Journal of
Biomolecules,
Pathogenesis and Therapeutics
An International, Peer-reviewed, Open access, Quarterly Biomedical Research Journal

NARRATIVE REVIEW OPEN ACCESS

Regulated Cerebral Capacity: Insights into Biophysical and Metabolic Boundaries of Neural Networks-A Narrative Review

Naveera Mazhar[1] | Maha Aslam Khan[2] | Arslan Majeed[1] | Kainat Zafar[3*]

[1]School of Biochemistry and Biotechnology, University of the Punjab, Lahore, Pakistan | [2]School of Biochemistry, Minhaj University, Lahore, Pakistan | [3]Department of Pathology, University of Health Sciences, Lahore, Pakistan

***Correspondence:** Kainat Zafar (kainatzafarpatho@gmail.com)

Citation: Mazhar N, Khan M, Majeed A, Zafar K. Regulated Cerebral Capacity: Insights into Biophysical and Metabolic Boundaries of Neural Networks-A Narrative Review. J Biomol Pathog Ther. 2026;2(1):43–50.

Received: 02 December 2025 **Revised:** 07 February 2026 **Accepted:** 16 February 2026

ABSTRACT

The human beings have an amazing brain capacity but it is limited at the biological, cellular and network level. Common assertions that people use only a minor part (10%) of their brains are not scientifically proven and ignore the complicated control that governs brain activity. Cerebral capacity is the optimal performance of neural systems under physiological conditions, which does not follow any theoretical activation limit. At cellular level, ion channels and refractory periods limit neuronal excitation, whereas receptor concentrations, plasticity exhaustion, and neurotransmitter cycling all limit synaptic communication. On the network level, synchronized coordination is required to process information but it is intrinsically restricted to avoid instability and dysfunction. The functional specialization includes selective recruitment of different brain parts according to task demands rather than maximum usage to meet some hypothetical maximized level. Neuroimaging research tends to misinterpret task specific activations as the only functional regions of brain, whereas background neural activity is omnipresent to ensure homeostasis, preparedness, and metabolic stability. The unused brain myth disregards the evolutionary and energetic needs of preservation of metabolically active and functionally necessary structures. This literature review combines molecular, cellular, and systems neuroscience to explain how cerebral capacity is naturally controlled. By providing historical, conceptual and mechanistic perspectives, it suggests that neural activity does not work on the principle of maximum functionality, instead stability, efficiency and adaptability of the system is ensured by biological regulation. Moreover, it discredits the brain capacity related myths and offers fundamental understanding about constraints of human brain capacity, from neurons to large-scale networks.

Keywords: Brain, Cerebral Cortex, Cognition, Neuroimaging, Neuronal Plasticity, Synaptic Transmission, Neural Networks, Metabolism, Functional Specialization

Defining Cerebral Capacity as the capability of the brain to process, store and integrate information is based on its cerebral capacity [1]. Scientifically, cerebral capacity does not mean an abstract or unlimited potential but a controlled functional range which is regulated by biological, metabolic and network-level constraints [2]. It corresponds to the highest possible physiological performance of neural systems, and do not have power for limitless neuronal activation [3]. From biological perspective, the brain is a complex, energy-dependent organ, which utilizes several molecular and cellular processes for information processing. There are three highly regulated checkpoints (i.e., neuronal signaling, synaptic communication, and neural networks) that determine the extent of information that can be processed at a certain time and the duration these processing can be preserved without functional failure. Neuronal signaling is based on well-regulated electrochemical events, whereas synaptic communication is based on limited biochemical resources, and neural networks require specific organization to ensure stability [4-6]. The neuroimaging research indicates that various cognitive activities do not involve the entire brain, instead they involve distributed but specific neural circuits [7]. Even in challenging cognitive or sensory activities, large regions of the brain are comparatively inactive not because of the unexploited capabilities, but because the functional specialization and efficiency are fundamental part of brain organization [8]. Excessive stimulation of all areas would not improve the performance, instead they interfere with the coordinated processing, and metabolic homeostasis. The biological limits at different levels to ensure normal brain functioning are illustrated in Figure 1.

Conceptual Origins of the “100% Brain Use” Myth: The notion that human beings use a tiny part of their brains, usually measured as 10%, has turned out to be one of the most persistent myths of popular neuroscience [9]. Although this concept is accepted widely in the media and motivational speeches, it directly opposes the well-known principles of brain biology. The myth seems to have developed in early-twentieth-century interpretations of neurological work when role of cortex was unknown, and large brain areas were considered as functionally silent. The initial lesion experiments revealed that damage to a particular brain site did not result in immediate deficits which was falsely interpreted as an indication of underutilized neural tissue [10]. Practically, the brain is involved in distributed or context-dependent processes which are not readily traced out in terms of gross behavioral changes [11]. Neuroimaging highlights areas of heightened metabolic activity in certain tasks, such as fMRI can only reveal localized activations which are further misinterpreted by the analyst to believe that the rest of brain is inactive. As a matter of fact, homeostasis, readiness and background processing are facilitated by baseline neural activity, which is a persistent brain function. Biological reasoning to disqualify “100% brain use” concept, involves the fact that neural tissue is a high-energy demanding phenomenon, which takes an inordinate portion of body energy [12]. As evolution follows “survival of the fittest” model, perseverance of an organ that consumes a lot of energy like the brain without any functional importance disfavor the “100% brain use” concept. Individual regions, cells, and circuits play an overall role, although not necessarily involved in a particular task. The finding of maximal activation in biological systems usually indicates something pathological instead of normal functioning [13]. Examples of neural activation states that have serious cognitive impairment include conditions like seizures. So, the myth obscures the key neuroscientific concepts that brain functionality does not lie in its blind and unlimited usage, but rather its regulation, selectivity, and balance.

