NBRC LENS | EDITION #2

NBRC LENS

a student run
NEWSLETTER

JULY, 2025

Degeneracy

The Backbone of Evolution

Atharva Ashutosh Parolekar

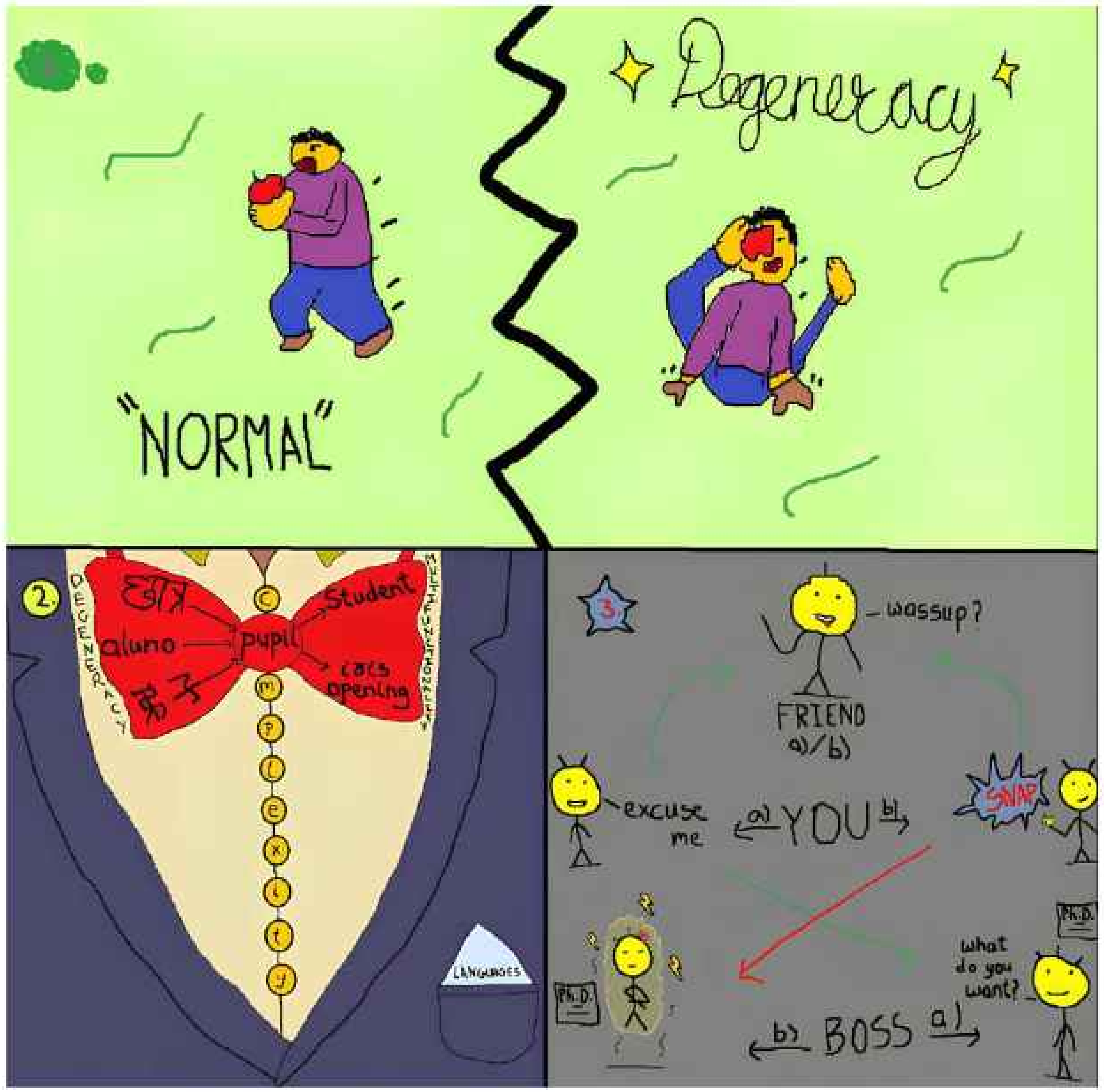
Believe it or not, each of us has brains brimming with degeneracy—no, I am not referring to the socially questionable and ethically dubious sort; that is a separate matter to consider. The word 'degeneracy,' often used to mean a decay in quality, is derived from the Latin degenerare, which simply translates to a deviation from the natural or generic state. Many of you might have become acquainted with this term in learning about degenerate atomic orbitals, which occupy the same subshells and are characterized by their equivalent energy states irrespective of different probability densities, or maybe about the degenerate genetic codon with multiple unique nucleotide sequences capable of translating the same amino acids.

