Discovering the Hidden Life of the Basal Ganglia

Book Review
The Hidden Life of the Basal Ganglia: At the Base of Brain and Mind

Andreas Horn[1*]

1. Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Movement Disorders and Neuromodulation Unit, Department of Neurology, Charitéplatz 1, 10117 Berlin, Germany.

** Corresponding Author*

Why study the basal ganglia? This question starts off the journey that Bergman puts ahead of us in *The Hidden Life of the Basal Ganglia: At the Base of Brain and Mind.*
In jest, he answers with an analogy quoting George Mallory[1]: *"Because they are there."* –
This beginning sets the tone of the book: A combination of deep insight with some of the finest humour.

Jokes aside, why *should* we become students of the basal ganglia? Bergman hurries to justify it further: To understand the brain, we should study all its parts. The basal ganglia constitute a central processing system involved in all cognitive processes we know of and involves causal links to quite a spectrum of brain disorders in the movement disorders and neuropsychiatric spectrum. Parkinson's Disease, Dystonia, Essential Tremor, Huntington's Disease, Schizophrenia, Obsessive Compulsive Disorder, you name it. Look for the basal ganglia and you may find (some) truth. The same goes for systems neuroscience: motor and reinforcement learning, risk-taking, decision making – look for the basal ganglia and you will see.

So, if you have been interested in the neocortex and these deep nuclei have been a closed book for you, you should open *The Hidden Life* to become illuminated. If you are already invested in basal ganglia research, the book is at least as much for you. Simply put: It may be one of the best, most up-to-date and most exhaustive monographs that exist on the topic.

Hagai Bergman has had a major impact in clinical neuroscience. When neurosurgeons in the pre-Bergman era performed *subthalamotomies* to treat Parkinson's Disease, this implicated lesioning tissue *below* (sub) the thalamus but exactly *sparing* the subthalamic nucleus (STN; out of fear of inducing hemiballism). Only following the seminal 1990 Bergman, Wichmann, DeLong Science article, the *STN itself* appeared on the map as a treatment target. Their article showed that STN lesions in the MPTP non-human primate model reduced "all of the major motor disturbances in the contralateral limbs, including akinesia, rigidity, and tremor". The publication coincided with the beginning of modern-day deep brain stimulation (DBS), when the Grenoble team demonstrated success of DBS to the thalamus for tremor. Following Bergman's results, they were able to establish STN-DBS for Parkinson's Disease.

[1] George Herbert Leigh Mallory (1886–1924) replied to the question "Why did you want to climb Mount Everest?" with the retort "Because it's there."

Hence, Bergman's findings paved the way to establish a highly effective treatment now applied to over 200,000 patients, worldwide [1].

From then on, Bergman's research involved similarly crucial insights that have steadily enhanced our understanding of basal ganglia cortico-thalamic loops, including the three-layer model of the basal ganglia [2], characterizing discharge rates of striatal projection neurons in health and disease states [3] and countless others. In concert with his neurosurgical colleague, Zvi Israel, Bergman has performed the electrophysiology on over nine-hundred DBS surgeries, hands-on, himself (**fig 1**). On top of that come countless animal experiments and research studies investigating basal ganglia electrophysiology. Hence, few people on this planet know their way in and around the human basal ganglia as well as Bergman does.

Figure 1: *Hagai Bergman in the operation room examining local field potentials recorded from the subthalamic nucleus (A) and controlling the microdrive to advance electrode trajectories into the target region (B). Photographs taken by Christian Lüscher, reproduced with permission.*

With the aim of compressing some of this wisdom into an algorithm, the company AlphaOmega recently introduced the *HaGuide* system, a real-time software solution designed to detect the STN region and its boundaries using microelectrode recording during surgery. But when Bergman's colleague, Renana Eitan, gave her lecture in a 2020 Stanford DBS meeting, she mentioned that while the system works and is helpful, having Hagai

Bergman in the operation room was “impossible to replace”. Apparently, while the *HaGuide* system may certainly help novices and experts alike, it seems we cannot put Bergman’s decade-long expertise into computer code, and his imminent retirement doesn’t help either.