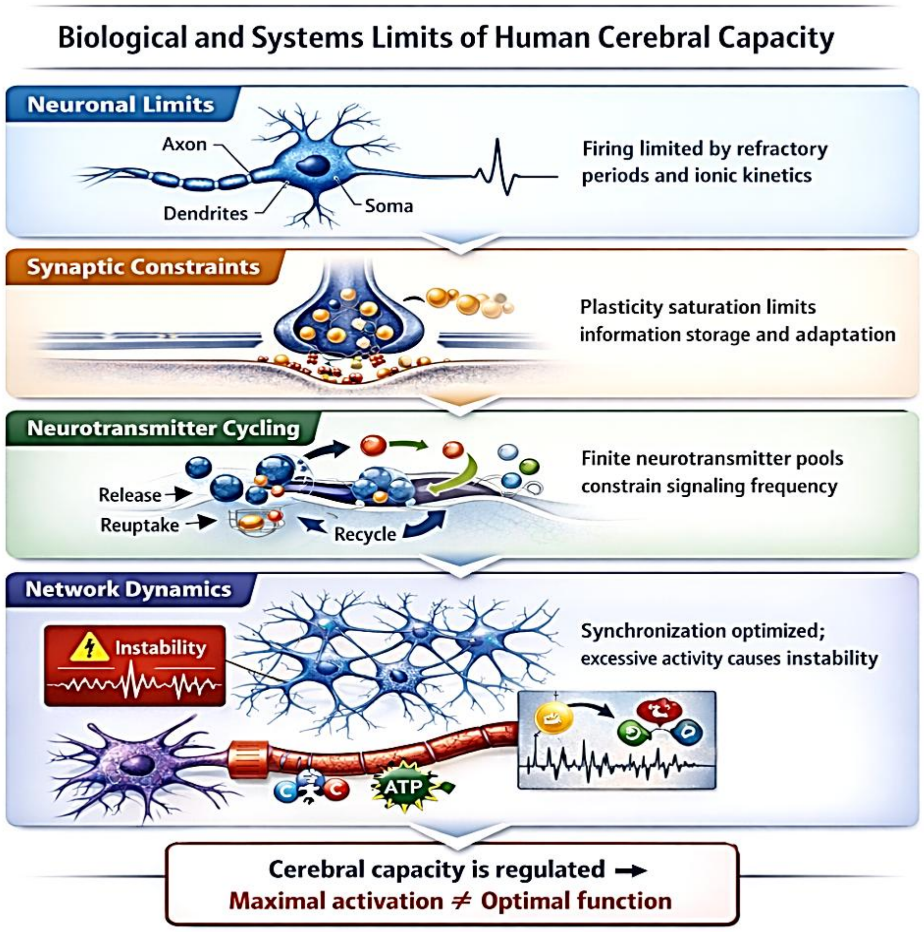

Figure 1. Biological and systems limits of human cerebral capacity. Neuronal firing is constrained by neuronal limits, synaptic constraints, neurotransmitter recycling and network dynamics. Together, these mechanisms regulate cerebral capacity, highlighting that maximal activation does not equal optimal function. (Image generated by ChatGPT 5.0)

Neuronal Excitability and Action Potential Constraints: The neuronal excitability sets a basic boundary for brain capacity. The ionic processes are highly regulated to produce action potentials, which are the primary source of information transfer in the nervous system [14]. Voltage-gated sodium channels trigger depolarization followed by repolarization through efflux of potassium ions. Following every action potential, neurons go into an absolute refractory period, in which no further spikes can occur and then a relative refractory period, in which only suprathreshold stimuli will cause a spike [15]. The intervals between these impulses usually lasts from of 1- 5 milliseconds in cortical neuron, providing significant constraint to the maximum firing rate. These biophysical limits not only affect individual neurons, but extend their impacts to network activity. Continuous stimulation signal results in conduction failures, spike jitter, and synaptic depression, reflecting that the information throughput is limited at the cellular and circuit levels [16].

Moreover, intrinsic and extrinsic factors such as density of ion channels, morphology of dendrites, and dynamics of local membrane potential, neuromodulators, temperature, and metabolic state, control neuronal excitability. Computational models revealed that continuous high-level firing are neither energy-inefficient nor functionally valuable. The neurons demand high levels of ATP to support ionic gradients through

Na+/K+ -ATPase activity and high neuronal activity raise the metabolic burden, boost reactive oxygen species, and put excitotoxicity at risk [17]. Therefore, the evolutionary pressure prefers a discontinued excitability mechanism to assure the complex thinking without excessive activation that would attenuate network stability. Generally, there are basic biophysical and metabolic constraints on neuronal firing. The maximum neuronal activation is temporary and situation-specific, and it cannot be compared to the overall brain capacity. Refractory dynamics and energy-sensitive signaling of neurons are highly controlled at cellular level, providing a screening layer that avoid indiscriminate or unlimited processing of information. These limits provide a mechanistic answer to popular myths that maximum levels of brain activation would be neither possible nor desirable for optimal cerebral activity.

