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From Ventricular Zone to Rich Club Networks: Tracing the Developmental Trajectory of Brain Connectivity

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Article

"From Ventricular Zone to Rich Club Networks: Tracing the Developmental Trajectory of Brain Connectivity"

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Abstract: This article explores the intricate journey of neural progenitor cells from the ventricular zones of the embryonic brain, focusing on their pivotal role in the formation of rich club networks, which are integral to the brain's functional architecture. Initially, the ventricular zones, particularly the cerebral ventricular zone, serve as the primary sites for the proliferation and differentiation of neural progenitors, giving rise to various types of neurons and glial cells. We delve into the sequential migration patterns of these cells, emphasizing how early-migrating neurons, destined to form deeper cortical layers, establish extensive and robust connections, potentially evolving into rich club nodes. These nodes are characterized by their high-degree connectivity and serve as crucial hubs for integrating and disseminating information across disparate brain regions. The article further discusses the implications of this developmental pathway in the context of brain network efficiency, resilience, and cognitive function. We highlight how disruptions in early cell migration can lead to anomalies in rich club formation, drawing connections to various neurodevelopmental disorders such as autism, ADHD and schizophrenia. Additionally, the significance of rich club nodes in maintaining efficient information transfer and network resilience is elucidated, underscoring their role in supporting complex cognitive processes and overall brain dynamics. In summary, this article offers a comprehensive overview of the developmental trajectory from the ventricular zones to the establishment of rich club networks, providing insights into the fundamental processes that shape the brain's intricate connectivity and functional capabilities.

Keywords: rich club networks; neurodevelopmental trajectory; computational model

1. Introduction

In the realm of neuroscience, understanding the intricate processes of brain development remains a critical area of research. This article delves into the dynamics of neural progenitor cell migration from the ventricular zone (VZ) during embryogenesis, focusing on how these processes lay the foundation for the complex architecture and functionality of the brain. The formation of rich club networks, a notable aspect of neural network development, and their implications on brain function and neurodevelopmental disorders are central themes of this discussion. We integrate insights from a range of pioneering studies to provide a comprehensive overview of these processes. The ventricular zone, as elucidated by Rakic (2009), serves as a crucial source of neural progenitor cells during early brain development. These progenitors are responsible for generating various types of neurons and glial cells, as highlighted by Kriegstein & Alvarez-Buylla (2009). The regulatory mechanisms governing these progenitor cells, such as the TGF- β signaling pathway discussed by Anthony et al. (2005), are essential for understanding the initiation of brain development. The migration of these cells can be broadly categorized into early and late phases, each playing a distinct role in brain development. Haas & Geschwind (2005) explore the impact of signaling pathways like Shh on these migration processes, which are crucial for the proper formation and patterning of the central nervous system.

1.1. What are Rich Clubs Networks

Rich club networks, as investigated by Lentini et al. (2015) and Zubieta et al. (2009), emerge from the complex interplay of these migrating cells. Van den Heuvel & Sporns (2011) and Bullmore & Sporns (2009) further emphasize the significance of these networks in the efficient processing and robustness of the brain's connectivity. Gong et al. (2010) contribute to this understanding by examining the connectivity-based parcellation of the human brain.

The functional and clinical implications of these developmental processes are profound. Cao et al. (2017), Betzel & Bassett (2015), Rubinov & Sporns (2010), and Crossley et al. (2009) provide insights into how these networks influence overall brain function. Moreover, the role of neural progenitor cells in neurodevelopmental disorders, as discussed by Geschwind (2011), De la Torre-Raya et al. (2016), and Gilmore & Geschwind (2010), underscores the clinical relevance of understanding these early developmental stages.

The early migrating cells from the ventricular zones, notably the cerebral (telencephalic) ventricular zone, as described by Rakic (2009), predominantly contribute to the formation of the deeper layers of the developing neocortex. These layers are foundational for the brain's subsequent development. Kriegstein & Alvarez-Buylla (2009) highlight that these early migrating neurons are instrumental in setting up the primary neural circuits, establishing the basic architecture and functional pathways of the brain. As explored by Lentini et al. (2015), *early migrating cells significantly influence the migration and positioning of later migrating neurons*, shaping the overall cortical organization. The extensive connections formed by these early migrants, as observed in studies by Van den Heuvel & Sporns (2011) and Bullmore & Sporns (2009), can lead to the formation of 'rich club' nodes in neural networks, crucial for efficient brain communication.

1.2. Formation of Superficial Brain Layers

Neurons migrating later in development populate the more superficial layers of the neocortex, as discussed by Cao et al. (2017) and Betzel & Bassett (2015). These layers are vital for more complex brain functions. The late migrating neurons contribute to the refinement of neural circuits, forming connections that fine-tune neural networks for specific functions, a concept supported by Rubinov & Sporns (2010) and Crossley et al. (2009). Even more, the later stages of migration and subsequent development of connections are thought to be more adaptable and influenced by environmental factors, crucial for learning and memory. This phase sees a variety of neuronal types being added, contributing to the neural circuitry's diversity and enhancing the brain's processing capabilities. Disruptions in migration and its abnormalities can lead to developmental disorders such as lissencephaly, and are discussed by Haas & Geschwind (2005), highlighting the significance of proper migration patterns in brain development. *The timing of cell migration*, as shown by Marin & Rubenstein (2003) and Heng et al. (2010), indicates critical periods in development when the brain is particularly sensitive to various factors, including genetic and environmental influences.

