A Computational Model of Information Processing in the Frontal Cortex and Basal Ganglia

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Abstract

■ Performance on the Wisconsin Card Sort Test (WCST) of patients with schizophrenia, Parkinson's disease (PD), and Huntington's disease (HD) was simulated by a neural network model constructed on principles derived from neuroanatomic loops from the frontal cortex through the basal ganglia and thalamus. The model provided a computational rationale for the empirical pattern of perseverative errors associated with frontal cortex dysfunction and random errors associated with striatal dysfunction. The model displayed perseverative errors in performance when the gain parameter of the activation function in units representing frontal cortex neurons was reduced as an analog of reduced dopamine release. Random errors occurred when the gain parameter of the activation function in units representing striatal neurons was reduced, or when the activation level was itself reduced as an analog of a striatal lesion. The model demonstrated that the perseveration of schizophrenic, Huntington's, and demented Parkinsonian patients may be principally due to ineffective inhibition of previously learned contextual rules in the frontal cortex, while the random errors of Parkinson's and Huntington's patients are more likely to be due to unsystematic errors of matching in the striatum. The model also made specific, empirically falsifiable predictions that can be used to explore the utility of these putative mechanisms of information processing in the frontal cortex and basal ganglia. ■

INTRODUCTION

The dorsolateral prefrontal cortex has been the subject of intense scrutiny by researchers in neuroanatomy (Goldman-Rakic, 1987), neuropsychology (Drewe, 1974), and neuropsychiatry (Berman & Weinberger, 1990; Taylor, Saint-Cyr, & Lang, 1986). This research has generated both broad theories of executive function (Fuster, 1989), and detailed computational models of specific functions putatively performed in the frontal cortex, including sustained attention (Cohen & Servan-Schreiber, 1993) and working memory (Dehaene & Changeux, 1989; Levine, Parks, & Prueitt, 1993). These models simulate performance on neuropsychological tests sensitive to frontal lobe dysfunction, such as the Wisconsin Card Sorting Test (WCST), which tests the ability to shift sets (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). However, that patients with subcortical lesions are impaired on the test indicates that some of the processes involved in WCST performance may be located subcortically (Caltagirone, Carlesimo, Nocentini, & Vicari, 1994; Taylor et al., 1986). Recent research demonstrating the integration of the frontal cortex in neuroanatomic loops through the basal ganglia and thalamus (Alexander, DeLong, & Crutcher, 1992) provided the framework for a computational model of WCST performance, which could integrate these findings into a more comprehensive scheme.

The WCST (Heaton et al., 1993) is an ideal tool for examining the information processing performed in the cortico-basal loops due to the extensive literature associated with the tool, including many studies with patient populations suffering dysfunction in different regions of the loops. The WCST requires subjects to sort a deck of 128 cards according to specific criteria. The cards contain figures varying along three dimensions: color, form, and number, each of which has four possible states. Thus, each card contains between one and four identical shapes, taking one of four forms (square, circle, triangle, cross), in one of four colors (red, yellow, green, blue). The subject must place each of the 128 stimulus cards, in turn, in front of one of four target cards, which never change. The subject is not told what rule to apply, and must infer the appropriate rule from the experimenter's response to each attempt. The experimenter will at first reply "Correct" if the subject sorts according to color. Once the subject has made 10 correct responses in a row, a category is achieved and the rule changes without warning. The test ends once all 128 cards have been placed, or once the subject correctly achieves six categories (Heaton et al., 1993).

Although the WCST has primarily been used as a test of frontal lobe (or executive) function (Lezak, 1995), patient populations with disorders putatively limited to nonfrontal regions of the cortico-basal loop also achieve significantly fewer categories than normal controls. Patients with Huntington's disease (HD) suffer selective destruction of the neurons of the striatum, the area of the basal ganglia that receives most of the afferent fibers originating outside the basal ganglia (Mendez, 1994). Parkinson's disease (PD) involves destruction of neurons of the substantia nigra (pars compacta), the major source of dopamine for structures of the basal ganglia (Boller, Mizutani, Roessman, & Gambetti, 1980). Severe deficits on the WCST have been found in samples of patients with HD (Weinberger, Berman, Iadarola, Driesen, & Zec, 1988) and PD (Taylor et al., 1986).

Impaired WCST performance has also been demonstrated in patients with dysfunction in the frontal lobes (Drewe, 1974), including schizophrenics (Weinberger, Berman, & Zec, 1986). Although schizophrenia has been associated with dysfunction in many areas of the brain, including regions of the basal ganglia, the limbic system, and the anterior cingulate cortex (Buchsbaum, 1994), the present model will only consider the possible effects of dopamine imbalance in the frontal cortex. With this caveat, it appears that there is a good body of empirical data for testing hypotheses about the particular processes performed in the different areas of the cortico-basal loops during the WCST.

Previous Models of the WCST

Two long-standing computational models of the WCST utilising neural network architectures to investigate frontal function have been reported in the literature (Levine et al., 1993; Dehaene & Changeux, 1989). Neither model was constructed on the basis of known structures in the frontal cortex. Instead, the authors suggested post hoc that the manipulation of particular parameters was analogous to frontal dysfunction. A more recent model was based on a neuroanatomic rationale (Monchi & Taylor, 1999).

Levine and Leven

Levine et al.'s (1993) model was a simplified form of an Adaptive Resonance Theory (ART) network (Carpenter & Grossberg, 1987), comprising six interconnected modules. For present purposes, the most relevant module was the bias module, which determined the attention given to the dimensions color, form, and number. The dimensions were represented by three mutually inhibitory units, only one of which could be active at a time. Information about dimensions represented by the inactive units was blocked. If the network's response on the previous trial was incorrect, the activity of the highly active unit was suppressed, allowing another unit to become active.

This model successfully simulated normal performance on the WCST. It reproduced the significantly lower number of achieved categories characteristic of patients with frontal lobe lesions by reducing the sensitivity of the bias module to success and failure. Levine et al. (1993) simulated frontal damage by reducing the strength of the rewarding or punishing signals representing success or failure. However, the role of the frontal cortex in this motivation system seems to be in the prediction of reward (Schultz, Dayan, & Montague, 1997), and the generation of responses to unexpected outcomes (Schultz, Apicella, Romo, & Scarnati, 1994) rather than in the generation or modification of the strength of reward or punishment. These putative functions suggest an alternative analogue of a frontal cortex lesion: A dysfunction in the bias module itself, which predicts the correct rule for sorting. The reduction of the effects of success and failure on the bias module might rather be expected to simulate dysfunction in reward pathways projecting to the frontal cortex. That the reduction of the rewarding effects of particular actions does not really describe the deficit in frontal dysfunction is supported by the fact that subjects with frontal lobe lesions do not have difficulty in learning all tasks involving reward, but only those that involve the maintenance of contextual information across time (Petrides, 1995; Goldman-Rakic, 1987).

