A deep dive into the origins of psychiatric disease: a multiscale perspective of nervous system organization

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The nervous system acts as a master controller of nearly all bodily functions, and is therefore at the center of human health.

The human nervous system is a complex network of cells that are capable of sending messages amongst each other, ultimately controlling movement, sensation, thought, emotion, and behavior. Cells in the nervous system are highly specialized. For instance, neurons are long-lived cells that are capable of transmitting chemical and electrical signals across large distances [1]. Its complexity is in large part attributed to intricate organization across multiple levels. The nervous system is organized at the level of molecules, to cells, to collections of cells forming distinct regions of the nervous system, including the peripheral and central nervous system. Understanding how these levels work together is essential for explaining normal brain function,shedding light on the origins of neurological disease, and opening new avenues for treatment. This review paper examines basic nervous system anatomy along with the diversity of brain cell types and molecules involved in neural communication. By exploring how disruptions in each level of complexity contribute to neurodevelopmental and psychiatric disorders, this paper builds an understanding of disease mechanisms affecting the nervous system.

The nervous system is heterogeneous and organized at multiple scales of size.

The human nervous system is anatomically heterogeneous, meaning it is made up of many different parts that work together. It is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and spinal cord and serves as the main control and integration center of the body [4]. The PNS consists of all nerves outside the CNS and relays sensory and motor information between the brain and the rest of the body through somatic (voluntary) and autonomic (involuntary) pathways [5]. The human brain is the most complex organ within our bodies and is crucial for human development and everyday functioning. The human brain is composed of the brainstem, cerebellum, cerebrum, and cerebral cortex. The brainstem connects the brain with the spinal cord and controls essential functions such as breathing and heart rate. The cerebellum, also known as “the little brain,” controls balance and coordination, while the cerebrum makes up most of the brain and includes the cerebral cortex [1]. The cerebral cortex is the outer layer of the cerebrum and is divided into four lobes. Each lobe is responsible for different functions. The frontal lobe controls movement, cognitive processes, social and emotional behavior, and speech production. The temporal lobe manages language comprehension and auditory processing. The parietal lobe is involved in sensory functions such as touch, spatial awareness, and pain, while the occipital lobe controls vision. The corpus callosum connects the left and right hemispheres of the brain, allowing for proper communication between both sides [1].

Without a functioning brain, human development would be severely limited and normal behavior would not be possible. Different regions of the brain carry out different tasks. The cerebrum is responsible for higher cognitive functions such as thinking and decision making, while the cerebellum primarily controls movement and coordination. Because of this organization, damage to specific regions can lead to specific deficits [4]. Injury to the frontal lobe may alter personality or decision making, cerebellar abnormalities can impair coordination and motor learning, and damage to the brainstem can disrupt vital autonomic processes like breathing. [2]

Neurodevelopmental diseases often involve underdevelopment of major brain structures. For example, problems with cerebellar development can affect movement and coordination. Prenatal infection with the Zika virus can also interfere with brain growth, causing microcephaly, where babies are born with smaller-than-normal brains. This happens because the virus damages developing brain cells, which can lead to long-term cognitive and motor difficulties [8]. Neurodevelopmental disorders demonstrate how proper organization of brain structures is crucial. Psychiatric and neurodevelopmental disease can also originate at different biological scales. Some disorders arise from macro-scale anatomical problems, when large brain regions fail to develop properly, such as when the cerebellum is too small or malformed, leading to impaired body function. Other conditions occur at a medium scale, when neurons fail to make the correct connections, disrupting neural circuits and information processing, as seen in autism spectrum disorder. Finally, disease can originate at the micro scale, at the level of synapses, where neurotransmitter imbalances or misfolded synaptic proteins contribute to disorders such as depression and schizophrenia [3].