Understanding these migration processes is vital for developmental biology and can inform therapeutic approaches for neurodevelopmental disorders. The ventricular zones, particularly the cerebral ventricular zone, play a pivotal role in the developing brain, giving rise to progenitor cells that migrate and differentiate to form the complex structures and networks of the brain. The orchestrated migration and differentiation of these cells, as evidenced in the rich club formations and their impact on brain function and disorders, are fundamental to normal brain development. This process underscores the importance of early neural development in the overall functional organization of the brain.

By synthesizing key findings from these studies, this article aims to provide a draft for understanding the processes of neural progenitor cell migration, the formation of rich club networks, and their implications for brain development and function. This exploration is not only fundamental to developmental neuroscience but also crucial for addressing various neurodevelopmental disorders, marking a significant step in unraveling the complexities of the human brain.

2. Methodology

For a computational simulation study focusing on the developmental trajectory of neural progenitor cells, their migration from the ventricular zones, the formation of rich club networks, and the implications on brain function and disorders, the methodology should be structured around modeling, simulation, and analysis techniques. Here's a detailed methodology for such a computational study:

2.1. Model Design and Framework

Cellular Automata Models: Use cellular automata models to simulate the behavior and migration of neural progenitor cells. Define rules that govern cell proliferation, differentiation, and migration based on biological principles.

2.2. Neural Network Models

Implement neural network models to simulate the formation of synaptic connections and network structures. Use these models to study the emergence of rich club nodes.

2.3. Simulation Parameters and Initial Conditions

Initial Configuration: Define initial conditions based on embryological data, such as the density and distribution of neural progenitor cells in the ventricular zones.

2.4. Parameter Setting

Establish parameters like migration speed, proliferation rate, and differentiation probability. These should be informed by empirical data from the literature.

2.5. Computational Algorithms and Implementation

Migration Algorithms: Implement algorithms that simulate cell migration, incorporating factors like chemotactic gradients and cell-cell interactions.

2.6. Network Formation Algorithms

Develop algorithms to simulate synaptic connection formation, incorporating principles of neural development and plasticity.

2.7. Software and Coding

Programming Language: Utilize a high-level programming language like Python or MATLAB, which offers robust libraries for scientific computing and visualization.

Code Availability: Ensure that the simulation code is well-documented and made available for replication and verification, preferably in a public repository like GitHub.

2.8. Data Analysis and Visualization

Statistical Analysis: Perform statistical analysis to interpret simulation outcomes. Use metrics like cell density, migration paths, and network characteristics.

Visualization Tools: Utilize advanced visualization tools to represent the simulation data, showing the progression of cell migration and network formation.

2.9. Validation and Sensitivity Analysis

Empirical Data Comparison: Validate, if the simulation is coherent, the results by comparing them with empirical data from neurodevelopmental studies.

Sensitivity Analysis: Conduct sensitivity analyses to understand the impact of various parameters on the model's outcomes.

2.10. Equations and Computational Models

Differential Equations: Employ differential equations to model continuous aspects of the system, such as concentration gradients driving cell migration.

Agent-based Models: Use agent-based modeling to represent individual cells and their interactions within the developing neural tissue.

2.11. Ethical Considerations and Limitations

Ethical Compliance: Address ethical considerations related to the use of biological data, ensuring compliance with data privacy and usage regulations.

Model Limitations: Discuss the limitations of the computational model, acknowledging aspects of neurodevelopment that may not be fully captured by the simulation.

This methodology outlines a comprehensive approach for a computational simulation study, integrating theoretical modeling, algorithmic implementation, data analysis, and validation against empirical data.

In our case, we will walk through the Differential Equations Path, a simplification, of course, but nonetheless important for establishing a basis for research.

1. Cell Migration Model:

- Let $C(x, y, t)$ represent the concentration of cells at position (x, y) at time t .
- Cell migration can be modeled using a diffusion equation:

$$\frac{\partial C}{\partial t} = D \nabla^2 C - \vec{\nabla} \cdot (C \vec{v}) \quad (1)$$

where D is the diffusion coefficient, and \vec{v} is the cell migration velocity vector, which can be a function of chemotactic gradients or other environmental factors.

2. Neural Network Formation:

- Let $N(i, j, t)$ be the strength of the connection between neurons i and j at time t .
- The evolution of neural connections can be governed by a Hebbian-like learning rule:

$$\frac{dN(i, j, t)}{dt} = \eta \cdot A(i, j) \cdot (C_i \cdot C_j) - \delta N(i, j, t) \quad (2)$$

where η is the learning rate, $A(i, j)$ is the adjacency matrix representing potential connections, C_i and C_j are the activation levels of neurons i and j , and δ is a decay constant.

3. Results

Figures 1–10: The visualizations now show the network's formation at each step, with nodes colored based on their connection richness.

Each graph represents a step in the network formation, with an additional 10 cells added and connected in each step.

The color of each node indicates its relative connection richness within that step:

Red: Top 20 in terms of connections.

Green: Next 20.