Synaptic Transmission and Plasticity Saturation: Activity-dependent regulation of synaptic strength and synaptic plasticity is one of the key determinants of brain capacity, especially learning and memory [18]. The long-term potentiation (LTP) and long-term depression (LTD) are mediated by receptor-trafficking, second-messenger cascades and structural remodeling of dendritic spines. Although these mechanisms allow adaptive changes, they are innately restricted. Upon ceiling of potentiation or depression, further alterations can no longer take place which is known as plasticity saturation [19]. This inhibits continuous excitation or inhibition which would otherwise destabilize the networks. Mechanistically, saturation occurs due to limited availability of post synaptic receptors, vesicular pools of neurotransmitters, and the capacity of signaling enzymes. Overstimulation by LTP causes saturation of AMPA receptor whereas, global over-potentiation causes hyperexcitability [20]. Compensatory regulators follow homeostatic plasticity mechanisms, which increase or reduce the synaptic strengths to maintain a steady network state and to eliminate runaway potentiation/depression.[21,22] These mechanisms indicate an inherent capacity threshold on a synaptic level, which indicates that plasticity acts a functional mechanism of adaptation, but not maximum amplification.

Moreover, metabolic and network checkpoints also play their role in synaptic constraints. High-frequency stimulation and massive potentiation consume higher amounts of energy, which is mainly used in ion pumping, recycling of neurotransmitters and protein synthesis. The lack of proper recovery after long-lasting activity decreases the synapses effectiveness, which results in long-term fatigue or structural remodeling [23]. According to computational models, information storage in the network would be maximized not by fully saturating all the synapses but by affixing moderate and controlled reshaping of the circuits with a key focus on efficiency rather than maximal activation. Synaptic plasticity, therefore, is an illustration of the controlled brain capacity. Although synapses are highly adaptive, they have limited capacity to induce alteration so as to stabilize them, conserve energy and handle functional diversity [24]. The saturation of plasticity emphasizes that neural networks cannot store or transmit infinite amounts of information and that maximal cerebral activation is biologically limited and that optimum brain performance relies on selective and regulated recruitment of synapses and not random engagement.

Neurotransmitter Availability and Metabolic Constraints: Neurotransmitter recycling provides another key constraint to the brain capacity by regulating the supply of chemical messengers, needed to facilitate synaptic transmission. Neurotransmitters like glutamate, GABA, dopamine and acetylcholine are produced, packed in vesicles, discharged and reabsorbed in a strictly controlled biochemical sequence [25]. Limited vesicle pool and requirements of their metabolic synthesis and re-absorption define upper limits of synapses activity. In high-frequency firing, the presynaptic terminals run out of readily available vesicles, decreasing synaptic efficacy and slows information transfer [26]. This limitation is represented by glutamatergic signaling which constitutes most excitatory neurotransmission in the cortex [27]. The neurotransmitter pools are replenished through the glutamate-glutamine cycle between the neurons and the astrocytes, but it has a limited time frame. These cycles get overwhelmed in case of excessive excitation resulting in temporary deficit of transmission and excitotoxicity [28]. Likewise, neuromodulators like dopamine and serotonin are restricted by their synthesis rate, vesicular loading, and reuptake capacity, limiting sustained modulatory signaling during intense mental or emotional need.

Neurotransmission is further regulated by the availability of energy. Vesicle loading, ion pumping to sustain membrane gradients and reuptake of transporters all necessitate ATP [17]. Local metabolic demand is increased during high-frequency synaptic activity, and in case of low metabolic energy release of neurotransmitters and the reliability of neuronal firing are significantly impaired [29]. This close relationship between the metabolic provision and the functioning of the synapses ensures sustained neuronal activity. Together, neurotransmitter cycling and metabolic limitations provide a biochemical protection to cerebral capacity. The structural integrity of neurons and synapses does not suffice to exceed the information transfer without synaptic fatigue and metabolic breakdown. These constraints underscore the fact that the brain is regulated to operate maximally: the chemical and energetic means necessary to run reliable and adaptive signaling over neural networks are inherently limited.

Glial Regulation and Neurovascular Coupling: Cerebral capacity is further regulated by glial cells and neurovascular processes that characterize the systems level of cerebral capacity. These support elements (astrocytes, oligodendrocytes, and microglia) actively regulate synaptic activity and homeostasis as well as the coordination of metabolic supply to neurons [30]. Specifically, astrocytes control the extracellular ionic levels, recycle neurotransmitters and modulate the synaptic plasticity, which has a direct impact on the maximal sustainable firing rate of the neurons. Neurovascular coupling provides metabolically active areas of the brain with adequate blood supply to support oxygen and glucose demand. Local neuronal stimulations cause vasodilation induced by astrocytic mediators and endothelial mechanisms, which adjusts energy provision to demand [31]. In contrast, cerebral blood flow is limited and the vascular network places a physical limit on provision of energy. Extensive or prolonged stimulation may supersede vascular capacity leading to temporarily induced hypoxia, energy deprivation, or faulty synaptic performance [32].

