International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Polytherapy in Drug-Resistant Epilepsy: Cellular and Molecular Mechanisms Underlying Cognitive Outcomes

Manasa Sankara Narayanan

School name: Greenwood High International School
Email: *manasa.msn9[at]gmail.com*

Abstract: ***Epilepsy is a chronic neurological disorder characterized by recurrent seizures and is frequently associated with long-term cognitive impairment. While monotherapy remains the first-line treatment, approximately one-third of patients develop drug-resistant epilepsy and require polytherapy with multiple antiepileptic drugs. Although polytherapy can improve seizure control, combined pharmacological exposure may influence cognitive function through effects on neurotransmission, synaptic plasticity, neurotrophic signaling, metabolic regulation, and neural network stability. This review examines the cellular and molecular foundations of cognition, the mechanisms by which epileptic activity disrupts these processes, and how polytherapy may further modify cognitive outcomes. By integrating evidence on neural signaling, plasticity, and network-level changes, this review highlights the need to balance seizure suppression with preservation of cognitive function. Understanding these mechanisms is essential for guiding rational treatment strategies and improving quality of life in individuals with drug-resistant epilepsy.***

Keywords: Epilepsy; Polytherapy; Antiepileptic drugs; Cognitive function; Synaptic plasticity; Neurotransmission; Neurotrophic signaling; Network connectivity

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, spontaneous seizures that arise from an imbalance between excitatory and inhibitory neuronal signaling. It is one of the most prevalent neurological disorders globally, affecting over 50 million individuals across diverse age groups and socioeconomic backgrounds (World Health Organization, 2023). Beyond seizure activity, epilepsy is associated with increased risks of premature mortality, psychiatric comorbidities, and long-term consequences for social and emotional well-being (Devinsky et al., 2018). For patients, epilepsy is not limited to episodic seizure events but represents a chronic condition that can interfere with education, employment, social relationships, and independence in daily life. This underscores the need for research that extends beyond seizure suppression to include broader quality of life outcomes.

The first-line treatment strategy for epilepsy typically involves monotherapy, defined as the use of a single antiepileptic drug (AED). Despite careful drug selection and dose optimization, approximately one-third of patients continue to experience seizures and are classified as drug-resistant (Kwan and Brodie, 2000; Chen et al., 2018). In such cases, clinical management often shifts toward polytherapy, which combines two or more AEDs with complementary mechanisms of action. While polytherapy can improve seizure control, the increased pharmacological load introduces complexity. Adjustments to one medication can intensify adverse effects of others, complicating the balance between therapeutic efficacy and patient safety.

Cognitive impairment is a well-documented feature of epilepsy, affecting domains such as attention, memory, executive function, and processing speed, even when seizures are partially controlled (Hermann et al., 2007; Holmes, 2015). The cognitive effects of polytherapy remain incompletely understood, particularly because it is difficult to separate impairments caused by epileptic activity from those arising due to medication interactions (Mula and Trimble, 2009). Factors such as AED mechanisms of action, pharmacokinetic interactions, and underlying neural pathology all contribute to variability in cognitive outcomes (Lagae, 2014). While seizure suppression remains the primary treatment goal, preserving cognitive function is essential for long-term patient well-being.

In this context, this review examines how polytherapy influences the cellular and molecular mechanisms underlying cognitive function in epilepsy. It aims to distinguish the therapeutic benefits of polytherapy for seizure control from its potential risks to neurocognitive health. The review first outlines the biological foundations of cognition, then explores how epilepsy disrupts these processes, and finally evaluates how polytherapy may further modify them. By synthesizing current evidence, this review provides a framework for understanding the cognitive implications of polytherapy and for guiding treatment strategies that balance seizure control with cognitive preservation.

2. Background

Epilepsy is defined as a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal, synchronous neuronal activity (Fisher et al., 2014). Seizures are classified as focal, generalized, or of unknown onset, reflecting differences in their spatial origin and underlying neural networks (Scheffer et al., 2017). The disorder arises from a wide range of etiologies, including genetic mutations, structural brain abnormalities, metabolic dysfunction, immune-mediated conditions, infections, and idiopathic causes. This etiological diversity contributes to

variability in clinical presentation and treatment response (Shorvon, 2011; Devinsky et al., 2018).

Globally, epilepsy affects more than 50 million individuals, with incidence rates highest during early childhood and late adulthood (World Health Organization, 2023). In addition to the immediate risks posed by seizures, epilepsy is associated with elevated rates of premature mortality, including sudden unexpected death in epilepsy and seizure-related injuries (Hesdorffer et al., 2011; Devinsky, 2011). The burden of epilepsy extends beyond seizure activity, encompassing cognitive, psychological, social, and functional impairments. These outcomes highlight that seizure suppression alone is insufficient to fully address the disorder's impact (Kwan and Brodie, 2000; Bell et al., 2011).

At the cellular level, epileptogenesis involves disruption of the balance between excitatory glutamatergic and inhibitory GABAergic signaling, leading to persistent network hyperexcitability (Staley, 2015). This imbalance is further amplified by altered receptor expression, dysfunctional voltage-gated ion channels, and disrupted intracellular signaling pathways (Noebels, 2015). Pathological activity can propagate through hippocampal circuits, thalamocortical networks, and broader cortical and subcortical systems, accounting for the heterogeneity of seizure types and clinical manifestations (Löscher et al., 2020).

