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The role of cortico-basal-thalamic loops in cognition: a computational model and preliminary results

Srini Narayanan

ICSI, 1947 Center Street, Berkeley 94704, USA

Abstract

Clinical and experimental research over the last decade has implicated neuroanatomic loops connecting the frontal cortex to the basal ganglia and thalamus in various aspects of planning and memory. We report on computational model whose central aspects are: (1) a model of cortical-striatal-thalamic loops in planning and executive control, and (2) a fine-grained model of basal-ganglia function that exploits specific component connectivity and dynamics. The model is biologically plausible given current literature on the neurophysiology and disease pathology of the relevant brain regions. Specifically, our model has implications for subjects with diseases affecting the relevant brain regions (Parkinson's disease and Huntington's disease).

1. Introduction

There is by now robust evidence that the pre-frontal cortex plays a key role in various aspects of working memory and executive control [3]. As Middleton and Strick [5] points out, there is also clear evidence that the basal ganglia are closely involved with prefrontal cortex activity. From a functional viewpoint, while damage to the basal ganglia seems to produce cognitive deficits comparable to prefrontal cortex malfunction, teasing out the individual contributions has proven more problematic.

This report describes an ongoing effort to build a computational model fleshing out the role of cortical-basal-thalamic loops in planning and executive control. A distinguishing feature of the approach is a fine-grained model of basal-ganglia function that exploits specific component connectivity and dynamics. After introducing the relevant

E-mail address: snarayan@icsi.berkeley.edu (S. Narayanan).

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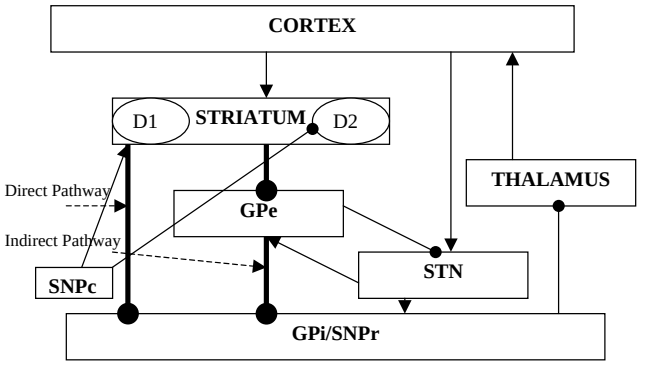

Fig. 1. This shows the block diagram view of the components and connectivity of the Cortico-basal loops. Inhibitory projections are shown with rounded tips while excitatory connections are shown with pointy tipped arrows. The direct and indirect pathways through the BG complex are highlighted and identified within the figure. The Striatum is shown with the two types of dopamine receptors D1 and D2. The Striatum, STN, GP (GPe and GPi), STN and SN (SNPr and SNPc) together comprise the primate BG complex.

biological facts, this report describes the model and preliminary results of applying the model to published behavioral data from Parkinson's (PD) and Huntington's (HD) subjects on a standard cognitive test (the Wisconsin card sorting task (WCST)).

1.1. The basal ganglia (BG) complex

The BG complex consists of several component structures; the *striatum*, the *subthalamic nucleus* (*STN*), the *globus pallidus internal* (*GPi*) *and globus pallidus external* (*GPe*) segments, and *the substantia nigra* (*par compacta* (*SNPc*) *and par reticula* (*SNpr*). Fig. 1 shows the various components and their interconnections. The description below is necessarily brief and the reader is referred to [1,4,5,6] for more details.

The striatum: receives excitatory input from many/all cortical regions (including ITP, PP, PFC, PMC, MC), from the midline and intralaminar nuclei of the thalamus, and from the limbic system (amygdala and hippocampus). Ninety percent of striatal cells are GABAergic medium spiny cells. The striatum provides phasic inhibitory output to other basal ganglia structures (GPe, GPi, SNr). Striatal cells have bistable states. In the tonic (steady) state, striatal cells do not respond to low levels of input (down state). In the presence of substantial, coordinated excitation, these cells can provide substantial output to low levels of additional input (up state). Dopaminergic transmission in the striatum is mediated by D1 (+) and D2 (−) receptors. While the striatum has in the order of 110 million cells, downstream structures including output structures of the BG complex have around 100,000 cells. Thus the *fan-in/fan-out ratio in the striatum is* > 1000, suggesting a fairly substantial data compression in the BG complex.