Dehaene and Changeux

Dehaene and Changeux's (1989) model of WCST performance was more biologically informed than Levine et al.'s (1993). Dehaene and Changeux's (1989) model also reasoned about the situation, in the limited sense that it could make the sorting decision on the basis of memories of past decisions, by selecting among sorting rules that would not have failed on the last incorrect response, or both.

Dehaene and Changeux (1989) also included in their model two features motivated by conditions within the brain. They suggested that the nature of the connection between two neurons (e.g., A and B) could be altered by another neuron (C) if that neuron (C) changes the state of receptors on the afferent neuron. Thus, when C fires it changes the shape of receptors on B, thereby either enhancing or diminishing the effects of A on B. Therefore, Dehaene and Changeux (1989) implemented a method of learning that has a neural analogue, whereas Levine et al. (1993) simply assumed that their bias units can gate information between input units and decision units in a way unmotivated by information processing in the brain.

In addition, Dehaene and Changeux (1989) allowed the state of particular units in their network to retain information. In most neural networks, information is retained in the relatively static connection weights between units. However, single-unit studies in primate

brains have demonstrated that working memory in the frontal cortex relies in part on the sustained activation of particular neurons (Goldman-Rakic, 1987). Dehaene and Changeux's (1989) model stored the current sorting rule by maintaining the activation of one of three units representing color, form, or number.

Monchi and Taylor

Monchi and Taylor (1999) described a model of working memory based on the neuroanatomic loops between the frontal cortex, the basal ganglia, and the thalamus. They developed the analogy between their modules and the neural substrate in considerable detail. This permitted examination of the mechanisms underlying deficits in working memory tasks including the WCST in patients with PD and schizophrenia, as well as those with frontal lobe lesions.

Monchi and Taylor's (1999) model of a three-target-card version of the WCST consisted of several parallel loops from the cortex through the basal ganglia and thalamus. Each of three loops maintained a representation of the currently active feature of one dimension of the WCST through recurrent feedback. Another loop maintained a representation of the current rule. The frontal lobe module integrated this information and selected a response.

This model was used in a qualitative investigation of possible mechanisms in disease states, without simulating empirical results in patient populations. Essentially, Monchi and Taylor (1999) suggested that Parkinson's patients perform poorly on the WCST because dysfunction in the striatum interferes with the accurate encoding of features within each loop. Dysfunction in the frontal cortex in schizophrenia was explained as the result of a dopamine-related dysfunction in the nucleus accumbens, which interfered with the ability of the network to settle on a single rule. However, this would appear to predict that schizophrenic patients would show random patterns of error, whereas empirical data suggest they tend to make perseverative errors (Weinberger et al., 1986). In the model, this would appear to be analogous to an inability to change a rule once selected, rather than an inability to settle on a particular rule. The explanatory value of the model would therefore be enhanced if it was used to simulate patient data.

Extending Understanding of Information Processing in WCST Performance

Both Levine et al. (1993) and Dehaene and Changeux (1989) were interested in the WCST as a tool for understanding the nature of information processing in the prefrontal cortex. However, patients with lesions confined to subcortical areas show deficits in performance on this task in the absence of global dysfunction. Such deficits have been demonstrated in patients with PD (Taylor et al., 1986) and HD (Weinberger et al., 1988). It would be difficult to extend the former models to explain the mechanisms of deficit in these diseases. While Monchi and Taylor (1999) provided a detailed anatomical rationale for their model, they did not simulate empirical results from studies with patient populations.

Thus, while these models provide compelling accounts of possible mechanisms of information processing in the frontal lobes, cortico-basal loops, and the performance of the WCST, they may not completely describe these domains. A network constrained by neuroanatomy and patient data might engender a finer level of description of processes involved in the performance of the WCST, and of the information processing performed in the frontal cortex and other areas of the cortico-basal loops.

Empirical Patterns

In order to investigate these concerns, the performance of subject samples with dysfunctions thought to be relatively localized inside and outside the frontal cortex was simulated. The present paper focuses on subject samples with schizophrenia (considered as an example of frontal cortex dysfunction), PD (striatal neurotransmitter imbalance), and HD (striatal lesion).

Empirical work with the WCST differentiates these patient populations (Table 1). Normal and control groups typically perform well, with almost all subjects completing all six categories within 128 trials (Berman et al., 1995). Schizophrenic patients without tardive dyskinesia (a motor disorder of abnormal involuntary movements thought to be related to neuroleptic use [Casey, 1995]) showed a high level of perseveration, tending to achieve few categories because they tended to apply previously correct categorization rules after the rule had been changed (Weinberger et al., 1986). Schizophrenics with tardive dyskinesia performed worse than those without, due to a greater proportion of perseverative errors (Waddington et al., 1995).

PD patients without dementia performed very poorly, but in contrast to the error patterns of schizophrenics; they tended to show high rates of random error, with a proportion of perseverative errors similar to that of the control group. PD patients with dementia showed high rates of random error as well as elevated rates of perseverative errors (Caltagirone et al., 1994).

HD patients also performed worse than normal controls, due to high levels of both perseverative and random errors (Weinberger et al., 1988). Thus, schizophrenia was associated mostly with perseverative errors, Parkinson's more with random errors, while patients with HD and PD with dementia made high levels of both sorts of error. Several researchers have tied the cognitive deficits in these disorders to dysfunctions in particular parts of the brain: schizophrenia to

Table 1. Empirical Results

Disorder	*Study*	*Groups*	*Categories*	*Perseverative errors (%)*
Schizophrenia	Weinberger et al. (1986)	Normal control	6	9
		Schizophrenic patients	1.5	27
	Waddington et al. (1995)	Schizophrenic patients	2.9	27
		Schiz.+Tardive dyskinesia	2.5	41
Parkinson's disease	Taylor et al. (1986)	Normal controls	6.1	15
		Parkinson's patients	3.7	16
	Caltagirone et al. (1994)	Parkinson's patients	5	20
		Parkinson's with dementia	2	27
Huntington's disease	Weinberger et al. (1988)	Normal controls	6.7	13
		Huntington's patients	1.4	38

frontal lobe dysfunction (Cohen & Servan-Schreiber, 1993), HD to a combination of frontal lobe and basal ganglia dysfunctions (Mendez, 1994), and PD to the basal ganglia (Bradshaw & Mattingley, 1995). In addition, dementia in PD has been shown to be associated with cortical degeneration similar to that found in Alzheimer's disease (Boller et al., 1980).