But if Bergman’s wisdom cannot be fit into an algorithm, maybe at least more of it fits into a book? The appearance of *The Hidden Life* constitutes a major event for our field. The decision process that led Bergman during the pandemic to sit down to write a monograph is a feast that we should certainly reinforce[2].

He starts our journey with a broad introduction which includes an unheard number of facts and figures about the boundary conditions that make up the basal ganglia: mm^3 volumes of different nuclei across species measured via MRI and histology, numbers and shapes of key neuron types, quantities of axon terminals and dendrites, sizes and shapes of their dendritic fields, gradients of receptive fields along the striatopallidofugal axis, etc. The section is followed by detailed information on afferents and efferents. Bergman reminds us about crucial facts that we may often try to forget when involved with our simplified box-and-arrow models – for instance that cortico-thalamic projections outnumber thalamo-cortical projections, that some thalamic nuclei heavily project to the striatum (which also projects to the cortex) and the existence of the reticular nucleus.

These sections alone are invaluable to ground our knowledge about the basal ganglia and make sure we are on the same page regarding their general properties. Bergman moves on to down-stream projections of cortical layers and the wide notion of axon collaterals that send efference copies to many midbrain and brainstem regions alike. In this context, we come to know the basal ganglia as a *dimensionality reduction system* [4]: From cortex to striatum, external to internal pallidum, information is compressed – only to be expanded again on its way back up to the cortex (via the thalamus). In my own notion, this is a very central and understudied concept which resembles the architecture of many successful artificial neuronal networks found today (such as U-Nets or autoencoders).

To quote Chris Eliasmith on exactly this universal “high-low-high” concept of the brain: “it is important to have those concepts of going from higher dimensions to lower dimensions and manipulating [content] in the lower dimensional space can be more efficient than in the higher dimensional space”[3]. As revealed by Bar-Gad and Bergman, the basal ganglia are true experts in the compression arm of this crucial process [4].

After briefly touching on Marr’s levels of understanding in neuronal systems and invaluable expert insights into basal ganglia recordings & data analysis, Bergman comes up with clear questions about the basal ganglia which he revisits throughout the rest of the book. Beyond further minor questions, the three major ones read:

- *What is the computational goal of the basal ganglia?*

---

[2] As you are reading this, I am opening all canisters of dopamine that I have left under my desk with the aim of motivating a second edition of the book.

[3] Eliasmith wrote another seminal book, “How to Build a Brain” in which he gives an overview about a cognitive architecture built around the concept of semantic pointers which hold specific (e.g. mixed, associative, motor, visual or sensory) content and can be manipulated in a low dimensional space but dereferenced to the uncompressed content. The quote stems from an interview found here https://braininspired.co/podcast/90/

- *How does the basal ganglia system do what it does?*
- *And how is the basal ganglia system physically realized?*

We now dive into a condensed and fascinating review about electrophysiological results and, later, the jungle of box-and-arrow basal ganglia models – which evolve throughout the book and will make increasingly more sense. Beginning with the original diagram by Albin, Young and Penney [5] and its first adaptation by Bergman, Wichmann and DeLong [6], he drastically cleans up what is there by acknowledging the STN as the second input node of the basal ganglia on the same level as the striatum [2]. The solution is much simpler, three layers in and out.

But, alas, the field of neurology and neurosurgery is not the only one with a passion for basal ganglia diagrams. There's a second group of neuroscientists that seem equally interested in them. You guessed it – our friends from the field of reinforcement learning! It may be fair to say that while the two fields do communicate, of course, they also develop things in separation. Off we go to explore "their" basal ganglia models in the next chapter. A new – and seemingly important box appears, with the caption *WORLD*.

But will Bergman be able to integrate and harmonize these *two worlds* of box and arrow models? He responds with a typically humorous anecdote:

There is an old Jewish joke about two neighbors who were fighting over a financial dispute and took their case to the local rabbi. The rabbi heard the first litigant's case, nodded his head, and said "You're right." The second litigant then stated his case. The rabbi heard him out, nodded again, and said "You're also right." The rabbi's wife was justifiably confused. "But Rebbe," she asked, "how can they both be right?" The rabbi thought about this for a moment before responding, "You're right too!"

I thought for a moment about the statements and problems of the two models of the basal ganglia and decided to adopt the same approach— "Yes, both are right."

