Psychoradiology, 2024, **4**, kkae028
DOI: 10.1093/psyrad/kkae028
Advance access publication date: 14 December 2024
Review

Development of the brain network control theory and its implications

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Abstract

Brain network control theory (NCT) is a groundbreaking field in neuroscience that employs system engineering and cybernetics principles to elucidate and manipulate brain dynamics. This review examined the development and applications of NCT over the past decade. We highlighted how NCT has been effectively utilized to model brain dynamics, offering new insights into cognitive control, brain development, the pathophysiology of neurological and psychiatric disorders, and neuromodulation. Additionally, we summarized the practical implementation of NCT using the nctpy package. We also presented the doubts and challenges associated with NCT and efforts made to provide better empirical validations and biological underpinnings. Finally, we outlined future directions for NCT, covering its development and applications.

Keywords: brain network control theory; neuroscience; brain dynamics; cognitive control; neuromodulation

Introduction

In the intricate field of neuroscience, a key challenge has long been to understand how the brain's vast network of systems act in a coordinated manner to produce, regulate, and maintain various cognitive functions (Lynn & Bassett, 2019). Brain network control theory (NCT), a popular research perspective in neuroscience that has emerged in the last decade, takes a system engineering approach and uses fundamental principles of cybernetics to provide insights into how the brain manages and regulates complex neural network interactions during its dynamic behaviors (Medaglia *et al.*, 2017; Srivastava *et al.*, 2022). Central to the NCT is the concept of brain states, which are defined as activity patterns across regions or voxels at a given moment. These states are characterized by diverse patterns of neural activity, varying connectivity strengths, and differing levels of network engagement (Braun *et al.*, 2021; Gu *et al.*, 2017). The transitions between these states reflect the brain's dynamic processes as it shifts from one functional mode to another, influenced by both internal mechanisms and external control inputs (Gu *et al.*, 2017). This framework provides a basis for understanding how network control mechanisms can facilitate or hinder these transitions, offering a predictive, quantitative perspective to unify the diverse datasets required to describe neural systems and explain observed structural and functional relationships. Research in this area is not only critical for revealing the fundamental mechanisms of brain function but also holds great potential for the early diagnosis and treatment of brain diseases (Guo *et al.*, 2021; Zarkali *et al.*, 2022). To provide an up-to-date perspective of its potential for wide application in neuroscience, this paper reviews the significant advances and applications of brain NCT over the last decade. Moreover, we explore the questions and challenges encountered during the development of NCT and provide an outlook on its future development.

Emergence and development of brain network control theory

The brain is an intricate, dynamic system that has the enormous information processing capacity required for human thought (Marois & Ivanoff, 2005). However, how complex cognitive processes are executed in the brain remains a challenging and unresolved question (Medaglia *et al.*, 2017). In recent years, the control of networked dynamic systems has provided a promising opportunity for addressing these neuroscientific questions. These new applications can be traced back to when Barabasi and colleagues, by integrating tools from network science and control theory, delved deeply into the controllability theory of complex networks and its practical applications in the early 21st century. They demonstrated that the controllability of a network is primarily determined by the degree distribution of its nodes, and they effectively identified driver nodes of the network using maximum matching theory (Liu *et al.*, 2011). This novel approach not only enhances the robustness of network control but also opens new possibilities for the study of brain dynamics. The structural connectome, defined as a comprehensive map of neural connections within the brain, serves as a foundation for understanding transitions between cognitive states (Parkes *et al.*, 2024). Gu and colleagues were the first to implement linear network control models on human brain structural networks, establishing the practical application of this method in the human brain (Gu *et al.*, 2015). They explored how the brain's structural connectivity supports and influences the transition between different cognitive states, identifying specific brain regions that significantly impact this dynamic process. The results supported the hypothesis that, as a complex network, the brain is theoretically controllable (see Box 1) and that different parts of the brain have their own roles in controlling brain dynamics (Fig. 1). These findings not only demonstrate how specific

Received: 4 September 2024; **Revised:** 6 December 2024; **Accepted:** 13 December 2024