The present model was constructed in order to test the hypothesis that perseverative errors on the WCST are primarily associated with frontal lobe dysfunction, and random errors are more associated with basal ganglia dysfunction. This hypothesis was tested by constructing the model on the basis of the neuroanatomic features of the cortex and basal ganglia reviewed in the next section, before comparing the performance of the model to that of several psychiatric populations. This method additionally allowed a description of the deficits of these psychiatric populations in terms of specific processes.

Information Processing in the Prefrontal Corticobasal Loop

Alexander et al. (1992) outlined the anatomy of several loops incorporating aspects of the frontal cortex, the striatum, the substantia nigra and globus pallidus, and the thalamus (Figure 1). They suggested that these loops are important in processing information used in motor and cognitive functions. The anatomical structure and information processing associated with each area of these loops is discussed in turn to establish the neural substrate of the present model of WCST performance.

The Prefrontal Cortex

The area of the cortex that lies in front of the motor areas on the dorsolateral surface of the frontal lobes, the dorsolateral prefrontal cortex, is considered the probable locus of many of the functions served by working memory (Fuster, 1989). One of the many processes that occur in the prefrontal cortex is the maintenance of information about a stimulus between its removal and the onset of a response cue in tasks such as delayed response, delayed alternation (Goldman-Rakic, 1987), and internally generated sequencing (Petrides, 1995). In the same way, the WCST requires subjects to make decisions based on information retained from previous trials.

Goldman-Rakic (1987) reviewed the evidence about this process of working memory. She recorded the activation of single neurons in various areas of the primate cortex, including the prefrontal, during various activities. During delayed response tasks, particular sets of prefrontal neurons remained active between the removal of a stimulus and the onset of the response cue. The active neurons were different depending on the nature of the stimulus.

Thus, it appears that one of the functions of the prefrontal cortex is to maintain contextual information that is required for future responses. In addition, as Goldman-Rakic (1987), and others (Petrides, 1995) have shown, this information is represented by the maintained activation of particular prefrontal neurons.

Neurons in the cortex are of two basic types: pyramidal and nonpyramidal. It is believed that the pyramidal cells are excitatory, that some nonpyramidal cells are inhibitory, and that most cells that project from the cortex to the basal ganglia are excitatory (Haines, 1995).

Another feature, which guided the construction of the current model is that cortical neurons are arranged in columns. Thus, there are functional associations of neurons involved in the representation and manipulation of particular sorts of information. The nature of these organizational units is not fully understood, but the general properties include dense connections within

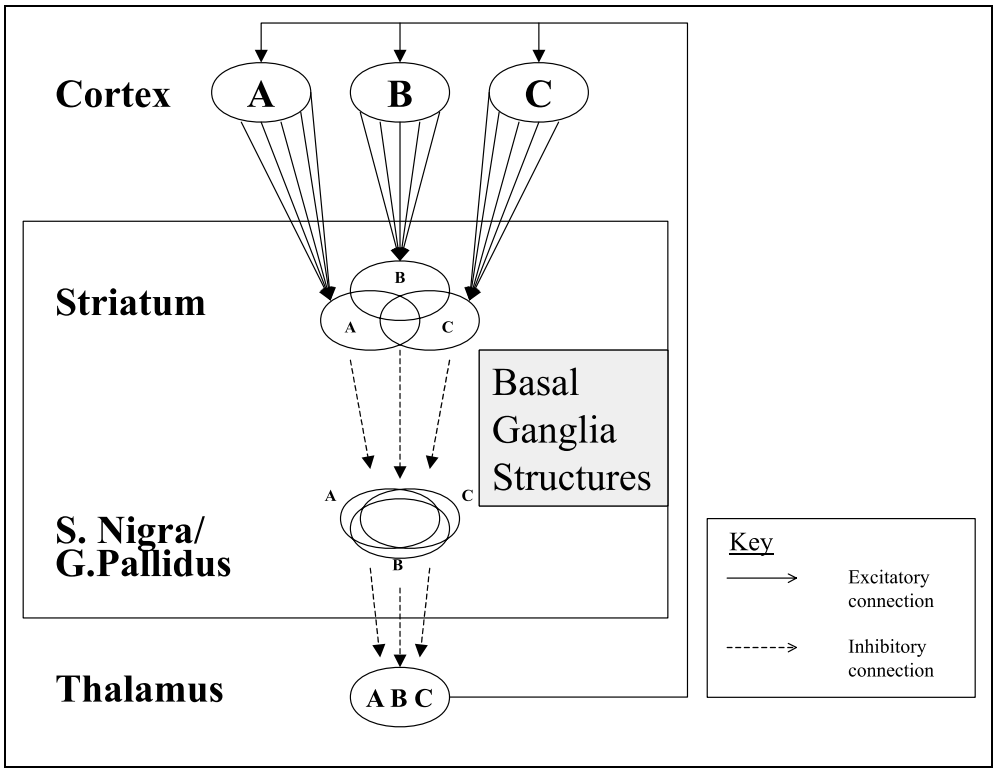

Figure 1. Basic form of the cortico-basal loop. Demonstrates the converging, topographic inputs from dispersed but related areas of the cortex (A, B, C) onto the striatum, and from the striatum to the output nuclei (S. Nigra/G. Pallidus). There are of the order of 1000 inputs to the striatum for each output from the striatum. Adapted from Alexander et al. (1986).

columns, and sparser connections to related units via mediating neurons (Calvin, 1995).

The Striatum

Cells in the striatum can be divided into two basic categories: medium-sized spiny neurons (about 95% of striatal cells), and all others (including large spiny and small aspiny neurons). It is generally accepted that medium-sized spiny neurons project inhibitory connections outside the striatum, with localized collaterals (Di Chiara, 1995).

The striatum receives almost all of the afferent fibers of the basal ganglia (Gerfen, 1992). As part of the corticobasal loop it projects to the substantia nigra (pars reticulata) (SN(r)) and globus pallidus (interna) (GP(i)) (Alexander et al., 1992). Projections to the striatum are topographically arranged such that distributed areas of the cortex devoted to representations of different aspects of the same construct project to the same area of striatum (Graybiel & Kimura, 1995). For example, the color and light intensity of the same area of the visual field are represented in different areas of the cortex, but project to the same area of the striatum. Projections from the striatum are also topographically organized (Graybiel & Kimura, 1995).

There are about 1000 projections to the striatum for every output (Berns & Sejnowski, 1995). The topographic nature of the projections strongly suggests that the striatum performs some form of integration, for example by gating information.