Degeneracy *is the ability of structurally disparate elements to give rise to virtually identical systemic output in select circumstances,* generating a many-to-one mapping. Gerald Edelman received the Nobel Prize in 1972 for his contributions to the discovery of antibody structure, which made it possible to realize that immune cells defend our bodies against xeno-agents by producing a vast and degenerate population of antigen-recognition sites that facilitate clonal selection. His further recognition of the ubiquitous presence of degeneracy at all levels of biological organization was pioneering—spanning gene networks, cellular, multicellular, systemic, and behavioral scales within and across individuals. Refer to Table 1 in Edelman & Gally, 2001, for a quick overview of cases.

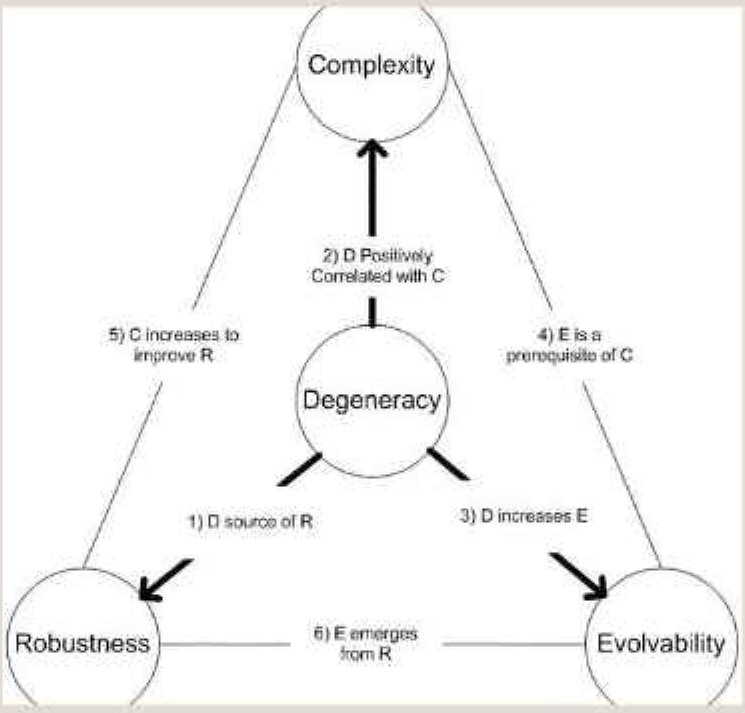
No biological system is as intricate as the human brain. It accommodates ~8.5×10^{10} glia and ~8.6×10^{10} neurons, where every neuron by itself is a complex dynamical system, with each being morphologically distinct. Furthermore, every neuron forms thousands of synapses, with estimates of aggregate connections approaching an order of 10^{15} across the brain. Throughout development, the brain undergoes extensive neurogenesis, migration, differentiation, synaptogenesis, myelination, pruning, cell death, and remapping.

This plethora of processes yields the unique patterns of structural and functional connectome that underlie its cognitive duties. When one ponders just how these connections could have combined, the possible permutations grow beyond astronomical. With so many heterogeneous constituents at its disposal, it is hardly surprising that the neural system would be a hotbed of degenerate processes. In fact, the past two decades have seen the development of new anatomical, electrophysiological, molecular, and statistical methods. And these technologies have greatly benefited the quest to gather empirical evidence of degeneracy in the brain—much of which could be found reviewed in Albantakis et al., 2024.

Is there a fitting reason that brains work in such confusingly uncertain ways without sticking to a prescribed set of solutions? Engineered devices like computers are built without useless parts, with all interactions planned out and errors mitigated by feedback control. Unlike them, the continually evolving brain does not operate in isolation and takes form without a priori assignments. Genetic factors dictate gross anatomy, but synaptic connectivity is orchestrated by tremendously stochastic developmental selection.



