global inhibition on ensemble activity in our model.
Figure 5.11: A network with global inhibition and recurrent connections under the influence of DA. This network also shows synchronous behaviour. Parameters: as for Figure 5.10 except cells which receive no initial input (and therefore no recurrent inputs) have $\Theta = 1.0$.

of a delay ensemble. Cells which do not receive recurrent input have an increased threshold, thus by increasing the value of $\theta$ for cells receiving no input in the model we can reproduce the desired conditions. Results are shown in Figure 5.11.

We can see that the average firing activity for inhibited and non-inhibited ensembles looks very similar, i.e. both show coherent firing patterns (compare Figures 5.10 and 5.11). However an examination of exactly which cells are firing (Figure 5.12) shows that only the ensemble with inhibition and recurrent connections maintains the correct spatial firing pattern. This can be contrasted with ensembles with DA but no GABA input (Figure 5.13), and ensembles with no DA input (Figure 5.14).

This model represents a biologically plausible weightless form of short-term memory, whereby spatial patterns can be accurately stored over time without any form of synaptic modification, dependent upon an intact dopaminergic input to PfCx and an intact and functional PfCx architecture.
Figure 5.12: This Figure shows a raster of firing times for 10 neurons in an ensemble of 100. Here the parameters are set to represent DA and GABA input to the ensemble ($\Theta = -2.0$ for neurons receiving recurrent input and GABA input, $\Theta = 1.0$ for neurons with only GABA input, $\gamma = 40.0$). It can be seen that as well as synchronous firing within the ensemble, the precise neural firing pattern is maintained.

It should be mentioned here that this model does not incorporate an accurate representation of the GABA interneuron. This has implications for the firing frequency of the pyramidal cells which are predicted to fire more slowly in an ensemble under the influence of DA (see chapters 6 and 9). Also, no account of the DA action on the $D_2$ receptors is included. It is not envisaged that these omissions will affect the information processing properties of the ensemble, as described above.

5.7 Schizophrenia: multiple pathologies lead to the same outcome

I have earlier looked at the evidence for PfCx involvement in working memory and schizophrenia (chapter 2). Now, in the light of my model of PfCx delay cells and the various components necessary for correct functioning of this model, we can consider in more detail the nature of PfCx dysfunction in schizophrenia. This will also be con-
Figure 5.13: Here we have the same input pattern as in Figure 5.12, with DA input but no GABA inhibition. Parameters are as in Figure 5.10. Here we can see synchronous firing, but no maintenance of the specific input pattern.

Figure 5.14: This Figure shows the case where there is no DA input and no GABA inhibition. The same input pattern is used as in Figures 5.12 and 5.13. Parameters as in 5.9. The Figure shows that in the absence of DA and GABA activity there is neither pattern maintenance nor synchronous firing.
Modelling the prefrontal cortex

sidered in chapter 8 in terms of the interaction between PfCx and other brain regions such as hippocampus and NAcc.

There is evidence that there is a reduction in D_1 receptor activity in the PfCx of schizophrenics (Okubo et al., 1997). From my model of delay cell activity we can see in a qualitative fashion exactly how this reduction in DA D_1 receptor activity affects the ability to hold spatio-temporal patterns online.

A reduction in the activity of D_1 receptors will have two main effects. One is that the coherence of firing patterns in the delay ensemble will be disrupted. This corresponds directly to a disruption in working memory ability. The other implication of a hypodopaminergic state is that the gating of inputs to the delay ensemble is reduced, leading potentially to extraneous activity in some of these cells. This could be construed as a reduction in attentional ability, another hallmark of schizophrenia. Overactivity of D_1 receptors would also lead to deranged prefrontocortical function through over-gating of inputs and preventing access to the delay ensembles. Many psychotomimetic drugs do raise DA levels e.g. amphetamine, cocaine, LSD (via serotonin), although their principal locus of action is probably in the NAcc. Interestingly, PCP, a drug which can induce behaviour identical to both the negative and positive symptoms of schizophrenia, causes an increase in NAcc DA and decrease in PfCx DA (Svensson et al., 1995). This is evidence in support of the theory that in schizophrenia there is hypodopaminergia in PfCx and hyperdopaminergia in subcortical structures, especially NAcc.

We can also see from the model, however, that defective PfCx function can arise from causes other than reduced DA action. A loss of global inhibition from GABA interneurons will prevent the maintenance of a spatial pattern over time although the delay ensemble activity will remain coherent. In line with this observation there is data to suggest that in schizophrenia there may be a reduction in the number of GABA interneurons and a reduction in inhibition (Benes et al., 1996). If we look at the converse case, where GABA cells are over-active we would expect to see poor performance on working memory tasks, and this is seen in studies assessing the cognitive effects of
Modelling the prefrontal cortex

benzodiazepines (Coull et al., 1995). Diazepam also reduces the novelty-induced release of DA in PfCx (Feenstra et al., 1995), however, so we cannot be sure exactly by which mechanism benzodiazepines reduce performance on working memory tasks. The third component of the model which is crucial to the formation of coherent firing activity in delay ensembles is the duration of the axonal delay ($\Delta^{ax}$). As discussed above, if the duration of the axonal delay is too short then coherent activity will not form in the network (except in conditions of zero noise, which do not exist in biological neural systems). Although there is no evidence for conduction defects in schizophrenia to affect the axonal delay, there is, however, some evidence for developmental abnormalities (Harrison, 1997). In particular for the hypothesis that excessive pruning of synapses in developing neocortex underlies schizophrenia (Keshavan et al., 1994), as discussed in chapter 4. If synaptic pruning proceeds by a distance rule where long and/or synaptically weak connections are removed, as suggested by Hoffman and Dobscha (1989), then we would see shorter connections maintained at the expense of longer and weaker connections. If this is the case then, assuming the general architecture is preserved, we would have delay ensembles composed of neurons with short axonal transmission times. Shortened axonal delays may prevent synchronous firing in an ensemble, as outlined earlier in the chapter. This would obviously prevent correct functioning of the delay ensemble and lead to working memory deficits. This provides an alternative to the attractor-based explanation for the consequences of over-pruning. In addition, there is a possible correlation between neonatal brain damage and the subsequent development of schizophrenia. It could be that a disruption in the development of frontal architecture, either in terms of altered axonal delays or disruption to the recurrent connections from layer V pyramidal cells to layer III stripes, is the mechanism behind this correlation.

It can be seen that multiple pathologies can all lead to the same or similar outcomes in terms of PfCx function. This in turn implies that these pathologies are involved in the pathogenesis of schizophrenia. This fits nicely with the growing view that schizophrenia is not one illness but a collection of illnesses or conditions with a common core pathology.
5.8 Summary

In this chapter I have investigated the neural basis of working memory by constructing a model based on the spiking properties of neurons. Using this model I have replicated experimental data for spiking patterns in rat PfCx pyramidal cells (delay cells). I have also replicated the effects of DA on the firing properties of individual cells. I have then connected several model neurons together to form a fully connected ensemble of delay cells. Using the same parameters as for single neurons I have shown the effect of the application of DA to the delay ensemble. DA allows the ensemble to fire coherently, which is a prerequisite for it to be able to store a pattern of information over time. In order for the pattern to be stored accurately it is necessary to have global GABA inhibition and recurrent re-activation of the correctly firing cells. Any change in: 1. DA activity in PfCx; 2. GABA interneuron activity; or 3. the recurrent connections from layer V to layer III, can result in PfCx dysfunction. Alterations in all three of these parameters have been observed in different studies of schizophrenics. Thus the model illustrates how multiple pathologies can lead to PfCx dysfunction, and so, ultimately, how they may underly some of the symptoms of schizophrenia.
Chapter 6

Modelling Dopamine Dynamics

6.1 Introduction

The aim of this chapter is to investigate the dynamics of the ventral DA system. The key structures in this system are the VTA, NAcc, and PfCx. The PfCx projects to the VTA, the NAcc also projects to the VTA, and the PfCx projects to the NAcc. Thus there are several inter-linked feedback loops which all contribute to the control of firing of VTA DA cells. In this chapter I will attempt to unravel some of the dynamics that arise from these loops, primarily looking at the effects of changing DA levels on the activity in PfCx and NAcc, but also looking at how changes in activity in PfCx can affect activity in VTA and NAcc. I will also look briefly at the effects of manipulating somatodendritic DA activity in the VTA.

The main idea is that we can investigate the dynamical interaction of brain regions through modelling the effects that variation in the concentration of neurotransmitter in one region can have on the concentration of neurotransmitter in another region. The model described below is composed of a set of first-order differential equations which describe the various pharmacological interactions in the pathways linking PfCx, NAcc and VTA. Certain external inputs are also included since this is not a closed system.
The model presented here is in effect a proof of concept, to which certain plausible assumptions have to be made. This is to say that this approach to modelling neurotransmitter dynamics has not been undertaken before and it can be seen as a novel way of exploring the possibilities of dynamic models. The equations utilised in the model can be solved using a numerical integrator. Specifically the model was implemented in C++, and a fifth order Runge-Kutta algorithm with adaptive stepsize control was used to numerically integrate it. This program was adapted from code in Press et al. (1992). All simulations referred to in this chapter were performed using this numerical integrator software.

### 6.2 Some dopamine neurobiology

The initial motivation for this model came from work by Kalivas (Kalivas, 1993) which describes the pharmacological control of activity in VTA DA cells. There are two distinct dopaminergic projections from the VTA, one to the PfCx (mesocortical), and one to the NAcc (mesolimbic). I have tried to capture the neurotransmitter actions relevant to schizophrenia which are involved in the control of DA release in PfCx and NAcc, and the effects which DA has on these structures. These are summarised in Figure 6.1.

I have discussed in chapter 3 Grace’s model of schizophrenia (Grace, 1991, 1993; O’Donnell and Grace, 1998) and the importance that somatodendritic DA has within that model for setting the tonic level of DA in the NAcc. The factors controlling somatodendritic DA release in the VTA appear to be the same as those controlling terminal release of DA (Kalivas and Duffy, 1991). This includes muscarinic (Gronier and Rasmussen, 1998) and 5-HT2 (Kalivas, 1993) actions. Recent evidence points to a lack of D2 autoreceptor inhibition of somatodendritic release however (Horger and Roth, 1996; Iravani et al., 1996; Cragg and Greenfield, 1997), so they are not incorporated into my model. In the model, then, there are separate terms for mesolimbic and mesocortical levels of somatodendritic DA release since these two populations of cells receive different inputs. The functional role of somatodendritic DA seems to be to enhance
both glutamatergic inputs to the VTA and GABA interneuron effects within the VTA, via D₁ receptors (see Figure 6.1). In Experiment 2. I will look at the effects of removing somatodendritic DA from the model.

The excitatory input to the VTA is considered to come from PfCx and external glutamatergic inputs. The PfCx input has a direct excitatory effect on, specifically, the
phasic actions of the DA neurons and increases the level of DA in the NAcc (Murase et al., 1993; Nisell et al., 1995; Rossetti et al., 1998) via its action on the VTA. From this I am assuming it has a similar effect on concentrations of DA in the PfCx. 5-HT acting at 5-HT2 receptors (Kalivas, 1993) has been shown to increase firing of VTA DA neurons by direct action on the neurons. Presynaptic effects in the VTA have also been shown to act on Glu afferents. These actions, by DA at D1 receptors (Kalivas and Duffy, 1995) and nicotine at nicotinic receptors (Schilstrom et al., 1998), have both been shown to increase the concentration of Glu in the VTA and also increase the level of DA in NAcc. In addition, presynaptic effects have been shown to occur on GABA afferents from the NAcc to the VTA. 5-HT, via 5-HT1B receptors, reduces GABA activity, thus having a disinhibitory effect on the mesolimbic DA neurons (Cameron and Williams, 1995). Conversely, DA via D1 receptors, increases the afferent GABA input from the NAcc and provides tonic inhibition on the mesolimbic DA neurons (Aceves et al., 1995). GABA interneurons have been shown to exist in the VTA but it is not clear exactly where the excitatory input to these cells comes from; however it is known that there is presynaptic enhancement of their activity by DA acting on D1 receptors (Kalivas and Duffy, 1995) and maybe a direct action on them via D2 receptors (David et al., 1997). In the model I have included separate mesocortical and mesolimbic populations of interneurons because there are different concentrations of somatodendritic DA in these two regions. Evidence for two distinct VTA regions also comes from Svensson et al. (1995), who describe different effects of PCP on the paranigral nucleus, projecting largely to NAcc and other limbic structures, and the parabrachial pigmented nucleus which projects largely to the PfCx.

The neurobiology of the NAcc and PfCx have been described earlier (chapter 3), and I mention here how this information has been incorporated into the model. The PfCx is considered to have reciprocally connected pyramidal (Glu) cells and GABA interneurons. The pyramidal cells also form the major projection out of the PfCx, therefore activity in these cells, as represented by the variable $Gl$, is extremely important for the rest of the model. DA has a modulatory action on both the pyramidal (via D1 receptors) and GABA (via D2, or maybe D4, receptors) cells. It facilitates activity via both of these receptors, thus indirectly inhibiting pyramidal cells via the GABA cells. The
Figure 6.2: Simplified connectivity within the NAcc. SN represents Spiny Neuron and i/n represents interneuron. These have mutually inhibitory actions on each other. SN collaterals are not explicitly modelled. Excitatory inputs come from hippocampus and PfCx, and other regions. Dopamine input from the VTA acts at D$_2$ receptors and has an inhibitory action, this includes D$_2$ autoreceptors. 5-HT$_{1B}$ receptors allow for presynaptic excitation of dopaminergic inputs.

precise action of DA on PfCx pyramidal cells remains contentious and is mentioned again in chapter 9. The results of these simulations may help to shed further light on this issue. The level of DA in the PfCx can be increased by the presynaptic action of 5-HT on 5-HT$_{2A}$ receptors on the DA afferents. This PfCx circuit has been studied as an independent sub-system and both analytical and simulation results are presented later in this chapter.