Another pathway has been described between the striatum and SN(r) and GP(i) through the globus pallidus (external) and subthalamic nucleus. It has been suggested that activation in this pathway modifies the effect of activation through the direct pathway from the striatum to the SN(r) and GP(i) (Starr, 1995). However, as recent reviews suggest that evidence for the existence of an indirect pathway is not conclusive, and as the actual function performed by this pathway is unclear (Parent & Hazrati, 1995b), it is not included in the model.

The Substantia Nigra (Reticulata) and the Globus Pallidus (Interna)

The SN(r) and the GP(i) are the principal output nuclei of the basal ganglia (Gerfen, 1992). They project to the thalamus, and thence relay information back to the cortex (Alexander et al., 1992). These nuclei (SN/GP hereafter) are tonically active, and their projections to the thalamus are inhibitory. To initiate movement, SN/GP cells must be inhibited by activity in the projections from the striatum, disinhibiting the thalamus and cortex, thus allowing activity to occur (Starr, 1995).

This architecture indicates that the functions of the SN/GP complex include those of initiating and maintaining activity (Graybiel & Kimura, 1995). Projections from the striatum to the SN/GP are topographically arranged so that areas within these nuclei receive projections from particular bands in the striatum. Graybiel and

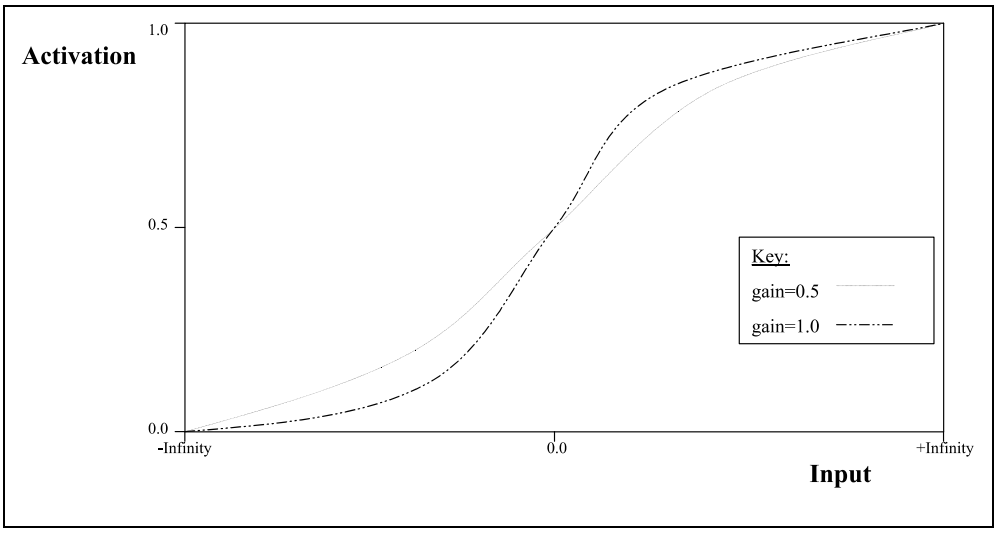

Figure 2. As gain increases, the activation function $f(x)=1/(1+e^{-gain*x})$ approaches a step function, increasing the signal-to-noise ratio.

Kimura (1995) suggest that this arrangement provides a distinct channeling of information from the cortex through the striatum to the SN/GP that allows information to be dispersed in the striatum then reintegrated in the SN/GP in order to select a particular activity in a ''winner-lose-all'' manner such that active striatal projections strongly inhibit only the neurons representing the selected action.

The Role of Dopamine in Neuronal Information Processing

Dopamine is an important neurotransmitter in the cortico-basal loops. Dopamine imbalance also plays an important part in the pathology of schizophrenia, PD, and HD. The substantia nigra (pars compacta) and nearby structures richly supply the striatum and the frontal cortex with dopamine (Starr, 1995). A dopamine imbalance has been hypothesized to be the primary dysfunction of schizophrenia, because the primary treatment involves manipulation of DA levels with neuroleptic medication.

Cohen and Servan-Schreiber (1993) showed that the putative dopamine deficit in the frontal cortex of schizophrenic patients could be simulated by manipulating the gain parameter of units in a network model describing frontal cortex function. By focusing on the frontal cortex, Cohen and Servan-Schreiber (1993) may have limited the descriptive power and scope of their model in a manner similar to Levine et al. (1993) and Dehaene and Changeux (1989). Nevertheless, Cohen and Servan-Schreiber (1993) convincingly supported the manipulation of gain as a tool for modeling the effects of dopamine (DA) dysfunction. They pointed out that DA potentiates the response of particular neurons to both excitatory and inhibitory afferents. Changing the gain parameter of the logistic activation function, which describes the input–output relationship of units in many networks, captures this potentiating effect of DA (Figure 2).

Principles Underlying the Model

A number of constraints from the foregoing discussion were used to structure the model. First, the module representing the frontal cortex should retain information over time by maintaining the activation of particular cells representing information important for future responses. It should use a columnar organization, with clusters of connected cells connected to other columns through mediating cells. Projections to the striatum should be excitatory.

Second, the module representing the striatum should integrate information from cortical representations. Its units should only respond to activity distributed across a number of afferent fibers. Striatal cells project inhibitory efferents to areas outside the striatum.

Third, the module representing the SN/GP should select a ''winner-lose-all'' response. The projections from this module are inhibitory, well segregated, and topographically organised.

Finally, the effects of reduced DA may be simulated by reducing the gain of activation functions representing affected neurons (Cohen & Servan-Schreiber, 1993).

The Model

Figure 3 gives an overview of the model. There were two sets of input, one representing the characteristics of the stimulus card for each trial, and one representing the target cards. As the target cards never change in the WCST, the inputs representing the target cards were fixed. The model examined the stimulus card with reference to a sorting rule (Frontal module), matched the stimulus card with one of the four target cards