The subthalamic nucleus (*STN*): is the major source of excitation in the BG. Receives projections from cortical regions as well as from the external segment of the globus palladus (GPe).

The globus palladus (*GP*): consists of two segments; the external segment (GPe) is an internal segment (GPi) participating with a loop with the STN. The internal segment is one of the two principal output nuclei of the BG with GABAergic (−) projections to functionally related areas in the ventral thalamus.

The subtantianigra (*SN*): has two component sub-structures, the SubtantiaNigra-ParsCompacta (SNPc) which provides dopaminergic input to the Straitum (+ or − depending on receptor type) and the substantianigraparsreticula (SNPr), which are the other (along with GPi) major output nuclei of the BG.

1.2. Multiple segregated cortico-basal-thalamic loops

A significant neuroanatomic fact about the primate BG complex is their involvement in five parallel cortical-thalamic loops namely two motor loops (skeletomotor and occulomotor), and three non-motor loops. The non-motor loops include a *dorso-lateral PFC loop*, a *lateral orbito-frontal loop* and an *anterior cingulate loop*. The *dorso-lateral pre-frontal loop* (DLPFC (area 9 and 10)-BG (caudate nucleus-Gpi-SNPr)-thalamus (VA,MD)-DLPFC) is believed to be involved in executive functions, planning and working memory. The *lateral orbitofrontal loop* (LPFC-BG (VM caudate-GPi-SnPr)-thalamus-LPFC) mediates empathetic and socially appropriate responses. Damage to this loop produces irritability, lack of empathy and is implicated in obsessive compulsive disorder (OCD). The *anterior cingulate loop* (Ant.Cing.Gyrus-BG (ventral striatum-rostromedial palladium-SNPr)-thalamus (MD thalamic nucleus)-ACC) is believed to be involved in communicating reinforcement signals from VT and SNpc. Damage to this loop may result in akinetic mutism (profound defects in movement initiation).

1.3. Model

Many recent models have identified the role of the basal ganglia as one of selective disinhibition [1,2,4,7]. [1] These models assume that cortical afferents are integrated by the striatum (the main input nuclei of the basal ganglia). Cells from the striatum project topographically through inhibitory connections to the palladal output nuclei of the BG. When a striatal match is found (where all the appropriate input cortical areas are active), The tonic activity of the appropriate palladal cells is suppressed through increased inhibition. This suppression in turn disinhibits the thalamus and through it the appropriate prefrontal region (through segregated and topographic projections). Thus, the main role of the basal-ganglia in these models is one of integrating inputs from multiple cortical areas through conjunctive cortico-striatal connections and then selectively disinhibiting particular areas in the prefrontal cortex based on the result of the match.

Our model of the basal ganglia differs from previous models in that it incorporates the specific connectivity and dynamics of the various basal ganglia modules. Specifi-

[1] The connection between this model and the other primary role of the BG complex in reinforcement learning is outside the scope of this paper.

cally, the model incorporates multiple pathways within the basal ganglia including (a) the direct pathway (Sriatum-Sbstantia Nra pars Rticula (SNPr)-Gobus Palladus interna Gpi, (b) the indirect pathway (striatum-globus pallidus externa (GPe) and SNPr/GPi), (c) the internal loop between GPe and the STN, and (d) direct excitation of the STN. In the model, SNr/GPi nuclei are tonically active and inhibit the thalamus. The projections from the SNr/GPi to the thalamus are topographically organized. When active, the direct pathway results in inhibiting the basal ganglia output nuclei and thus disinhibiting the thalamus and the appropriate cortical column. The indirect pathway modifies this behavior by exciting the output nuclei and inhibiting the thalamus and cortical outputs. In our model, the direct pathway is involved in gating (through selective disinhibition) while the indirect pathway and other circuits regulate the selection process by controlling the amount of activation to scale to contextual factors controlled by the afferent cortical activity (similar to [4]). Our model is consistent with known disease pathologies (such as decreased amplitude movements or tremors) in certain PD patients. The model makes specific predictions about the role of different pathways and circuits within the basal-ganglia and potentially offers computational explanations for the mysterious success of certain interventions (such as deep brain stimulation of the STN [6] for PD).