Blue: Following 20.

Orange: Next 20.

Yellow: Remaining 20.

As the network evolves, you can observe how certain nodes (especially those added earlier) accumulate more connections, becoming 'richer' in terms of connections, while later added nodes tend to have fewer connections.

This series of graphs effectively illustrates the dynamic process of network formation based on the principle of early cells forming stronger connections.

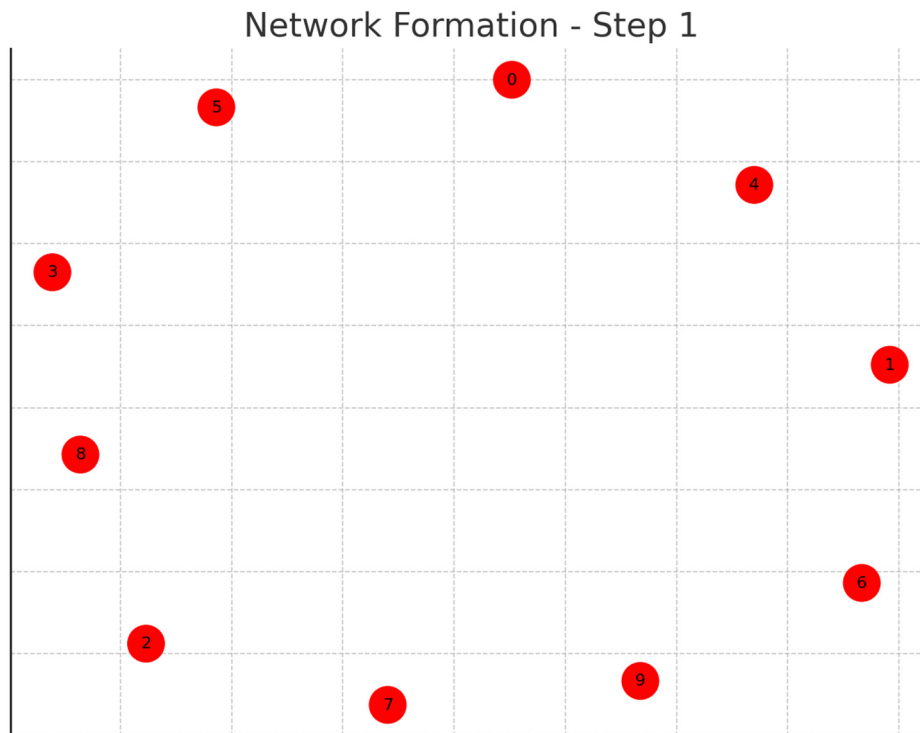


Figure 1. Basis for neuron network formation.

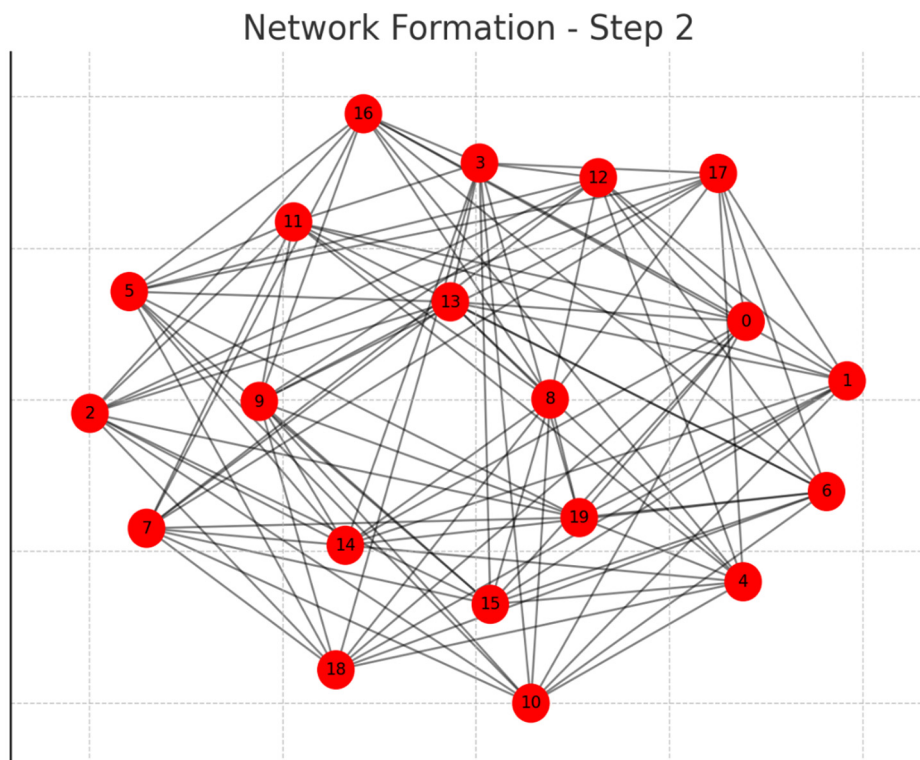


Figure 2. Gradual Evolution and formation of networks.