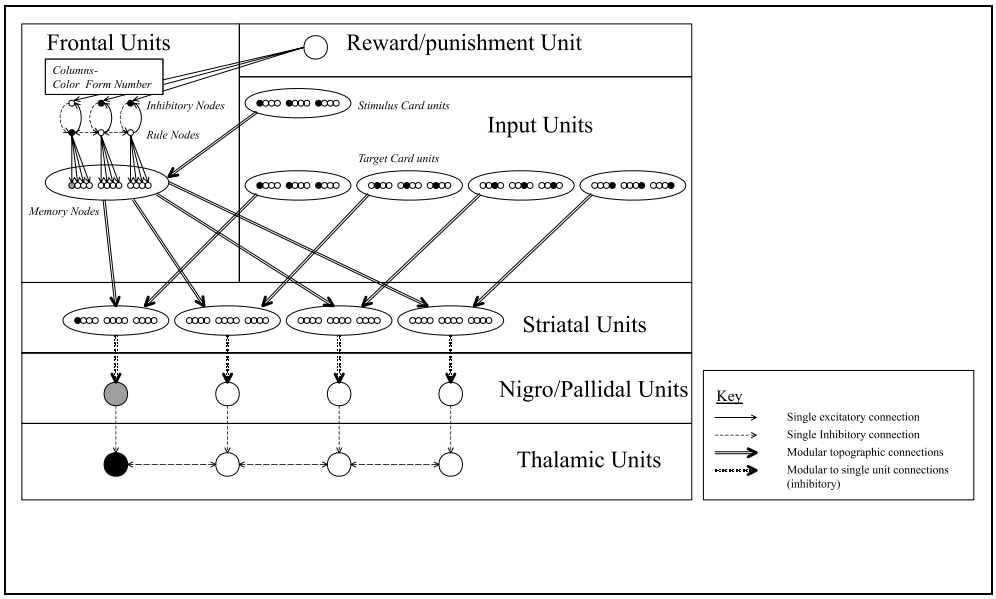

Figure 3. Model structure; by the anatomic features of the cortico-basal loop. The frontal module is organized into columns; the striatal module receives topographic projections from the frontal module and input units; there are converging projections onto the striatal and nigro/pallidal modules. Action is disinhibited at the thalamic module.

according to that rule (Striatal module), then retained or changed the sorting rule (Frontal module) depending on the success of the action (SN/GP and Thalamic modules). The activation equations of all units are given in the Appendix.

The model does not include projections between the thalamic and cortical modules. Thus, it cannot reproduce effects due to feedback of information through the cortico-basal loops described by Alexander et al. (1992). Monchi and Taylor's (1999) model used three feedback loops to select and maintain the features of each dimension on the present stimulus card. This is a different approach, and it would be interesting to use Monchi and Taylor's (1999) model to simulate empirical results from patient populations to see how well their approach accounts for quantitative data. The present model also does not attempt to simulate the information routing performed by the thalamus; in the present model, the thalamus acts as a target for information representing the action selected in the SN/GP. These simplifying assumptions comprise two possibilities for extending the model. In particular, completing the loop would allow more complex integration of information in the frontal cortex, including the comparison of predicted results with actual outcomes. Monchi and Taylor (1999) did not include such a function in their frontal module, although their approach might readily be extended in this way.

Association Cortex

Following Levine et al. (1993) and Dehaene and Changeux (1989) stimulus and target cards were represented by three sets of four units representing the four possible states of each of the three dimensions (Figure 4). This level of representation is assumed to occur in the association area of the visual cortex (Levine et al., 1993).

Frontal Module

The frontal module stored and applied the model's current sorting rule. Inputs to the frontal module synapsed on units organised into three columns representing color, form, and number (Figure 3).

Each column contained memory units, rule units, and inhibitory units. Each column had four memory units with one connection from the corresponding unit of the input card, and one connection from the column's rule unit. A highly active rule unit would excite the memory units in the column, increasing attention to the column's attribute. The rule units were mutually inhibitory, so only one could be active at a time (Figure 3).

Each column contained an inhibitory unit that made an inhibitory synapse with the rule unit, which reciprocated with an excitatory synapse. Each inhibitory unit also received an excitatory synapse from a single punishment unit, which fired if the last trial was unsuccessful (Figure 3). This accommodated the fact that the general signal of presence or absence of expected reward from the ventral tegmental area projects unselectively to much of the prefrontal cortex and limbic system (Oades & Halliday, 1987). In the model, an inhibitory unit would only become active if both the general punishing signal occurred and the specific related rule neuron was currently highly active.

This architecture instantiated a win-stay, lose-shift strategy. The mutual inhibition of the rule units would cause the most active unit to suppress the other two. Mutual excitation between the rule unit and the memory units in its column maintained the activity of the rule unit. If a trial ended in failure, the active

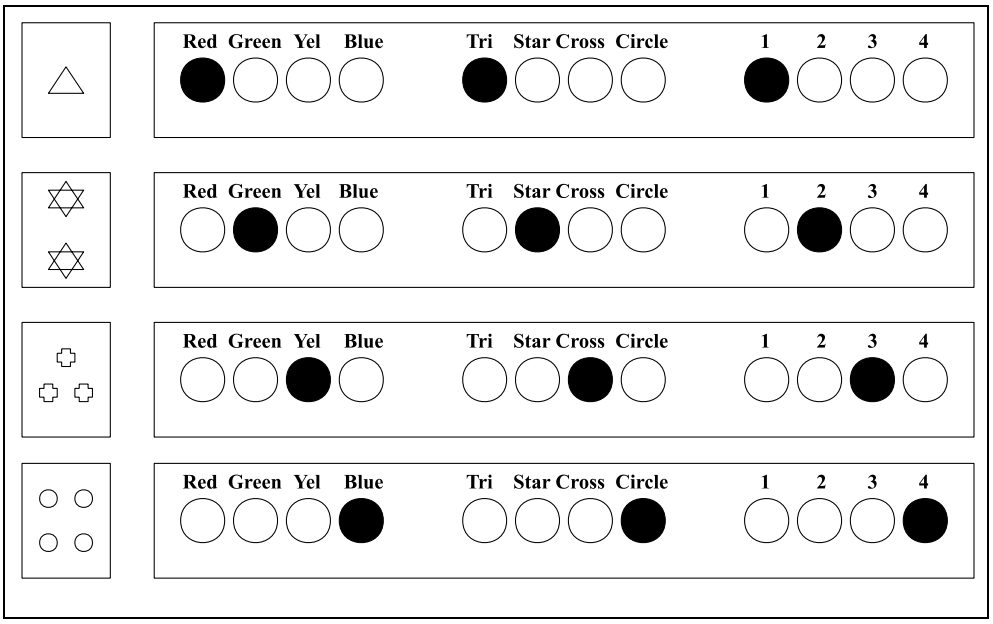

Figure 4. The characteristics of each card are represented by the activity across twelve nodes. Four nodes represent color, four represent form, and four represent number. In each group of four, one node is active, representing the characteristic present in the card, and the other nodes are inactive.

rule unit was inhibited, allowing another unit to become active.

Striatal Module

Units representing the target cards projected to the striatal module. Additionally, the units representing each characteristic of the stimulus card in the frontal cortex projected to the same units as the analogous characteristics of the target cards (Figure 3), mirroring the topographic nature of corticostriatal projections (Graybiel & Kimura, 1995). The striatal module integrated this information in a way that detected matches. Only units with active afferents from both the frontal lobe module and the target cards would themselves become active.