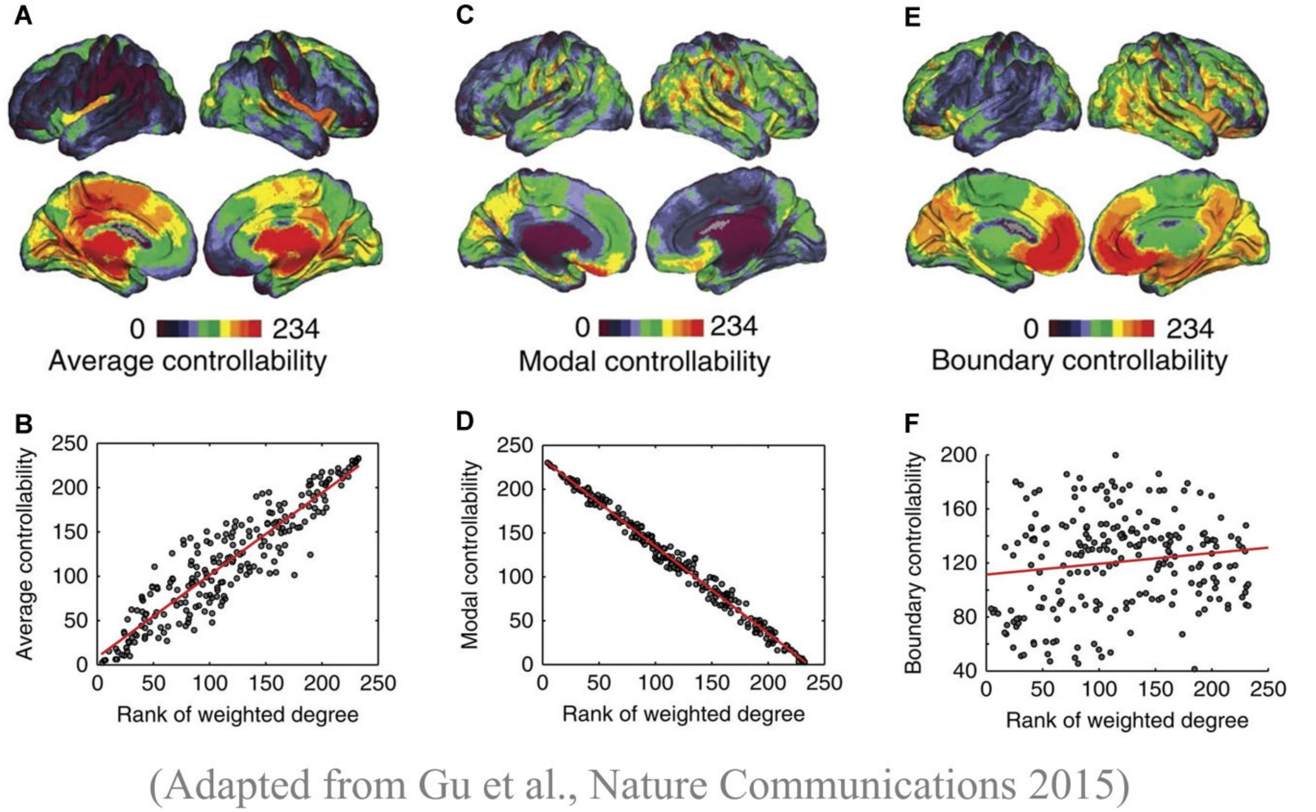

Figure 1: Elucidating brain network control properties through diverse metrics. (A, B) Average controllability describes the ability of brain regions to drive the network state toward various easily reachable states. Correlation scatter plots show a strong positive correlation between the weighted degree (a measure of connectivity strength) of brain regions and their average controllability, suggesting that regions with higher connectivity are more effective in driving the network to easily reachable states. (C, D) Modal controllability focuses on controlling the network to reach difficult-to-achieve states. Scatter plots reveal a strong negative correlation between the weighted degree and modal controllability, indicating that regions with lower connectivity are crucial in driving the network to hard-to-reach states. (E, F) Boundary controllability quantifies the ability to decouple or integrate network modules. Correlation scatter plots indicate a weak positive correlation between the weighted degree and boundary controllability, suggesting that regions with slightly greater connectivity may play a role in the dynamics of network module integration (Gu et al., 2015).

regions contribute to overall cognitive flexibility and control but also lay the foundation for future studies into the relationships between individual differences in network controllability and behavioral, cognitive, clinical, and genetic variables (Gu *et al.*, 2015).

Box 1 Controllability

Controllability in NCT refers to the capacity of specific brain regions, via control inputs, to guide brain states along a designated trajectory—i.e. to move from an initial state to a target state following a predetermined path (Cai *et al.*, 2021; Gu *et al.*, 2015). This concept introduces possibilities for understanding the mechanisms of cognitive control. To explore this, the first essential question is whether the brain is controllable in principle. This is a foundational inquiry within the NCT framework, as it provides a basis for determining whether interventions can indeed alter the system's state.

To address this question, the concept of global controllability is introduced to assess whether the brain network can be guided to a target state through inputs to a single node, effectively altering the overall network state. Furthermore, we must determine which brain regions are most influential in either constraining or facilitating changes in brain state trajectories. Three diagnostic measures of regional controllability provide insights into this question: average controllability, modal controllability, and boundary controllability. Each of these methods captures distinct control objectives (Gu *et al.*, 2015; Karrer *et al.*, 2020; Tang & Bassett, 2018).