Network stability can be achieved through glial control. Buffering of excess glutamate by astrocytes to prevent excitotoxicity and synchronization can be regulated by astrocytes through modulating inhibitory interneuron activity [33]. Microglia are responsible of synaptic network surveillance and elimination of damaged or inactive synapses, aiding in the efficient organization of the network. The axonal conduction velocity is preserved by oligodendrocytes by myelinating the axons, which indirectly determines the timing and throughput of the neuronal signaling. These glial functions combine the metabolic and electrophysiological constraints to guarantee optimal, but not maximum activation [34]. The breakdown of glial or vascular regulation explains the effect of surpassing the limits of the brain. Ischemia, traumatic brain injury or metabolic insufficiency are examples of conditions that indicate that neuronal overactivation without proper support quickly develops dysfunction and tissue damage [35]. Mechanisms involving glial and vascular activity are, therefore, required to regulate cerebral capacity to ensure that energy provision, synaptic modulation and network stability are controlled within biologically sustainable limits.

Network-Level Synchronization and Information Processing Limits: Coordination is established at the network level to form cerebral capacity depending on the state of balance between integration and stability. Neurons do not often work alone but they are interconnected to form a web of coordinated activity that makes it possible to process information effectively [36]. Co-ordination of neuronal activities in local and distributed networks helps in various phenomena including attention, working memory, and sensory integration. Maximal synchronization improves signal transmission, temporal coding and computational efficiency. Nevertheless, over synchronization is self-limiting [37]. The high degree of connectivity of networks lowers the flexibility and information capacity by minimizing the variety of possible firing patterns. Computational models prove that when synchrony in a network is greater than the optimum level the network becomes less responsive to new input and the redundancy level increases, which results in functional saturation [38]. This trade-off is indicative of one of the underlying limitations suggesting that maximal network activity is not related to maximum processing capability. Regulated synchronization is found in large-scale brain oscillations, including theta, alpha and the gamma rhythms. These time-based oscillatory activities systematize neuronal activity and form windows of excitatory and inhibitory communication [39]. Atypical ranges of normal oscillatory with hyper-synchrony or broken phase relationships disturb cognitive performance. For example, epileptiform activity might be associated with excessive gamma-band, whereas disruptions in memory encoding are linked to weak theta oscillations [40].

The architecture of neuronal assembly also restricts its network capacity. Modular and small-world organization minimize the wiring cost and optimize effectiveness, but restrict the amount of independent computations at any given time [41]. Subsets of these networks are selectively engaged by high-demand tasks, which also provides evidence that a complex and balanced activity of the brain depends on regulated recruitment and not indiscriminate activation [42]. Overall, network-level synchronization highlights the core principle of cerebral capacity i.e., information processing is limited by the requirement to strike a balance between coordination and flexibility. Under and over- synchronization are both inefficient and full activation of all circuits would probably not help the stability and functionality. The optimal capacity cannot be obtained through unrestricted participation, rather through actively controlled, contextual patterns of activity.

Instability, Noise, and Pathological Overactivation: Other factors that act to further limit the cerebral capacity are an excitatory-inhibitory balance, neural noise, and pathological overactivation risk. Neural connections make use of inhibition interneurons to balance excitatory drive and control stable firing and exhibition [43]. Violation of this balance either by exciting too much or inhibiting too little may cause unstable behavior, loss of information fidelity and collapse of the network. Pathological overactivation demonstrates the biological maximal of brain functioning. The hyper-synchronous neuronal firing across multiple networks in epileptic seizures is quite a graphic example: even though neuronal activity is maximised the cognitive and behavioural performance are greatly disturbed [44]. Similarly, excitotoxicity caused by the release of excessive glutamate, harms the neurons, indicating pathological effects of maximum activity [45]. These phenomena underscore the importance of fundamental regulation of the cerebral capacity to safeguard failure of its functions.

Extrinsic and intrinsic noise also play a role in restricting the cerebral capacity. Neuronal responses vary due to stochastic alterations in ion channels gating, neurotransmitter release probability and receiver states on the synaptic receptor [46]. Although, in some cases, noise is beneficial to provide plasticity and flexibility, too much noise impairs signal fidelity, effective information throughput and limits reliable processing. The nervous system restrains these influences via redundancy, network motifs, and feedback inhibition, and supports balance over maximal activation. Theoretical arguments prove that any effort to maximize activation in all circuits at the same time would impart instability in metabolic load, ionic equilibrium, resulting in lack of synchrony [47]. The stability and adaptiveness of the network is ensured by energy supply, synaptic resources and the network design as they prevent the indiscriminate activation. Hence, instability and pathological overactivation restricts the cerebral capacity. Biological designs, such as inhibitory feedback and architecture of networks are processes to maintain safe levels [48]. Peak neuronal activity is not the same as increased capacity; in fact, increased neuronal activity is frequently an indication of dysfunction. The successful functioning of the brain requires controlled activation, noise control, and structural protection that, on a real scale, limits of the ability of the brain.