The basic assumptions behind the model are:

(1) When excited the striatal input to the output nuclei results in promoting specific action structures through *disinhibition* while *maintaining inhibitory control* over others. The direct and indirect pathway work through a "*push-pull*" model of control. Specific disease pathologies may contribute to degradation of the push or pull aspects depending on whether they impact the direct of indirect pathways.

(2) Projections in the parallel cortico-basal-thalamic loops are topographically organized.

(3) The role of the BG complex in cognitive control is analogous to its role in motor control. The basic operation is *selectively disinhibit specific cognitive synergies* (*analogous to their role in selectively disinhibiting specific motor synergies*).

1.4. Model implementation

Our model of the BG complex is implemented on a simulation framework based on Stochastic Petri Nets. A Petri Net is a bipartite graph containing *places* (drawn as circles) and *transitions* (drawn as rectangles). Places hold *tokens* and represent predicates about the world state or internal state. Transitions are the active component. Transitions spread activation by firing (based on a stochastic firing function). The most relevant features of Petri Nets for our purposes are their ability to model events and states in a distributed system and to cleanly capture sequentiality, topographically structured connections, inhibition, concurrency and event-based asynchronous control. Fig. 2 shows the basic computational primitive (node in the network) of the BG model.

Our extensions to the basic Petri Net formalism include typed arcs, hierarchical control, durative transitions, parameterization, typed (individual) tokens. For this paper, the crucial fact about our representation is the ability of SPNs to capture structured connections, complex temporal dynamics. Using this basic model, we implement the various

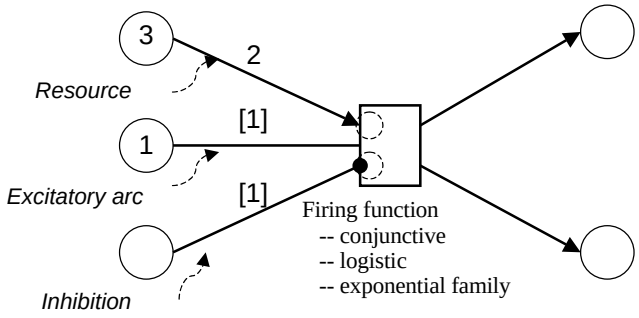

Fig. 2. The Basic Model of collections of BG cells. The input sites may be excitatory, inhibitory or weighted (the resource link). The firing of cells can be conjunctive (there is excitation in all the excitatory cites, no inhibition and sufficient activation in the resource arcs, then the cell fires). Weights on the output links (default 1) represent the *Gain* parameter. Different regions in the BG are modeled by different types of nodes in the model. The striatal cells in the model are conjunctive matching cells. Other excitatory nuclei (such as STN) use the logistic firing function used in many neural network models. Other inhibitory cells (such as the output nuclei) use other firing functions based on the exponential family of functions. Also, different deficits of specific regions in the BG are modeled changing the gain, firing function and weights of the relevant region in the model.

components and connections of the BG in our computational framework. Specific components use specific firing functions (striatal cells use the conjunctive firing function, STN cells use the logistic firing function and other nuclei use negative exponential firing functions (all the functions are from the exponential family of functions).

2. Results

We applied the model to data from normal, PD, HP and schizophrenic patients on the WCST to compare our model predictions to previous results [1]. Since we were mainly interested in the role played by the basal ganglia, out model of the prefrontal cortex is similar in many respects to [1].