Altogether, disease can emerge from larger-scale structural malfunctions, medium-scale circuit abnormalities, or small-scale synaptic dysfunction. While brain size and structure matter, especially when major regions do not develop properly, the plasticity of the nervous system is also critical, particularly early in life. This means the brain can sometimes adapt and compensate for structural problems. Because of this, understanding the nervous system at a large scale is important, since its overall organization supports how brain cells communicate and function.

The nervous system is composed of diverse cell types: a focus on glia.

At a cellular level, the brain is composed of neurons and glial cells, which communicate through electrical and chemical signals. On a molecular level, genes in the brain produce proteins that help shape neurons and regulate neurotransmitter release, allowing communication throughout the nervous system. Externally, the brain supports memory, thought, emotion, and other functions that allow humans to experience everyday life. There are many different types of cells found in the nervous system. Neurons are a class of cells that can carry electrical signals and make up the majority of the functional nervous system. However, support cells that are non-neuronal are equally important. In this paper, I choose to focus on reviewing glial cells because neuronal cell types have been thoroughly studied, while glial cell types lack sufficient investigation. Glial cells are a diverse group of non-neuronal cells that play an essential role in the nervous system. Broadly, glia support, regulate, and modulate neuronal function in both the central nervous system (CNS) and peripheral nervous system (PNS). While neurons are responsible for sending and receiving electrical signals, glial cells create the conditions that allow neurons to function properly. Therefore, to understand how the brain works in health and disease, it is necessary to understand both major classes of cells in the nervous system: those that send signals (neurons) and those that do not send signals but support and shape signaling (glia) [3]. Historically, more attention has been given to the roles for neurons in disease, however, glia potentially play an equally important role because of their ability to regulate electrical signaling.

Glial cells vary widely by location, shape, developmental origin, molecular composition, and function. This diversity allows different glial cell types to perform specialized roles that are essential for normal nervous system activity. Here, we review the types of glial cells and their known functions in regulating the nervous system. Astrocytes are the most abundant glial cells in the CNS and originate from neural precursors during development [2]. Structurally, astrocytes have many fine, branching processes that occupy distinct territories and closely interact with both neurons and blood vessels. This unique structure allows astrocytes to regulate molecular processes at the scale of individual neurons. One of their major roles is participation in the neurovascular unit, where they help regulate blood flow and energy metabolism in response to neuronal activity. Astrocytes are also critical for maintaining ion and water balance in the brain. They regulate extracellular potassium levels and control water movement through specialized ion and water channels, which is essential for preventing abnormal neuronal firing. In addition, astrocytes contribute to the formation, maintenance, and refinement of synapses [6]. Even though astrocytes are not electrically signaling, they play a direct role in which electrical signals take place because of their shaping of synapses. Although astrocytes were once considered passive, they are now recognized as major contributors to brain activity and information processing. Dysfunction of astrocytes has been linked to a range of neurological disorders, including epilepsy and neurodegenerative diseases, highlighting their importance in maintaining normal brain function [6].

A second class of glial cells are oligodendrocytes and Schwann cells, which are primarily responsible for myelinating axons needed for fast electrical signal transduction, in the central nervous system (CNS) and peripheral nervous system (PNS). Myelin is an insulating layer that wraps around axons and allows electrical signals to travel rapidly and efficiently along nerve fibers. Oligodendrocytes are capable of myelinating multiple axons at once, whereas Schwann cells typically myelinate only a single axon segment. In addition to insulation, myelin helps organize ion channels at gaps known as nodes of Ranvier, which further increases the speed of signal transmission. These glial cells also provide important metabolic support to axons, helping to maintain their long-term health. Dysfunction of myelinating glia is directly linked to disease. Multiple sclerosis (MS) is a CNS disorder characterized by immune-mediated damage to oligodendrocytes and myelin. This loss of myelin disrupts signal conduction, leading to symptoms such as muscle weakness, sensory disturbances, and impaired coordination. Studying oligodendrocytes and myelin biology has therefore been critical for understanding the mechanisms of MS and for developing therapeutic strategies aimed at protecting or restoring myelin. Similarly, diseases affecting Schwann cells in the PNS demonstrate how glial cell dysfunction can severely impair nervous system function. Guillain-Barré syndrome (GBS), is an autoimmune disorder that causes a rapid onset of weakness that can ultimately lead to hospitalization and dangerous paralysis/breathing difficulties [3].