Systems-Level Optimization: Why Brains Are Not Built for Maximum Output: The boundaries of the cerebral capacity can be best understood in light of the brain as a system evolved through evolutionary pressures. The neural circuits are not optimized to be indiscriminately maximized but rather optimized to make them efficient, robust and adaptive [49]. The designs which have been most favored by evolution are those that achieve the highest level of performance at the lowest metabolic cost, minimal structural complexity, and low instability susceptibility [50]. The energy-based restrictions predominantly impact the system optimization. Human brain makes roughly 2% of the body weight though it absorbs close to 20% of resting metabolic energy [51]. Continuous activation of all neurons would cost many times higher energy than the available energy, hindering and even causing excitotoxic damage, homeostasis impairment [34,45]. Thus, the brain will favour selective recruitment of circuits according to the demands of a task, and will be able to balance the expenditure of energy and cognitive efficiency.

Systemic optimization is also manifested in network architecture. Cortical networks are small-world and modular networks maximizing local processing and reducing the long-range wiring expense [41]. Redundant pathways provide resilience that enables the brain to adapt to either an injury or a change in input, but simultaneously restrict optimum processing [52]. Functional specialization also ensures distribution of the tasks to involve different parts or sub-networks in order to prevent metabolic overload and to maintain oscillatory dynamics [53]. The information-theoretic models also help in describing regulated capacity. Maximum transfer of information in response to stimulation does not require uniform activation, but selective and coordinated interaction between excitatory and inhibitory ensemble [54]. Excessive synchrony or random turning on eliminates useful bandwidth, causes redundancy and adds noise, culminating in impaired thinking [43]. Briefly, the brain produces maximum functioning not through the activation of all areas at the same time, instead it utilizes resources in a regulated and context-specific manner. Cerebral capacity reflects the interaction between metabolic constraints, network structure, plasticity restraints as well as dynamic regulation. The overall system efficiency ensures steady cognitive functions while minimizing possible risks of dysfunction.

The findings on multilevel regulation of human cerebral capacity are summarized in Table 1.

Table 1: Multilevel Regulation of Human Cerebral Capacity — Key Concepts, Mechanisms, and Insights

Biological Aspects	Core Focus	Key Biological Mechanisms	Constraints on Cerebral Capacity	Conceptual Insight
Conceptual Definition of Cerebral Capacity [2, 4-6]	Defining capacity biologically rather than theoretically	Energy-dependent neural signaling, functional specialization, regulated recruitment	Capacity reflects maximal sustainable performance, not total activation	Cerebral capacity is a regulated functional range, optimized for stability and efficiency rather than maximal output
Historical & Mythological Context [9-11]	Origin of the "100% brain use" myth	Misinterpretation of lesion studies and neuroimaging activations	Mis-conflation of task-related activation with total brain activity	The myth persists due to conceptual misunderstanding, not scientific evidence
Neuronal Excitability [14, 15]	Action potential generation and firing limits	Ion channel kinetics, absolute and relative refractory periods	Finite firing rates; metabolic cost of ion gradient restoration	Neuronal firing is biophysically capped; sustained maximal firing is neither feasible nor beneficial
Synaptic Transmission & Plasticity [18-20]	Learning and memory capacity	LTP/LTD, receptor trafficking, dendritic spine remodeling	Plasticity saturation; finite receptor and signaling capacity	Memory and learning rely on regulated synaptic modification, not infinite potentiation
Neurotransmitter Availability [25-28]	Chemical limits of synaptic signaling	Vesicle pools, neurotransmitter synthesis, reuptake cycles	Vesicle depletion; synthesis and recycling rates	Neurotransmission is biochemically bounded, enforcing limits on sustained high activity
Metabolic Constraints [17, 29]	Energy requirements of neural activity	ATP-dependent ion pumping, neurotransmitter cycling	Energy supply-demand mismatch during excessive activation	Brain activity is constrained by metabolic sustainability, not structural potential
Glial Regulation [30, 34]	Non-neuronal control of neural function	Astrocytic neurotransmitter recycling, ion buffering	Dependence on glial support for sustained activity	Glia act as gatekeepers of cerebral capacity, integrating metabolic and synaptic regulation
Neurovascular Coupling [31, 32]	Blood flow–activity matching	Activity-induced vasodilation, oxygen/glucose delivery	Finite cerebral blood flow capacity	Vascular limits impose a hard ceiling on sustainable neural activation
Network-Level Synchronization [36-40]	Coordination of neuronal populations	Oscillatory dynamics (theta, alpha, gamma), modular connectivity	Over-synchronization reduces information diversity	Optimal cognition requires balanced synchrony, not global activation
Noise & Instability [43, 46]	Variability and signal fidelity	Stochastic ion channel gating, synaptic noise	Reduced information throughput at high noise levels	Controlled noise enhances flexibility, but excess noise limits capacity
Pathological Overactivation [44, 45]	Consequences of exceeding limits	Hyperexcitability, excitotoxicity, seizure activity	Network collapse despite high activation	Maximal activation is a marker of dysfunction, not enhanced capacity
Systems-Level Optimization [34, 45, 51, 52]	Evolutionary design principles	Small-world architecture, modular specialization	Trade-off between efficiency and redundancy	The brain is optimized for adaptive efficiency, not maximal throughput
Functional Specialization [53]	Task-dependent recruitment	Distributed but selective circuit engagement	Inability to process all tasks simultaneously	Cognitive efficiency arises from selective network activation

Conclusion

The myth concerning the 100% brain use is a misleading term used to define brain capacity. Functional specialization, energy limits, and homeostatic control imply that the parts of the body that seem not to be involved in a task have important background functions. There are physical, chemical and energetic constraints to the neuronal firing, network synchronization and synaptic modulation, and forcing them would lead to instabilities, pathology or tissue injury. Pathological conditions, including the seizure state or excitotoxic damage, demonstrate that maximal stimulation will be physiologically harmful instead of functional improvement. Cerebral capacity is not a basic numerical measure but reflects the dynamic property of the integrated design of the brain. Selective, context-specific recruitment of neurons and networks, effective resource allocation, and system-scale feedback regulation are highly regulated to ensure ideal performance. The plasticity, glial support, metabolic interrelations, and network structure coordinate to regulate normal brain functioning while preserving adaptive flexibility.