The NAcc has two components in the model: spiny projection neurons and interneurons, both of which are inhibitory GABAergic neurons (see Figure 6.2). The interneurons inhibit the spiny neurons. In addition, DA has an inhibitory effect on both of the cell-types via D$_2$ receptors (Yamamoto and Davy, 1992; Matsui et al., 1998). Also,
there are strong presynaptic effects on DA release in the NAcc through excitatory 5-HT action via 5-HT1B receptors (Hallbus et al., 1997) and DA autoinhibition through D2 receptors (Wieczorek and Krul, 1995). Excitatory input to the NAcc, to both interneurons and spiny cells, is from PfCx and hippocampus. There is some confusion in the literature over the presynaptic interactions between afferent Glu and DA inputs to the NAcc. For example, there is evidence for:

1. presynaptic reduction in [Glu] by DA (Kalivas and Duffy, 1997);
2. presynaptic increase in [Glu] by DA (Dalia et al., 1998);
3. presynaptic reduction in [DA] by Glu (Taber et al., 1996);
4. presynaptic increase in [DA] by Glu (Ohno and Watanabe, 1995);

Although there is most support for condition 4, in view of the lack of agreement in the neurobiology literature on the nature of the DA-Glu presynaptic interaction in the NAcc, no treatment of this interaction was included in the model.

The foregoing describes the effects this model is intended to capture. In the next section I will present the equations and some explanation of the methodology and assumptions therein.

6.2.1 Assumptions and justifications

The equations used in the model describe the rate of change in concentration of neurotransmitters in the relevant brain regions. It is assumed that these rates of change are continuous. This means that no account of the firing patterns of neurons is taken into account. Ultimately this is undesirable because it reduces the accuracy of the model, which weakens the explanatory power of any results the model produces. However,
the complexity of a model which takes firing patterns and neurotransmitter concentrations into account would be very great. It would be necessary to have either complex equations which can represent the different firing states of neurons in a single equation, or multiple equations for each cell-type, with one equation per firing state. The escalation in numbers of parameters would also reduce the accuracy of such a model. Crucially, however, including firing patterns would not necessarily provide any more information regarding brain function since the relationship between neural firing patterns and brain function remains far from clear. In addition, the relationship between brain regions is much better understood in terms of neurotransmitter levels than it is in terms of neural firing patterns, thus the firing pattern level of detail is generally not available for inclusion in the model.

The equations in the model here represent the excitatory and inhibitory actions of the various neurotransmitters described above. To represent the clearance, reuptake and general decay in the concentration of neurotransmitter at the synaptic cleft, I have included a negative term proportional to the square of the relevant neurotransmitter. Modelling the timecourse of neurotransmitters in the synaptic cleft is in itself a very complex issue (Clements, 1996) and the approximation I have used here seems reasonable since none of the equations I have used are asymptotic. A discussion of possible alternative formulations can be found at the end of this chapter.

The general form of the equations is that excitatory influences on the production of neurotransmitter are positive quantities modified by appropriate rate constants and combined additively. Inhibitory influences are represented similarly as negative quantities which are subtracted. In order to deal with presynaptic actions I have treated these as being combined multiplicatively. Presynaptic effects in general occur through increasing \( Ca^{2+} \) influx which stimulates extrusion of neurotransmitter containing vesicles (Kandel et al., 1991). Impulse dependent release of neurotransmitter also works through increasing \( Ca^{2+} \) influx. The flow of \( Ca^{2+} \) can be considered to be proportional to both variables and so the two are combined multiplicatively. From the foregoing it is apparent that some of the equations contain terms which are occurring
in different physical locations. Specifically, presynaptic and clearance terms act distally at the site of transmitter release whereas actions affecting impulse driven release act proximally on the dendrites and soma of the relevant cell.

6.2.2 The equations

<table>
<thead>
<tr>
<th>Variable/parameter</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_n$</td>
<td>[DA] in NAcc. Includes presynaptic actions on DA input to NAcc.</td>
</tr>
<tr>
<td>$D_p$</td>
<td>[DA] in PfCx. Includes presynaptic actions on DA input to PfCx</td>
</tr>
<tr>
<td>$D_{vl}$</td>
<td>terminal [DA] due to phasic firing in mesolimbic part of VTA</td>
</tr>
<tr>
<td>$D_{vc}$</td>
<td>terminal [DA] due to phasic firing in mesocortical part of VTA</td>
</tr>
<tr>
<td>$D_{sdlt}$</td>
<td>[DA] due to somatodendritic release in mesolimbic part of VTA</td>
</tr>
<tr>
<td>$D_{sdc}$</td>
<td>[DA] due to somatodendritic release in mesocortical part of VTA</td>
</tr>
<tr>
<td>$G_{asn}$</td>
<td>terminal [GABA] due to firing of spiny neurons in NAcc</td>
</tr>
<tr>
<td>$G_{a\text{inn}}$</td>
<td>[GABA] due to GABA interneurons in NAcc</td>
</tr>
<tr>
<td>$G_{a\text{p}}$</td>
<td>[GABA] due to GABA interneurons in PfCx</td>
</tr>
<tr>
<td>$G_{a\text{vol}}$</td>
<td>[GABA] due to GABA interneurons in mesolimbic part of VTA</td>
</tr>
<tr>
<td>$G_{a\text{vc}}$</td>
<td>[GABA] due to GABA interneurons in mesocortical part of VTA</td>
</tr>
<tr>
<td>$G_l$</td>
<td>terminal [Glu] due to pyramidal neurons in PfCx</td>
</tr>
<tr>
<td>$G_{lh}$</td>
<td>Glutamatergic input from hippocampus</td>
</tr>
<tr>
<td>$G_{lexl}$</td>
<td>Glutamatergic input from external sources to mesolimbic dopamine neurons in VTA</td>
</tr>
<tr>
<td>$G_{lexc}$</td>
<td>Glutamatergic input from external sources to mesocortical dopamine neurons in VTA</td>
</tr>
<tr>
<td>$S_{1B}$</td>
<td>Action of 5-HT on 5-HT1B receptors in NAcc and PfCx</td>
</tr>
<tr>
<td>$S_2$</td>
<td>Action of 5-HT on 5-HT2 receptors in VTA</td>
</tr>
<tr>
<td>$S_{2A}$</td>
<td>Action of 5-HT on 5-HT2A receptors in PfCx</td>
</tr>
<tr>
<td>$N$</td>
<td>Action of ACh on nicotinic receptors in VTA</td>
</tr>
<tr>
<td>$M$</td>
<td>Action of ACh on muscarinic receptors in VTA</td>
</tr>
</tbody>
</table>

Table 6.1: Explanation of variables and parameters
The equations for the model are listed below. Table 6.1 lists the variables and parameters of the system and their actions.

\[ D_n = D_{cl}(k_2 S_1 B - k_1 D_{cl}) \]  
\[ D_p = k_3 S_1 B D_{vc} \]  
\[ D_{sii} = k_9 D_{el} \]  
\[ D_{sdc} = k_{10} D_{vc} \]  
\[ \frac{dG_{asn}}{dt} = k_{11} Gl + 2k_4 Gl_h - k_{17} D_n - k_{23} G_{ain} - k_{24} G_{asn}^2 \]  
\[ \frac{dG_{ain}}{dt} = k_{11} Gl + 2k_4 Gl_h - k_7 D_n - k_{26} G_{ain}^2 \]  
\[ \frac{dD_{cl}}{dt} = k_{14} D_{sdt} Gl + k_{15} N Gl - k_{19} G_{aet} - k_{18} D_{et} G_{asn} + k_{19} S_1 B G_{asn} + k_{20} S_2 + k_{21} M + k_{13} G_{et} D_{sdt} - k_{29} D_{et}^2 \]  
\[ \frac{dD_{vc}}{dt} = k_{14} D_{sdc} Gl + k_{15} N Gl - k_{23} G_{ave} + k_{20} S_2 + k_{27} M + k_{22} G_{exc} D_{sdc} - k_{36} D_{vc}^2 \]  
\[ \frac{dG_{ael}}{dt} = k_{28} D_{sdt} Gl - k_{37} G_{ael}^2 \]  
\[ \frac{dG_{ave}}{dt} = k_{28} D_{sdc} Gl - k_{38} G_{ave}^2 \]  
\[ \frac{dG_{ap}}{dt} = k_{34} D_p + k_{35} Gl - k_{10} G_{ap}^2 \]  
\[ \frac{dGl}{dt} = (k_{32} + k_{30} D_p)(Gl + G_{cc}) - k_{31} G_{ap} + k_{33} S_2 A Gl - k_{39} Gl^2 \]
6.2.3 Selection of rate constants

It was initially intended to calculate the rate constants from data available in the neuroscience literature relating to release of neurotransmitters in certain brain regions relevant to these models in response to the application of a different neurotransmitter in another relevant brain region, e.g. measuring the release of dopamine in the PfCx in response to the application of Glutamate in the VTA. These experiments were performed in rats or guinea pigs and were intended to show functional links between different brain regions. There are several problems with these experiments which detract from using the data in the models.

1. There is not enough data to calculate all the rate constants in this manner. In fact, fewer than half of them could be calculated in this way.
2. Most of the experiments rely on the application of very large amounts of neurotransmitter, far in excess of the amounts released in vivo.
3. The experiments are all performed in rats or guinea pigs.

Therefore it seems unrealistic to assume that the dynamics of neurotransmitter release in these experiments reflect the dynamics of neurotransmitter in the human brain. Rate constants were selected on an ad hoc basis to provide a working model. This is in keeping with other models using systems of differential equations to model biological processes (Edelstein-Keshet, 1988).

6.3 Results

Having constructed the model, three experiments were carried out. These do not in any way represent an exhaustive investigation of the properties of the model, but give some interesting and useful results and serve to illustrate the potential of the model.

Figure 6.3 shows the model at rest. All the variables are in equilibrium. It is unlikely that this situation ever arises in vivo but it is important for a model to start from such an equilibrium state.
Figure 6.3: \textbf{(Time = ms)} Equilibrium states for: (a) $D_n$, (b) $D_p$, (c) $G_{asn}$, and (d) Gl. Note that activity in NAcc is so heavily damped that the resting value for $G_{asn}$ is very low. All the other quantities exhibit damped oscillation.

6.3.1 Experiment 1: The action of DA in NAcc

The aim of this experiment was to illustrate the potential switching between ensembles that Pennartz \textit{et al.} (1994) describe (see chapter 3). Figure 6.4 shows the effects of a pulse of excitation applied to the mesolimbic VTA on the NAcc while the NAcc is in the resting state and also while it is under the influence of excitatory input.
Figure 6.4: (Time = ms) In Figures (a) and (b), a pulse of excitatory input to the mesolimbic DA cells is applied ($G_{\text{exc}} = 1$). This causes a corresponding increase in $D_n$ but no increase in $G_{\text{dsn}}$, thus no activation of NAcc spiny neurons. Figures (c) and (d) illustrate the application of a pulse of excitatory input to the NAcc ($G_{\text{hl}} = 5 \times 10^{-6}$). This does cause increased activity in NAcc as seen in Figure (d). Figures (e) and (f) illustrate the simultaneous activation of mesolimbic DA cells and NAcc cells. The DA pulse transiently halts activity in the NAcc.
Under resting conditions, increasing $D_n$ has no effect on the activity of the NAcc. This is due to the strong resting inhibition in the NAcc. Excitatory inputs can induce activation of the medium spiny neurons in the NAcc (Figure 6.4 (d)). Under these excitatory conditions the activation of mesolimbic DA cells causes a DA pulse which inhibits the action of the medium spiny NAcc neurons (Figure 6.4 (f)). It should be noted that DA only has an effect on the NAcc medium spiny neurons in the presence of a depolarising input from the hippocampus which lifts the NAcc projection neurons out of their extremely negative resting potential. This has been called the gating of action of the hippocampus by O'Donnell and Grace (1995), and has been mentioned as necessary for the induction of LTP and LTD in the neostriatum by Wickens et al. (1996).

Since the model only operates at the neurochemical level it is difficult to reconcile these results precisely with the theory of Pennartz et al. (1994). However, certain statements can be made. The overall effect of DA on the excited NAcc is inhibition. From Figure 6.5 we can see there is little effect of DA on $G_{a_{in}}$.

The GABA interneurons are thought to provide feedforward inhibition between en-
sembles, and reducing this inhibition could allow different ensembles to compete and a new one to become activated, thus effecting switching between ensembles. The results from my model, however, do not support this theory because the action of DA on $G_{ain}$ is not strong enough. An alternative and similar possibility is that through transiently inhibiting the activity of an ensemble, this will allow another ensemble to become activated depending upon the pattern of excitatory inputs.

Finally, I have looked at two forms of increased DA in the NAcc. The results are shown in Figure 6.6.

In both cases the excitatory input to the mesolimbic DA cells is increased. In one instance it is raised to a uniform level throughout the experiment. This is intended to represent increased tonic DA in the NAcc, with a loss of phasic activity. Figure 6.6 (a) and (b) shows that this has the effect of preventing the normal excitatory action from hippocampal afferents. In the other case the excitatory input to the VTA is only increased during the phasic release. This is intended to represent a relative increase in the phasic release of DA in the NAcc. Figure 6.6 (c) and (d) shows that in this case the expected excitation of NAcc projection neurons from hippocampal input occurs, but there is no DA-induced disruption in the level of $G_{asn}$. Thus, in the latter case, there will be a loss of switching. It should be pointed out that Figure 6.6 (c) shows two very small peaks of $D_n$ with a dramatic fall in concentration between the two peaks. This fall is due to the autoreceptors becoming highly activated and effectively switching off all DA release in the NAcc. It is not clear how biologically plausible this is, but it is discussed in a later section of the chapter.

It is interesting to compare the situation of increased phasic DA in the NAcc with an increase in hippocampal input to the NAcc. This simulation was carried out and the results are shown in 6.7.

It can be seen that, in my model at least, an increase in phasic DA in the NAcc has a similar effect on NAcc activity as an increase in the hippocampal input to the NAcc.
Modelling Dopamine Dynamics

Figure 6.6: (Time = ms) Figures (a) and (b) represent uniformly increased mesolimbic input ($G_{ext} = 1$). The hippocampal input ($G_{h} = 5 \times 10^{-6}$) has no effect on NAcc activity ($G_{sn}$ stays low). Figures (c) and (d) show the effect of increasing mesolimbic input only during the intended period of DA activity ($G_{ext} = 100$ for duration of excitatory pulse, otherwise at basal value $1.62 \times 10^{-8}$).

That is, they both allow excitation of NAcc projection neurons but no dopaminergic inhibition, and so no switching, occurs. This suggests that hippocampal overactivity can prevent the normal action of DA in the NAcc from occurring. This provides another link between hippocampal dysfunction and consequent NAcc and DA dysfunction, and has implications for schizophrenia.
In this simulation an increased excitatory pulse from hippocampus is applied ($G_{lh} = 5 \times 10^{-3}$), and the usual mesolimbic pulse is also applied ($G_{lex} = 1$). The latter induces a pulse of DA in the NAcc (Figure (a)), but this fails to inhibit the NAcc projection neurons. Compare with Figure 6.6 (c) and (d).