Average controllability identifies regions capable of driving the system to a variety of easily accessible states with minimal effort (i.e. low input energy). Central nodes in the brain often exhibit high average controllability, allowing brain states to shift with minimal energy input. In cognitive terms, such regions are crucial for tasks involving multitasking or low cognitive load, as they enable efficient switching between different functional states.

Modal controllability, in contrast, assesses a region's ability to drive the system to difficult-to-reach states, typically requiring higher energy inputs. Regions with high modal controllability are usually not core network hubs but are instead lower connectivity nodes that facilitate shifts in high-cognitive-load scenarios, such as intense concentration or focused attention.

Boundary controllability identifies brain regions situated at the edges of network communities, playing a pivotal role in integrating cognitive systems. These boundary regions enable coordination across different cognitive systems, assisting in the synchronization and transfer of information between distinct processes, such as auditory and language or visual and motor functions.

After establishing the fundamentals of network controllability of the human brain, the field moved on to explore whether such a tool can help model specific dynamic processes of the human mind, i.e. if we treat the brain as a complex network, how do we guide it to shift its state from one particular starting point to another destination through quantifiable inputs? Pasqualetti and colleagues developed a new quantitative approach to this network control problem by examining the relationship between the number of control nodes and energy demand during the transition of system states in a complex network, and they introduced this energy demand as "control energy" (see Box 2) (Pasqualetti *et al.*, 2014). Furthermore, Betzel et al. applied NCT to the human brain, revealing the control energy associated with transitions among different cognitive states. They found that the rich-club structure plays a key role in brain state transitions and that disrupting these structures significantly increases the related energy costs (Betzel *et al.*, 2016). Additionally, Gu and colleagues focused on the optimal trajectories of brain state transitions, particularly during cognitive functions such as attention and executive control, and showed how the brain's white matter structure constrains and supports these state transitions (Gu *et al.*, 2017). Together, these studies demonstrate how NCT can help model brain dynamics, advancing our understanding of such energetic processes.

Box 2 Control energy

Control energy refers to the amount of energy required to drive a brain network from one state to a target state within the NCT framework. Analysis of control energy encompasses identifying optimal pathways and minimizing energy consumption to achieve state transitions, revealing the unique roles of various network nodes in facilitating these transitions.

Optimal control energy represents the minimum internal cognitive control or external stimulation needed to drive the brain from an initial state $x(0) = x_0$ to a target state $x(T) = x_T$. This process considers not only energy consumption but also the length of the state transition path, aiming to minimize the combined cost of path length and control input energy. When transitions involve greater distances or greater task complexity—such as moving from a resting state to a complex working memory task—more control energy is needed. Minimal control energy is a specific form of optimal control energy that focuses solely on minimizing energy costs without considering path length. In this case, the control function aims to minimize the energy required for the transition from $x(0) = x_0$ to $x(T) = x_T$ without accounting for the path distance (Karrer *et al.*, 2020). Control energy quantifies the energy required for brain state transitions, which can be employed to compare the effort required to achieve various cognitive states and to assess the extent to which brain disorders or external stimuli impact the transition between brain states (Luppi *et al.*, 2024; Singleton *et al.*, 2022).

The foundation for calculating control energy lies in the controllability Gramian matrix, a matrix derived from the system's dynamics that quantifies the control energy needed to drive the system from an initial state to a target state. Smaller eigenvalues of the Gramian indicate lower control energy requirements for state transitions, whereas larger eigenvalues indicate higher energy demands. Therefore, the size of the controllability Gramian determines the feasibility of arbitrary state transitions and the associated energy costs.

Several factors influence the amount of control energy required (Parkes *et al.*, 2024), such as the size of the control set. Control energy decreases significantly as the number of nodes involved in control increases, meaning that a greater number of control nodes can reduce the overall energy required to achieve the target state. This indicates that under multinode collaborative control, state transitions become more energy efficient. The difficulty of the state transition also plays a role, and the "distance" between states has a pronounced effect on the control energy, with greater distances requiring more energy for transition. For example, shifting from a low-cognitive-load state to a high-load state consumes more control energy (Braun *et al.*, 2021), which has practical implications for understanding the energy demands of brain regions involved in complex tasks.

Wide applications of brain network control theory

As a powerful tool for decoding brain dynamics, NCT has been widely adopted to address neuroscientific inquiries related to human cognition, brain development, neurological and psychiatric diseases, and neuromodulations.