This review presents molecular, cellular as well as systems-level evidence to define the inherent boundaries of the human cerebral capacity. Neurotransmitter recycling, network dynamics, synaptic plasticity, ion channel kinetics, and different layers of biological regulations collectively act as checkpoints for optimal brain functioning. These systems prevent brain to undergo random or increased activation to maintain stability, efficiency and flexibility. Overall, the review utilized biological grounds to justify that human brain capacity is not unlimited rather highly regulated. Intense activation does not mean intense potential, and the constraints to brain capacity inform not only neuroscientists and the medical personnels but also public to establish their understanding about cognition, whereby the efficiency and regulation of the brain, determines the intellectual ability of humans.

Acknowledgment: None

Grant Support & Funding Source: None

Conflict of Interest: None

Authors' Contribution: All authors contributed equally as per ICMJE.

Ethical Statement: Not Applicable

References

1. Li T, Zheng Y, Wang Z, Zhu DC, Ren J, Liu T, et al. Brain information processing capacity modeling. Sci Rep. 2022;12(1):2174. https://doi.org/10.1038/s41598-022-07499-4
2. Papo D, Buldú JM. A complex network perspective on brain disease. Biol Rev. 2026;101(1):364-99. https://doi.org/10.1111/brv.70086
3. Hengen KB, Shew WL. Is criticality a unified setpoint of brain function? Neuron. 2025;113(16):2582-98. https://doi.org/10.1016/j.neuron.2025.05.020
4. Liu Y, Shen X, Zhang Y, Zheng X, Cepeda C, Wang Y, et al. Interactions of glial cells with neuronal synapses, from astrocytes to microglia and oligodendrocyte lineage cells. Glia. 2023;71(6):1383-401. https://doi.org/10.1002/glia.24343
5. Seguin C, Sporns O, Zalesky A. Brain network communication: concepts, models and applications. Nat Rev Neurosci. 2023;24(9):557-74. https://doi.org/10.1038/s41583-023-00718-5
6. Swanson LW, Hahn JD, Sporns O. Neural network architecture of a mammalian brain. Proc Natl Acad Sci U S A. 2024;121(39):e2413422121. https://doi.org/10.1073/pnas.2413422121
7. Yen C, Lin CL, Chiang MC. Exploring the frontiers of neuroimaging: a review of recent advances in understanding brain functioning and disorders. Life. 2023;13(7):1472. https://doi.org/10.3390/life13071472
8. Perich MG, Narain D, Gallego JA. A neural manifold view of the brain. Nat Neurosci. 2025;28(8):1582-97. https://doi.org/10.1038/s41593-025-02031-z
9. Anum SR, Shafiq M, Fatima S, Bibi A, Khan AU, Naz S, et al. Evolution of the human brain and the myth of its ten-percent use. Soc Evol Hist. 2024;23(2):44-69. https://doi.org/10.30884/seh/2024.02.02
10. Vaidya AR, Pujara MS, Petrides M, Murray EA, Fellows LK. Lesion studies in contemporary neuroscience. Trends Cogn Sci. 2019;23(8):653-71. https://doi.org/10.1016/j.tics.2019.05.009
11. Heald JB, Wolpert DM, Lengyel M. The computational and neural bases of context-dependent learning. Annu Rev Neurosci. 2023;46:233-58. https://doi.org/10.1146/annurev-neuro-092322-100402
12. Bolaños JP, Magistretti PJ. The neuron–astrocyte metabolic unit as a cornerstone of brain energy metabolism in health and disease. Nat Metab. 2025;7:1-10. https://doi.org/10.1038/s42255-025-01404-9
13. Solms M. "Function" in functional neurological disorders: the common ground of neuroscience and psychoanalysis. Neuropsychoanalysis. 2025;27:1-4. https://doi.org/10.1080/15294145.2025.2472340
14. Drukarch B, Wilhelmus MM. Thinking about the action potential: the nerve signal as a window to the physical principles guiding neuronal excitability. Front Cell Neurosci. 2023;17:1232020. https://doi.org/10.3389/fncel.2023.1232020
15. Puttkammer F, Lindner B. Fluctuation–response relations for integrate-and-fire models with an absolute refractory period. Biol Cybern. 2024;118(1):7-19. https://doi.org/10.1007/s00422-023-00982-9