In the WCST, subjects sort a deck of 128 cards according to specific criteria. Cards vary by color (4 values), form (4 values), Number (4 values) (ex. red triangle 2). The subject places each of the 128 stimulus cards in front of a target card and gets a correct/incorrect response from the experimenter. Once the subject has made 10 correct responses a category is achieved and the rule (sort according to one of the features) is arbitrarily changed. The test is completed when 6 categories are achieved or all 128 cards are used.

Many results show patients with frontal damage including schizophrenics perform poorly on the WCST. Patients with *Huntington's disease* (*HD*) which affects striatal cells show impaired performance. Patients with *Parkinson's disease* (*PD*) which affect the substantia nigra have been shown to exhibit impaired performance. Normals tend to do well, almost all subjects complete the six categories. Schizophrenic patients exhibit perseverative errors. PD patients without dementia show erratic/random errors.

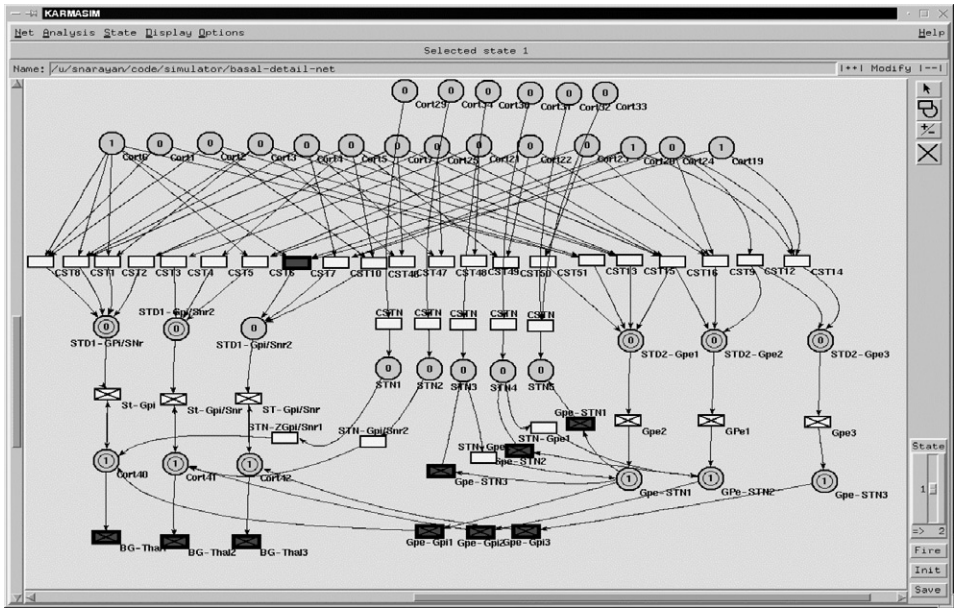

Fig. 3. Implementation and computational simulation of the BG complex. The figure shows part of the Basal Ganglia model. The striatal match cells are implemented as conjunctive transitions (shown as CorticalStriatal (CS) transitions in the Stochastic Petri Net based model). The striatal cells are bi-stable, and when in the up state can inhibit the output nuclei (the St-Gpi transitions) with input. This is the direct pathway which results in disinhibiting the thalamus (through the BG-thal transitions in the model. The inhibitory effect of the indirect pathway can be seen through the GPe cells. Other pathways include the direct stimulation of STN and the STN-GPe loops.

PD patients with dementia show both random and perseverative errors. HD patients show both perseverative and random errors.

2.1. Baseline model

Most computational models of the WCST are concerned with PFC details and deficits. Some models attempt to include the PFC-BG-Thalamus-PFC loop. Amos [1] surveys the state-of-the-art and introduces a model that explicitly deals with the published behavioral data on PD, HD and Schizophrenic patients on the WCST task. Amos describes and implements a model for the cortical–basal–thalamic interaction for the WCST test. The model of the BG complex in this work is relatively simple and considers *only the direct pathway*. Our initial results reported in this paper use the Amos model as a baseline. All parts of the model except for the BG are kept similar to the baseline. We replaced the BG part of the baseline with the more biologically realistic model implemented as shown in Fig. 3. We then simulated the various deficits (HD and PD) in our model and compared it both to the behavioral data and to previous modeling results.