### 6.3.2 Experiment 2: Somatodendritic dopamine

In this experiment, the aim was to investigate the effects of somatodendritic DA in the VTA. Since I am assuming there are no VTA DA autoreceptors based on the evidence cited above, it is unclear exactly what influence somatodendritic DA might have on DA release. I have simulated both an increase and a decrease in VTA somatodendritic DA. Results are shown in Figures 6.8 and 6.9.

In both situations the DA concentration in the NAcc is not as high as would be expected, given the excitatory inputs to the VTA. In the case of increased somatodendritic DA this is due to the activation of autoreceptors. In the case of reduced somatodendritic DA there is a general loss of responsivity of VTA DA neurons to excitatory input. In the face of increased excitatory input to the VTA, especially the mesolimbic section, this reduction in responsivity may help restore normal DA transmission. This may be part of the therapeutic action of atypical neuroleptics, such as clozapine, which have a high affinity for $D_1$ receptors. This will be discussed further in chapter 9.
Figure 6.8: (Time = ms) This Figure represents an increase in somatodendritic DA. Mesocortical and mesolimbic inputs are set at $G_{l_{exc}} = 0.0005, G_{l_{ext}} = 1, G_{l_{h}} = 5 \times 10^{-6}$ to simulate the normal inputs which induce DA release in PfCx and NAcc. $D_{s_{eff}}$ and $D_{s_{dec}}$ are increased by a factor of 1000. Figure (a) shows an increase in the simulated level of DA in the PfCx while Figure (c) shows a decrease in the level of DA in the NAcc. Figures (b) and (d) show the consequent changes in simulated levels of Glu in the PfCx and GABA in the NAcc.

6.3.3 Experiment 3: Excitation of mesocortical VTA cells

In this experiment I simulated excitation of the mesocortical VTA cells in order to see what effects this has on PfCx DA concentrations and also PfCx Glu and GABA concentrations. Figure 6.10 shows the results.

We can see that excitation of mesocortical DA cells can increase the DA concentration in PfCx and this induces oscillations in the levels of Glu and GABA. This may correspond to the functional synergism and information processing properties described.
earlier in chapter 5. In the next section I will explore the origins of these oscillations more fully and show, analytically and through simulations, the conditions under which they may arise.

6.4 Focussing on PfCx dynamics

6.4.1 The simplified model

The 12-equation model described earlier allows us to change specific parameters and observe the changes in the whole system in a quantitative way. If we want to know,
however, how the system behaves qualitatively then we must use a simplified system. The reason for this is that mathematical analysis is in general only tractable for systems with 2 variables. In order to investigate qualitatively the dynamics of the PfCx I have taken equations 6.11 and 6.12 in isolation and treated DA as a continuous parameter which may be varied. In this way we can investigate the effects of increased and reduced DA in the PfCx. Specifically, we can investigate the hypotheses that functional synergism exists between PfCx GABA interneurons and PfCx pyramidal cells, as suggested by Wilson et al. (1994) and my model of the PfCx described in chapter 5; and that the concentration of DA in the PfCx can alter the nature of GABA cell-pyramidal cell interactions, in effect acting as a control parameter.

Equations 6.11 and 6.12 are re-written here in terms of the variables Gl and Ga_p for convenience:

\[
\frac{dG_a_p}{dt} = -k_{40}Ga_p + (k_{35} + k_{34}D_p)Gl \quad (6.13)
\]
\[ \frac{dG_l}{dt} = -k_{39}G_l^2 + (k_{32} + k_{33}S_{2A} + k_{30} D_p)G_l - k_{31}G_{ap} + (k_{32} + k_{30} D_p)G_{cc} \]  (6.14)

The same values of rate constant were used as in the global model.

### 6.4.2 Analysis of the simplified model

Given equations 6.13 and 6.14 we can analyse the dynamics of the system as DA is varied. The techniques used in this section are described fully in Edelstein-Keshet (1988). The starting point for the analysis is the **Linearisation Theorem**. Informally, this states that the behaviour of a non-linear system close to its fixed point(s) approximates to a linearised version of the system (see Arrowsmith and Place (1992) pg 77). The fixed point of a system is simply where there is no change i.e. the rate of change of both variables is 0. By setting \( \frac{dG_{ap}}{dt} = 0 \) and \( \frac{dG_l}{dt} = 0 \) we get the following quadratic equations defining the fixed points of my system:

\[ -k_{40}G_{ap}^2 + (k_{35} + k_{34} D_p)G_l = 0 \]  (6.15)

\[ -k_{39}G_l^2 + (k_{32} + k_{33}S_{2A} + k_{30} D_p)G_l - k_{31}G_{ap} + (k_{32} + k_{30} D_p)G_{cc} = 0 \]  (6.16)

The above equations are known as **nullclines**. From 6.15:

\[ G_l = \frac{-k_{40}G_{ap}^2}{(k_{35} + k_{34} D_p)} \]  (6.17)

Substituting the term for \( G_l \) in 6.17 into equation 6.16 we get:
Modelling Dopamine Dynamics

\[-k_{39} \left( \frac{-k_{40} Ga_p^2}{k_{35} + k_{34} D_p} \right)^2 + (k_{32} + k_{33} S_{2A} + k_{30} D_p) \frac{-k_{40} Ga_p^2}{k_{35} + k_{34} D_p} - k_{31} G a_p + (k_{32} + k_{30} D_p) G_{cc} \]  

(6.18)

This has given us a polynomial in \( G a_p \). Although it cannot easily be solved analytically, precise values for its roots can be obtained numerically for specific values of \( D_p \) using the MATLAB software package. The values obtained for \( G a_p \) can then be plugged back into equation 6.17 to yield the fixed point value for \( G1 \). From equation 6.18 we can see that there may be up to 4 fixed points for this system.

Having determined the fixed points of the system (for a given value of \( D_p \)) we can look at the behaviour of the system around these fixed points.

A nonlinear 2 \( \times \) 2 system \( f_1(x, y), f_2(x, y) \) at a steady state \((x_0, y_0)\) behaves much like a linear one:

\[
\frac{dx}{dt} = a_{11} x + a_{12} y
\]

(6.19)

\[
\frac{dx}{dt} = a_{21} x + a_{22} y
\]

(6.20)

The Jacobian of such a linear system at the steady state is given by:

\[
J(x_0, y_0) = \begin{pmatrix}
    a_{11} & a_{12} \\
    a_{21} & a_{22}
\end{pmatrix}
= \begin{pmatrix}
    \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} \\
    \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y}
\end{pmatrix}
(x_0, y_0)
\]

(6.21)

My system gives the Jacobian:
$$J = \begin{pmatrix} -2k_{40}G_a p & k_{35} + k_{34}D_p \\ -k_{31} & -2k_{39}G_l + k_{32} + k_{30}D_p + k_{33}S_{2A} \end{pmatrix}$$ (6.22)

This can then be evaluated at the various fixed points \((G_a p, G_l)\) dependent upon the value of \(D_p\). The behaviour of the system around these fixed points, and the stability of the fixed point, can be determined by examining the trace \((Tr)\), determinant \((det)\), and discriminant \((disc)\) of \(J\) (see Edelstein-Keshet (1988) pp 186-191 for full details). These are given by:

$$Tr(J) = -2k_{40}G_a p - 2k_{39}G_l + k_{32} + k_{30}D_p + k_{33}S_{2A}$$ (6.23)

$$det(J) = -2k_{40}G_a p(-2k_{39}G_l + k_{32} + k_{30}D_p + k_{33}S_{2A}) + k_{31}(k_{35} + k_{34}D_p)$$ (6.24)

$$disc(J) = Tr(J)^2 - 4det(J)$$ (6.25)

With these tools at my disposal I was able to examine the behaviour of the Glu-GABA interactions in the PfCx model for various values of \(D_p\). The results are presented in table 6.2.

Here the stability condition refers to the geometry of the phase plane. In other words, the shape of the plot if \(G_l\) is plotted against \(G_a p\).
Table 6.2: This table shows the fixed points in the phase plane for different values of $D_p$, and the stability conditions at these points. Note that the saddle point and the stable node have the same $Tr$ and $disc$ signs. The difference is that a stable node has two negative eigenvalues, while the saddle point has one negative and one positive eigenvalue.

### 6.4.3 Bifurcations

The results in 6.2 suggest the existence of two bifurcations. I will briefly describe why this is so, and in the next section present simulation results which support the occurrence of these bifurcations.

As the value of $D_p$ is increased the nature of the stability conditions around the fixed point changes from being a stable spiral to an unstable spiral. This is predicts the existence of a Hopf bifurcation, and if that is the case then a limit cycle will be found close to the fixed point, according to the Hopf bifurcation theorem (Arrowsmith and Place, 1992). A limit cycle is seen as a closed orbit in the phase-plane and is of interest because it indicates stable oscillation of the two variables in the system. The conditions for the existence of a Hopf bifurcation are as follows:

1. a stable fixed point becomes unstable as some parameter (upon which the fixed point depends) is varied;
2. the steady state has complex eigenvalues;

3. the eigenvalues have a non-zero real part;

4. as the parameter passes through a critical value \( D_p^* \) the sign of the real part of the eigenvalue changes (from \(-\) to \(+\) if going from stable to unstable).

The Hopf bifurcation theorem predicts the occurrence of a limit cycle close to the fixed point if these criteria are met. It does not say anything about the stability of the limit cycle, or what happens in phase space far away from the fixed point. From Table 6.2 we can see that condition 1. is met as \( D_p \) is increased. The eigenvalues for my system can be calculated from the \( Tr \) and \( disc \) of the Jacobian using the following formula:

\[
\lambda_{1,2} = \frac{Tr \pm \sqrt{disc}}{2}
\]  

The critical value, \( D_p^* \), cannot be calculated directly for my system because the expressions for \( Tr \) and \( disc \) depend on the fixed point values of \( G_{ap} \) and \( Gl \), and, as discussed above, there is no simple expression relating the fixed point values to the value of \( D_p \). By repeated calculation of the eigenvalues, however, I was able to determine that:

\[
4.8 \times 10^{-10} < D_p^* < 4.9 \times 10^{-10}
\]  

The eigenvalues of the system either side of \( D_p^* \) (for the values in equation 6.27) are: \(-1.45 \times 10^{-6} \pm 1.52 \times 10^{-4}i\) and \(7.24 \times 10^{-7} \pm 1.53 \times 10^{-4}i\). We can see that all the criteria for a Hopf bifurcation are met. The simulation results in the next section illustrate this and show that a stable limit cycle comes into existence with this bifurcation. We would intuitively expect the limit cycle to be stable since the fixed point is unstable, and so points in the phase plane close to the fixed point will be repelled from the fixed point. This would suggest that they are attracted to the nearby limit cycle, making it a stable limit cycle.
The second bifurcation in the system has less functional significance but is still of interest because it suggests what might happen when the concentration of DA in the PfCx is very high. From Table 6.2 we can see that there are values of $D_p$ for which there are three fixed points in the phase space. From repeated calculation of the fixed points (equations 6.17 and 6.18) the two extra fixed points arise as $D_p$ passes above $1 \times 10^{-5}$. As indicated in Table 6.2 the stability condition for the lower-valued fixed point is a saddle point. We can tell this because the eigenvalues for the system at this fixed point have one positive and one negative value. As the value of $D_p$ is increased the saddle point moves towards the lowest-valued fixed point (unstable spiral). When $D_p$ is fractionally greater then $9.584 \times 10^{-5}$ both of these fixed points disappear. One of the ‘symptoms’ required for a saddle-node bifurcation ((Arrowsmith and Place, 1992), pg 226) is that two fixed points move together, merge into one, and then disappear entirely. The interim single point just described is the bifurcation point. The other condition is that the linearised system at the bifurcation point has one zero and one non-zero eigenvalue. Since I cannot calculate directly where the bifurcation point is, I cannot show its existence or verify that it satisfies the eigenvalue requirement. Thus this change in the fixed points of my system is possibly a saddle-node bifurcation, but can only be demonstrated to be so by analytically solving the polynomial defining the $Gl$ fixed point. Regardless of this, the fact remains that for $D_p > 9.584 \times 10^{-5}$ the system has only one (high-valued) fixed point which is a stable node. The importance of this is that there can be no oscillations in the system above this value of $D_p$.

6.4.4 Results: DA as a control parameter

In this section simulation results are presented which support the analysis of the preceding section. Figure 6.11 show the system at rest and the appearance of a limit cycle. It is quite clear from Figure 6.11 that the limit cycle is indeed stable, as was anticipated. This means that for the range $4.8 \times 10^{-10} < D_p < 9.584 \times 10^{-5}$ there are stable coupled oscillations of the values of $Ga_p$ and $Gl$. I will discuss the functional implications of this in subsequent sections.
Figure 6.11: (Time = ms) Figure (a) shows the nullclines for $G_{a_p}$ and $G_l$ for $D_p = 3.0 \times 10^{-10}$, the resting value. The * represents the starting point of the system, in this case the system is in equilibrium and so there is no movement from the starting state. Figure (b) shows the temporal evolution of the system ($G_l$ in red (upper trace) and $G_{a_p}$ in blue (lower trace)). Figure (c) shows the system with $D_p = 4.9 \times 10^{-10}$. The nullclines are almost identical to those for the resting state, however the dynamics of the system around the fixed point are considerably different. The two *'s represent two alternative starting points which both converge onto a stable limit cycle (thick line), which confirms the occurrence of a Hopf bifurcation. The inner (green) trace starts from the resting values of $G_{a_p}$ and $G_l$, the outer (magenta) trace starts from $(2.0 \times 10^{-8}, 2.95 \times 10^{-7})$. Figure (d) depicts the time evolution of the system starting from resting values of $G_{a_p}$ and $G_l$. It shows there is stable oscillation between $G_{a_p}$ (lower blue trace) and $G_l$ (upper red dashed trace).
Figure 6.12: (Time = ms) Time plots for (a) $D_p = 3.0 \times 10^{-7}$ and (b) $D_p = 3.0 \times 10^{-2}$, with the system starting from the resting values of $G_{av}$ and $Gl$. The top (blue) trace is for the time evolution of $G_{av}$ and the lower (red) trace is for the time evolution of $Gl$. In Figure (a), we can see there are still stable oscillations and so the limit cycle still exists (and is reachable when starting from resting values). Figure (b) shows that the oscillations have disappeared and the system has converged on a stable node. The values of $G_{av}$, $Gl$ and $D_p$ involved in Figure (b) are very high and represent an upper limit of activity.