A. Degeneracy in domains of behavior: **1. Motor:** Morphologically dissimilar upper and lower limbs can facilitate both travel and grasping objects, but nature selects for speed and dexterity outcomes, respectively, to assign their prevalent roles. **Visual:** Cursive and block handwriting styles, despite their structural differences, elicit the same mapping of letters. In fact, no two written letters are exactly the same. **2. Semantics:** Different phrases—across or within languages—can convey the same meaning, while identical words may imply different things based on context. In tandem, this degeneracy and plurifunctionality form a bow-tie structure that underlies linguistic complexity. **3. Decision-making:** Verbalizing and finger-snapping could work equally well to get the attention of your friend, but one of them has the latent ability to create a radically unpredictable aftermath in your guide's office.



B. Interrelations of complexity, degeneracy, evolvability, and robustness. Reproduced from Whitacre, 2010, under CC by 2.0

This process organizes its landscape into numerous functionally specialized clusters of neurons that are highly intraconnected and relatively secluded from the rest. Additionally, afferent constraints continually modify cluster topography throughout the organism's life, which themselves are recurrently modulated by successful outputs. Experiential selection essentially allows the generated dynamic system to flexibly map spatio-temporal events onto respective neuronal assemblies. Moreover, coordination athwart groups is mediated by ***reentry**, a dynamic process of ongoing spatio-temporal correlation between maps facilitated by selective yet massively parallel reciprocal signals*. This bidirectional communication throughout the cortex integrates diverse features like senses, memory, decision-making, and motor control. Reentry might be the enabler of conscious experience by facilitating distributed processing of information across areas in addition to their isolated roles. High computational efficiency in the brain is a virtue of its *hierarchical architecture, assimilating both segregated subsystems and collective functions, forging its* ***complexity***. Consequently, it is by nature emergent over scales and self-organizing over time.

Encoders like the brain exhibit two key features: 1. Resilience to homeostatic disruption and stable preservation of previously learned abilities. *The degree of insensitivity of systemic functional states to diverse conditions is termed* ***robustness***. 2. Flexible adaptability to the changing repertoire of environmental stimuli and ability to produce novel responses, heeding their necessity.

This attribute improves the organism's ***evolvability***, which is *the capacity to generate heritable phenotypic variation*. While they appear to be at odds, biological systems are nonetheless evolving and resilient. Man-made simplex instruments drive their robustness by employing ***redundancy**, a fail-safe design mechanism that is marked by the presence of duplicate sets of identical elements that give rise to the same functions and ensure stability*. However, biological systems relying solely on redundancies would cease to evolve. Since they only protect against minor disturbances or increased functional demand, if any alteration uproots essential mechanisms, it could preclude survival. On the other hand, degenerate motifs bestowing similar phenotypic traits via distinct mechanisms conserve their organizational purpose in the face of change. Degeneracy promotes evolvability as well by providing distinct structural sites with unique susceptibilities towards evolutionary molding, with the potential for hidden adjustments. Even if the random environment-induced changes sparked at one type of site disrupt its preexisting abilities, others could compensate for its duties. And if the modification is beneficial to the system's survival, it might be selectively retained and inherited in future iterations. Information-theoretic and causal computational models have shown that complexity concomitantly elevates with degeneracy but not with redundancy. This operating method is vastly more efficient for enduring context-dependent reforms than redundancy-featuring determinant prescriptivism.

Degeneracy is not simply a selected feature of evolution but rather an essential prerequisite for the process of natural selection itself, which explains its seeming omnipresence. In addition, the reentrant nature of the circuitry bestows ***plurifunctionality*** on the system, identified by *the ability of a structural constituent to carry out multiple roles*, forming a one-to-many mapping. It is conceptually equivalent to pleiotropy in genetics. Together, degeneracy and multifunctionality conjure a many-to-many mapped causal framework that promotes irreducible high-order interactions among its distinct elements. The bowtie-like convergent and divergent forces in these distributed systems support the homeostatic mechanisms essential for complexity and aid the further emergence of novel degenerate motifs. In complex systems, the range of interactions of segregated modules that yield a particular network motif is neither uniquely determined nor completely random. Their manifold of intermediate randomness functions as a specific set of interchangeable unit combinations that, together, can compensate for induced stochastic changes. Worth noting also is that biological systems are multiscale and scale-rich, meaning that systems exist within systems, each inherent with unique components and behaviors. Changes at one scale can drive them at the others, yet the plasticity at each level helps sustain function. Discovering the mechanisms of compensatory interactions between scales is a worthwhile open endeavor.