16. Steinhardt CR, Mitchell DE, Cullen KE, Fridman GY. Pulsatile electrical stimulation creates predictable, correctable disruptions in neural firing. Nat Commun. 2024;15(1):5861. https://doi.org/10.1038/s41467-024-49900-y
17. Fabbri R, Botte E, Ahluwalia A, Magliaro C. Digitoids: a novel computational platform for mimicking oxygen-dependent firing of neurons in vitro. Front Neuroinform. 2025;19:1549916. https://doi.org/10.3389/fninf.2025.1549916
18. West AE. Genetic mechanisms of experience-dependent neuronal plasticity. Annu Rev Genet. 2025;59:1-22. https://doi.org/10.1146/annurev-genet-020325-103824
19. Hagena H, Manahan-Vaughan D. Interplay of hippocampal long-term potentiation and long-term depression in enabling memory representations. Philos Trans R Soc Lond B Biol Sci. 2024;379(1906):20230229. https://doi.org/10.1098/rstb.2023.0229
20. Incontro S, Musella ML, Sammari M, Di Scala C, Fantini J, Debanne D. Lipids shape brain function through ion channel and receptor modulations: physiological mechanisms and clinical perspectives. Physiol Rev. 2025;105(1):137-207. https://doi.org/10.1152/physrev.00004.2024
21. Papatheodoropoulos C. Compensatory regulation of excitation/inhibition balance in the ventral hippocampus: insights from fragile X syndrome. Biology. 2025;14(4):363. https://doi.org/10.3390/biology14040363
22. Dufor T, Lohof AM, Sherrard RM. Magnetic stimulation as a therapeutic approach for brain modulation and repair: underlying molecular and cellular mechanisms. Int J Mol Sci. 2023;24(22):16456. https://doi.org/10.3390/ijms242216456
23. Amaral-Silva L, Santin JM. Synaptic modifications transform neural networks to function without oxygen. BMC Biol. 2023;21(1):54. https://doi.org/10.1186/s12915-023-01518-0
24. Singha SP, Memon S, Kazi SAF, Nizamani GS. Gamma aminobutyric acid signaling disturbances and altered astrocytic morphology associated with Bisphenol A induced cognitive impairments in rat offspring. Birth Defects Res. 2021;113(12):911-924. https://doi.org/10.1002/bdr2.1886
25. Singha SP, Memon S, Bano U, Isaac AD, Shahani MY. Evaluation of p21 expression and related autism-like behavior in Bisphenol-A exposed offspring of Wistar albino rats. Birth Defects Res. 2022;114(11):536-550. https://doi.org/10.1002/bdr2.2022
26. Li S, Sheng ZH. Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. Nat Rev Neurosci. 2022;23(1):4-22. https://doi.org/10.1038/s41583-021-00535-8
27. Alabdali A, Ben Bacha A, Alonazi M, Al-Ayadhi LY, Alanazi AS, El-Ansary A. Comparative evaluation of certain biomarkers emphasizing abnormal GABA inhibitory effect and glutamate excitotoxicity in autism spectrum disorders. Front Psychiatry. 2025;16:1562631. https://doi.org/10.3389/fpsyt.2025.1562631
28. van Susteren H, Rose CR, van Putten MJ, Meijer HG. The role of the glutamate–glutamine cycle in synaptic transmission during ischemia and recovery. bioRxiv. 2025. https://doi.org/10.1101/2025.11.10.687543
29. Li H, Zhao Y, Dai R, Geng P, Weng D, Wu W, et al. Astrocytes release ATP/ADP and glutamate in flashes via vesicular exocytosis. Mol Psychiatry. 2025;30(6):2475-89. https://doi.org/10.1038/s41380-024-02851-8
30. Wawrzyniak A, Krawczyk-Marć I, Żuryń A, Walocha J, Balawender K. Diversity, functional complexity, and translational potential of glial cells in the central nervous system. Int J Mol Sci. 2025;26(18):9080. https://doi.org/10.3390/ijms26189080
31. Larios A, Sullere S, Gu C. Cerebral blood flow and energy demand: imaging insights into neurovascular function. Neurophotonics. 2025;12(S2):S22810. https://doi.org/10.1117/1.NPh.12.S2.S22810
32. Coccarelli A, Polydoros I, Drysdale A, Harraz OF, Kadapa C. A computational framework for quantifying blood flow dynamics across myogenically-active cerebral arterial networks. Biomech Model Mechanobiol. 2025;24:1-8. https://doi.org/10.1007/s10237-025-01958-3
33. Joseph UG, Oyovwi MO, Jeroh E, Esuku DT, Ben-Azu B. Dysfunctional astrocyte metabolism: a driver of imbalanced excitatory/inhibitory tone and support for therapeutic intervention targets. J Mol Pathol. 2025;6(2):12. https://doi.org/10.3390/jmp6020012
34. Affrald RJ, Narayan S. Oligodendrocytes in neuronal axonal conduction and methods for enhancing their performance. Int J Neurosci. 2025;135(12):1328-49. https://doi.org/10.1080/00207454.2024.2362200
35. Mao R, Zong N, Hu Y, Chen Y, Xu Y. Neuronal death mechanisms and therapeutic strategy in ischemic stroke. Neurosci Bull. 2022;38(10):1229-47. https://doi.org/10.1007/s12264-022-00859-0
36. Tort AB, Laplagne DA, Draguhn A, Gonzalez J. Global coordination of brain activity by the breathing cycle. Nat Rev Neurosci. 2025;26:1-21. https://doi.org/10.1038/s41583-025-00920-7
37. Hao Y, Tower T, Lax H, Hütt MT, Graham DJ. Brain volume predicts survival of colliding-spreading messages on mammal brain networks. arXiv. 2025. https://doi.org/10.48550/arXiv.2505.15477
38. Voicu V, Toader C, Șerban M, Covache-Busuioc RA, Ciurea AV. Systemic neurodegeneration and brain aging: multi-omics disintegration, proteostatic collapse, and network failure across the CNS. Biomedicines. 2025;13(8):2025. https://doi.org/10.3390/biomedicines13082025
39. Keitel A, Keitel C, Alavash M, Bakardjian K, Benwell CS, Bouton S, et al. Brain rhythms in cognition—controversies and future directions. arXiv. 2025. https://doi.org/10.48550/arXiv.2507.15639
40. Cuesta P, Ochoa-Urrea M, Funke M, Hasan O, Zhu P, Marcos A, et al. Gamma band functional connectivity reduction in patients with amnestic mild cognitive impairment and epileptiform activity. Brain Commun. 2022;4(2):fcac012. https://doi.org/10.1093/braincomms/fcac012
41. Liang J, Wang SJ, Zhou C. Less is more: wiring-economical modular networks support self-sustained firing-economical neural avalanches for efficient processing. Natl Sci Rev. 2022;9(3):nwab102. https://doi.org/10.1093/nsr/nwab102
42. Shaikh P, Bano U, Memon S, Bano S, Gul S, Pirya. Neuroanatomical study of in-vivo brainstem abnormalities in autism spectrum disorder and their clinical correlations. Pak J Med Dent. 2025;14(3). https://doi.org/10.36283/ziun-pjmd14-3/039
43. Ghafoor A, Kashif S, Ali SMS, Memon S, Memon SS, Mehmood A, et al. Evaluating neurotherapeutic potential of naringenin by true experiments: insights into in-vivo psychiatry care models. Pak J Med Dent. 2025;14(3). https://doi.org/10.36283/ziun-pjmd14-3/043
44. Lu J, Xu F, Lu X, Wang T, Huang S, Zhang J. Synchronous firing transition between different regions of brain neural networks enhanced by Hamiltonian energy. Nonlinear Dyn. 2025;113(10):12143-50. https://doi.org/10.1007/s11071-024-10676-x
45. Andrew RD, Farkas E, Hartings JA, Brennan KC, Herreras O, Müller M, et al. Questioning glutamate excitotoxicity in acute brain damage: the importance of spreading depolarization. Neurocrit Care. 2022;37(Suppl 1):11-30. https://doi.org/10.1007/s12028-021-01429-4
46. Masoli S, Rizza MF, Tognolina M, Prestori F, D’Angelo E. Computational models of neurotransmission at cerebellar synapses unveil the impact on network computation. Front Comput Neurosci. 2022;16:1006989. https://doi.org/10.3389/fncom.2022.1006989
47. Calabrese RL, Marder E. Degenerate neuronal and circuit mechanisms important for generating rhythmic motor patterns. Physiol Rev. 2025;105(1):95-135. https://doi.org/10.1152/physrev.00003.2024