Figure 6.12 shows time plots for the evolution of the variables $G_{av}$ and $Gl$. In order to ascertain the number of fixed points in the system as $D_p$ is increased simulations were performed with the value of $D_p$ increasing by a factor 5 each time. Figure 6.13 shows the system when 3 fixed points exist. The saddle point effectively divides the phase-plane into two attractor basins; one with high values of $G_{av}$ and $Gl$ and a stable node, and the other with low values of the variables and a limit cycle.

6.5 Criticism of the model

The results obtained from the above models are all dependent on the precise formulation of the equations and the values of the parameters and rate constants used. The results are, at best, quantitatively approximate and in general illustrate what could, qualitatively, occur given a certain set of circumstances.
Figure 6.13: (Time = ms) In Figures (a)-(d) $D_p = 3.0 \times 10^{-5}$. Figure (a) shows the $G_{a_p}$ and $G_l$ nullclines, respectively in blue (dot-dashed) and red (solid). The three fixed points of the system are marked on (a) with O's. Figure (b) shows the two nullclines (red and blue dotted lines) and the phase-plane trajectories of the system starting from 2 adjacent points ($(2.0 \times 10^{-5}, 4.0 \times 10^{-6})$ and $(4.0 \times 10^{-5}, 3.0 \times 10^{-6})$, marked by *'s). The two points are both very close to a saddle-node fixed point. The attracting manifold of this fixed point lies roughly parallel to the $G_{a_p}$ axis, so the two plots are initially attracted towards the fixed point. Once they encounter the repelling manifold, which runs roughly in the $G_{a_p} = G_l$ plane, they are repelled away from the fixed point. Since the two starting points are effectively on different sides of the saddle, they are repelled in opposite directions. The upper (green) trace is attracted to a stable node. The time evolution of this trace is shown in Figure (d) ($G_{a_p}$ in blue (upper) and $G_l$ in red (lower)). The lower (magenta) trace in Figure (b) is attracted to the limit cycle which exists around the lowest fixed point (time evolution shown in Figure (c) (representation as for Figure (d)). This fixed point has the stability condition of an unstable spiral and has had this characteristic since the Hopf bifurcation occurred. The other two fixed points are new and indicate the possible occurrence of a saddle-node bifurcation.
One of the outstanding issues with the equations used in the model is that they are not intrinsically asymptotic. That is, the general form for the representation of a particular neurotransmitter is to add a set of positive ‘release’ terms and a set of negative ‘inhibition of release’ terms, and a quadratic uptake term. These are reasonable terms to use but do not necessarily cause the concentration of the neurotransmitter to vary between fixed lower and upper limits. Thus it has been necessary to impose a lower limit on all concentrations of $1 \times 10^{-18}$ Mol. Accordingly the presynaptic autoreceptor term in equation 6.1 may not be realistic in that for very high values of $D_{ul}$ the value of $D_n$ hits the imposed lower level rather than increasing above the upper fixed limit as we might expect. In other words, it is not possible to saturate the autoreceptors and raise the simulated level of DA in the NAcc above the homeostatic upper limit. Instead, the autoreceptors come to dominate the dynamics of the accumbal dopamine release. It is not clear that this happens in vivo. Two alternative approaches could possibly have been used for the basic neurotransmitter dynamics:

1. I could have used a simple sigmoidal function. This would have given the release dynamics the desired asymptotic minima and maxima, but it would not be possible to use the biological data to generate the rate constants. More importantly, it would also not generate the anticipated autoreceptor dynamics.

2. The other option would be to use a much more sophisticated set of equations, having a separate differential equation for release, uptake, diffusion and degradation. This would make the model far too complex and unwieldy. In addition, for most parameters, the biological data does not exist to give them appropriate values.

In support of my approach, Garris and Wightman (1994) use a similar formulation. For the caudate-putamen and NAcc they assume rate of uptake is governed by Michaelis-Menten kinetics because values for $K_m$ are available for these regions. However, for Michaelis-Menten kinetics have the property of saturation and take the general form: $\frac{dX}{dt} = \frac{K_{max}C}{K_m + C}$, where $X$ and $C$ are variables; $K_{max}$ is the upper limit for $\frac{dX}{dt}$ when $C$ is large; and $K_m$ is the rate constant for the production of $C$. 

\footnote{Michaelis-Menten kinetics have the property of saturation and take the general form: $\frac{dX}{dt} = \frac{K_{max}C}{K_m + C}$, where $X$ and $C$ are variables; $K_{max}$ is the upper limit for $\frac{dX}{dt}$ when $C$ is large; and $K_m$ is the rate constant for the production of $C$.}
the PfCx and amygdala they approximate rate of uptake with a first-order process characterised by a rate constant $k$. Their final formulation for PfCx is:

$$\frac{d[DA]}{dt} = [DA]_p f - k[DA]$$  \hspace{1cm} (6.28)

where $[DA]_p$ refers to the concentration of DA released per stimulus pulse and $f$ is the stimulation frequency. This is quite similar to my formulation, the main difference being that I have not taken into account any frequency data, and I have used a quadratic uptake term. The reason for this was that the uptake curves shown in Clements (1996) and Garris and Wightman (1994) (pg447) appear to be fit better this way. Future work could address these issues.

It was mentioned earlier that no term for PfCx autoreceptors was included. This was based on two pieces of evidence. One is from Garris and Wightman (1994), who conclude that PfCx DA release does not tend to steady state. They consider DA concentrations in the PfCx to be 'release driven', whilst those in NAcc and caudate-putamen are 'uptake driven'. The second piece of evidence is that the density of D$_2$ receptors in the PfCx is 10 times lower than that of D$_1$ receptors, and much lower than the density of D$_2$ receptors in the striatum. Since autoreceptors are known to be D$_2$ receptors and many of these are located on GABA neurons this suggests that, while autoreceptors have been shown to exist in the PfCx (Bean et al., 1990), they may only present in small quantities in the PfCx and play a limited role in modulating DA release.

Another point to be made is that certain interactions were left out of the model. For example, noradrenaline is not included at all in the model. Also, α-1, D$_1$, and D$_2$ interactions are not included either. These may be important in relation to the mode action of neuroleptics (Gioanni et al., 1998). In addition, not all the parameters in the model were utilised in the experiments and clearly there is a whole host of other experiments which could have been carried out.
6.6 Interpretation of the results

A 12-equation model encapsulating significant interactions between the VTA, NAcc and PfCx with respect to the control of DA release in these regions was constructed. The 12-equation model allowed me to investigate certain changes in the control of DA release from the VTA. Experiment 1 illustrates a potential switching role for DA via D2 receptors in the NAcc. Large increases in either the level of DA in the NAcc or the excitatory hippocampal input to the NAcc effectively remove this switching effect. Switching appears to be a necessary part of any alteration in reward-based responses, such as in a spatial discrimination with reversal task. In schizophrenia, there is often a loss of ability to switch responses appropriately, and perseveration ensues. This is one example of how aberrant DA activity in NAcc may be involved in schizophrenia. The NAcc also has other potential roles in schizophrenia. One is as the locus of action of neuroleptic drugs; this is discussed in chapter 9. The other is as a site for reward-based learning using DA acting on D1 receptors as an error signal. This is discussed in chapter 8.

Experiment 2 illustrates the effects of increasing or reducing the somatodendritic release of DA in the VTA. The effect of reducing somatodendritic release in VTA is to reduce the effect of excitatory inputs to the VTA. Thus the normal PfCx and NAcc pulses of DA in response to VTA excitation are absent. An increase in somatodendritic DA increases PfCx DA and NAcc DA, although the latter is is reduced by the severe action of D2 autoreceptors in the NAcc. All these actions are assumed to be presynaptic effects acting via D1 receptors on excitatory and inhibitory afferents to the VTA DA cells. The results suggest that the main role of somatodendritic DA is to amplify the excitatory inputs to the VTA and ensure adequate terminal release of DA.

Experiment 3 was a simple illustration of the normal release of DA in the PfCx following the application of an excitatory pulse to mesocortical VTA cells. The ensuing release of DA in the PfCx caused reciprocal oscillations in the activity of the pyramidal and GABA cells in the PfCx. This is hypothesised to reflect functional synergism, as suggested by Wilson et al. (1994).
Following on from this, a 2-variable sub-system of the global model was investigated. This sub-system comprised variables representing the activity of pyramidal and GABA cells in the PfCx, with the ascending DA input as a continuous parameter of this system. A model composed of 2 ODE's is amenable to mathematical analysis, and this was undertaken. The analysis revealed the existence of a Hopf bifurcation, which was demonstrated with simulations. A Hopf bifurcation implies the existence of a stable limit cycle, which in turns implies that the oscillations in Glu and GABA are stable. Further analysis revealed the upper and lower values of the DA parameter for which the stable limit cycle existed. Above and below these values the system tends to a fixed point. These results confirm the hypothesis of Williams and Goldman-Rakic (1995) that there is an optimal level of DA in the PfCx.

If functional synergism is necessary for normal PfCx function, as demonstrated in chapter 5, then from the foregoing both raised and reduced levels of DA in PfCx can prevent normal PfCx function. This has a bearing on schizophrenia, as discussed earlier.

It is very interesting to consider the changes in the values of Gl and Ga, as Dp is varied, in the light of the discussion on the role of DA in the PfCx in chapter 3. Thierry's work implies that DA has an inhibitory effect on pyramidal cells via D2 receptors. This could be via GABA interneuron inhibition. Yang's work implies that DA acting on D1 receptors enhances the firing of pyramidal cells, and this work has been the basis for the model in chapter 5 which illustrates how the PfCx can store information online, crucially requiring GABA interneurons for maintaining spatial resolution of stored patterns. Now if we look at the values of Gl and Ga in the 2-variable model in this chapter we can see, from Table 6.2, that the value of Gl for which there is a stable spiral (and so a stable limit cycle nearby), falls initially, and then rises slightly. In this model DA has an enhancing effect on the pyramidal cells and yet the level of pyramidal cell activity appears to fall. Since we know, from information presented in chapters 3 and 2, that DA in PfCx is necessary for working memory function and that increased activity in PfCx is observed during working memory tasks, it would appear that the increased activity in PfCx is due to increased firing of GABA interneurons. If we can
accept that a fall in the level of \( Gl \) in the model has less functional significance than the appearance of oscillations then we can almost tie up the contradiction between Thierry's and Yang's work. The final point to make is that in the work of Thierry, experiments are not performed on animals performing working memory tasks and measurements are generally done at the single cell level. I have suggested that a crucial part of performing a working memory task is the *ensemble* activity of a group of pyramidal cells (chapter 5). From this it is possible to suggest that the reason Thierry does not see any pyramidal cell firing at all when applying DA to the PfCx is because there is no ensemble activity to overcome the DA-induced GABAergic inhibition.

Commenting on the above, we see that, once again the role of the GABA interneuron seems pivotal in PfCx function, and so any disruption to the distribution and functioning of GABA interneurons may also contribute to PfCx dysfunction. Also, hypo-functionality of the PfCx may in fact reflect a reduction in GABA cell activity and DA afferent input, not necessarily a reduction in pyramidal cell activity.
Chapter 7

Modelling the Tower of London task

7.1 Preface to chapters 7 and 8

The aim of this chapter and the next is to look at possible functions of the PfCx and NAcc in the cognitive domain. This chapter looks at the PfCx and uses the Tower of London task as a paradigm for modelling the cognitive function of the PfCx. The following chapter uses reinforcement learning as a means to illustrate a possible mechanism for the function of the NAcc. Both chapters use the Tower of London task as the data-set to be modelled. It is very important to stress, however, that in this chapter I am modelling performance of the Tower of London task directly as a model of PfCx function, whereas in the following chapter (chapter 8) I am simply using the Tower of London data-set as an example of a set of sequences to be learned. I am not suggesting that the NAcc is involved in the way in which humans learn to perform this task, merely that the NAcc may be involved in the learning of sequences by a reinforcement or reward-based learning mechanism. The set of sequences used in the model in chapter 8 is the Tower of London data-set so that a comparison between a standard
reinforcement learning approach and that of Dehaene and Changeux’s (1997) model can be made. In terms of modelling the function of NAcc, any set of sequence data could have been used. Thus the PfCx model (this chapter) is a model of performance on a planning task and the NAcc model (next chapter) is a model of sequence learning. In certain situations these two processes may intersect, for example when playing chess, where tactical planning abilities (PfCx) are used in conjunction with previously acquired strategic skills (putatively the NAcc).

The models in this and the next chapter are subsequently lesioned in a fashion intended to mimic possible psychological or biochemical changes in people with schizophrenia, and the results are then interpreted in the context of schizophrenia at the end of chapter 8

7.2 Introduction

As already discussed, the PfCx is involved in planning and ‘thinking ahead’ activities. One task which taps these properties is the Tower of London planning task. In this chapter the model presented represents PfCx function in solving this task.

7.3 The Tower of London planning task

The Tower of London task taps planning ability and in doing so utilises working memory. Several studies have shown that the PfCx is active during the Tower of London task (Morris et al., 1993; Baker et al., 1996; Owen, 1997) and also that performance is impaired in patients with either frontal lobe damage or schizophrenia (Morice and Delahunty, 1996). Thus it can be used as a measure of the preservation of these functions in various normal and patient populations.
The aim of the Tower of London task (which is a simplified version of the more general Tower of Hanoi problem) is to go from an initial configuration of discs on pegs to a target configuration in a specified (minimum) number of moves (See Figure 7.1). Moves consist of removing one disc/piece from the top of its stack and placing it in the lowest unfilled position on another peg. With the three-disc task, different starting and goal configurations can be used to give a set of 1260 problems ranging in difficulty from 1 to 8-moves. Subjects are asked to try and work out a solution to the problem mentally before they actually make any moves. Problems requiring few moves (less than 3) are easy to solve and do not really tax the PfCx. Accordingly, frontal lobe patients and schizophrenics are not especially impaired on these problems. However, problems with greater than 3 moves are increasingly difficult, as shown by the fact that the time taken to solve them increases monotonically with number of moves.