Microglia are the resident immune cells of the brain and have distinct developmental features compared to other glial cells. They have a uniquely branched shape that allows them to constantly survey the brain environment for signs of injury or infection. When disease or injury occurs, microglia change shape and become activated. In this state, they help protect neurons by releasing signaling molecules, clearing cellular debris, and removing damaged cells. They also play essential roles in normal brain development by pruning synapses and shaping neural circuits. This synapse removal process helps refine neural connections and ensures efficient communication between neurons. Dysregulation of microglial activity has been seen in neurodevelopmental and neurodegenerative disorders, emphasizing their role in maintaining brain health and their potential use for therapeutic purposes [3].

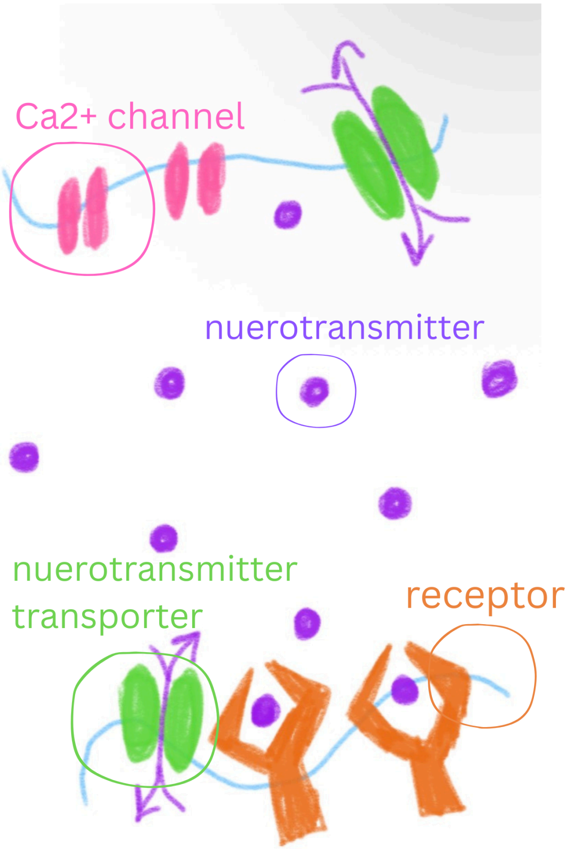
Overall, acknowledging glial cell classes is critical to understanding disease in the nervous system. Because glial cells actively influence neuronal health, connections, and communication, their dysfunction can lead directly to neurological disease. Modern scientific techniques have revealed that different glial cell types possess unique molecular and protein shapes/structures that reflect their specialized functions. Although studying glial cells remains technically challenging, continued research into their roles is essential for developing a more complete understanding of brain function and finding new treatments for neurological disorders.

Neurotransmitters' impact on psychiatric diseases: disruptions in the synapse.

Psychiatric disorders develop frequently from disruptions in neurotransmitter signalling at the molecular and synaptic level. Neurotransmitters are the chemical messengers that enable neurons to communicate, and their precise regulation is essential for maintaining normal cognition, mood and behavior. When neurotransmitter release, receptor binding, or signal termination is altered, neural communication can become dysregulated, leading to abnormal circuit activity underlying many psychiatric and neurodevelopmental disorders. Neurotransmitters are released by neurons and travel across synapses to bind with receptor sites on adjacent neurons. Once bound to these receptors, neurotransmitters either trigger or inhibit electrical signals, determining how the brain processes information and regulates various bodily functions.