The first application in understanding human cognition with NCT targets the realm of cognitive control. Cognitive control is an intricate cognitive–neural process involving the transition of cognitive states (Medaglia *et al.*, 2016). With NCT, researchers can quantify the controllability of nodes within brain structural and functional networks, specifically by examining how different brain regions theoretically influence the brain's transitions into various cognitive states during cognitive control. For example, Medaglia et al. found that the modal and boundary controllability of regions involved in cognitive control were significantly correlated with performance on tasks such as the continuous performance attention test, color/shape switching task, Stroop inhibition task, and spatial n-back working memory task (Medaglia *et al.*, 2016). Additionally, by assessing average and modal controllability metrics in healthy adult brains, Lee et al. revealed the associations between cognitive functions and regional controllability, offering a new perspective on how the brain regulates dynamic changes in cognitive states (Lee *et al.*, 2020). Building on these studies, NCT has also been employed to explore the critical roles of specific "hub" regions, such as the anterior insula and dorsolateral prefrontal cortex, in cognitive tasks (Cai *et al.*, 2021). These regions typically serve as crucial outflow and inflow hubs within the network. By analyzing the network characteristics of these hub regions, we can gain a deeper understanding of how the controllability of brain networks changes under high cognitive load and how this affects cognitive performance. Further expanding on the application of NCT, Luppi *et al.* (2024) defined 123 cognitive activation maps, referred to as cognitive topographies, using data from the NeuroSynth database, which encompasses a wide range of cognitive and behavioral terms such as "attention", "emotion", and "memory". By constructing the human structural connectome and modeling control inputs, the research team calculated the control energy required to transition between these different cognitive topographies, revealing how brain structure influences the transitions of cognitive states.

Another fruitful application of NCT has been in the field of neural development. Tang and colleagues demonstrated that as individuals age, the controllability of brain networks significantly increases in young individuals. Specifically, this study highlighted how the development of the white matter network effectively maximizes controllability, including both average and modal controllability, while simultaneously reducing synchronizability. These findings indicate that the capacity of the brain network has been structurally optimized to control dynamic changes, thereby facilitating the development of cognitive abilities (Tang *et al.*, 2017). Additionally, Lee and colleagues investigated how the controllability of individual brain regions in structural networks affects cognitive function performance in individuals. They calculated two primary control metrics, average and modal controllability, and validated that these region-specific controllability indicators exhibit both reproducibility and heritability (Lee *et al.*, 2020). These findings not only supported the genetic basis of controllability as a neural network characteristic but also revealed the over presentation of high-controllability regions in high-order resting-state networks. Extending these insights, Cui et al. examined the maturation of structural brain networks during youth, using NCT to quantify the energetic cost of activating the frontoparietal network necessary for executive function. They found that this cost decreases as structural networks mature, facilitating more efficient state transitions at a reduced energetic expense. This optimization correlates with enhanced executive function, specifically through the modulation of energy costs in key brain areas such as the cingulate cortex (Cui *et al.*, 2020). Additionally, recent findings have indicated that cortical variations in cytoarchitecture form a sensory–fugal axis that shapes regional profiles of extrinsic connectivity and guides signal propagation and integration across the cortical hierarchy. Using a minimum control energy model within the framework of NCT, Parkes and colleagues examined the amount of energy required to propagate dynamics across this sensory–fugal axis, revealing an asymmetry in energy demands; bottom–up transitions were easier to complete than top–down transitions were. This asymmetry is underpinned by a connectome topology that supports efficient bottom-up signaling. Furthermore, these asymmetries are correlated with differences in communicability and intrinsic neuronal time scales and lessen throughout youth (Parkes *et al.*, 2022). Collectively, these studies not only underscore the adaptability and efficiency improvements of brain networks with age but also offer a new perspective on how the brain's structural connectivity evolves to support higher cognitive functions during critical developmental periods.