The striatal module contained four separate representations of twelve units each, analogous to the four target cards (Figure 3). However, what was represented here was not a card per se, but the pattern of match between the stimulus card and each target card, modified by the level of attention given to each attribute in the frontal module.

Nigral Module

Projections from the striatum to the SN/GP are also topographic (Parent & Hazrati, 1995a). In the model, each of the four match patterns of the striatal module projected to a single nigral module unit representing one of the four possible actions (Figure 3). The nigral units were tonically active, and the synapses were inhibitory. Therefore, the greater the strength of match in the striatal units, the lower would be the level of activity of the corresponding nigral unit. The nigral unit with the lowest activation level was thus inhibited, and the corresponding action (i.e., placing the stimulus card before a particular target card) chosen by the network by disinhibiting the appropriate thalamic unit.

Simulations

The model was first constructed to simulate the WCST performance of a normal population (Berman et al., 1995). This architecture was then used to simulate the performance of samples of schizophrenics with (Waddington et al., 1995) and without (Weinberger et al., 1986) tardive dyskinesia; PD sufferers with (Caltagirone et al., 1994) and without (Taylor et al., 1986) dementia; and HD patients (Weinberger et al., 1988). In all cases, the function of different modules was selectively altered by modifying parameters analogous to the dopamine deficit or lesion known to mediate the particular syndrome.

Simulating Dysfunctions of Schizophrenia, PD, and HD

Cohen and Servan-Schreiber (1993) simulated dopamine imbalances by reducing the gain of the activation function of the units of their model. They argue that this modification is analogous to altering the signal-to-noise ratio of the cell, potentiating both excitatory and inhibitory inputs (Figure 2). Dopamine also tends to cause neurons in the frontal cortex to become more excited due to modulation of the membrane properties of the postsynapic neuron (Penit-Soria, Audinat, & Crepel, 1987). To simulate decreased dopamine in schizophrenia and PD, the bias against firing in frontal units was increased, and the gain decreased.

HD arises from the destruction of projection neurons in the striatum (Mendez, 1994). This was approxi-

mated in the model by reducing the output of striatal neurons (i.e., reducing the activation of Equation (4) in the Appendix). This assumes that each model unit represents many neurons, and that information is disrupted rather than destroyed by lesions.

RESULTS

Parameter manipulations for all simulations are provided in Table 2.

Schizophrenic Samples

Normal performance (Weinberger et al., 1986) was simulated by manipulating noise in the network. Noise was constant and random across the entire network, all activation functions having the general form: Activation(t) = $1/(1+e^{-\text{gain}*(\text{Sum of inputs})+\text{bias}+\text{Noise}})$. Holding all other parameters constant, the schizophrenic pattern was produced by reducing the gain and increasing the bias of all units in the frontal module. Perseverative errors increased as gain was reduced and bias increased in the frontal module, due to decreasing probability that the inhibitory unit would be active enough to inhibit the active rule unit. This might be seen as decreased sensitivity to punishment signals.

To simulate the differences between schizophrenic patients with and without tardive dyskenesia (Waddington et al., 1995) two possibilities were explored. The poorer performance of those with TD may be due to dysfunction in the frontal cortex or the striatum caused by the dopamine antagonist effects of neuroleptic medication. This was simulated by reducing the gain of the striatal module (Striatal Model), and by reducing the gain and increasing the bias of the frontal module (Frontal Model).

As Table 3 demonstrates, the Frontal Model produced a better fit to the data than the Striatal Model. The former interfered with performance by increasing the proportion of perseverative errors while the latter increased the proportion of random errors.

Parkinson's Samples

Table 4 presents the results of the simulations of PD patients. Cognitive decline with age has been related to a decline in dopamine production and release (Arnsten, Cai, Steere, & Goldman-Rakic, 1995). As the control group in Taylor et al.'s (1986) study was age-matched to the PD patients, striatal and frontal gain were reduced, and noise increased, to reproduce the normal pattern. The PD pattern was simulated by decreasing striatal gain. This increased the proportion of random errors, while perseverative errors remained at about the same level. As the striatal module essentially performs matching, increasing the effect of noise by decreasing gain tended to cause unsystematic errors.

Table 2. Parameter Manipulations

Disorder	*Study*	*Simulated group*	*Frontal gain*	*Frontal bias*	*Striatal gain*	*Striatal output*
Schizophrenia	Weinberger et al. (1986)	Normal controls	1.0	6.4	1.0	1.0
		Schizophrenic patients	0.9	7.7	1.0	1.0
	Waddington et al. (1995)	Schizophrenic patients	0.9	6.6	1.0	1.0
		Schiz.+Tardive Dyskinesia (Frontal Model)	0.85	7.8	1.0	1.0
		Schiz.+Tardive Dyskinesia (Striatal Model)	0.9	6.6	0.95	1.0
Parkinson's Disease	Taylor et al. (1986)	Normal controls	0.99	6.6	0.98	1.0
		Parkinson's patients	0.99	6.6	0.95	1.0
	Caltagirone et al. (1994)	Parkinson's patients	1.0	6.6	0.97	1.0
		Parkinson's with dementia (Frontal Model)	0.88	6.6	0.97	1.0
		Parkinson's with dementia (Striatal Model)	1.0	6.6	0.95	1.0
Huntington's Disease	Weinberger et al. (1988)	Normal controls	1.0	6.5	1.0	1.0
		Huntington's Patients (Striatal Model)	1.0	6.5	1.0	0.9
		Huntington's Patients (Frontal Model)	0.95	6.5	1.0	1.0
		Huntington's Patients (Fronto-striatal Model)	0.96	6.5	1.0	0.92

Table 3. Simulations of the Performance of Schizophrenic Samples

		Weinberger et al. (1986)	
		Data	*Striatal Model*
Categories	Normal	6.0	6.0
	Schizophrenic	1.5	1.5
Perseveration	Normal	9%	9%
	chizophrenic	27%	26%

		Waddington et al. (1995)		
		Data	*Frontal Model*[a]	*Striatal Model*[b]
Categories	No TD	3.9	3.8	3.8
	TD	2.5	2.5	2.5
Perseveration (%)	No TD	27%	27%	27%
	TD	41%	41%	29%

[a]Frontal Model involved decreased frontal gain and increased frontal bias.
[b]Striatal Model involved decreased striatal gain.

Caltagirone et al. (1994) found that nondemented PD patients performed worse than demented PD patients due to a higher level of perseverative errors. The performance of nondemented PD patients was approximated by adjusting the noise parameter. In addition, the striatal gain parameter was reduced to mimic the reduction in striatal dopamine that causes PD. Two different hypotheses were explored by matching the total number of errors of the demented patients by reducing frontal gain (Frontal Model) and by reducing striatal gain (Striatal Model). The Frontal Model matched actual performance more closely than the Striatal Model (Table 4).