Neurotransmitters are generally categorized as either excitatory, stimulating brain activity, or inhibitory, calming brain activity. However, neurotransmitters can produce either excitatory or inhibitory effects depending on the specific receptors they bind to. At a synapse, the presynaptic neuron is responsible for sending the signal, while the postsynaptic neuron receives the signal. Neurotransmitter signaling is terminated through a process known as reuptake, in which specific transporter proteins remove neurotransmitters from the synaptic cleft and end the synaptic action, or through enzyme based degradation. Smaller molecular changes like altered transporter efficiency, receptor sensitivity or synthesis rates can significantly impact brain function [6].

Figure 1. An overview of the synaptic cleft



Caption: Pictured above is the synaptic cleft, in which messages are transferred between two neurons, signified by the blue lines. The pink figures in the top left are the Ca2+ channels, where neurons' action potentials are translated into chemical signals which are then able to be transferred. The purple figures are neurotransmitters, which are how the chemical messages are sent between the neurons into the receptors, which are the orange figures. The receptors bind the neurotransmitters to trigger inhibitory/excitatory responses, while the green figures, neurotransmitter transporters, terminate the transmitters once they have completed their signal for reuse.

Disorders such as depression, anxiety, schizophrenia, ADHD and other neurodevelopmental conditions have all been linked to imbalances in key neurotransmitter systems. Psychiatric disorders are not caused by a single neurotransmitter imbalance, but rather by disruptions in multiple molecular signaling pathways that affect neural circuits. Changes in neurotransmitter synthesis, release, receptor binding, or reuptake can interfere with normal brain communication and lead to abnormal cognition and behavior. The following sections focus on major neurotransmitters involved in psychiatric and neurodevelopmental disorders and explain how their molecular dysfunction contributes to diseases.

Serotonin is the neurotransmitter mainly regulating the human mood and other mental health disorders in relation to depression and anxiety. Molecularly, serotonin is a monoamine neurotransmitter, meaning it's a small organic molecule synthesized with the amino acid tryptophan. This neurotransmitter is found across the body, with 90% being in the gut, as well as through the central nervous system and within blood platelets. Serotonin is released from presynaptic neurons, crossing the synaptic cleft, and binds to specific serotonin receptors across postsynaptic neurons/cells, triggering different effects. The serotonin transporter protein SERT, removes the neurotransmitter from the synapses to terminate the signal. Serotonin stabilizes our moods, promoting calmness and regulating balance-oriented functions such as sleep and digestion, differentiating itself from other neurotransmitters by having both excitatory and inhibitory effects (as a regulatory neurotransmitter). [7]

Dopamine is the neurotransmitter that the brain is dependent on for its reward and pleasure systems. It is another regulatory catecholamine, meaning it has both excitatory and inhibitory effects. Since it regulates motor functions such as motivation and attention, its levels fluctuate in response to rewarding stimuli that enhance its effects (such as eating, socializing or achieving a goal). Molecularly, dopamine is a catecholamine neurotransmitter, meaning it's a monamine with catechol structure, initially composed of the amino acid tyrosine. This amino acid is converted toL-DOPA by an enzyme and then loses a carboxyl group to form the neurotransmitter. Dopamine is located in vesicles (where it is stored) and released into synapses by binding its receptors on other neurons, triggering different signals. The dopamine transporter (DAT) removes the neurotransmitter from the synapse to terminate the signal, or it is broken down. As stated prior, dopamine is different from other neurotransmitters because it is a regulatory monamine that can have stimulating or calming effects. [7]

Norepinephrine is the brain's stress response regulator, a neurotransmitter involved in the body's fight-or-flight response. In response to stressful situations, norepinephrine increases heart rate, blood pressure, and energy levels. Molecularly, norepinephrine, also known as noradrenaline, is another monoamine, also formed from the amino acid tyrosine. The structure of this neurotransmitter is both similar to dopamine and adrenaline, following the initial phases of dopamine structure and then finally being hydroxylated into its own neurotransmitter. Norepinephrine can be found in the central nervous system while acting as a neurotransmitter. While working in synapses, this monoamine binds to alpha and beta adrenergic receptors, and then the signal is terminated by NET transporter or degraded by enzymes. Norepinephrine is different from other neurotransmitters as it acts as both a major neurotransmitter acting on brain focus and alertness, as well as a hormone dictating fight-or-flight responses. [7]