Slowly, but steadily, we rediscover familiar elements in the reinforcement models and are delighted that things can indeed be integrated (**fig 2**). We learn about the actor and critic (or teacher) and how two systems make sense of data if one can reinforce the other. Here, again, network architectures from the AI literature come to mind, including the popular generative adversarial networks – and of course (deep) reinforcement learning networks.

The idea to pair two (or more) systems and have each pursue different parts of the task has been invented by nature long before humans existed – in fact since the very early days of the brain [7]. But if there's one actor and one teacher, Bergman rightfully asks: "Who Is the Teacher of the Teacher?" He comes up with a convincing answer that I will not spoil by divulging here. We move on to multiple critics and multiobjective optimization, soon to find out that it's not really all about dopamine:

"If a worse than expected situation happens (you enter the classroom and find the most terrible teacher at the university), it is time for your basal ganglia serotonin to rise. It will induce the same change in the motor vigor as dopamine (so you can escape from the class). But the change in the plasticity would be different (you will change your behavioral policy to

avoid repeating the same mistake again and having to take this class with the awful lecturer).”

Beyond dopamine, we know that acetylcholine, serotonin and histamine also play crucial roles in the reinforcement mechanism of the basal ganglia. Bergman concludes the physiological part of the book with a broad view summary on the role of the basal ganglia and proposes they could embody the *fast System 1* described by Daniel Kahneman (while the cortex could mainly represent the *slow System 2*). Competing and equally interesting concepts have been proposed, before [8,9], but following Bergman’s stream of reasoning on this matter is both insightful and instructive.

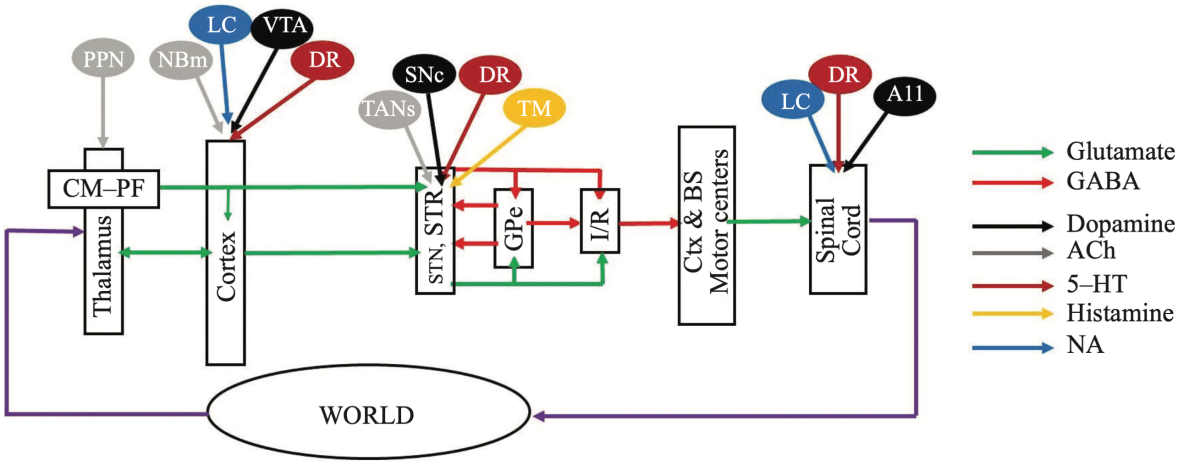

Figure 2: *The “final iteration” of box-and-arrow models from The Hidden Life incorporates a successful marriage between the three-layer model of the basal ganglia (central), that is integrated as the actor (main axis) with multi-objective critics (arrows sprouting in from the top) into a reinforcement learning model. The structures of the main axis are CM/PF, centromedian and parafascicular thalamic nuclei; STN, subthalamic nucleus; STR, striatum; GPe, external segment of the globus pallidus; I/R, internal segment of the globus pallidus and substantia nigra reticulata; BS, brain stem; Ctx, cortex. The critics are PPN, pedunculopontine nucleus; NBm, nucleus basalis of Meynert; LC, locus coeruleus; VTA, ventral tegmental area; DR, dorsal raphe; TANs, striatal tonically active neurons; SNc, substantia nigra compacta; TM, tuberomammillary nucleus; A11, posterior peri- ventricular and intermediate hypothalamic nuclei. Red arrows, excitatory main axis connections; green arrows, inhibitory main axis connections. Black, gray, orange, yellow, and blue arrows: dopamine, acetylcholine (ACh), serotonin (5-HT), histamine, and noradrenaline (NA). Figure reproduced, with permission, from The Hidden Life (MIT press).*