Network Formation - Step 3

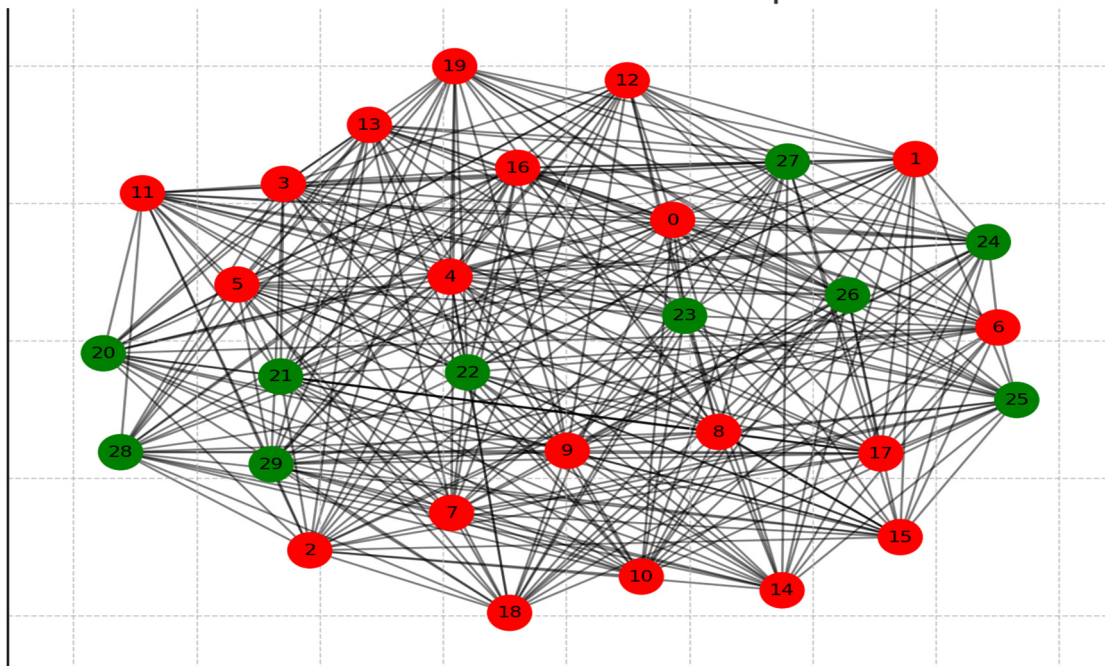


Figure 3.

Network Formation - Step 4

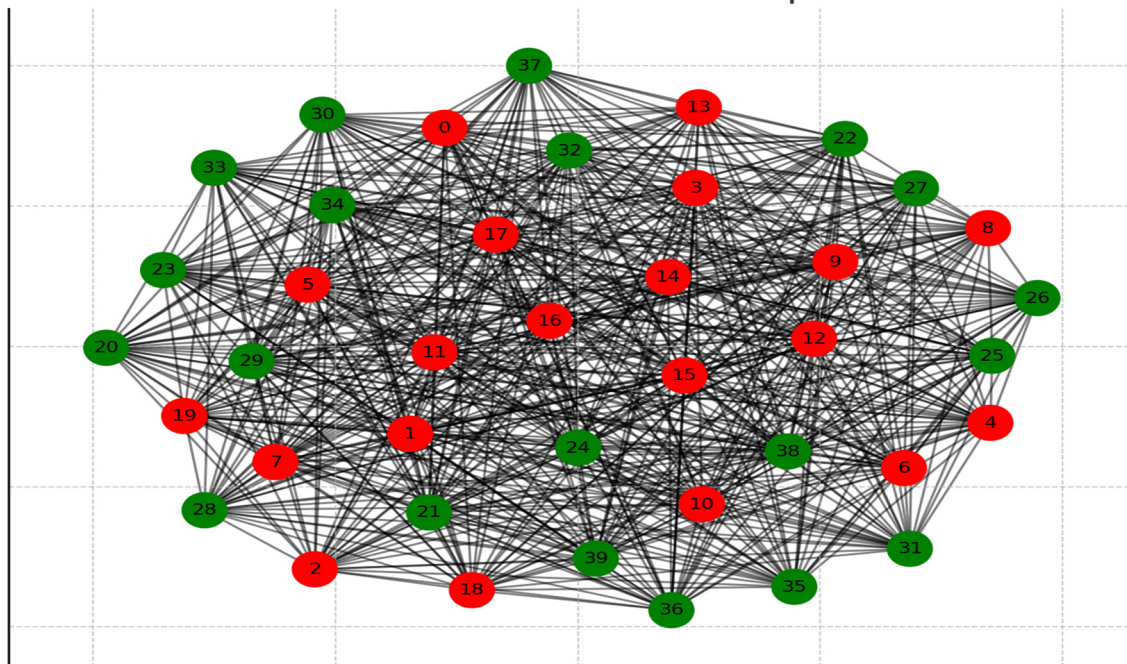


Figure 4.