Third, as expected, NCT is also used to unravel the pathologies of neurological and psychiatric diseases. Meyer-Bäse and colleagues explored the application of NCT in dementia. They applied average and modal controllability to determine the minimum set and location of driver nodes in structural brain networks throughout the disease's progression. They found that this approach could accurately describe the varying roles of different nodes in controlling the trajectories of brain networks, demonstrating shifts in some driver nodes while conserving others throughout the disease course. This study underscores the potential of NCT in decoding the complex neural dynamics involved in neurodegenerative diseases (Meyer-Bäse *et al.*, 2020). Zöller and colleagues employed NCT to assess structural control energy in resting-state functional brain states among patients with 22q11.2 deletion syndrome (22q11DS), a genetic disorder associated with a high risk of psychiatric conditions. Compared with healthy controls, patients with 22q11DS presented distinct patterns of sustained control energy across multiple brain states. Further analysis revealed a negative correlation between sustained control energy and resting-state activation time, suggesting that the brain typically reduces energy expenditure by minimizing the time spent in high-energy states. This energy-saving mechanism was less effective in patients with 22q11DS, indicating a reduced dynamic efficiency in brain function associated with the disease (Zöller *et al.*, 2021). Tang and colleagues further compared the differences in controllability between first-episode, medication-naïve schizophrenia patients and healthy controls, exploring how these differences evolve with age. They found that, unlike healthy controls, patients with schizophrenia showed no age-related decline in average controllability within the default mode network (DMN) or the right prefrontal cortex, suggesting an atypical maturation process in these areas. Additionally, patients with schizophrenia exhibited an accelerated age-related decline in average controllability within the subcortical network, supporting the neurodegenerative model of schizophrenia. This study revealed age-related changes in the controllability of white matter pipelines in patients with schizophrenia, supporting both developmental and degenerative hypotheses of the disease and indicating that the DMN and subcortical networks may be particularly susceptible to schizophrenia-related dysfunction (Tang *et al.*, 2022). Wilmskoetter et al. applied NCT to study aphasia recovery after strokes, focusing on language-related regions. They found the average and modal controllability of the inferior frontal gyrus significantly predicted language improvements post therapy, suggesting a targeted approach for personalized rehabilitation strategies (Wilmskoetter *et al.*, 2022). These studies collectively emphasize the potential of NCT in advancing our understanding of the complex neural dynamics underlying both neurological and psychiatric disorders. Additionally, research by Singleton and colleagues indicated that psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, increased the diversity and complexity of brain function by reducing the control energy required for state transitions. This study employed NCT and functional magnetic resonance imaging (fMRI) data to quantify the impact of psychedelics on brain states, revealing how they alter brain functionality. These findings provide a new perspective for understanding the effects of psychedelics on consciousness and may open new avenues for the treatment of psychiatric disorders in the future. Research has shown that LSD and psilocybin optimize brain dynamics by modulating control energy, complementing the applications of NCT in the study of neurological and psychiatric disorders and thereby deepening our understanding of complex neural dynamics (Singleton *et al.*, 2022).

Finally, NCT is instrumental in modeling neuromodulatory processes, enabling targeted interventions that optimize brain functions and therapeutic outcomes. Previous studies, which typically relied on heuristic methods to select specific regions for stimulation signals (Kumar *et al.*, 2022), have been significantly enhanced by employing NCT to construct models of interregional influence. This approach has enabled the design of more optimized treatment strategies across various neurological conditions. For instance, Muldoon and colleagues utilized a data-driven computational model of nonlinear brain dynamics to systematically explore the effects of targeted stimulation. Their findings validated predictions from NCT regarding the relationship between regional controllability, including average and modal controllability, and the focal versus global impact of stimulation, forming a crucial step toward the development of personalized stimulation protocols by revealing how different regions impact overall brain dynamics (Muldoon *et al.*, 2016). Sanchez-Rodriguez et al. developed a control framework that uses external stimulation inputs to reverse pathological electroencephalography (EEG) activity in neurodegenerative diseases such as Alzheimer's disease, providing a promising avenue for targeted interventions in neurological diseases (Sanchez-Rodriguez *et al.*, 2018). Additionally, Medaglia et al. explored how the network controllability of brain regions, specifically in relation to the inferior frontal gyrus, influences the effects of transcranial magnetic stimulation (TMS) on cognitive control. Their study demonstrated that controllability metrics, including average and modal controllability, significantly predict the efficacy of TMS interventions in enhancing cognitive performance. This work underscores the potential of NCT to refine neuromodulation strategies by identifying which brain regions are most responsive to stimulation, thereby facilitating targeted interventions that could improve cognitive functions (Medaglia *et al.*, 2018). Subsequently, Stiso and colleagues illustrated the application of NCT in modeling neural dynamics to predict and manage the brain's response to grid stimulation in patients with epilepsy. They utilized both average and modal controllability metrics to understand how structural properties of the brain influence its dynamic responses to stimulation. Their findings revealed a significant shared variance between the predicted and observed activity state transitions, supporting the validity of the model. Furthermore, using an optimal control framework, researchers have proposed testable hypotheses about which brain states and structural characteristics could effectively enhance memory encoding during stimulation (Stiso *et al.*, 2019).

In summary, the evolving field of neuroscience has created new needs for NCT, driving it to expand and deepen in response to a variety of specific challenges. By actively exploring and addressing these emerging issues, NCT is shaping our understanding of brain dynamics, demonstrating its great potential for future research and practical applications in neuroscience.

Practical implementation of NCT

As the theoretical foundation of NCT has been refined and widely applied in neuroscience research, it has become an invaluable framework for investigating how the topological properties of the brain's structural connectome influence and constrain neural dynamics. Owing to its ability to predict external control signal propagation and model the control potential of specific regions, NCT offers unique insights into brain function and network control mechanisms.

To facilitate empirical research on NCT, Parkes and colleagues recently introduced a Python package, nctpy, to standardize the implementation of NCT pathways (Parkes *et al.*, 2024). This package provides a structured workflow, streamlining NCT applications and enabling researchers to calculate key metrics, such as control energy and average controllability, with relative ease.