There are several factors which make these problems harder. One is that the number of decision points increases. A decision point occurs when it is not clear what the next move should be i.e. it is not possible to place any disc in its goal position and there is more than one possible move. Ward and Allport (1997) refer to moves like this as sub-goal chunks. In order to solve the problem efficiently it is necessary to store a decision point temporarily in working memory and also to remember which move was made from it. This means it is possible to backtrack and try alternative moves if the first choice of move was not successful. The time taken to solve a problem, and hence its difficulty, depends on the number of sub-goal chunks (or decision points). Another factor which adds to the degree of difficulty of a problem is whether there is any goal-subgoal conflict (Goel and Grafman, 1995; Morris et al., 1997). A goal-subgoal conflict arises when the correct move required to solve the problem efficiently takes a disc.
out of its goal position, or fails to place the disc in its goal position when there is an opportunity to do so. There is conflict because the *instinctive* choice of move is always to put a disc in its goal position. In order to solve certain problems it is necessary to *inhibit* the instinctive 'going for goal' behaviour when goal-subgoal conflict occurs. We can see now why the PfCx is necessary for efficient performance of the Tower of London task. It is required to generate the plans to solve the Tower of London task. Specific aspects of this function include holding decision-points in working memory and inhibiting instinctive behaviour in certain situations.
7.4 Review of Dehaene's model

Dehaene and Changeux (1997) have produced a very complex neurally inspired model which solves the Tower of London task. Their model starts from raw sensory input and proceeds through a 'gesture' level and an 'operation level' to a 'plan level'. All these levels are given biological analogues, e.g. the plan level represents PfCx function. Basic knowledge of the structure of the Tower of London task is coded into the gesture and operation levels. It is not clear why these levels have to be distinguished, other than to increase the complexity of the model and lend it further, probably spurious, biological association. Their model solves the 3-disc Tower of London task and is tested on problems ranging from 1-6 moves, as are commonly used in psychological testing. Ward and Allport (1997) believe that people can cope with more complex forms of the Tower of London task, and use a 5-disc version with up up to 10 moves.

There are several problems with Dehaene and Changeux's model. The most fundamental is that it does not appear to be able to solve problems with a goal-subgoal conflict, even with the inclusion of a working-memory module. This is because it uses a 'remaining goals' statistic which has to decrease. If this value increases then this triggers an error which causes the move to be abandoned. In the case of goal-subgoal conflict a piece has to be moved out of its correct position, causing 'remaining goals' to go up temporarily, in order that the problem may be correctly solved. This temporary increase in 'remaining goals' can be likened to an annealing process, where the error must ultimately decline but small and transient increases in the error are permitted. Dehaene and Changeux claim that their model can solve these problems given enough time, due to the inclusion of noise in the activation function. It is still not clear how this allows moves to be made which increase the activity in the 'remaining goals' unit.

In addition, in assessing the model's performance Dehaene and Changeux do not appear to take into account the fact that it is always possible to get to the correct goal configuration in more than the minimum number of moves. In fact, this seems to be a feature of their data-set since they state that their data-set represents 2081 problems,
but there are only 1260 minimum-move problems. This implies that some of the problems they have used require a task to be solved in more than the minimum number of moves. This is never done in psychological testing, and would certainly require some sort of move-counter to keep track of the number of moves taken. Their model does not have such a move-counter. Also, they do not state exactly how the performance of their model is assessed, however in some of the examples they give of correct performance it can be deduced that the goal was not achieved in the minimum number of moves. Thus it is not clear exactly how well Dehaene and Changeux’s model matches the psychological data with which they compare it.

Another potential flaw in Dehaene and Changeux’s model is that it implicates reward-based learning in the solution of the Tower of London task. As mentioned earlier in this chapter, planning and reward-based learning are very different processes and there is no evidence that the latter is involved in planning activities. If this was the case then a standard reinforcement learning model would produce as good, if not better, results than Dehaene and Changeux’s complex system (as shown in chapter 8).

One interesting finding of Dehaene and Changeux is that their model does show that solution time and error rate depend on the number of direct and indirect moves, rather than the total number of moves. A direct move is where a disc is placed in its target position, an indirect move is any other move. This confirms the findings of Ward and Allport (1997) on psychological testing. My models were not assessed on this issue.

7.5 Basic components of the model

In both this model and the one in the following chapter it is assumed that given any particular configuration, all the moves which can be made from it can be seen. In other words, we consider that knowing which discs can physically be moved does not constitute part of the cognitive process of solving the task but belongs in the realm of primary sensorimotor processing. This is represented in the models as a set of pre-learnt
associations between current state and possible moves. This corresponds to the gesture and operation levels in Dehaene and Changeux's model. These associations are represented in neural networks trained with a standard back-propagation algorithm (e.g., Hertz et al., 1991). Since changes in primary sensorimotor processing are not fundamental features of schizophrenia these network representations are not altered in any of our simulations. In order to cope with the mapping from current state to possible moves, which is a one-to-many mapping, I have introduced an intermediate level of coding, which can be thought of as a binding code (see Figure 7.3). Activation of a single unit in the binding code layer represents a whole configuration, which is itself represented as a pattern of activity in 18 state-units. The state-units provide a description of the 6 possible locations of the 3 different discs, using 18 units. The input layer of the model is composed of 18 state-units, plus 18 context units which hold the target configuration. Context is necessary when the network already has stored knowledge in order to disambiguate the possible moves. Between 2 and 4 units in the output layer will be active given any particular input configuration. Another network acts to translate the binding code back to 18-bit activity patterns which can then be used in other parts of each model for hypothesis testing and/or learning.

It is worth mentioning that for the model presented in this chapter this neurally inspired input set-up is not a key feature of the model, and a different way of inputting patterns could equally have been chosen without losing anything from the model. The choice of the neural network input arrangement was much more relevant to the model of the NAcc in the next chapter, which is intended to be more neurally accurate. To simplify the simulation process, the same neural network input system was used for both models however.

7.6 The PfCx model

This model is rule-based and requires working-memory components to function. The PfCx model uses the heuristic suggested by Ward and Allport (1997) (pg 69) on the
OUTPUT

BINDING CODE

Figure 7.3: The network in this diagram maps from specific configurations to possible moves from that configuration. This architecture and 'move knowledge' is common to the models in this chapter and the next. The state-units represent a particular configuration of the Tower of London task using an 18-bit code. The context units represent a particular context (the target state). The binding code converts a particular position into between 2 and 4 possible moves which can be made from that position.

basis of their psychological experiments. First a target disc is designated. This is the first, lowest, incorrectly placed, disc as we scan the puzzle from right to left and is effectively the most difficult disc to place. If this disc is covered then we look to see if its target location is occupied. If the target location can be freed then that move is selected, otherwise we move the discs above the target disc until it can be moved. This heuristic is combined with rules regarding the “goodness” of a move (see Table 7.1) to select a move. This heuristic is similar to the perceptual strategy of Goel and Grafman (1995).

It is important to note that a move which places a disc in its goal position is always taken. This can give rise to goal-subgoal conflict, as described above. Other features of the model are that it stores in a working memory any position where there is more than one possible move after applying the criteria in Table 7.1, i.e. it stores decision points. It also remembers which move is made subsequent to the decision point. If following a particular trail of moves leads to a dead-end (i.e. no legal move) then the model backtracks to the decision point and chooses a different move. Figures 7.4 and
Modelling the Tower of London task

<table>
<thead>
<tr>
<th>Score</th>
<th>Move Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Moves a disc to its goal position</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>Moves target disc, but not to goal location</td>
</tr>
<tr>
<td>1</td>
<td>Moves disc away from goal location</td>
</tr>
<tr>
<td></td>
<td>Moves disc not designated as target disc</td>
</tr>
<tr>
<td>0</td>
<td>Moves the same disc twice on successive moves</td>
</tr>
</tbody>
</table>

Table 7.1: Scoring of different move types. Higher scoring moves take precedence over lower scoring moves

7.5 illustrate the process of storing decision points and backtracking using an 8-move problem. Another feature of the model is that if the number of items stored in working memory exceeds the minimum number of moves of the puzzle then the model restarts the puzzle from the beginning, although the time is not reset to zero. Also, the only non-deterministic aspect of this model is in the value given to moves which score between 1.5 and 2.5 points.

Results for the basic model are summarised in Figure 7.6. A one-way within-subjects ANOVA comparing time against number of moves showed a clear main effect, $F(7, 367) = 54.7, p < 0.0001$. Tukey HSD pairwise comparisons of the main effect showed significant differences between (3 and 4) and (1 and 2), (5 and 6) and (1, 2 and 3), and (7 and 8) and (1-5). This shows that performance time does increase significantly with the number of moves in the task. This compares with a similar finding from testing real subjects (Ward and Allport, 1997)

Errors are classed as relative if the problem is solved but not in the minimum number of moves, and absolute if the problem is not solved at all. The results for error rates with the PfCx model are qualitatively similar to those from real subjects although quantitatively much worse. This can be accounted for by the fact that we used a 3-disc problem which has a higher decision-point to goal ratio than the 5-disc problem. Also, my model also did not have an explicit move-counter, although to compensate for this
Figure 7.4: This diagram illustrates the concept of decision points and backtracking. The problem is an 8-move problem. The black lines represent the moves taken by the model. Red (dashed) lines represent backtracking to the decision point (DP). It can be seen that at some decision points the correct move is made (e.g., 21 and 14) and there is no backtracking to these points. Having made the initial move from 21 to 19, the model is committed to moving to 18 since this puts the middle (gold) piece in its correct position. In order to escape from position 18 it is necessary to backtrack to 19 and inhibit the 'going for goal' move that selects position 18. This illustrates goal-subgoal conflict which requires inhibition of the automatic response for its resolution.
Figure 7.5: This diagram shows the trajectory through state-space of the model solving the same problem as in Figure 7.4.

Figure 7.6: Results for the PiCx model. Solid (blue) line gives correct sequences; dashed (red) line shows relative errors; dot-dashed (green) line shows absolute errors. I used a randomly selected problem set consisting of 6 types of each problem, with problems ranging from 1-move to 8-moves. 10 simulations were run using this problem set giving a total of 480 data points. This table shows mean performance times and the average error rate. Error rate is calculated as the number of problems which are solved in greater than the minimum number of moves over the number which are solved with the minimum number of moves. One of the 7-move problems could not be solved. See Appendix B for the data-set.
Figure 7.7: Graph of results taken from Ward and Allport (1997). They have used tasks with 1, 2, 3, 5, 7, and 10 moves on a 5 disc task, with 6 different tasks for each move category. This gives a data-set of 48 puzzles, which was presented to 10 subjects.

it was able to restart a problem when the number of items stored in working memory exceeded the minimum number of moves.

The results from the basic model correspond reasonably well with the data from Ward and Allport’s study, thus making it a reasonable model of a cognitive process. In a later section of the chapter I will alter some of the parameters of the model in order to simulate potential schizophrenic deficits.

7.7 Lesions of the PfCx Tower of London model

I have investigated three conditions representing PfCx dysfunction:

- Condition 1: loss of inhibition of ‘going for goal’ instinct

- Condition 2: reduction in the number of items that can be stored in working memory
Figure 7.8: Top graph shows results for condition 1. (no inhibition); lefthand graph shows results for condition 2. (reduced working memory capacity, from 9 items to 2 items); righthand graph shows results for condition 3 (disruption to working memory). Solid (blue) line = correct sequence; dashed (red) line = relative error; dot-dashed (green) line = absolute error.

- Condition 3: disruption to the integrity of memories stored in working memory

Results are shown in Figure 7.8. The three conditions were effected as follows: condition 1 was a straightforward removal of the inhibitory response. This meant that tasks requiring goal-subgoal resolution would not be solvable. Condition 2 had the working memory capacity reduced from 9 items to 2 items. Smaller reductions in capacity were also tested but did not produce particularly noticeable results. Condition 3 was where working memories were disrupted. Patterns stored in working memory were replaced with randomly generated patterns to simulate disintegration of working memory representations. The random patterns still represented genuine configurations within the Tower of London task, but were not legal moves, rather random configurations. This was intended to represent a failure at the level of appropriate representation rather than a fundamental failure in cognitive processing which might occur in more organic brain conditions such as in a confusional state.
In all three conditions performance on shorter problems is relatively preserved. Also the number of absolute errors is higher than in the control condition. With loss of inhibition (condition 1) we see a marked deterioration in performance on the longer problems, 7 and 8-move problems are not solved at all. Reduced working memory capacity (condition 2) has a similar, although more gradual effect. The error rate is not as high as in conditions 1. and 3. and the overall degradation in performance is not as severe as for the other two conditions. Disruption to the contents of working memory (condition 3) produced a deterioration in performance very similar to that in condition 1. Comparing the success rates in each of these conditions reveals that condition 1. and 3. have very similar profiles (Figure 7.9). This is interesting because one of the ideas being presented in this thesis is that the attentional and inhibitory functions of the PfCx may be different interpretations of the same process. The similarity between these simulation results shows that disruption of working memory ability, which can be considered part of an attentional process, has a similar effect on a cognitive process as loss of inhibition. In the simulation these two processes are implemented independently because this model does not attempt to be biologically plausible. However it is entirely possible that the process of holding information online can act to inhibit instinctive processes, which are not necessarily performed by the PfCx.
Modelling the Tower of London task

The disruption of working memory also produced an interesting 'jump' phenomenon when working memory was utilised, illustrated in Figure 7.10. This was where the corrupted memory stored in the PfCx led to a bizarre jump to a new and unrelated position. In the context of the Tower of London task this jump does not make much sense other than to ascribe failure. However in a more general sense it is reminiscent of Knight’s Move in thinking, a symptom characteristic of psychosis. Condition 3 also gives results which accord well with observed performance of schizophrenics on the Tower of London task (Moric and Delahunty, 1996). PfCx deficits alone are very similar to the symptoms of the psychomotor poverty syndrome suggested by Liddle et al. (1992) and Kaplan et al. (1993).

Figure 7.10: Four examples of jump phenomena occurring with disrupted working memory. Solid circle represents the starting point and the star represents the target state.
7.7.1 Relevance to schizophrenia: Summary

The relevance of this model and the model of NAcc function in the next chapter are discussed fully at the end of that chapter (chapter 8), however, a summary of the main findings from this model are presented here:

- Disruption to the integrity of memories stored in the PfCx causes behaviour on the Tower of London task similar to Knight's move thinking seen in schizophrenia.