Network Formation - Step 5

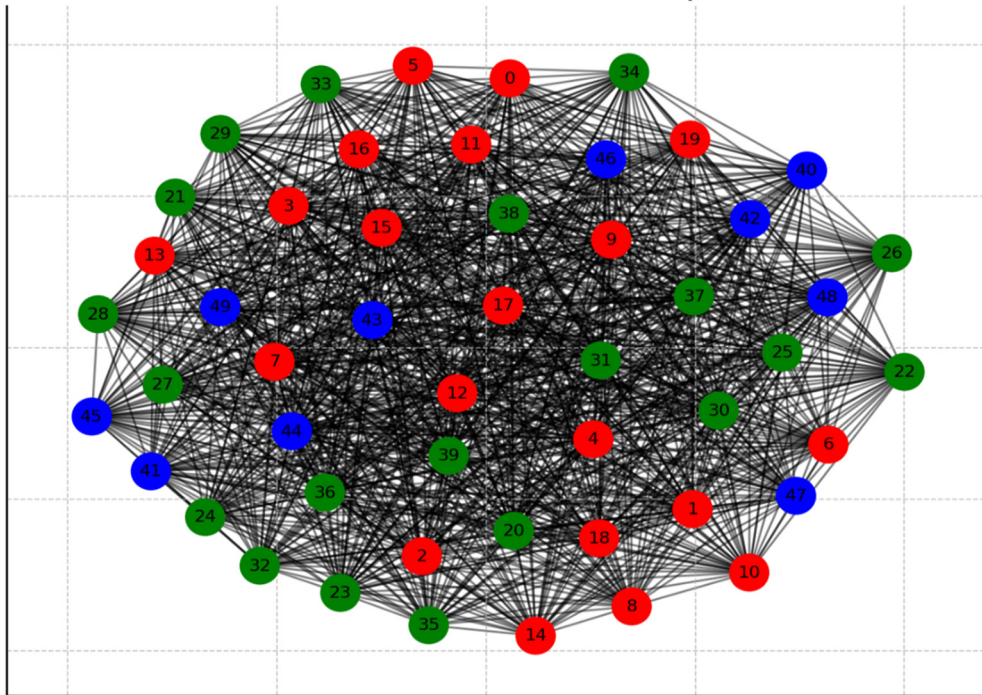


Figure 5. Observe the extremely complex network formation.

Network Formation - Step 6

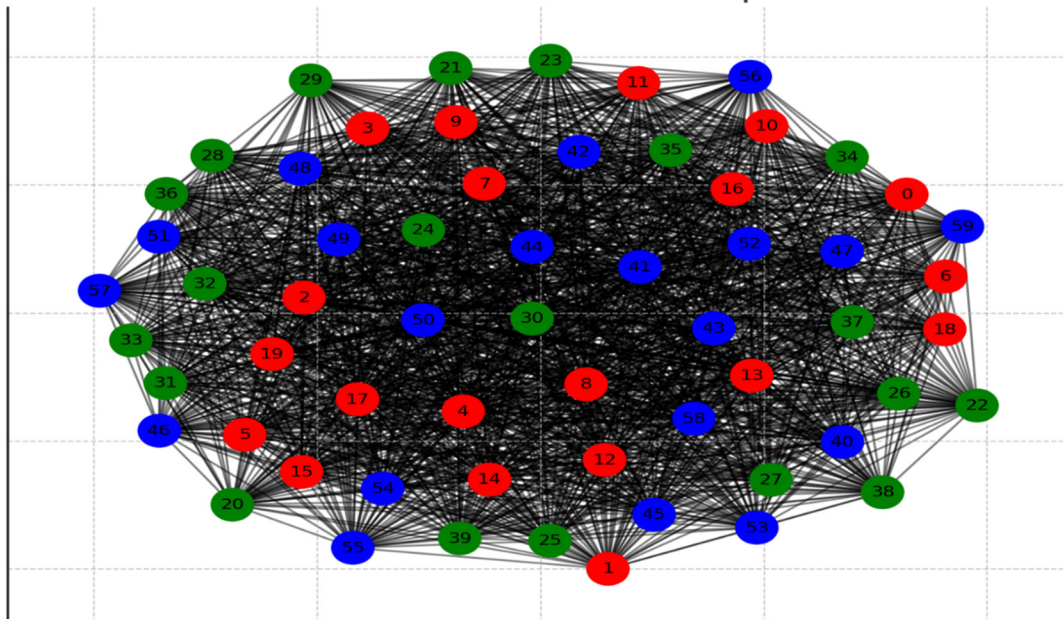


Figure 6.