To reiterate, biological systems like the brain are known to malleably adapt to new demands via systemic integration and resist loss of abilities via segregation of solutions. The implementation of degeneracy at all organizational scales makes the systems evolvable and robust, which leads to Darwinian selection, making them increasingly complex. This complexity creates positive feedback by sustaining degeneracy through recurrent communication. Now, while redundancy and degeneracy are often portrayed as alternates striving towards robustness, I am personally of the belief that there is no such thing as redundancy in nature—but only the illusion of it. Simply put, I think that even if multiple elements are apparently structurally identical and give rise to a function in the same way, say, a "type" of neuron, if one peeks at the scale underlying them, massive heterogeneities between each case could be found. It is plausible to think that degeneracy is found hidden under every "redundant" scenario in subsequently finer scales of observation, at least until we hit the subatomic limits, challenging our current understanding of particle- and meta-physics. Regardless, degeneracy is highly relevant in many domains of life, and it is prudent to incorporate its understanding in neuroscience research—from molecular to systems and cognitive levels.

The author with a butterfly that was unable to fly properly, likely due to neurodegeneration.

Correspondence: atharva.parolekar@gmail.com; critical feedback and questions welcome!

Why mentors: my mentors, women mentors

Dhananjay Huilgol, PhD

Ever since I entered graduate school, I have dreamt of establishing my own lab, following the science I enjoy, and experiencing the privilege of mentoring students and crafting careers. With the fortune gods smiling upon me, I write this as a faculty member at NBRC, seeing my dream take form! I share the joy of addressing questions that pique my curiosity with people much younger than me and at the beginning of their careers. While I pen my thoughts and prerogative, I ask myself who brought me here? Who are my mentors? Who actually is a mentor? While I am still thinking about the last question, I quote an insightful thought from Ben Barres, who was an excellent glial biologist and an even more phenomenal mentor -

> *"If your advisor does not know how to be a good scientist or does not know how to train you to be a good scientist, you are unlikely to become a good scientist".*

So, even though some of us are still grappling with the idea of how to be a good mentor, we can surely spot one miles away.

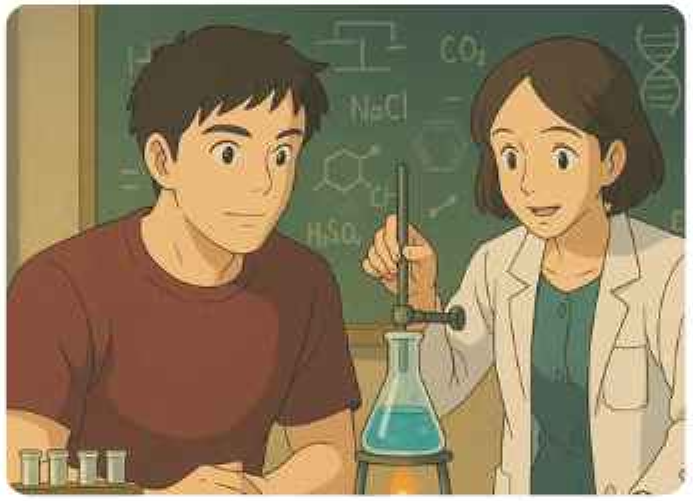
Throughout my scientific career, I ended up benefiting from remarkable mentors by sheer Brownian motion and dumb luck – and most of them were women. In the process, I learned that women mentors and role models are absolutely necessary not only for a woman's career (kind of obvious), but also for a man's. Here's what I understood: i) successful women teach endurance/resilience because they have to work twice as hard and fight more barriers, thanks to societal constraints, ii) women are unconventional in their approach to addressing scientific questions and quite resourceful since the traditional route doesn't support their success. Hence, women mentors teach creativity, iii) training with women mentors makes one a more empathetic and inclusive mentor because one cannot turn a blind eye to their struggles.

Let me briefly walk you through my journey in science, the people responsible for kindling my interest in fundamental biology, and enabling me to envision it as a career choice. I have had a privileged upbringing in an "equal opportunity for all" joint family, and hence, all the grown-ups in my household were my friends. Casual conversations about my school classes became a topic of in-depth discussions, helping me see the importance of a deeper understanding of my interests. My induction into science and biology started early with my paternal aunt, a botanist by training. We used to go for long walks among trees and plants in agricultural universities or at the foothills of the Himalayas, and somehow managed to make a herbarium of economically useful plants from our walks every single time!