- Disruption to PfCx function may lead to both disruption of information stored online (i.e. working memory processes), and to loss of the inhibitory function performed by the PfCx. Disruption of both these processes may occur through the same biological mechanism. Both of these processes are disrupted in schizophrenia.
Chapter 8

Modelling the function of the Nucleus Accumbens with reinforcement learning

8.1 Introduction

As outlined in the previous chapter, the model in this chapter uses reward based or reinforcement learning as a means to illustrate the possible function of the NAcc. The model can then be lesioned in order to simulate schizophrenic deficits and we can examine how potential pathology in the reinforcement learning process may be related to the symptoms and signs of schizophrenia. The data-set used in this chapter is the same as that from the previous chapter, i.e. the Tower of London set of moves. As already mentioned, however, any set of sequences could have been used as this is not a model of performance on the Tower of London task but rather a model of sequence learning. The Tower of London data-set was used so that a comparison could be made between this model and that of Dehaene and Changeux (1997).
8.2 The reinforcement learning model

This model is a reward-based model which uses the adaptive-critic form of reinforcement learning (Barto et al., 1983; Barto, 1995; Kaelbling et al., 1996) to solve and learn the correct sequence of moves for the Tower of London task. It has been suggested that the dorsal striatum operates under such a learning scheme (Houk et al., 1995), and I am suggesting that this learning principle can be extended to the ventral striatum i.e. the NAcc. Also, Montague et al. (1996) have shown how the temporal difference error signal acts analogously to dopamine in reward-based learning. They did not state specific anatomical correlates for their model, however they did suggest that the weight-learning locus might be in the basal ganglia or ventral striatum. In chapter 9 I will discuss the issue of 'where exactly is the adaptive critic'?

The function of the NAcc has been discussed in some detail in chapter 3. It should be emphasised that all situations are both potential learning and performance situations. Performance does not necessarily entail physical enactment and could instead be mental rehearsal. I have used the Tower of London task as an illustration of sequence learning here. It is unlikely that the solutions to the task are actually memorised, but if I had modelled chess playing, as mentioned, it would not be unrealistic to envisage memorisation of sequences of moves as well as calculating optimal de novo sequences.

The NAcc model utilises the same input code and binding code arrangement as the PfCx model. For full details of adaptive critic reinforcement learning see Barto et al. (1983) and Barto (1995). Some important details of the algorithm will be described here however.

Figure 8.1 illustrates the basic architecture of a reinforcement learning system using an adaptive critic. Essentially, there are two learning elements in this system: the adaptive critic which makes predictions regarding the expected reward a particular move will bring, and whose output is the temporal difference error; and the actor, who
Modelling the function of the Nucleus Accumbens with reinforcement learning

Figure 8.1: This diagram illustrates the fundamental architecture of an adaptive critic reinforcement learning system. The environment can be either internal or external to the learning agent. The fixed critic supplies the primary reinforcing signal.

The critic learns which are good moves to make in a particular situation under the guidance of the critic. The critic receives primary reinforcing signals from the environment which it combines with its predictions to provide an effective reinforcement signal (equation 8.1).

$$\hat{r}_t = r_t + \gamma P_t - P_{t-1}$$  \hspace{1cm} (8.1)

In equation 8.1, $r_t$ represents the primary reinforcement from the environment (0 at all times except when the target is achieved, when it is 1); $P_t$ represents the prediction of the critic at time $t$, discounted by a factor $\gamma$ (0.95 in my simulations) to allow the effects of reward to propagate through time but to eventually decay; and $P_{t-1}$ is the prediction at the previous time-step. The temporal difference error ($\hat{r}_t$) represents a DA signal in these models. $P_t$ is dependent on the weights in the adaptive critic and is produced by the following equation:
Modelling the function of the Nucleus Accumbens with reinforcement learning

\[ P_t = \sum_{i=1}^{m} w_t^i x_t^i \quad (8.2) \]

where \( x_t^i \) refers to the activity in input unit \( i \) at time \( t \) and \( w_t^i \) refers to the synaptic weight on unit \( i \) at time \( t \). Both actor and critic are forms of neural network. The actor takes 36-bit input and produces as output activation of a single unit in the binding code layer. The critic takes a 36-bit input and has a single unit as an output. This unit provides the scalar \( \hat{r}_t \) quantity. The learning rules for setting the weights of these two components both take the same form, given by:

\[ w_t^i = w_{t-1}^i + \eta \hat{r}_t x_{t-1}^i \quad (8.3) \]

Where \( x^t \) refers to the input to unit \( i \) and \( \eta \) is a learning rate given by:

\[ \eta = \frac{1}{\sqrt{10t}} \quad (8.4) \]

All units in both networks use a standard squashing activation function to convert input into output, which is given by:

\[ O_t = \frac{1}{1 + e^{-\sum_{i=1}^{m} w_t^i x_t^i}} \quad (8.5) \]

for an input pattern with \( m \) bits in it. Clearly \( \eta \) in equation 8.4 is time-dependent, thus the learning rate decreases with time. This is necessary to prevent random fluctuations in the later stages of learning from effectively undoing a lot of the earlier learning. I would suggest that the decrease in learning rate could be tied to the decrease in TDE as learning proceeds. This would negate the need for invoking external factors to control the learning rate. The fundamental nature of the reinforcement learning process is that the actor network randomly selects an output unit, with some bias provided by
the weights in the network. Initially the weights are set to small random values (between \(-0.01\) and \(+0.01\)), thus there is no guidance on selecting outputs. The network randomly selects outputs until the target state is reached, at which point some information enters the system regarding which moves will lead to the target. This has the effect of modifying the weights of the preceding moves. The most recent states of the actor net are modified by the largest amount, with a gradual reduction in the degree of modification the more temporally distant a particular state is from the goal. The shape of this decline in weight modification is given by \(\gamma\). \(\gamma = 0\) means that only the previous state is modified whereas \(\gamma = 1\) means all previous states are modified.

8.2.1 Problems with the reinforcement learning analogy

There are several problems with the analogy between reward-based learning in the striatum with DA as the error signal, and reinforcement learning. One is the precise anatomical correspondence of the various components, which will be touched on again in chapter 9. Another is the fact that \(r_t\) does not correspond in a quantitative way to DA concentrations in the NAcc and elsewhere, thus it can become negative, for example. Also, there is a problem with what is known as the eligibility trace. This is effectively a local memory which states which synapses are eligible for updating. In the model the terms \(P_{t-1}\) and \(x_{t-1}^i\) represent the remembered information, however it is not clear what the biological mechanism for this would be. Houk et al. (1995) and Wickens and Kötter (1995) both discuss this issue to some extent. There is some consensus that the timing of input signals may be important in this. Friston et al. (1994) have introduced a model which in fact predates that of Montague et al. (1996). Friston et al use the term value dependent learning to model a simple neural system which has not only innate values but experience dependent values also. These terms are similar to the primary reward and effective reward terms of the adaptive critic reinforcement learning model. Temporal difference learning can be viewed as a special case of value dependent learning. One of the advantages of value dependent learning is that there is no need to specify an extrinsic discount factor as the decay in learning potency with time arises as an automatic feature of the value dependent learning formulation.
8.2.2 Results of the NAcc model

The results from the basic NAcc model are shown in Figure 8.2.

The NAcc model (reinforcement learning) is assessed on whether it has learnt the correct sequence or not, in contrast to the PfCx model which is assessed on performance. Thus the NAcc model may be producing the correct sequence for some time before the testing point is reached, however this does not indicate that that sequence has been learnt. The testing point is determined as the time when the TDE for the target configuration goes below zero. The maximum number of iterations is arbitrarily set at 5000.

Although a direct comparison between the model in this chapter and the one in the preceding chapter is not really valid since they are designed to carry out different tasks, the results profile of the NAcc model is similar to that of the PfCx model but the solution times are much greater. In terms of solving the problems outright, regardless of number of moves, as a comparison with Dehaene and Changeux’s model,
Modelling the function of the Nucleus Accumbens with reinforcement learning

both models perform very well. Their results, such as are available from the literature, are presented in Figure 8.3. As can be seen, the results from my models compare favourably with their results. As mentioned earlier, it is not clear what measure of success they have used, however I have shown the total error for my models to present them in the least favourable light. The PfCx model is more computationally intensive and requires a working memory in order to perform back-tracking, however solution times (in terms of number of iterations) are much quicker than the reinforcement learning model. The reinforcement learning model also does not solve the higher move tasks as consistently as the PfCx model.

8.3 NAcc lesions

I have investigated one main effect in the NAcc model. This was to see how abnormal alterations in the level of dopamine (i.e the TDE) affect learning. There were two different conditions within this effect. One is to have a consistently raised TDE, and the other is to have the TDE fluctuate randomly. The precise nature of these conditions
was as follows: TDE is consistently raised by a factor of 5; or TDE is altered by a random factor of between 0 and 5 (using real values). It should be noted that these values are not quantitatively accurate representations of the biological values of DA concentration, but, as noted above, this is one of the flaws of the analogy between standard reinforcement learning and biological reward-based learning. These two conditions are of interest because they distinguish between two different pathologies in the DA innervation of the NAcc. Most DA theories of schizophrenia posit a raised level of DA, or phasic DA, as the principle pathology which directly leads to psychosis. An alternative hypothesis is that it is inappropriate firing of DA cells, leading to fluctuations in the concentration of DA, which directly or indirectly induces psychotic symptoms, as suggested in chapter 3. The results from the following simulations may shed some light on how these two pathologies would affect NAcc function.

With a raised value of TDE an interesting phenomenon occurs. Although the TDE is only raised by a factor of 5, it soon leads to an explosion in synaptic strengths in both the actor and the critic. The weights in the adaptive critic dictate the output of the critic and so the value of the TDE also rises until it hits an imposed ceiling value (set at $1 \times 10^{100}$). This ceiling value represents a maximum level of DA which we know will occur in the NAcc (Garris and Wightman, 1994). The effects on learning are shown in Figure 8.4.

In the case of raised TDE the learning time actually falls as the number of moves increases. The reason for this is that the number of successfully learnt sequences is very small (see Figure 8.5), and so the few occasions that the sequence is successfully learnt are due to rapid convergence of the learning algorithm on the correct sequence. This simulation also has a very poor success rate in terms of learning (Figure 8.5). In contrast, the variable TDE situation gives a more gradual deterioration in performance (Figure 8.5), with the learning times remaining roughly stable.

It is not totally clear how these results should be interpreted. A raised TDE leads to a massive increase in synaptic strengths and a dramatic failure to learn all but the simplest of sequences. A varying TDE leads to a gradual worsening of learning. In terms
Modelling the function of the Nucleus Accumbens with reinforcement learning.

Figure 8.4: Upper graph shows results for TDE increased by a factor of 5. Lower graph shows results for variable TDE (altered by a random factor of 0 to 5 at each iteration). These results are the average of 10 simulations using the 48-problem data-set in Appendix B.

of this model representing the NAcc and the TDE-DA analogy, this means that consistently raised DA would lead to very strong synaptic connections in the NAcc and there would be no ability to learn to relate motivational states and contexts in a goal-driven way. Single step ‘conditioning’ type of connections would be made but nothing else. On the other hand, a fluctuating level of DA would lead to a deterioration in this ability to connect sequences but not an outright failure.
8.4 Relevance to schizophrenia

The relevance of the models in this chapter and the preceding chapter to schizophrenia is discussed here. In addition, suggestions regarding the involvement of the hippocampus in PfCx and NAcc function are raised. Lesions of the PfCx model suggest that loss of inhibition and disruption to the information stored online in the PfCx both produce similar effects on performance on the Tower of London task. This may be tentatively taken as evidence that disruption of these two processes may occur through the same biological mechanism. For example, disruption in the ability of the PfCx to hold information online, as may occur through the means outlined in chapter 6, could clearly lead to corruption of information stored online. If this occurred due to loss of DA in the PfCx then this would prevent the inhibitory effect of DA on PfCx output from occurring. This could, in turn, be the mechanism for causing loss of PfCx inhibition on instinctive and/or subcortical processes. This would assume that the 'going for goal' behaviour is instinctive or automatic, which is reasonable. Hypofunctioning of the PfCx has been associated with the psychomotor poverty syndrome of schizophrenia (Liddle et al., 1992; Friston et al., 1992), and some overlap between this syndrome and the reality distortion syndrome is observed (Friston et al., 1992). This correlates with the demonstration of Knight’s move type of jumps in PfCx processing.
under conditions of disruption to the integrity of memories stored in the PfCx.

The NAcc model is intended to represent the learning of goal-driven strategies which utilise a contextual input (from hippocampus) and a motivational input (from amygdala). Such a learning process is thought to rely intrinsically on DA. An interesting question which has not often been raised is 'how exactly do the (positive) symptoms of schizophrenia arise from alterations in the level of DA in the NAcc?'. In attempting to address this question I have simulated two variations in DA during reward-based learning in the NAcc. The raised DA condition leads to extremely poor learning of sequences. Barely any sequences other than one step associations were learnt. In addition the value of DA in the model, and the synaptic strengths went through a very rapid increase until a ceiling value of DA was reached. It is not clear what the biological analogue of this behaviour would be. We may expect to see some sort of damage to the synapses, or an increased number of dendritic spines (Arbuthnott and Ingham, 1993). The other simulated condition was for a random variation in the level of DA in the NAcc and led to a more gradual deterioration in learning in the NAcc. Both conditions thus led to a reduction in the ability to learn goal-driven strategies. It has been suggested (see chapter 3) that such a loss would lead to a failure to build up a coherent world view, with a general loss of understanding for the meaning of behaviours and the consequence of actions. This could be the basis for the symptoms which form the disorganisation syndrome of schizophrenia (Liddle et al., 1992). Another interpretation might be that it leads to a failure of meta-representation which Frith (1992) has suggested underlies the psychological basis for schizophrenic symptomatology (see chapter 2). If the NAcc has the role described above, then the drastic loss of function resulting from consistently raised DA may give rise to cognitive losses which are too extreme for schizophrenia. This all ties in with the disconnection hypothesis (Friston, 1998), which is discussed further in chapter 9. Also, raised levels of DA have never been detected in schizophrenia. I would speculate that it is fluctuations in the level of DA that causes a significant but not overwhelming loss of reward-based learning in the NAcc. There are no clinical studies to date which address the question of impairment of reward-based learning in schizophrenia. Another possibility, however, is that in more extreme cases of schizophrenia where the degree of psychosis is severe
and unremitting, the level of DA is persistently raised, whereas in less severe cases the level of DA is fluctuating.

The third brain region implicated in schizophrenia, the hippocampus, has not really been incorporated into the simulations in this chapter. As discussed in chapter 3, the hippocampus is considered to provide context for learning in the NAcc. In the model of NAcc in this chapter, contexts are only required when the network already has data stored in it and there is a need to disambiguate previous associations from new ones. The hippocampus has been linked to the reality distortion syndrome of schizophrenia (Friston et al., 1992), although the (left) temporal lobe is linked with all three syndromes. A hypothesis on the nature of the hippocampal dysfunction is presented in chapter 3. A consequence of this is that its context-generating ability is affected. This could have consequences for both PfCx and NAcc function. A hypothesis concerning the origin of DA fluctuations in the NAcc can be re-presented, having been mentioned originally in chapter 3. I will call this the fluctuating dopamine hypothesis.