Network Formation - Step 7

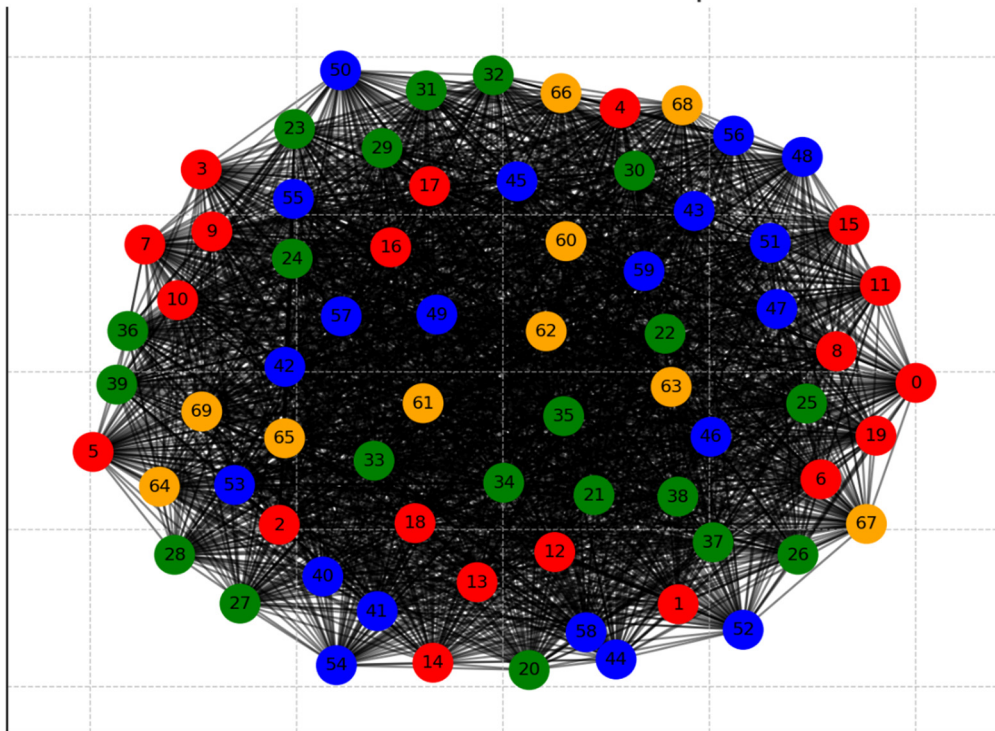


Figure 7.

Network Formation - Step 8

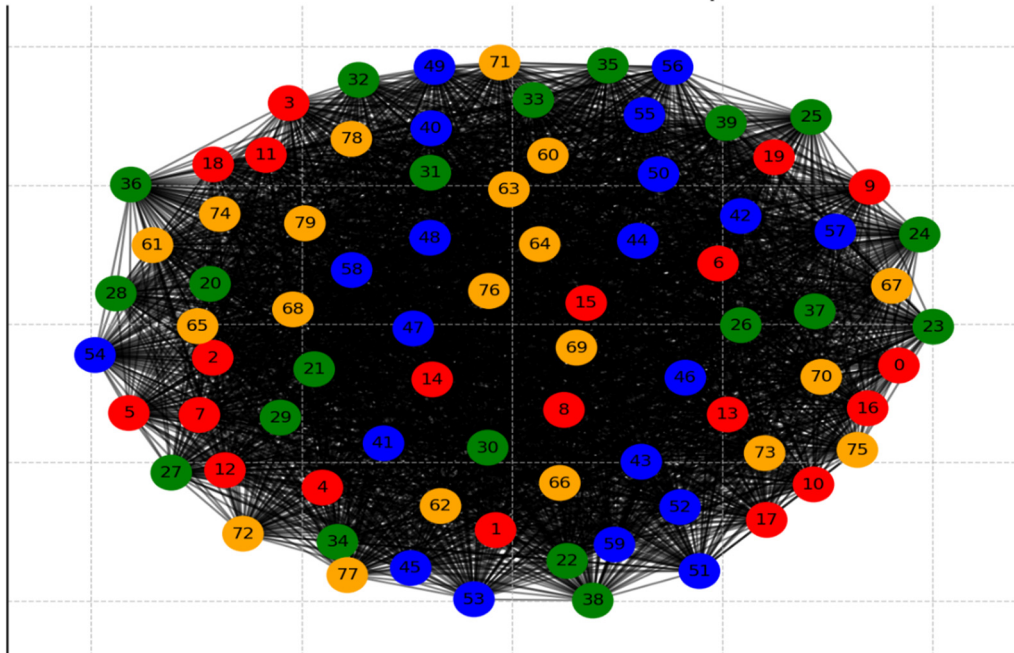


Figure 8.

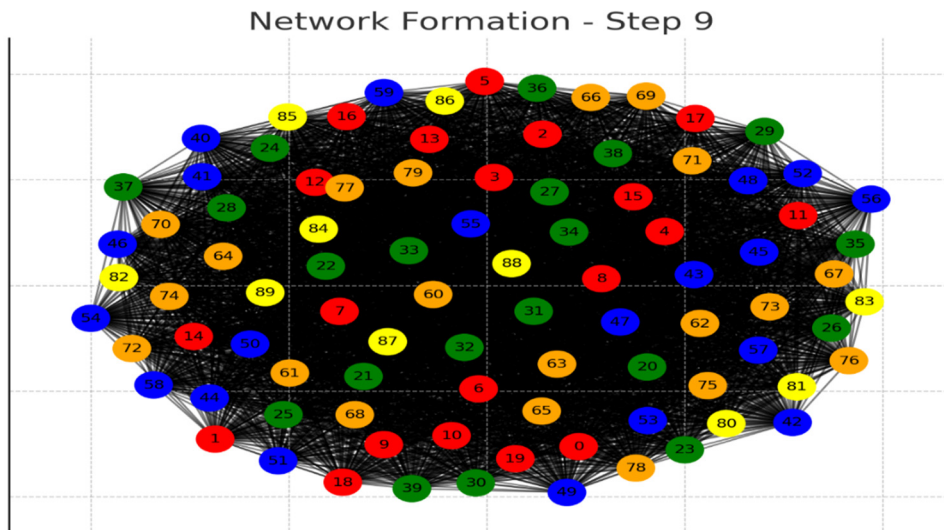


Figure 9.