I started seeing life sciences as part of my daily routine, and by high school I knew I wanted to study 'life', but not medicine (the traditional choice). My aunt was the guiding light for me to follow my dreams **against convention.**

After high school, my scientific outlook and research are a product of the higher education schools I have attended, the labs where I obtained my training, and now, the students I have the honor of mentoring. My undergrad education was very fulfilling, and this one was a very new honors course in modern biology introduced by the University of Delhi. Information in biology is inevitable, however, the motto of our course was – "your strength as a scientist lies in the strength of **your fundamentals**", and one particular teacher was a living example. She put in the effort of staying back after-hours and designed experiments for teaching us the excitement of hypothesis-driven research and how to build a hypothesis from observations. She went to the extent of even incorporating these experiments for the future batch of students, which wasn't easy, given it was a university-recommended curriculum. She leads by example, and there has been no student in the last 25 years who hasn't immediately been excited by her teaching and research prowess.

A big thanks to my undergrad education, I next entered the best possible phase of my scientific life, where the learning curve was steep.



My Integrated MSc and PhD at TIFR had an unusually large influence on my outlook towards science and mentorship. I was in a department with an equal number of men and women faculty, which is an exception to date across the globe! To add a cherry on top, all four members of my thesis (doctoral) committee were women, including my PhD advisor.

Collectively, they had a very powerful mantra, which went beyond what they thought was good for me. They identified my relationship with my environment, enabling me to achieve the best I could from that interaction. Understanding my **individual strengths** was the key – what is it that this student can bring to the table, to this project, to the lab, and even to the department? These terrific women scientists taught me how to be **innovative** in research despite having limited resources, how to make **strong requests** instead of demands, the philosophy of **people over productivity,** and to recognize that **collective science** is better than an individual's thought.

As I highlight the lessons learnt during my training phase, I remind myself of the responsibility to provide a creative and vibrant scientific atmosphere for my trainees, with unconventional approaches to doing stellar work. However, I must not lose sight of the legacy I may have in the form of young scientists whom I mentor.

New paper out !

Uncovering a Potential Therapeutic Strategy for Huntington’s Disease: Targeting Pten to Ameliorate Neurodegeneration

Deepti Thapliyal

We are excited to share the findings of our recent study, where our team investigated potential therapeutic approach for Huntington’s disease (HD)—a devastating, dominantly inherited neurodegenerative disorder. In this study, we found that targeting Phosphatase and Tensin Homolog (Pten), a key regulator of cell survival pathways, can significantly ameliorate disease phenotypes in both fruit fly and cell line HD models. HD is caused by the abnormal expansion of CAG, resulting in mutant Huntingtin (mHtt) proteins with expanded polyglutamine polyQ tracts. These proteins form aggregates that lead to progressive neuronal dysfunction and cell death. Despite extensive research, no current treatment effectively halts or reverses disease progression.

To explore potential genetic modifiers of HD, we utilized transgenic Drosophila models expressing HTT.ex1.Q93 and mRFP-HTT.588.Q138 constructs, which harbour 93 and 138 polyQ repeats, respectively. These flies exhibit classical HD features, including degeneration of photoreceptor neurons in the eye, neurodegeneration in the brain, and defects in motor neurons, providing a robust platform for screening. Previous research has implicated impaired growth factor signaling in HD pathology, particularly involving insulin and receptor tyrosine kinase (RTK) pathways. Pten is a well-known negative regulator of this signaling cascade, especially the PI3K/AKT pathway, which promotes cellular survival and growth. In our study, we downregulated Pten and observed a significant rescue in HD phenotypes.

The photoreceptor neuron loss in the eye was reduced, brain morphology improved, and motor neurons at the neuromuscular junction were rescued with Pten downregulation. At the molecular level, Pten downregulation led to a noticeable decrease in mHtt aggregates and reduced levels of caspase 1, an important marker of apoptosis. These results suggest that modulating Pten not only improves the HD-related phenotype but also suppresses the underlying mutant protein aggregation and further neuronal degeneration. We further utilised a small-molecule Pten inhibitor, VO-OHpic, to solidify our findings with pharmacological interventions. Similar to the genetic knockdown, this treatment improved motor behavior and reduced both aggregate levels and apoptotic markers. Notably, when tested in a mouse-derived HD inducible N2a neuronal cell line. VO-OHpic decreased mHtt aggregate formation, supporting its therapeutic potential in the higher mammalian cell line system.