If the hippocampus does not provide adequate contextual information to the NAcc then the ability of the NAcc to learn appropriate goal-driven strategies may be impaired. Since it is assumed that this learning process depends on a DA signal to indicate how likely an action is to lead to reward, and this DA signal is activated only during learning i.e. when rewards are unexpected, or the outcome of an action is unknown, then the DA signal falls as learning proceeds. If learning does not proceed properly, then rewards always remain unexpected to a certain degree and the DA neurons are activated inappropriately, leading to inappropriate fluctuations in the level of DA. These changes in DA, more subtle than it being consistently raised, could cause disruption to NAcc function, as suggested above, and lead to the symptoms of the disorganisation syndrome. If the origin of these DA fluctuations was dysfunction in the hippocampus then there are now two potential symptom sets. In addition, it has been shown in animals that neonatal damage to the hippocampus leads to dysfunction of the medial PfCx in adulthood (Lipska et al., 1993, 1998). Thus it is possible to tie hippocampal dysfunction with PfCx dysfunction and the third set of symptoms, the psychomotor poverty syndrome. The fluctuating DA hypothesis would also account
for the lack of observed increases in DA levels in subcortical regions. In this scenario neuroleptic drugs would work by stabilising the level of DA in the NAcc rather than actively reducing it, as suggested by Egan et al. (1996).

This hypothesis remains very speculative, however a recent scanning study has shown that both hyper- and hypo-perfusion of brain regions correlate with the positive symptoms of schizophrenia (Sabri et al., 1997). Bearing in mind the potential role of DA in the control of blood flow in cerebral microvasculature, this result may reflect inappropriate fluctuations in DA levels in various brain regions, rather than a fixed increase/decrease. Future modelling work could include incorporating context effects into the reinforcement learning process and trying to induce fluctuations in the TDE through loss of context. It would also be interesting to investigate the direct influence of the PfCx on subcortical processes.

### 8.4.1 Conclusion

In summary, I have tried here to provide an account of the symptomatology of schizophrenia in terms of the individual breakdown in PfCx and NAcc function, suggesting that these correspond, respectively, to the psychomotor poverty and disorganisation syndromes. In addition I have looked at the interaction between NAcc and hippocampus. If hippocampal function is aberrant then this could lead directly to the third syndrome, reality distortion, and also indirectly to dysfunction of PfCx and NAcc, and so to the other two syndromes. Clearly more than one dysfunction can co-exist, and this allows for the overlap in the syndromes.
Chapter 9

Discussion

Several issues have arisen during the preceding chapters which have not been dealt with fully and have implications for the interpretation of my results. The first part of this chapter will discuss these issues, and the second part will summarise the ideas and results obtained in this thesis.

9.1 Some dilemmas and hypotheses

The action of DA in the PfCx

It is not exactly clear what the role of DA is in the PfCx. Yang and Seamans (1996) have shown that bath application of DA acting on D1 receptors in rat PfCx can increase and regularise the firing rate of these cells when they receive a depolarising input. Their data was used in the model presented in chapter 5. This is in contrast to the results of Thierry and others (Thierry et al., 1990; Pirot et al., 1992; Gioanni et al., 1998) who show that both iontophoretic application of DA to PfCx cells, and stimulation of the VTA, reduce the spontaneous and depolarising current-induced firing of PfCx cells, probably via D2 receptor mechanisms. In addition Kolachana et al. (1995) have shown
that the application of DA in the PfCx reduces DA release in the striatum, and Karler et al. (1998) have shown that this reduces the locomotion induced by raising DA in the NAcc. This ties in with other observations that stimulation of PfCx can induce burst firing in VTA DA cells and increase DA in the NAcc (Murase et al., 1993). It has also been shown that application of DA D1 receptor antagonists to the dorsolateral PfCx of a monkey performing a delayed response task impairs performance on the task (Sawaguchi and Goldman-Rakic, 1994) but also increases firing of the delay cells (Williams and Goldman-Rakic, 1995), although in the latter case the dosage of the drug was not sufficient to affect performance on the task. Finally, DA D2 receptors have also been implicated in working tasks. There seems to be an improvement in working memory function with D2 agonists (Luciana et al., 1992; Arnsten et al., 1995), and it has also been noted that bromocriptine, a D2 agonist, can both improve working memory performance and reduce PfCx activity as measured with fMRI (Kimberg et al., 1998).

Attempting a synthesis of the above facts, my model assumes that the action of DA at distal D1 receptors is to reduce the excitability of the PfCx pyramidal cells, but its action at proximal/somatic D1 receptors is to increase and regularise the firing rate. This serves to isolate the pyramidal cell and to filter out all but the strongest inputs. If the cell receives adequate input then it will continue to fire regularly. However, reciprocal connections with GABA interneurons will cause the firing rate of the cell to fall, but functional synergism will be maintained. This helps to reconcile the above data. There is also some evidence of D1 receptors on GABA interneurons, which would allow for a direct action on these cells (Muly et al., 1998). This hypothesis can be tested by assessing the action of D1 agonists and antagonists on the firing of PfCx pyramidal cells in the presence of GABA antagonists. These experiments have not, to my knowledge, been performed.

**Oscillations in PfCx output allow switching between delay ensembles**

Thus DA acts via both D1 and D2 receptors to facilitate working memory, and that DA actions in the PfCx reduce the firing of pyramidal neurons. This implies that dur-
ing working memory tasks the output from the dorsolateral PFCx (and maybe other PFCx regions) is reduced. The dynamical systems model in chapter 6 shows how the functional synergism between GABA and pyramidal cells in the PFCx can lead to a reduced level of glutamate in that region, while the model in chapter 5 shows how the synergism may underly working memory processes. These models are assumed to be localised to the dorsolateral PFCx, but it is possible that a similar process occurs in other regions of the PFCx, despite the fact that there are evolutionary and functional distinctions between at least the ventral and dorsal areas of the PFCx. It is quite possible that a general functional characteristic of the PFCx is to hold information online, since most of the functions ascribed to it require this ability to some extent. Goldman-Rakic and Selemon (1997) are of this opinion and believe that the functional differences between PFCx regions are a matter of modality. If this is the case then it is possible to suggest that the holding of information online simultaneously has the effect of reducing PFCx output to other areas, as well as isolating the PFCx, via DA action at the distal dendrites, from further input. This can be considered the attentional function of the PFCx. It is not clear how strong DA induced reduction in PFCx output is, i.e. can it be overcome by strong excitatory input from other cortical regions and/or the hippocampus? This certainly corresponds with it having a role in selective attention however. If this is the case then the inhibitory function of the PFCx could also be considered to be the lack of PFCx input to subcortical structures. It is interesting that the PFCx has such a strong controlling effect on the release of DA from the VTA. Since DA is involved in working memory processes, it seems that the PFCx-VTA-PFCx loop provides self-limiting control of the duration of working memory. The following scenario applies: if the PFCx is activated, by thalamic activity say, then this would cause a burst of activity in VTA DA cells leading to release of DA in the NAcc and the PFCx. DA in the PFCx allows working memory processes to occur but also reduces the output from the PFCx, thus reducing DA input and limiting the duration for which items can be stored online. Extending this, it can be suggested that the oscillatory nature of the PFCx output during working memory tasks actually allows for intermittent firing of the VTA cells. This would allow the contents of the working memory to be altered during periods of low DA input. Thus DA is involved in a switching mechanism again, although in a
different way to its involvement in the NAcc switching process. This has relevance to true working memory and planning tasks which require the ability to hold online, and to manipulate, information.

There are problems with this account, however, in particular it is not clear that the output of the PfCx under the influence of DA ever reaches threshold level. Thus, in the model in chapter 6 the maximum value of Gl while oscillating was still significantly lower than the resting value (derived from spontaneous firing). This could be due to a flaw in the model, since many assumptions were made in its construction. If the output of the PfCx does not reach threshold level in vivo it is still possible that subthreshold oscillations in the membrane potential of the PfCx afferent could interact with the presynaptic release factors in the VTA, especially ACh acting at nicotinic receptors, to cause a pulsatile release of Glu and activation of the DA cells in the VTA. Another problem with the oscillating PfCx account is that oscillations in delay cell activity are not observed in vivo. There are two possible explanations for this. One is that the tasks which are utilised in the studies are not complex enough to require switching between ensembles. This is because single electrode measurements of individual cell firing can only be performed on non-humans and the complexity of tasks which even macaque monkeys can perform is significantly simpler than the highly complex planning processes humans can perform. Another, perhaps more plausible, explanation is that oscillations entail switching between ensembles, and single cell recordings can only capture the activity in one cell of one ensemble. Thus the recordings cannot follow the switching between ensembles. If the above theory of PfCx-VTA-PfCx control is correct then we need to explain how the PfCx is activated in the first place, and this leads to another tentative hypothesis.

The PfCx is the locus of the adaptive critic

The DA neurons in the VTA respond to unpredictable reward or unexpected reinforcers of reward and this leads to the analogy between reward-based learning in biological systems and the computational reinforcement learning algorithm, as discussed
in chapter 8. If the PfCx is largely responsible for the control of VTA DA cell firing then, in the reinforcement learning analogy, this would make it the locus for the adaptive critic. This concept is worth exploring further. The adaptive critic requires access to the TDE (DA) signal as part of its learning process, so this could be a secondary function of the DA innervation of the PfCx. The amygdala has strong reciprocal connections with the anterior cingulate and PfCx and has been shown to learn primary stimulus-reward associations (Kesner and Williams, 1995), thus it is well-placed to provide a primary reinforcing signal. The pyramidal cells in the PfCx will be required to learn the associations that the adaptive critic makes i.e. to make predictions about the value of a particular action in relation to a particular goal, and in a given context. If we assume that context is supplied by the hippocampus, then this hypothesis becomes more tenable with the discovery that stimulation of the hippocampus can induce LTP in the PfCx. Thus, it is known that the CA1 and subicular regions of the hippocampus can induce LTP in the prelimbic and infralimbic regions of rat PfCx (ventral PfCx in humans) (Jay et al., 1995; Mulder et al., 1997). There are also reciprocal connections between the dorsolateral PfCx and the subiculum. If this is the case then we would expect the PfCx to be activated during situations where the outcome of an action does not have the results which are expected, or where there are no predictions available. Such situations would certainly include those in which the PfCx is implicated such as planning and internal representation. In this sense this makes the PfCx the seat of strategic activities as the adaptive critic acquires ‘knowledge’ of appropriate strategies for obtaining goals.

It is not suggested, however, that the PfCx performs the exact computation used in the temporal difference model of reinforcement learning. This is because of the biological inaccuracy of the reinforcement learning algorithm. The PfCx does seem suited to the role of adaptive critic, though, and Pennartz (1997) has come to a similar conclusion, although he uses a different formulation of reinforcement learning which does not rely on DA to provide an error signal. Other research has suggested that the anterior cingulate is a locus for error-detection during working memory and other tasks requiring controlled information processing (Carter et al., 1998). This leads to the question of whether the whole of the PfCx acts as an adaptive critic or whether it is the func-
tion of a specialised region. Performing the function of the adaptive critic necessarily entails learning, and this would interfere with the working memory model proposed in chapter 5, where uniform synaptic weights are assumed. Further elucidation of the specific PfCx and cingulate regions which project to the VTA would help to answer this question.

The concept of the PfCx as adaptive critic also agrees loosely with Frith (1992)'s tentative suggestion for the circuitry underlying his theory of metarepresentation. He mentions the amygdala, orbitofrontal PfCx and dorsolateral PfCx as key sites. It could be that the PfCx maintains information which is crucial in determining self. From this, a dysfunction in the PfCx will clearly lead to a failure of metarepresentation and all the ensuing consequences as described in chapter 2. At a more general level, if the adaptive critic does not function correctly then this will lead to the learning of inappropriate associations or at least a failure to learn appropriate associations. This in turn would lead to a loss of automatic processing and the cognitive compensation, again, as discussed in chapter 2. It can also be seen as a form of disconnectionism, to be discussed later.

Ascribing the role of adaptive critic to the PfCx could have implications in terms of personality traits, which are significantly altered when the PfCx is damaged. The suggestion here is that personality is composed of the strategies used to solve problems, and the set of events which are considered novel of surprising, the complement of which would be the set if events for which there are automatic actions not requiring any planning.

The idea that the adaptive critic is located in the PfCx also makes sense from a learning theory perspective. It is known that the PfCx is active during learning of tasks but not once they have been learnt. This corresponds to the role of the adaptive critic in reinforcement learning. In terms of DA dysfunction in schizophrenia, abnormal functioning of the PfCx could lead to aberrant firing of the DA VTA cells and this could lead to the sequelae described in the fluctuating DA hypothesis, namely a cycle of
learning inappropriate associations leading to a loss of predictability and so inappropriate firing of the VTA DA neurons.

This account is highly speculative and although it fits in with accounts of PfCx as a central executive and locus of working memory, it does not sit so easily with the account of the PfCx as a component in the selection of actions via activity in the cortico-striato-pallido-thalamic-cortex loops. It is worth noting, however, that this last role of the PfCx is much more related to rodent studies, while the first two paradigms relate to humans and higher primates. Certain questions also arise: how to account for previous predictions? Are these generated by PfCx? Where are they held? Could the adaptive critic be localised to single cells rather than ensembles of cells? Nevertheless, I hope that the above account may sow the seeds of ideas which can be extended and investigated empirically. Studies using patients who have undergone amygdalo-hippocampectomy would be particularly useful, for example.

9.1.1 Neurodevelopmental Hypotheses

It is worth mentioning a few extra points regarding the possibility that disturbances in normal brain development may underly schizophrenic pathology.

Normal development of dendritic spines in the striatum is dependent on DA, with reduced DA leading to fewer spines. It is possible that reduced DA in the PfCx during the development of this brain region, which matures in adolescence, could lead to reduced numbers of dendritic spines, which would in turn lead to the observed increase in cell density (Selemon et al., 1995). As well as impaired working memory function and all that that entails, another consequence of alterations in the dendritic field during development could be, according to the constructivist perspective (Quartz and Sejnowski, 1997), a direct disruption to the acquisition of cognitive skills. This theory suggests that the acquisition of cognitive abilities, including language skills, proceeds in tandem with cortical development and that the two processes directly interact to shape each other through time. It particularly focusses on the dendritic field as the
site of flux whose shape can be directly affected through activity-dependent processes and which is responsible for the synaptic connectivity which underlies cognitive function. There are several problems with this theory (Hurford et al., 1997), but setting these aside, it provides a clear link between dendritic deformity and cognitive dysfunction. Pathological developmental changes could account for early onset forms of schizophrenia which are generally rapidly progressive and respond very poorly to anti-psychotic medication.