Huntington's Disease

Table 5 shows the results of the simulation of HD patients. Weinberger et al. (1988) demonstrated that HD patients made many perseverative errors. The striatal lesion was simulated by reducing the activation of all striatal units (Striatal Model); as the level of striatal output was increasingly impaired, performance decreased due to an increasing number of random errors, leaving perseverative errors more or less stable. This pattern was quite different from that of the data. In light of the suggestion that HD may involve some retrograde dysfunction in the frontal cortex (Mendez, 1994), the effects of a reduction in frontal gain was explored as an alternative (Frontal Model). This manipulation caused a much higher level of perseverative errors than occurred in the patient sample. Finally, a combination of striatal lesion and reduced frontal gain was explored (Fronto-Striatal Model). This combination did reproduce the pattern of poor performance caused by high levels of perseverative and random errors.

DISCUSSION

A model based on the architecture of the corticobasal loops proposed by Alexander et al. (1992) successfully simulated the WCST performance of patients with frontal and striatal dysfunctions. All parameter changes were motivated by neurotransmitter imbalances and lesions thought to be associated with the disorders. The model demonstrated that the association between frontal lobe dysfunction and perseverative errors, and subcortical dysfunction and random errors, corresponds to differences in the neuroanatomy, neurochemistry, and cognitive function of these areas.

One of the greatest strengths of computer simulations is their ability to illustrate the mechanisms that may underlie the behavioural deficits associated with particular brain dysfunctions. In the present case, the simulations suggested that a dopamine deficit in the frontal lobe would tend to cause perseverative errors because of its effect on the inhibition of learned rules, while a dopamine deficit or lesion in the striatum would tend to cause random errors by interfering with the efficiency of matching.

It is clear from the work of Goldman-Rakic (1987) that neurons of the frontal lobes are involved in short-term retention of contextual information needed to make a decision. Frontal lobe patients (Drewe, 1974) and schizophrenics (Weinberger et al., 1986)

Table 4. Simulations of the Performance of Parkinsonian Patients

		Taylor et al. (1986)	
		Data	*Striatal Model*
Categories	Normal	6.1	6.1
	Parkinsonian	3.7	3.7
Perseverative Errors	Normal	19	19
	Parkinsonian	21	21
Total Errors	Normal	17	18
	Parkinsonian	29	28

		Caltagirone et al. (1994)		
		Data	*Frontal Model*[a]	*Striatal Model*[b]
Categories	Non-demented	5.0	4.9	4.9
	Demented	2.0	2.0	3.1
Perseverative Errors (#)	Non-demented	25	26	36
	Demented	34	36	36
Total Errors	Non-demented	42	40	40
	Demented	58	56	58

[a]Frontal Model attempted to simulate Demented performance by decreasing frontal gain.
[b]Striatal Model attempted to simulate Demented performance by decreasing striatal gain.

tend to make perseverative errors, defined as the continued application of a rule after it has been changed.

The present model suggests an alternative to Levine et al.'s (1993) explanation that frontal lobe patients do not unlearn a rule because the punishment signal is not strong enough to overcome their response bias, and Monchi and Taylor's (1999) explanation that schizophrenic patients suffer from a diminished capacity to valorize a particular sorting rule due to a loss of salience of reward and punishment in a loop including the nucleus accumbens. The present model suggests instead that decreased gain and excitation in frontal units reduces the likelihood of any particular unit firing. As the rule units are mutually inhibitory, these conditions do not affect the dynamics of rule maintenance:

Table 5. Simulations of the Performance of Huntington's Patients

		Weinberger et al. (1986)			
		Data	*Fronto-Striatal Model*[a]	*Striatal Model*[b]	*Frontal Model*[c]
Categories	Normal	6.7	6.6	6.6	6.6
	Huntington's	1.4	1.3	1.3	1.3
Perseveration (%)	Normal	13%	16%	16%	15%
	Huntington's	38%	36%	18%	45%

[a]Modeled Huntington's performance by a combination of striatal lesion and reduced frontal gain.
[b]Modeled Huntington's performance by striatal lesioning alone.
[c]Modeled Huntington's performance by reduced frontal gain alone.

once a rule unit is strongly switched on, it inhibits the excitation of the other rule units. However, decreased gain and excitation does affect the influence of the inhibitory units, making it less likely that a punishing signal will cause an inhibitory unit to inhibit its rule unit enough to switch the system to another rule. Thus, in information processing terms, decreased dopamine to the frontal lobes may cause perseverative errors by interfering with the inhibition of a learned rule.

Unlike Monchi and Taylor (1999) and Levine et al. (1993), the present model emphasizes the importance of inhibitory processes in mediating the effects of frontal lobe dysfunction. This is critical because it demands a closer examination of the relationship between inhibitory and excitatory neurons of the frontal cortex. Currently we know a lot about the behavior of the inhibitory and excitatory neurons of the frontal cortex in various contexts: their firing patterns, membrane properties, and so on (Schultz et al., 1997; Petrides, 1995; Goldman-Rakic, 1987). However, almost nothing is known about the mechanisms which terminate the firing of units that retain information about a vanished context. The simulations suggest that this is an important factor in dysfunction involving perseverative errors. Dysfunction affecting the rule units themselves should produce random patterns of error. Only when a rule unit is not effectively inhibited should large numbers of perseverative errors occur.

The striatum integrates information from all parts of the cortex and projects to output ganglia in the substantia nigra and globus pallidus. A simple analogy elaborated in the model is that the striatum performs a kind of pattern matching, cells firing only if conceptually linked parts of different areas of cortex are active.

Previous models that only considered the functions of the frontal lobes did not address the role of the striatum in information processing during performance of the WCST. The present model demonstrates that the effect of lesioning or decreasing the gain of neurons in the striatum may be to reduce the effectiveness of matching, increasing the proportion of random errors. In contrast, Monchi and Taylor's (1999) model suggests that striatal dysfunction may affect performance by interfering in the selection of features in feedback loops through the thalamus and frontal cortex. Simulation of quantitative data from patient populations may help differentiate the explanatory value of these approaches.

Implications and Predictions

The model makes a number of falsifiable predictions. First, the simulations suggest that the patterns of error generated by dopamine dysfunction in the frontal cortex and striatum will differ in go/no–go and switching–attention tasks. Dopamine deficiency in the frontal cortex will produce perseverative errors, while dopamine deficiency in the striatum will produce random errors. This could be tested on samples of monkeys performing analogues of the WCST and the CPT before and after selective impairment of the release of dopamine in the striatum and frontal cortex.