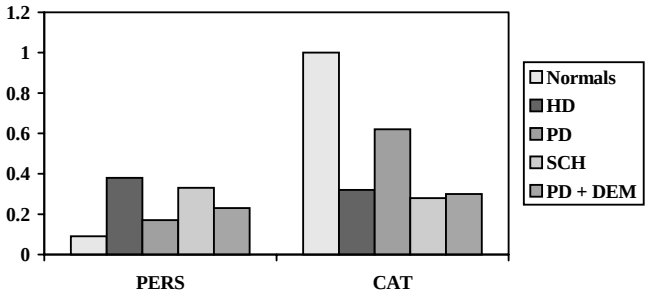

Fig. 4. The model's performance of the different patient data. The PERS label in the chart shows the relative performance of different populations in terms of the perseverative errors. Notice that the model predicts high percentage of perseverative errors for the HD and Schizophrenic patients compared to the normals. Notice also that the normals perform quite well in that the get all the categories right (percentage of categories right is shown by the value corresponding to the label CAT. Notice as well that the model performs badly for all other patient populations.

Fig. 4 shows the results made by our model based on specific deficits in the patient populations. PD was modeled as a decreased gain (see Fig. 2) of the indirect pathway and the SN regions, HD as noisy striatal matching coupled with decreased gain in the direct pathway, and Schizophrenia by decreasing the frontal bias as well as decreasing the output gains of the Substantia Nigra cells. Fig. 5a and b show the model predictions compared to the empirical data on the different patient populations (from data surveyed in [1]).

Our model showed results that suggested increased perseveration (with respect to card sorting strategy) for schizophrenic patients, erratic shifting of strategies for PD patients and a combination of errors for HD patients. While the overall results are compatible with previous efforts, our model predicts that the role of the basal ganglia is far more intricate than previously described. Our results showed that the complex dynamics both from the modifying influence of the indirect pathway and the projection back from the thalamus on the probability of shifting or maintaining the current strategy captured much finer grained detail than previous work. In particular, our model predicts greater erratic errors for PD patients due to a combination of inappropriate matching at the striatum (low dopamine levels decrease the gain and hence the efficacy of a clear winner match) as well as enhanced inhibition provided by the indirect pathway. HD patients, in contrast our model also makes empirical predictions that match experimental evidence on different stages of PD [6]. None of the previous models are able to make such detailed predictions. Interestingly, degradation of the Substantia Nigra regions in our model in combination with the frontal deficits produces a better match to the data of schizophrenic patient populations (compared to previous purely frontal lobe models). This is an intriguing finding of our work which we are subjecting to more detailed analysis.

Results from our model suggest that the basal ganglia may be involved in problem solving and planning that have complex dynamics and require prediction or simulation.