Other evidence of the effect of inadequate levels of DA in the PfCx during development comes from Diamond (1996) who has studied the effects of phenylketonuria (PKU) on working memory ability. PKU is an inborn error of metabolism which reduces the synthesis of DA in the CNS by limiting the amount of tyrosine (a DA precursor) available. PfCx neurons are very sensitive to reduced levels of tyrosine. Children who do not receive dietary treatment for PKU go on to have lower IQ's and are particularly bad at working memory tasks such as the A-not-B task, delayed non-matching to sample and a stroop-like task. Although this implies that schizophrenia does not arise purely from a reduced DA input to the PfCx during early development, it is possible that disruptions to DA input later in development may have more subtle and complex effects and be involved in the genesis of schizophrenia. In addition, this may support the fluctuating DA hypothesis in that strictly reduced levels of DA in the PfCx during early development do not lead to schizophrenia.

Another hypothesis which relates to the effects of DA on the PfCx pertains to the development of GABA interneurons. I have shown the necessity for intact GABA interneurons and recurrent connections from layer V of PfCx. There is evidence that GABA interneuron terminals in layer III develop synchronously with pyramidal cell dendritic spines (Sesack et al., 1995). The correct interaction between these two structures may well be at risk if there is any disruption to the normal developmental course. In addition it has been shown that in models of neural development inhibitory cells are necessary for the overgrowth of neurites (van Ooyen and van Pelt, 1994). The size of the neuritic field is reduced in the absence of inhibition, thus a failure of adequate inhibition during development may induce shorter axonal connections in the mature
neurons. Other factors, including D$_1$ receptor activity, are responsible for neurite outgrowth. It is possible that either a primary loss of GABA interneurons or a reduction in D$_1$ receptor function could give rise to altered connectivity of mature PfCx neurons. Both reduced D$_1$ receptors in the PfCx (Okubo et al., 1997) and reduced numbers of GABA interneurons in the anterior cingulate (Benes, 1993) have been observed in schizophrenics. From the model in chapter 5 we can see that any or all of these effects: reduced dopamine, shorter axonal connections, and reduced numbers of GABA interneurons, will disrupt PfCx function and potentially lead to schizophrenia.

A final comment on the origin of neurodevelopmental deficits in the PfCx is in order. As mentioned earlier, it has been shown that neonatal excitotoxic damage to the ventral hippocampus (including the subiculum) can cause hyperlocomotion in response to novelty and amphetamines in rats (Lipska et al., 1993, 1998), which is considered to be an animal model of schizophrenia. Neonatal damage to the medial PfCx does not produce this effect, however destroying adult medial PfCx removes the overresponsiveness. This suggests that the PfCx may have developed abnormally under the influence of altered hippocampal input and may be responsible for the abnormal behaviour. In the light of evidence that the hippocampus is overactive and has reduced volume in schizophrenics this suggests that changes in PfCx architecture may be secondary to hippocampal changes.

Disconnectionism

In chapter 3 I introduced the disconnection hypothesis (Friston, 1998), or disconnectionism, as an underlying theme of this thesis. One of the main tenets of disconnectionism is that if reward-based learning ceases to occur properly then there is an uncoupling between sensory and cognitive experiences and appropriate actions. I have localised the process of reward-based learning to the involvement of the brain regions implicated in schizophrenia and suggested that the NAcc may be viewed as the actor, making associative connections between sensory input and motivational states and actions given a particular context supplied by the hippocampus. I have also suggested
that the PfCx may be the locus of the adaptive critic, and so be the brain region where knowledge about the ‘goodness’ of an action is stored.

I have also looked at specific abnormalities in specific brain regions and shown how these may give rise to aberrant functioning of that brain region and lead to failures in the normal processes that region undertakes. This is not in accordance with the disconnection hypothesis, another crucial point of which is that schizophrenia arises due to a failure of integration between brain regions rather than failures within specific brain regions. Several comments can be made on this. Firstly, physical abnormalities can arise through developmental abnormalities (as mentioned above). There is no hard cut-off point between development and learning, particularly in brain regions such as the PfCx, which is not fully developed until late adolescence (Huttenlocher, 1990). This is also the time when the symptoms of schizophrenia often start to appear. Thus, while it is true that schizophrenia nearly always presents in adulthood, changes in the brains of schizophrenics are not necessarily restricted to the post-developmental period. In the PfCx, development and experience-dependent plasticity co-occur for a significant period of time. Thus the PfCx may be at special risk of abnormal development because it has a longer exposure to potentially disruptive environmental influences. Here are the main lesions and abnormalities which I have looked at in this thesis:

- fluctuating DA in PfCx and NAcc

- changes in recurrent collaterals of PfCx

- reduction in GABA neurons in PfCx/ant.cingulate

- reduced nicotinic activity on hippocampal interneurons

Some of these could certainly arise as a result of developmental abnormalities in the PfCx. Fluctuations in DA, changes in recurrent collaterals and morphology of GABA
interneurons can all interact during development to produce a dysfunctional PfCx architecture. It is hard to see how changes in the function of $\alpha_7$-nicotinic receptor subtypes could occur secondarily to developmental disturbances, but this brings me to the next point: schizophrenia is a very heterogeneous condition, and there is considerable overlap between some of the symptoms of schizophrenia and other psychiatric and neurological conditions. Disconnectionism could account for what might be termed idiopathic schizophrenia, however disorders of specific brain regions may account for sub-groups of schizophrenia with stronger aetiological claims. For example, the familial cases of schizophrenia which show genetic linkage to $\alpha_7$-nicotinic receptor defects. Severe mental handicap is also linked with a higher incidence of schizophrenia, or psychotic behaviour, which may be associated with functional impairment in specific brain regions.

9.1.2 The mechanism of action of neuroleptics

I have made very little mention of neuroleptics so far. The reason for this is that it is still very unclear how they work. Their pharmacological actions are fairly well understood but it is difficult to translate this to anti-psychotic efficacy. They have, however, been crucial in providing evidence for the DA hypothesis and any theory of schizophrenia needs to take into account the fact that neuroleptics do help relieve a lot of symptoms in a lot of cases, but not all symptoms in all cases. The traditional neuroleptic, such as haloperidol, blocks D$_2$ receptors and has little affinity for D$_1$ receptors. The locus of activity is thought to be the NAcc, but it is also active in the striatum, where long-term use of the drug can lead to Parkinsonian side-effects. Traditional neuroleptics can relieve the positive symptoms of schizophrenia but are very poor at lifting the negative symptoms, and sometimes make them worse. On the other hand, atypical neuroleptics, such as clozapine, have a different pharmacological profile and are effective in treating both the positive and negative symptoms. These drugs are thought to work more specifically in the shell region of the NAcc (Deutch et al., 1992) and have a weak affinity for D$_2$ receptors but a strong affinity for D$_1$ and a very strong affinity for 5-HT2A receptors (Meltzer, 1989; Nordström et al., 1995).
The other mode of action of neuroleptics, however, is thought to be through a depolarisation block of the DA neurons in the midbrain (Grace and Bunney, 1986). This takes several weeks to occur and is thought to account for the delay between starting drug treatment and relief from symptoms, since receptor blockade occurs very quickly. Recently there seems to be some controversy over whether this phenomenon exists (Gessa and Mereu, 1997; Melis et al., 1998). Interestingly, Egan et al. (1996) suggest that depolarisation block occurs, but only leads to reduced firing rates rather than a complete block, and crucially does not lead to changes in the impulse-driven release of DA. They suggest that the depolarisation block may serve to smooth the release of DA, implying that the fundamental DA deficit in schizophrenia is a fluctuation in DA release. This provides further support for the fluctuating DA hypothesis.

9.2 Summary of findings

The main ideas and findings of this thesis are summarised in a list here and illustrated in Figure 9.1.

- DA controls the occurrence of functional synergism (oscillation) between pyramidal cells and GABA cells in the PFCx. This synergism is necessary for the working memory properties of the PFCx

- Alterations in the level of the DA, in the number of GABA cells, and changes in the recurrent collaterals can all compromise PFCx working memory function. These changes could be developmental in origin.

- Reinforcement learning provides a model for the function of the NAcc. In this model the actor is the NAcc and the adaptive critic is the PFCx.
Figure 9.1: This diagram illustrates the main effects investigated in this thesis. These are: synergistic action between PfCx pyramidal and GABA cells and their role in working memory; the role of DA in reward-based learning in the NAcc; the control of DA release from the VTA by the PfCx, implying that PfCx may be the locus for the adaptive critic; disruption of ACh action on inhibitory interneurons in the hippocampus may be linked to schizophrenia.

- Fluctuations in the level of DA in NAcc and PfCx are behind the pathogenesis of schizophrenic symptoms, rather than a fixed increase in phasic DA responses. Fluctuations could arise either from PfCx or hippocampal discrepancies.

- Disruption of reinforcement learning due to DA fluctuations could lead to a failure of metarepresentation, and so to the symptoms of schizophrenia.
9.3 Concluding remarks

The amount of data pertaining to schizophrenia across many different spheres of research is almost overwhelming and makes it impossible to give every issue the attention which it deserves. There are also many theories of schizophrenia, not all of which have been addressed in this thesis.

I have focused on certain areas of the brain and have attempted to elucidate some of the mechanisms through which these regions perform information processing. I have used computational models operating at several different levels, from the firing properties of individual neurons in the PfCx through neurotransmitter interactions between brain regions to the influence of DA on the learning properties of the NAcc, to investigate these mechanisms. I have also made suggestions as to how various brain regions interact in normal situations. From the models it has been possible to show how a) information processing can go awry; and b) the consequences of abnormal interactions between brain regions. I hope that this work has addressed some interesting questions and even provided one or two answers. Perhaps more importantly, however, I hope that this work poses some interesting questions for which others may find answers.
Published Work


### Chapter 10

**Dopamine dynamics: 12 equation model**

#### 10.1 Rate constant values

<table>
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<tr>
<th>Rate constant</th>
<th>Value / ms$^{-1}$</th>
<th>Action</th>
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<tr>
<td>$k_1$</td>
<td>58924</td>
<td>$D_2$ autoreceptor</td>
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<tr>
<td>$k_2$</td>
<td>125011416</td>
<td>presynaptic 5-HT1B receptor in NAcc</td>
</tr>
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<td>presynaptic 5-HT1B receptor in PfCx</td>
</tr>
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<td>$k_4$</td>
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<td>hippocampal Glu input to NAcc</td>
</tr>
<tr>
<td>$k_7$</td>
<td>$1.058 \times 10^{-7}$</td>
<td>DA reduces GABA from NAcc i/neurons</td>
</tr>
<tr>
<td>$k_9$</td>
<td>0.333</td>
<td>somatodendritic DA in mesolimbic VTA cells</td>
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<tr>
<td>$k_{10}$</td>
<td>0.167</td>
<td>somatodendritic DA in mesolimbic VTA cells</td>
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<td>$k_{11}$</td>
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<td>action of glu on NAcc cells</td>
</tr>
<tr>
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<td>presynaptic action of somatodendritic DA on external Glu input to mesolimbic DA neurons</td>
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<td>presynaptic action of somatodendritic DA in VTA on [Glu]</td>
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Continued overleaf...
Dopamine dynamics: 12 equation model

<table>
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<th>Action</th>
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<td>presynaptic effect of 5-HT on GABA input to VTA</td>
</tr>
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<td>$1 \times 10^{-7}$</td>
<td>action of 5-HT on VTA cells</td>
</tr>
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<td>$2.3 \times 10^{-7}$</td>
<td>action of ACh via muscarinic receptors on VTA mesolimbic cells</td>
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<td>presynaptic action of somatodendritic DA on external Glu input to mesocortical DA neurons</td>
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<td>action of GABA on pyramidal cells in PfCx</td>
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<td>action of external Glu inputs on pyramidal cells in PfCx</td>
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<td>action of Glu in PfCx on [GABA]</td>
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10.2 Variable initial values

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<tr>
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<tr>
<td>$D_p$</td>
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<tr>
<td>$G_{\alpha_{el}}$</td>
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</tr>
<tr>
<td>$G_{\alpha_{vc}}$</td>
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<td>$G_{\alpha_p}$</td>
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10.3 Parameter values

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<td>$N$</td>
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<tr>
<td>$M$</td>
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Chapter 11

Data set for Tower of London Task

Moves refer to the positions described in diagram 7.2.

1-move problems

\[
\begin{align*}
10 & \rightarrow 12 \\
11 & \rightarrow 7 \\
21 & \rightarrow 23 \\
16 & \rightarrow 15 \\
2 & \rightarrow 1 \\
33 & \rightarrow 31
\end{align*}
\]

2-move problems

\[
\begin{align*}
29 & \rightarrow 31 \\
11 & \rightarrow 16 \\
35 & \rightarrow 4 \\
6 & \rightarrow 8 \\
33 & \rightarrow 30
\end{align*}
\]

3-move problems

\[
\begin{align*}
26 & \rightarrow 20 \\
26 & \rightarrow 30 \\
29 & \rightarrow 21 \\
34 & \rightarrow 2 \\
15 & \rightarrow 20 \\
15 & \rightarrow 10
\end{align*}
\]
4-move problems

\[
\begin{align*}
35 &\rightarrow 24 & 6 &\rightarrow 10 & 25 &\rightarrow 18 \\
21 &\rightarrow 27 & 17 &\rightarrow 7 & 5 &\rightarrow 31
\end{align*}
\]

5-move problems

\[
\begin{align*}
15 &\rightarrow 5 & 21 &\rightarrow 33 & 30 &\rightarrow 5 \\
11 &\rightarrow 36 & 15 &\rightarrow 25 & 16 &\rightarrow 3
\end{align*}
\]

6-move problems

\[
\begin{align*}
29 &\rightarrow 1 & 25 &\rightarrow 12 & 35 &\rightarrow 11 \\
30 &\rightarrow 17 & 35 &\rightarrow 20 & 12 &\rightarrow 25
\end{align*}
\]

7-move problems

\[
\begin{align*}
29 &\rightarrow 11 & 20 &\rightarrow 1 & 11 &\rightarrow 30 \\
20 &\rightarrow 34 & 12 &\rightarrow 27 & 35 &\rightarrow 19
\end{align*}
\]

8-move problems

\[
\begin{align*}
16 &\rightarrow 35 & 21 &\rightarrow 6 & 20 &\rightarrow 6 \\
34 &\rightarrow 18 & 11 &\rightarrow 28 & 1 &\rightarrow 21
\end{align*}
\]