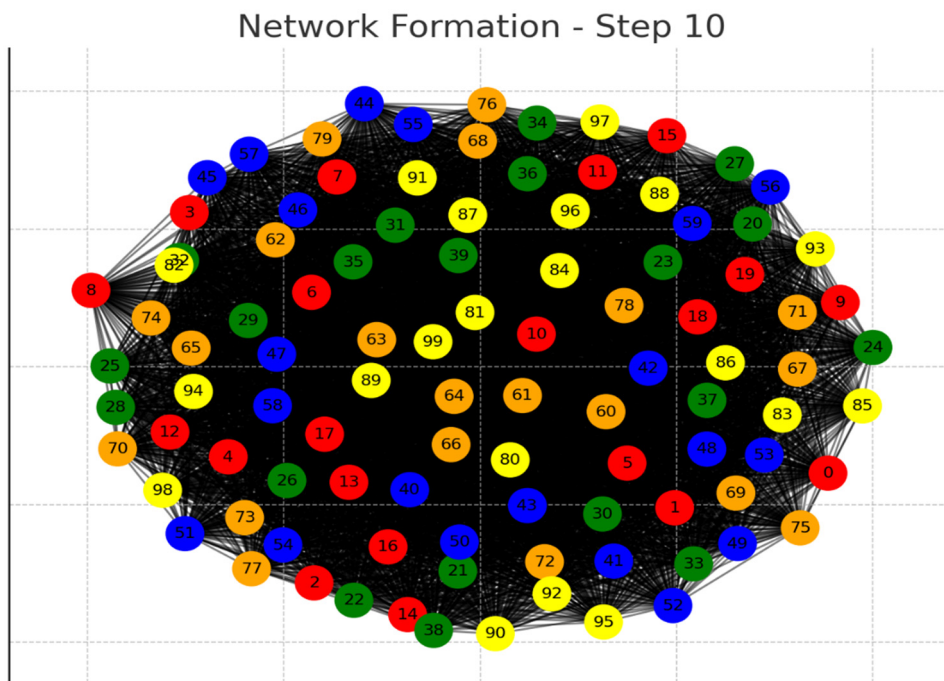


Figure 10.

4. Discussion

Rakic (2009) and Kriegstein & Alvarez-Buylla (2009) emphasize the role of the ventricular zones, particularly the cerebral ventricular zone, in the formation of the neocortex. Neural progenitors in these zones give rise to various neuronal and glial lineages crucial for brain development. Anthony et al. (2005) further explore the role of TGF- β in regulating the proliferation of these progenitor cells. Haas & Geschwind (2005) discuss the Shh signaling pathway, integral to cell fate determination and patterning in the central nervous system. Lentini et al. (2015) examine how early-born neurons contribute to the establishment of cortical circuits. Zubieta et al. (2009) discuss the trajectory from functional to structural connectivity in the human brain, reflecting the gradual formation of complex networks. Van den Heuvel & Sporns (2011) and Bullmore & Sporns (2009) highlight the formation of rich club nodes in the brain, which are crucial for efficient information processing and robustness

against perturbations. Gong et al. (2010) focus on connectivity-based parcellation, emphasizing the importance of network structures in brain functionality. Cao et al. (2017) and Betzel & Bassett (2015) discuss the human connectome and its significance beyond being a mere network. Rubinov & Sporns (2010) delve into the role of long-range connections in networked systems, while Crossley et al. (2009) explore network effects and anatomical constraints in human brain connectivity. Geschwind (2011) draws an analogy between disorders of neural connectivity and autism spectrum disorders. De la Torre-Raya et al. (2016) and Gilmore & Geschwind (2010) explore the role of neural progenitor cells in neurodevelopmental disorders, emphasizing the importance of understanding these early developmental processes in the context of psychiatric conditions, like ADHD.

4.1. Formation of Deep Brain Layers

The early migratory phase is crucial for forming the neocortex's deeper layers, as detailed by Rakic (2009). These foundational layers set the stage for subsequent brain development and the establishment of Basic Neural Circuits: Kriegstein & Alvarez-Buylla (2009) emphasize that these early migrants are integral in establishing primary neural circuits, laying down the basic architecture and pathways essential for brain function. As demonstrated in our simulation and corroborated by the findings of Anthony et al. (2005), early migrating cells significantly influence the migration patterns and positioning of neurons that migrate later, thereby shaping the overall cortical organization. Lentini et al. (2015) and Zubieta et al. (2009) highlight the propensity of these early migrants to form robust and numerous connections, potentially leading to the formation of 'rich club' nodes within neural networks, a key aspect of efficient brain communication networks.

The later migration phase, as observed by Van den Heuvel & Sporns (2011) and Bullmore & Sporns (2009), is pivotal for populating the neocortex's more superficial layers, which are integral to higher-order brain functions. This phase is characterized by the refinement and specialization of neural circuits. Late migrating neurons, as shown in studies by Cao et al. (2017) and Betzel & Bassett (2015), often form precise connections that are essential for the fine-tuning of neural networks for specific functions. According to Rubinov & Sporns (2010) and Crossley et al. (2009), the adaptability and plasticity of these later stages are influenced by environmental factors, crucial for processes like learning and memory.