In summary, our findings identify Pten as a promising therapeutic target in Huntington’s disease. Both genetic downregulation and pharmacological inhibition of Pten significantly rescue HD-related phenotypes, suggesting that modulating this pathway could provide a new direction for therapeutic development. We are hopeful that this work will serve as a foundation for future investigations into drug targeting the PI3K/AKT pathway modulators in the context of HD.

This research was led by women scientists Deepti Thapliyal, Nisha, and Bhavya Gohil.

Here is a link to our research-
https://pubmed.ncbi.nlm.nih.gov/40042729/

Find us at our lab page:
https://www.nbrc.ac.in/newweb/research/groups/mdhruba

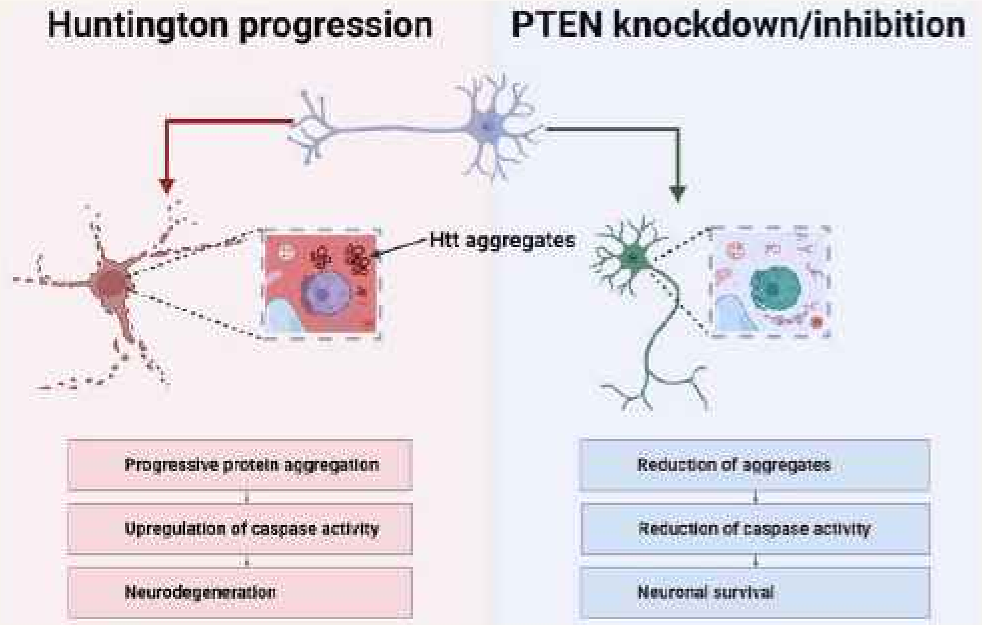
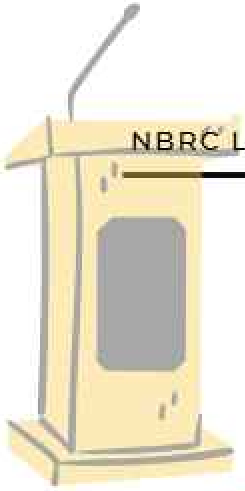