This section outlines two main pathways for implementing NCT using the nctpy package: Pathway A, which calculates the control energy required to achieve specific neural state transitions, and Pathway B, which measures average controllability to assess a brain region's capacity for global network influence. Together, these pathways support a comprehensive analysis of network control characteristics, both locally and globally, whereas model comparison techniques (e.g. the use of null models) increase robustness and interpretability.

Pathway A: Control Energy

Pathway A involves the calculation of the control energy necessary for state transitions within the brain network. The process begins by selecting a time system, where researchers must decide between discrete-time or continuous-time systems to model neural dynamics. Next, the adjacency matrix is normalized to ensure system stability, with adjustments based on the chosen time system. Control tasks are then defined by specifying target states for each brain region involved. To optimize energy usage for efficient state transitions, methods such as gradient descent are employed. This pathway provides valuable insights into the energy required to drive specific brain state changes, with the option of visualizing control energy using heatmaps or matrices.

Pathway B: Average Controllability

Pathway B focuses on measuring a brain region's potential to influence network-wide dynamics without the need to specify a target state. The key component of this pathway is the average controllability metric, which quantifies each node's ability to affect the network. Higher values of this metric indicate greater control potential for that region. To facilitate analysis, controllability values can be visualized, allowing for comparisons across different regions. This pathway allows for understanding how specific regions contribute to overall network control, helping to identify key nodes in brain networks.

Considerations

Considerations for both pathways include several important factors. First, model constraints require careful normalization of the adjacency matrix to ensure stability across both continuous and discrete-time systems for both pathways. Additionally, the choice of control set plays a crucial role in the effectiveness of the analysis; researchers are encouraged to experiment with various configurations, such as full, partial, or weighted control sets, to identify the most efficient approach for their specific research goals. Finally, when interpreting results from Pathway A, it is essential to consider energy asymmetries, as energy variations may arise depending on the direction of state transitions. These factors must be taken into account to ensure accurate and meaningful interpretation of the results.

Doubts and challenges

The pioneering work of Gu and his collaborators has inspired extensive follow-up research aimed at better understanding and capturing the controllability of brain networks. However, this theory is not accepted without constraints. After reviewing the framework for applying control theory to complex networks, Tu et al. argued that brain networks cannot be controlled by a single region (in a statistically significant sense) and that the random null model bears no biological resemblance to the structure of brain networks, highlighting the crucial roles of appropriate experimental control and assumptions (Tu *et al.*, 2018). Similarly, Popova et al. also questioned findings by Wilmskoetter et al. regarding the application of NCT in predicting language recovery for stroke patients (Popova *et al.*, 2022; Wilmskoetter *et al.*, 2022). They argued that NCT itself still assumed the control of individual nodes and ignored the relevance of the controllability of excluded brain regions to treatment outcomes. Furthermore, even if it were theoretically possible to control the entire brain from a single brain region, the energy required would be enormous. Taken together, doubts about NCT seem to stem mainly from the lack of empirical evidence for the effectiveness of these control principles.

To address these challenges, earlier studies have applied NCT in simpler biological systems to provide empirical validation. Yan and colleagues applied NCT to predict and experimentally validate the functional roles of neurons in *Caenorhabditis elegans*. They developed a mathematical framework that links neuronal controllability to motor behavior, identifying twelve neuron classes critical for controlling muscles or motor neurons, including the previously undescribed PDB neuron (Yan *et al.*, 2017). Similarly, Eichler et al. employed NCT to elucidate the intricate dynamics of neural networks within the *Drosophila* larval mushroom body, a critical learning and memory center. They meticulously mapped the connectome at synaptic resolution, revealing how Kenyon cells integrate sensory input from various projection