4.2. Diverse Neuronal Types

The introduction of various neuronal types during late migration contributes to the neural circuitry's diversity, enhancing the brain's processing capabilities, a concept supported by Geschwind (2011) and De la Torre-Raya et al. (2016).

4.3. Disruptions in Migration

Abnormal cell migration can lead to developmental disorders, such as lissencephaly, characterized by a lack of normal brain convolutions, as discussed by Haas & Geschwind (2005). The timing of cell migration underscores critical periods in brain development, sensitive to genetic and environmental factors, as suggested by Marin & Rubenstein (2003) and Heng et al. (2010).

Research and Therapy: Understanding these migration processes is key in developmental biology and therapeutic approaches for neurodevelopmental disorders, an area highlighted by recent research in the field.

In summary, the orchestrated migration of cells from the ventricular zone during embryogenesis lays the groundwork for the brain's complex structure and function. The distinct timing of this migration significantly impacts the neural circuits' development and organization, shaping both the structural and functional maturation of the brain.

5. Conclusion

In this study, we have developed a computational simulation that integrates key aspects of neural progenitor cell migration, rich club network formation, and brain development, drawing upon

a wide array of neuroscientific research. Our model, grounded in principles of diffusion and Hebbian learning, offers a novel perspective on how simple cellular processes can lead to the formation of complex and efficient neural networks.

The simulation underscores the pivotal role of early neural progenitor migration, resonating with the findings of Rakic (2009) and Kriegstein & Alvarez-Buylla (2009), and highlights the emergence of rich club nodes as a potential mechanism for efficient information processing in the brain, aligning with the observations of Van den Heuvel & Sporns (2011) and Bullmore & Sporns (2009). This approach provides a computational framework for exploring the intricacies of neural network development and the formation of critical brain structures.

Importantly, the model also offers insights into how disruptions in these early developmental processes could lead to the formation of atypical network structures, contributing to our understanding of neurodevelopmental disorders. This aspect of the study is particularly relevant in the context of the work by Geschwind (2011) and De la Torre-Raya et al. (2016), emphasizing the importance of early brain development in neuropsychiatric conditions.

While the simulation provides a valuable tool for understanding complex neurodevelopmental processes, it is imperative to acknowledge its limitations, particularly in terms of the simplifications inherent in computational modeling. Future research should aim to incorporate more detailed biological data, explore the impact of various types of cell-cell interactions, and refine network formation algorithms to more closely mimic the biological reality of neural development.

This study contributes significantly to the field of computational neuroscience, offering a unique lens through which to view the early development of the brain. By synthesizing key concepts from a range of neuroscientific research, the simulation enhances our understanding of the fundamental processes that shape the brain's structure and function, paving the way for future research in this dynamic and vital field.

6. Attachment

Python Code

```
import numpy as np

import matplotlib.pyplot as plt

# Parameters

D = 0.01 # Diffusion coefficient for cell migration

eta = 0.05 # Learning rate for neural connections

delta = 0.01 # Decay rate for neural connections

time_steps = 100 # Total number of simulation steps

grid_size = 50 # Size of the simulation grid

num_neurons = 100 # Number of neurons

# Initialize cell concentration and neural connections
```

```
cell_concentration = np.random.rand(grid_size, grid_size)
neural_connections = np.random.rand(num_neurons, num_neurons)

def laplacian(Z):
    Ztop = np.roll(Z, -1, axis=0)
    Zleft = np.roll(Z, -1, axis=1)
    Zbottom = np.roll(Z, 1, axis=0)
    Zright = np.roll(Z, 1, axis=1)
    return (Ztop + Zleft + Zbottom + Zright - 4 * Z)/4.0

def update_concentration(concentration, D):
    # Apply diffusion equation to update cell concentration
    return concentration + D * laplacian(concentration)

def update_connections(connections, concentration, eta, delta):
    # Update neural connections based on Hebbian-like learning rule
    for i in range(num_neurons):
        for j in range(num_neurons):
            connections[i, j] += eta * concentration[i//(grid_size//num_neurons),
j//(grid_size//num_neurons)]
            connections[i, j] -= delta * connections[i, j]
    return connections

# Simulation loop
for t in range(time_steps):
    # Update cell concentration
    cell_concentration = update_concentration(cell_concentration, D)

    # Update neural connections
```

```
neural_connections = update_connections(neural_connections, cell_concentration, eta, delta)

# Visualization of final state (example)

plt.imshow(neural_connections, cmap='hot', interpolation='nearest')

plt.title("Neural Connection Strengths After Simulation")

plt.colorbar()

plt.show()
```

Conflicts of Interest: The Author declares no conflicts of interests.

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Sporns (2011, 2013) explores the structure and function of complex brain networks.

Sporns et al. (2005) introduce the concept of the human connectome, describing the brain's neural connections.

Swanson & Lichtman (2016) offer a historical perspective on our understanding of brain connectivity.

Van den Heuvel & Sporns (2011) explore network hubs in the human brain and their behavioral connections.

Zubieta et al. (2009) suggest that early connections by migrating neurons might seed rich club networks.

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