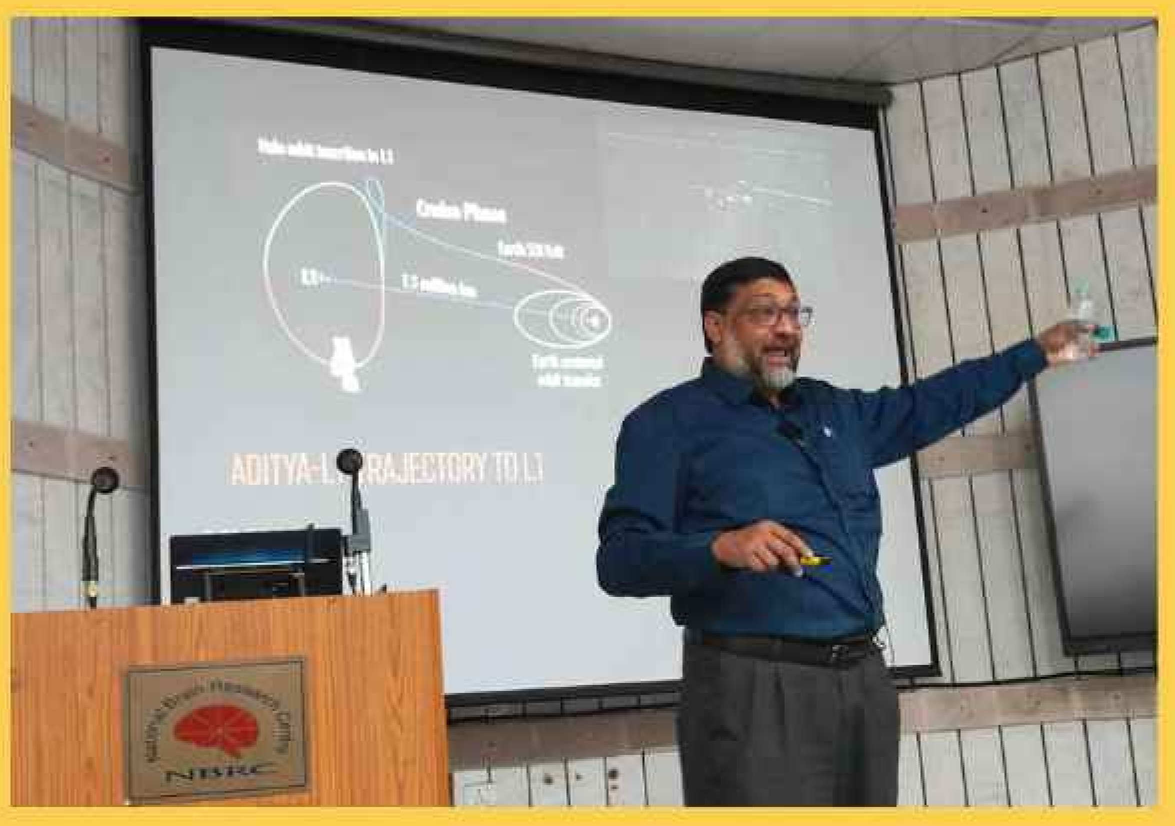
Fig. Knockdown or inhibition of Pten reduces the level of Htt aggregates and cell death.

Share your latest research /news from your lab for next edition!

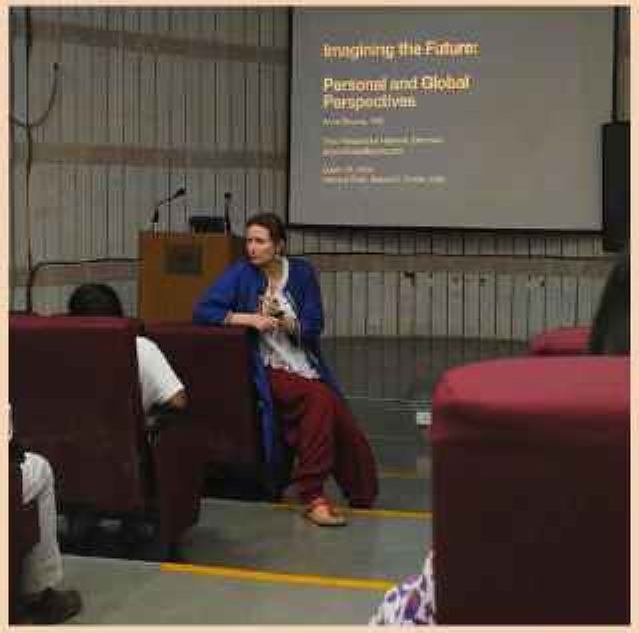
From the NBRC Podium...



Prof. Shubha Tole, DBS, TIFR Mumbai, visiting NBRC to deliver a lecture on control of cell fate and morphology in the developing brain. She also engaged with students on navigating the graduate school journey, offering guidance on their responsibilities, what they can expect from their supervisors, and how institutions can design strategies to better support academic growth.



Prof. Dipankar Banerjee, Director of the Indian Institute of Space Science and Technology (IIST), Thiruvananthapuram, delivering a talk at NBRC. He presented intriguing findings from the Aditya-L1 Mission, shedding light on our understanding of the Sun, and emphasized the potential of interdisciplinary research in advancing scientific frontiers.



Dr. Anna Sircova, an independent researcher from Denmark, conducting an interactive session with the students and faculty at NBRC. She explored the perception of time and introduced the emerging concept of futurization, discussing how personal and global future perspectives vary across different populations.