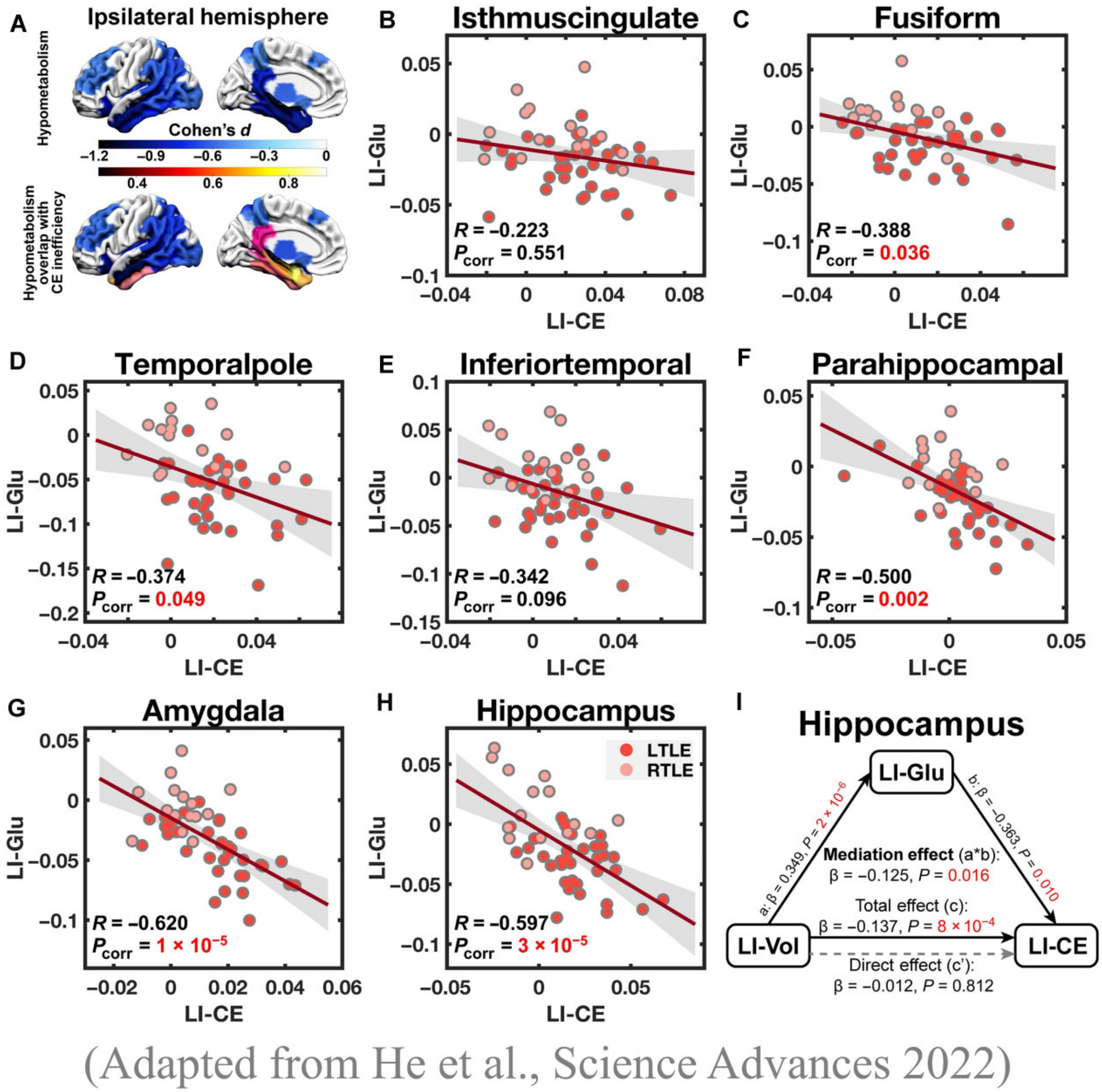

Figure 2: Associations between regional control energy consumption and glucose metabolism in patients with temporal lobe epilepsy. (A–E) Significant correlations were identified between the laterality indices of glucose uptake and control energy consumption across different brain regions, notably in limbic areas, indicating that regions with lower metabolic rates demanded more control energy. This was established through Pearson correlations adjusted for multiple comparisons, with significant results highlighted. (F) Mediation analysis in the hippocampus revealed that the laterality of glucose uptake fully mediated the relationship between gray matter volume laterality and control energy consumption (He et al., 2022).

neurons, which encode diverse stimuli, including olfactory, thermal, and visual signals. By demonstrating the structured yet adaptable interactions within these networks, their findings highlighted the utility of NCT in comprehending complex neural activities across different organisms. Such insights are pivotal for advancing our understanding of brain network responses to environmental changes and stimuli, thus providing a robust framework for potential translational neuroscience applications (Eichler *et al.*, 2017).

Another challenge lies in the absence of a biological basis for this theory, i.e. what exactly controls energy in the human brain. He and colleagues used unilateral temporal lobe epilepsy as a lesion model, integrating multimodal neuroimaging techniques such as diffusion-weighted imaging and positron emission tomography (PET), to reveal the association between control energy and glucose metabolism (He *et al.*, 2022). By modeling various state transitions in the brain with NCT, this work linked the increased control energy demands associated with disease-related inefficiency to glucose hypometabolism and gray matter loss in the hippocampus, offering a novel theoretical framework that integrates gray matter integrity, metabolism, and neural dynamics (Fig. 2). With the biological basis provided for NCT, this study not only laid a solid foundation for the further application and development of NCT in neuroscience but also provided strong support and validation for previous works (Menara *et al.*, 2018; Pasqualetti *et al.*, 2019).

In summary, despite existing skepticism, this growing body of literature highlights the potential of NCT to enhance our understanding of neural dynamics and responses to changes. However, as NCT has broader applications, it is crucial to continue rigorously validating its principles and assumptions to ensure robust and biologically relevant outcomes.