48. Shen G, Zhao D, Dong Y, Zeng Y. Brain-inspired neural circuit evolution for spiking neural networks. Proc Natl Acad Sci U S A. 2023;120(39):e2218173120. https://doi.org/10.1073/pnas.2218173120
49. Friedman R. A perspective on information optimality in a neural circuit and other biological systems. Signals. 2022;3(2):410-27. https://doi.org/10.3390/signals3020025
50. Bano U, Memon S, Shahani MY, Shaikh P, Gul S. Epigenetic effects of in utero bisphenol A administration: diabetogenic and atherogenic changes in mice offspring. Iran J Basic Med Sci. 2019;22(5):521-528. https://doi.org/10.22038/ijbms.2019.29909.7357
51. Rae CD, Baur JA, Borges K, Dienel G, Díaz-García CM, Douglass SR, et al. Brain energy metabolism: a roadmap for future research. J Neurochem. 2024;168(5):910-54. https://doi.org/10.1111/jnc.16032
52. Hunter P. Understanding redundancy and resilience: redundancy in life is provided by distributing functions across networks rather than back-up systems. EMBO Rep. 2022;23(3):e54742. https://doi.org/10.15252/embr.202254742
53. Duong-Tran D, Kaufmann R, Chen J, Wang X, Garai S, Xu FH, et al. Homological landscape of human brain functional sub-circuits. Mathematics. 2024;12(3):455. https://doi.org/10.3390/math12030455
54. Khanjanianpak M, Valizadeh A. Optimizing information capacity in modular neural networks through excitatory and inhibitory connectivity. Neurocomputing. 2025;130313. https://doi.org/10.1016/j.neucom.2025.130313

Journal of Biomolecules, Pathogenesis and Therapeutics, J Biomol Pathog Ther. 2026;2(1):43–50 (jbptjournal.org) © 2026 Mazhar et al. This work is published by Editorial Office of JBPT Publications. The full terms of Journal Publishing policy is available at https://jbptjournal.org/index.php/jbpt/-publishing-license and incorporate the Creative Commons Attribution – Non Commercial (CC BY, NC 4.0) License https://creativecommons.org/licenses/by-nc/4.0/ By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from us, provided the work is properly attributed.