Having established a good understanding about how these deep structures in our brain seem to function, Bergman – in typical fashion – goes about breaking them down again. The pathological part of the book begins, first by means of animal models in rodents and nonhuman primates, then in (human) Parkinson’s Disease. We learn how their function can (partly) be recovered by studying the effects of pharmacotherapy and DBS. Bergman does so by including increasingly complex box-and-arrow models. But they suddenly do not feel as complex anymore, we rediscover the same components that have since become familiar. He touches upon emerging concepts such as closed-loop DBS – and even speculates about “dreams and delusions” of DBS for schizophrenia (including appropriate warnings and an overview of the dramatic stories in the history of the disease).

After this roller-coaster ride full of insights and eureka-moments, what remains left to say? The book ends with a chapter on free will and human responsibility, followed by an extensive section of notes and advice on further reading including anecdotes and insights covered throughout the book. *The Hidden Life* is a stimulating and enjoyable read for anyone

interested in brain function, particularly if they aim to understand how different cognitive systems could be integrated by the obscure and hidden population of nuclei in the base of the brain. The book is interesting to readers from all fields but especially from the motor system in health and disease, decision making and reinforcement learning, as well as neuro-inspired AI. Given its exhaustive nature and the many deep and up-to-date insights it brings on all levels, the book will significantly push our understanding of the basal ganglia, going forward.

References

1. *Vedam-Mai V, Deisseroth K, Giordano J, et al. Proceedings of the Eighth Annual Deep Brain Stimulation Think Tank: Advances in Optogenetics, Ethical Issues Affecting DBS Research, Neuromodulatory Approaches for Depression, Adaptive Neurostimulation, and Emerging DBS Technologies. Front Hum Neurosci. 2021;15. doi:10.3389/fnhum.2021.644593*

2. *Deffains M, Iskhakova L, Katabi S, Haber SN, Israel Z, Bergman H. Subthalamic, not striatal, activity correlates with basal ganglia downstream activity in normal and parkinsonian monkeys. Elife. 2016;5:4854. doi:10.7554/eLife.16443*

3. *Valsky D, Heiman Grosberg S, Israel Z, Boraud T, Bergman H, Deffains M. What is the true discharge rate and pattern of the striatal projection neurons in Parkinson's disease and Dystonia? Gittis AH, Ivry RB, Gittis AH, Turner RS, eds. eLife. 2020;9:e57445. doi:10.7554/eLife.57445*

4. *Bar-Gad I, Morris G, Bergman H. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Prog Neurobiol. 2003;71(6):439-473. doi:10.1016/j.pneurobio.2003.12.001*

5. *Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci. 1989;12(10):366-375.*

6. *Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science. 1990;249(4975):1436-1438. doi:10.1126/science.2402638*

7. *Cisek P. Resynthesizing behavior through phylogenetic refinement. Atten Percept Psychophys. 2019;81(7):1-23. doi:10.3758/s13414-019-01760-1*

8. *Eliasmith C. How to Build a Brain: A Neural Architecture for Biological Cognition. Reprint edition. Oxford University Press; 2015.*

9. *Shine JM. The thalamus integrates the macrosystems of the brain to facilitate complex, adaptive brain network dynamics. Prog Neurobiol. Published online November 23, 2020:101951. doi:10.1016/j.pneurobio.2020.101951*

Acknowledgements

A.H. was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, Emmy Noether Stipend 410169619 and 424778381 – TRR 295) as well as Deutsches Zentrum für Luft- und Raumfahrt (DynaSti grant within the EU Joint Programme Neurodegenerative Disease Research, JPND). A.H. is participant in the BIH-Charité Clinician Scientist Program funded by the Charité –Universitätsmedizin Berlin and the Berlin Institute of Health.