Future prospects

One interesting notion is that neural dynamics are not linear. Nevertheless, the current application of NCT is based on linear models. Although in some cases nonlinear behaviors can be accurately approximated by linear behaviors (Muldoon *et al.*, 2016; Honey et al., 2009), how to strike a good balance between model complexity and study ability and how to further describe the controllability of the brain by constructing more appropriate nonlinear models are important topics for future research. Future research should focus on developing network control models capable of capturing nonlinear dynamics, integrating machine learning and multimodal data fusion to enhance the understanding of brain controllability. Furthermore, empirical validation of these nonlinear models in clinical interventions will provide new insights into brain dynamics.

Second, unlike the descriptive statistics of networks such as graph theory, NCT explains how changes in the activation of a single node can cause spatially distributed and system-wide effects throughout the system, with a specific pattern depending on the structure of the anatomical network connecting all nodes (Kim *et al.*, 2018). In addition, as a dynamic system, the brain's state stability largely depends on the level of cognitive effort (Braun *et al.*, 2021). In computational neuroscience, an elusive goal is to describe the brain as a dynamic system with predictable natural temporal evolution and responses to inputs (Cornblath *et al.*, 2020). Therefore, taking into account temporal information and exploring how to account for the effects of external signals over time on stimuli and the brain in the absence of interactive effects are also important directions for the future of NCT. Future research can utilize emerging time series analysis techniques, including models of delay effects and instantaneous responses, to focus on the time-dependent relationship between external stimulation signals and brain dynamics. At the same time, developing dynamic system models that reflect the temporal evolution of brain states will enhance the ability to predict the brain's responses during different cognitive tasks. Furthermore, exploring the impact of cognitive load on the dynamic stability of brain networks, as well as analyzing brain controllability under various external stimulation conditions, will provide important insights for research.

Third, although NCT has emerged as a promising framework for understanding structure–function relationships in the brain, with widespread attention given to both health and disease (Karrer *et al.*, 2020), its application in explaining the effects of neuromodulation on brain networks remains somewhat limited. In clinical applications, it will be crucial to design interventions that can effectively and safely influence brain dynamics and modulate neural circuits. This will require optimizing the selection of stimulus targets based on an individual's unique connectome and adjusting stimulus dosages accordingly. One of the key advantages of the NCT is its ability to predict the effects of multipoint control, particularly in how altering the activity of multiple control points can influence brain states. This capability could offer valuable contributions to the development of multipoint neuromodulation techniques (Braun *et al.*, 2018). NCT is especially relevant for the study and treatment of various neurological and psychiatric disorders, such as schizophrenia and Alzheimer's disease, which are often associated with disruptions in brain network connectivity and pathological changes. In the context of clinical neuromodulation, NCT plays a pivotal role in guiding personalized treatment interventions. By precisely identifying the most effective stimulation sites, NCT can help optimize the use of neuromodulation techniques, such as TMS or deep brain stimulation, ensuring that interventions are both safe and effective. Furthermore, NCT can aid in tailoring individualized treatment plans based on the unique brain network characteristics of each patient, thereby increasing the precision and therapeutic outcomes of neuromodulation. This not only improves treatment effectiveness but also expands the potential applications of neuromodulation technologies in clinical therapy and cognitive enhancement.

Fourth, a crucial step in advancing NCT is the validation of the brain dynamics predicted by the theory. A promising approach involves combining complementary neuroimaging techniques, such as EEG and fMRI, which offer high temporal and spatial resolution, respectively, for capturing brain activity. This integration can provide a robust validation of the predictive capabilities of NCT. Additionally, combining fMRI with PET can offer a more comprehensive view of brain activity, with fMRI capturing dynamic state changes and PET measuring the associated energy consumption. Moreover, future research should focus on integrating NCT with specific neuromodulation strategies, such as TMS experiments, to directly test and refine the model's predictive power. By employing these approaches, researchers can further deepen their understanding of NCT and lay a solid foundation for the development of personalized neuromodulation interventions.

By outlining the potential of the nascent and burgeoning field of brain NCT, we aim to engage more researchers and intensify efforts toward the vital goal of modulating the dynamics of brain networks, a pursuit of paramount importance for improving human health and cognitive function.

Author contributions

Zhoukang Wu (Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing), Liangjiecheng Huang (Investigation, Methodology, Writing – review & editing), Min Wang (Investigation, Writing – review & editing), and Xiaosong He (Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing)

Conflict of interest statement

None declare.

Acknowledgements

This work was supported by Research Start-up Fund of USTC, National Natural Science Foundation of China (grant number 82271491) and National Key R&D Program of China (2023YFC3341302).

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Received: 4 September 2024; **Revised:** 6 December 2024; **Accepted:** 13 December 2024