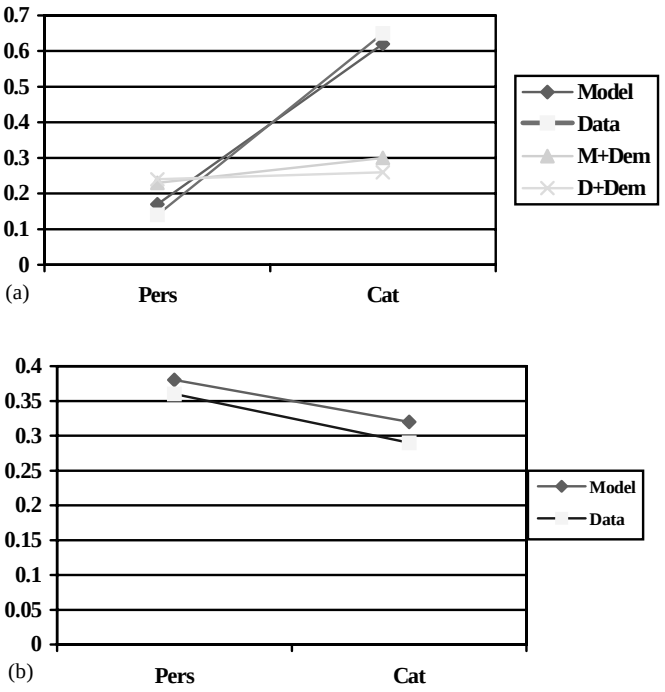

Fig. 5. (a) Performance of Model (M) compared to published data (from [1]) on the *PD* patient population. The chart shows the comparison of the model predictions with the data for patients with and without dementia. (b) Performance of Model (M) compared to published data (from [1]) on the *HD* patient population. The chart shows the comparison of the model predictions with the data for patients with and without dementia.

To better understand the implications and evaluate our model, we are continuing efforts in the following directions: (1) Design cognitive tests for which our models of planning, working memory and executive control are likely to predict non-obvious results. (2) Apply these tests on subjects with and without diseases affecting relevant brain regions (PD,HD) and evaluate the model with respect to the results.

2.2. Comparison to the baseline

The more detailed model described here is able to explain HD and PD data fitting the actual quantitative data better (where available). The model is able to explain differences in different stages of PD (something the baseline model is unable to do and to incorporate feedback from Thalamic input to the cortex, so makes finer-grained predictions about perseveration. Crucially, the model makes different predictions about the possible deficits in Schizophrenic patients, suggesting (unlike the baseline) that BG deficits may play a role in their cognitive performance. Some evidence that supports our model comes from [7]. After surveying the literature on the clinical symptoms of

a variety of types of Schizophrenic patients (both negative and positive, and unmedicated/medicated) Middleton and Strick [5] conclude:

> We propose that dysfunction of SNPr can lead to all of these symptoms. At the very least, we believe that abnormal activity in the nigral output channels participates in the symptoms associated with Schizophrenia.

3. Discussion

Cortico–basal–thalamic loops are increasingly being implicated in a variety of seemingly unconnected cognitive (as opposed to motor) disorders including obsessive compulsive disorder, Tourette's syndrome, Autism, Schizophrenia, attention deficit disorder (ADD), and even certain forms of depression. Our model indicates that

(1) The Basal Ganglia are part of a execution/simulation loop, where the next motor/cognitive action is selected based on *striatal matching of context* and the push-pull interaction of the two main pathways. The result is a *selective disinhibition* of the thalamus and cortical regions (both motor and non-motor depending on the specific loop involved).

(2) *Thought selection and updating* uses the *same sub-cortical structure* (*different loops*) *and mechanism* as action selection and updating.

(3) Detailed computational modeling can explicate this hypothesis and make specific and testable predictions.

The work described in this paper, while preliminary, suggests the utility of detailed modeling. We are addressing several shortcomings in the model as well as trying to identify, acquire data and test our model on cognitive tasks that have a greater temporal aspect such as planning or language understanding. Modeling such tasks, we believe is the next step to understanding the role of Cortico-subcortical interactions in cognition.

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Srini Narayanan is a Senior Research Scientist at ICSI, Berkeley where he works on neural models of cognition. He obtained his Ph.D. from the University of California, Berkeley in 1998. As part of his dissertation, Dr. Narayanan implemented a neural model which made specific predictions on the role of motor control representations in abstract thought including reasoning about metaphoric discourse. As part of an interdisciplinary group at ICSI/UC Berkeley, Srini Narayanan (http://www.icsi.berkeley.edu/∼snarayan) has continuing collaborations with Experimental and Clinical Neuroscientists as well as Computer Scientists and Linguists testing and refining the model and building new computational models exploring the Neural Theory of Language and Thought (NTL) (http://www.icsi.berkeley.edu/NTL).