Acetylcholine is a neurotransmitter that assists the body's memory formation, learning and attention, essential in cognitive processes and heavily involved in both the central and peripheral nervous systems. This neurotransmitter regulates functions like muscle contractions and heart rate, as well as having other cognitive roles. Molecularly, acetylcholine is a small organic molecule known as an ester, made of acetic acid and choline. It transmits nerve impulses across synapses, bridging communication between nerve cells and target cells, and its receptors are between two types: nicotinic (often excitatory) and muscarinic (both excitatory or inhibitory). When this neurotransmitter binds, it triggers a response, such as muscle contraction or slowed heart rate. Acetylcholine's synaptic actions are terminated by enzymes breaking down, rather than reuptake, which is common to many monoamine neurotransmitters. This neurotransmitter is different from others as it was the first one discovered, synthesized by dietary choline, acting at both neuromuscular junctions and in the brain. [7]

GABA, shortened from Gamma-Aminobutyric Acid, is the primary inhibitory neurotransmitter in the brain. This non-protein amino acid calms neural activity and assists in reducing anxiety and promoting relaxation. Its inhibitory functions allow it to calm the overexcessive brain activity that is stimulated from other external sources. Molecularly, GABA is distinct from other protein-building amino acids because of its structure, and is synthesized in the brain from the excitatory neurotransmitter glutamate (another amino acid), by the enzyme glutamic acid decarboxylase. Synaptically, this acid binds to GABA-A AND GABA-B receptors on the receiving neurons, and these receptors inhibit action potential from within the neuron or trigger slower, longer-lasting inhibitory effects through their proteins. By slowing down ion flow with its receptors, GABA inhibits nerve impulses, reducing overall brain activity. GABA is terminated by enzymes as well as reuptake into the presynaptic neuron/nearby glial cells. This amino acid is different from others as it is the primary inhibitory non-protein neurotransmitter, and works to inhibit/slow excitatory neurotransmitter signals/actions. [7]

Glutamate is an excitatory neurotransmitter, and the primary amino acid involved in learning, memory and cognitive function. This amino acid is crucial in synaptic plasticity, which is the process that involves neural connections weakening/strengthening over time, key for learning and adapting to new information. Molecularly, this amino acid is acidic, due to its extra carboxyl group on its side chain. Glutamate is synthesized in the brain from precursors like glutamine, and packaged into vesicles and released into synapses. It binds to various receptors such as AMPA/NMDA on the postsynaptic neuron, making the neurotransmitter more likely to fire, exciting the next cell. This reaction causes most excitatory signals in the brain, and assists in strengthening connections that underlie memory formation. Glutamate differs from other neurotransmitters because it's the primary excitatory neurotransmitter, in contrast to the inhibitory amino acid GABA. [7]

Conclusion/Discussion:

Overall, psychiatric and neurodevelopmental diseases highlight the multiscale organization of the nervous system. Normal brain function depends on coordinated processes within the nervous systems, including within glial cells and neurotransmitters. Disruptions at micro, medium and macro levels can interfere with neural communication and ultimately produce disease. Large-scale abnormalities in brain development can alter the organization of major brain regions, while cellular dysfunction in neurons or glial cells can disrupt circuits that regulate behavior and cognition. At the smallest scale, molecular changes affecting neurotransmitter release, receptor activity, or synaptic protein function can further destabilize communication between neurons.

Because these biological levels are interconnected, effective treatments for psychiatric disease must also consider multiple scales of nervous system organization. Future therapeutic research should therefore combine molecular approaches targeting neurotransmitter systems with methods that assess cellular activity and structural brain organization. Integrating this interdependence will be critical for developing more effective strategies to understand and treat disorders of the nervous system.

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