Regional Young Investigators Meet 2025

NBRC, in collaboration with Ashoka University, Sonipat, co-hosted the Regional Young Investigators Meet (**RYIM 2025 - 19 Mar - 21 Mar**) for the Delhi-NCR region—a three-day event dedicated to scientific exchange, networking, and fostering future collaborations.

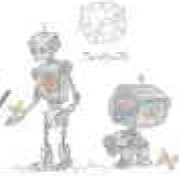
CCLAS 2025

This year again, NBRC hosted the **Certificate Course on Laboratory Animal Science (CCLAS 2025)** workshop, held from April 23 to May 2, 2025. Esteemed speakers from across the country addressed the participants on a wide range of topics—from animal handling ethics to designing experiments using animal models. Participants from diverse academic backgrounds took part in the workshop and received hands-on training with laboratory animals at NBRC's in-house Animal Facility, making it a comprehensive and enriching learning experience.

New Milestones

The **Mouse Cryopreservation Facility** at NBRC was inaugurated by
Dr. Sagar Sengupta (Director, NBRC – Additional Charge),
Prof. Subeer Majumdar (Director General, Gujrat Biotechnology University),
Prof. Taru Sharma (Director, NIAB), and
Dr. S.K. Dutta (Joint Commissioner, Animal Welfare),

Tantrika 2025 - celebrating Science & culture



Tantrika 2025, the annual fest of the National Brain Research Centre (NBRC), was a vibrant blend of science, culture, and fun. Organized by the second-year PhD students to welcome the incoming batch, the fest brought the entire NBRC community together in the true spirit of celebration.

Fun Fair

The festivities kicked off with a lively fun fair, complete with food stalls and games for children, creating a joyful and welcoming atmosphere.

Fun Fair

Faculty vs Students cricket

The sports events were equally thrilling, including badminton, table tennis, volleyball, football, and the much-anticipated student vs faculty cricket match, which saw the students winning in an energetic and fun-filled game.

Volleyball

Lab Clash

A major highlight was the Lab Clash Quiz, where teams from different labs competed in a friendly but intense battle of knowledge. Dr. Arpan Banerjee's lab emerged as the proud winner of this exciting event.

Treasure Hunt

Cultural activities like Antakshari, general quiz, poster making, and a Treasure Hunt—added excitement and creativity to the fest. The Bollywood night, was followed by a vibrant Cultural Night, with a wide range of performances from various student groups, showcasing incredible talent in music, dance, theatre set the stage for celebration.

Cultural night

Tantrika 2025 was more than just a festival—it was a celebration of talent, unity, and joy. It upheld the tradition of Tantrika as a memorable and cherished event at NBRC.

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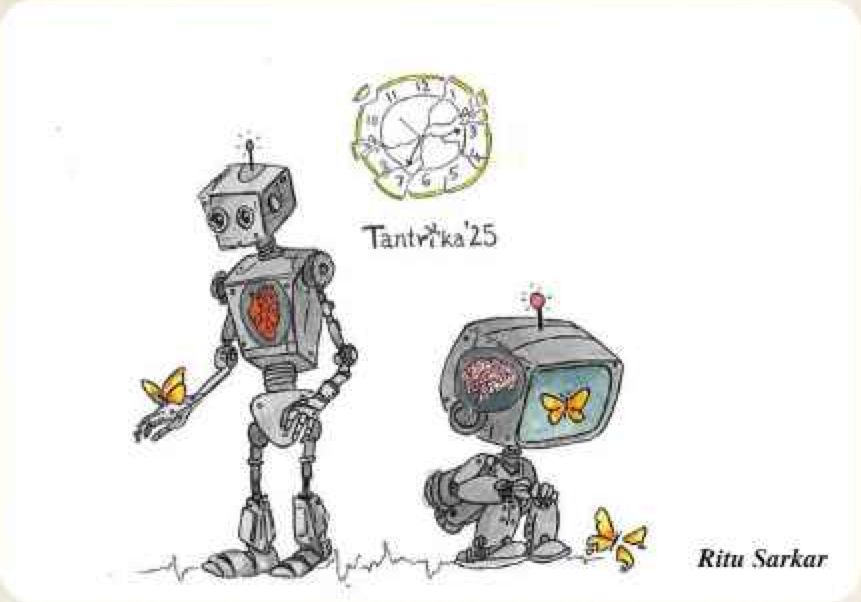
The Bulletin Board

Creative Corner

Rajyashree Basu



Ritu Sarkar

Meme of the edition!

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Dhey Vyas

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