A single-unit study of the same samples should be able to identify a population of neurons in the frontal cortex analogous to the inhibitory units of the models with firing patterns that are inversely correlated, and temporally lagging, with the firing patterns of neurons that retain contextual information. The effects of dopamine deprivation could then be examined as a function of the modified response of each of these populations; the model predicts that dysfunction in the inhibitory population would be associated with perseverative errors, while dysfunction in the context population would be associated with random errors.

The simulations also suggest a number of more fundamental tests of the nature of dysfunction in the different diseases, based on Luria's method of examining external mediation of cognitive functions (as discussed by Cole, 1990). This technique attempts to discover which processes are dysfunctional in deficit states by gradually supplying to subjects more external tools or information, which would replace internal processes which might be damaged (Cole, 1990). The current simulations predict that different sorts of external mediation would correct the deficits in the different patient groups.

As the model suggests that schizophrenic patients suffer from the inability to efficiently inhibit a prepotent response, it would predict that the poor performance of these patients could be improved (1) by having the experimenter allow only nonperseverative responses; (2) by making the rule change explicit; or (3) by increasing the salience of the punishment for an incorrect response. Levine et al.'s (1993) model would predict that only the last of these modifications would improve performance in schizophrenic patients.

If, as the model suggests, Parkinson's patients perform poorly because of a failure of matching, the modifications outlined in the previous paragraph should not greatly affect their performance. However, the model would predict that these patients' performance would be improved by supplying external information replacing the internal matching taking place in the striatum. For example, the presentation of each stimulus card could be supplemented with explicit instructions demonstrating which target cards were matched on each attribute of color, form, and number. If the frontal functions of rule maintenance and switching are retained in Parkinson's patients, this manipulation should improve their performance by compensating for their deficiency.

Finally, if, as the model implies, Huntington's patients suffer deterioration both in frontal and striatal functions, the performance of these patients should be improved by both types of manipulation.

Schizophrenia, PD, and HD

The simulations further suggest a possible relationship between schizophrenia, PD, and HD. It is clear that one of the factors dividing these different disorders is the locus of dysfunction. PD is primarily associated with degeneration of the dopamine producing cells of the substantia nigra which project to the motor areas of the striatum (Bradshaw & Mattingley, 1995); HD with degeneration of neurons in motor areas of the striatum (Mendez, 1994); and schizophrenia has been associated with dysfunctions of both the frontal cortex and many other areas of the brain (Bradshaw & Mattingley, 1995).

However, it is also clear that there is a degree of overlap between the symptomatology of these diseases. HD and PD involve many of the same cognitive deficits, while they exhibit opposite motor dysfunction: PD comprising marked reduction of motor activity, HD uncontrolled and violent motion (Bradshaw & Mattingley, 1995). Schizophrenia, if it is considered as a cluster of three independently varying syndromes, has subtypes which share affective, cognitive, and motor components with both HD and PD. Andreasen, Roy, and Flum (1995) review evidence suggesting that schizophrenia involves symptoms from three main syndromes: Psychosis (e.g., hallucinations and delusions), Thought Disorder (e.g. fragmented cognition and pressured speech), and Negative symptoms (depressions of emotion, pleasure, and cognitive processes). HD is not uncommonly complicated by psychosis and thought disorder, whereas PD shares many of the vegetative features of the Negative syndrome of schizophrenia in Andreasen et al.'s (1995) model.

The present simulations suggest that this symptomatological overlap may be explained as a result of the common pathway in each disease. Thus, although HD and PD share primarily subcortical dysfunction, while schizophrenia may be mostly characterized by cortical dysfunction, Huntington's has been linked with cortical degeneration (Mendez, 1994), Parkinson's with cortical dementia (Taylor et al., 1986), and schizophrenia with dysfunction in almost every part of the brain (Buchsbaum, 1994). Thus, the symptoms of these diseases may be the results of diffuse pathology within an integrated system.

Appendix: Equations in the Model

Frontal Module

As shown in Figure 3, the frontal module consists of three types of cells distributed across three columns. The memory units receive afferents from the stimulus card units and from the associated rule unit. Their activity is determined by the formula:

$$x_i = 1/(1 + e^{-frontal\ gain^*(R_s + I) + bias + Noise}) \quad (1)$$

where i represents the 12 memory units (1–4 in the Color column; 5–8 Figure; 9–12 Number), R_s represents the level of activity of the related rule unit (i.e., Color (R_1) for x_{1-4}, Form (R_2) for x_{5-8}, and Number (R_3) for x_{9-12}), and I represents the level of activity of the associated stimulus card unit.

The rule units each receive afferents from all the rule units including themselves, and the relevant inhibitory unit. Their level of activity conforms to the formula:

$$R_s(t) = 1/(1 + e^{-frontal\ gain^*(-R_{s_{t-1}} + N_s + (Sum)) + bias + Noise}) \quad (2)$$

where N_s represents the level of activity of the related inhibitory unit, and Sum represents the sum of activity of the other two rule units.

The inhibitory units receive afferents from their rule unit and from a reward unit common to all. They are activated according to the formula:

$$N_s(t) = 1/(1 + e^{-frontal\ gain^*(-N_{s_{t-1}} + R_s) + bias + Noise}) \quad (3)$$

Striatal Module

The units of the striatal module each receive afferents from the frontal module and from input units representing features of the target cards. Hence,

$$S_{jk}(t) = 1/(1 + e^{-striatal\ gain^*(-X_j + A_j k) + bias + Noise}) \quad (4)$$

where $S_{jk}(t)$ represents the activity of the striatal units, j = 1–12 enumerates the 12 features of the associated inputs, and k = 1–4 enumerates the associated target card.

Nigral Module

The units of the nigral module each receive afferents from the striatal module. These inputs are subject to shunting inhibition (following Carpenter & Grossberg, 1987). Thus,

$$G_k(t) = 1/(1 + e^{-nigral\ gain^*(\Sigma S_{jk}) + bias + Noise}) \quad (5)$$

where ΣS_{jk} represents the sum of all 12 (j = 1...12) striatal units associated with the kth target card.

Thalamus

The four thalamic units receive input from the associated nigral unit. They iterate 20 times according to the formula:

$$T_k(t) = 1/(1 + e^{-thalamic\ gain^*(Sum_k) + bias + Noise}) \quad (6)$$

$$Sum_k = T_{k(t-1)} - 0.5(O_{k(t-1)} - G_{k(t-1)}) \quad (7)$$

Where $O_{k(t-1)}$ is the sum of all thalamic units other than T_k at time $t-1$.

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