Epilepsy also has substantial effects on cognitive function, including impairments in attention, memory, executive function, and processing speed, even in patients with controlled seizures (Holmes, 2015; Hermann et al., 2007). Psychiatric comorbidities, particularly anxiety and depression, further exacerbate cognitive dysfunction and reduce quality of life (Mula and Schmitz, 2009; Kanner, 2016). These deficits arise from interactions between underlying neuropathology and seizure-induced disruptions of cellular homeostasis, synaptic plasticity, and network connectivity (Bernhardt et al., 2015). Collectively, these findings position epilepsy as a disorder with systemic neurocognitive consequences rather than solely a seizure condition.

3. Foundations of Cognitive Function

Cognitive function arises from the coordinated activity of cellular, molecular, and network-level processes that support information processing, learning, and memory (Kandel et al., 2014). These processes depend on stable excitatory-inhibitory balance, efficient synaptic communication, and adaptive plasticity mechanisms. Understanding these foundations is essential before examining how epilepsy and its treatments influence cognition.

3.1 Cellular and Molecular Mechanisms Supporting Cognition

At the cellular level, cognition relies on neurotransmitter-mediated communication between neurons. Glutamate and gamma-aminobutyric acid (GABA) serve as the primary excitatory and inhibitory neurotransmitters, respectively. Glutamatergic transmission strengthens synaptic connections and facilitates information flow across neural circuits, while GABAergic inhibition stabilizes network activity by preventing excessive neuronal firing (Isaacson and Scanziani, 2011). Maintaining equilibrium between these systems is critical for accurate information processing and network stability (Turrigiano, 2012).

Ion channels and receptor subtypes further regulate neural signaling. Voltage-gated sodium, potassium, and calcium channels control action potential initiation and propagation, while synaptic receptors such as AMPA, NMDA, and GABA_A receptors mediate excitatory and inhibitory transmission (Hille, 2001; Traynelis et al., 2010). These components enable synaptic plasticity, including long-term potentiation and long-term depression, which form the cellular basis of learning and memory (Malenka and Bear, 2004; Bliss and Collingridge, 2013). Disruption of these mechanisms impairs experience-dependent synaptic modification and contributes to cognitive deficits in neurological conditions (Neves et al., 2008).

Neurotrophic factors also play a key role in cognitive function. Brain-derived neurotrophic factor supports neuronal survival, dendritic growth, synaptic maintenance, and activity-dependent plasticity, linking molecular signaling to long-term network reorganization (Binder and Scharfman, 2004; Park and Poo, 2013; Lu et al., 2013). Deficits in neurotrophic signaling can impair learning and memory and increase susceptibility to neurological disorders, including epilepsy.

Cognitive processing is metabolically demanding, requiring efficient mitochondrial function to sustain synaptic transmission and plasticity. Neurons rely heavily on ATP production and oxidative stress regulation to maintain signaling fidelity. Disruptions in mitochondrial function can compromise synaptic communication and contribute to cognitive decline (Kann and Kovács, 2007; Harris et al., 2012).

3.2 Brain Circuits and Regions Underlying Cognition

Cognition depends on the coordinated activity of distributed neural networks. The hippocampus plays a central role in episodic memory formation and spatial navigation, supported by synaptic plasticity mechanisms such as long-term potentiation (O'Keefe and Nadel, 1978; Bliss and Collingridge, 2013). The prefrontal cortex supports executive functions, including working memory, planning, and decision-making, by integrating information from cortical and subcortical regions (Miller and Cohen, 2001).

Thalamocortical circuits regulate attention and sensory processing by coordinating rhythmic communication between the thalamus and cortex (Sherman, 2016). Disruption of these circuits is associated with attentional deficits and slowed cognitive processing. Additional networks, such as the default mode network, support internally directed cognition, including memory retrieval and self-referential processing, and rely on coordinated metabolic and rhythmic activity (Raichle et al., 2001; Buckner et al., 2008).

Subcortical structures, including the basal ganglia and cerebellum, contribute to procedural learning, cognitive

flexibility, and temporal processing. The cerebellum supports predictive timing and error correction across motor and cognitive tasks, while basal ganglia circuits influence action selection and reinforcement learning through corticostriatal loops (Ito, 2008; D'Angelo and Casali, 2013). Effective communication between these regions depends on white matter integrity and myelination, which determine conduction speed and network synchrony. Disruption of these pathways reduces processing efficiency and cognitive performance (Fields, 2008; Bartzokis, 2011).

3.3 Developmental Considerations

Brain development plays a critical role in shaping cognitive vulnerability in epilepsy. During childhood and adolescence, synaptogenesis, dendritic arborization, and myelination establish the structural and functional foundations for learning, memory, and executive function (Huttenlocher and Dabholkar, 1997; Tau and Peterson, 2010). These processes occur on different developmental timelines, with prefrontal cortical maturation extending into late adolescence, while hippocampal and sensory regions mature earlier (Gogtay et al., 2004; Casey et al., 2005).

During sensitive developmental periods, neural circuits are particularly plastic and responsive to environmental input. Disruption by epileptic activity during these windows can produce long-lasting cognitive impairments. Early-onset epilepsy is associated with greater deficits in memory, attention, and language compared to later-onset seizures (Berg et al., 2010; Hermann et al., 2006). These outcomes reflect interference with network refinement, synaptic pruning, and plasticity dynamics (Ben-Ari, 2006; Holmes, 2015).

Genetic, epigenetic, and environmental factors further contribute to individual variability in cognitive development and recovery. This variability underscores the importance of personalized treatment approaches, particularly when considering polytherapy in pediatric epilepsy (Johnson et al., 2008; Lenroot and Giedd, 2006).

4. Epilepsy as a Disruptor of Cognitive and Cellular Function

Epilepsy disrupts the cellular and circuit-level foundations of cognition, affecting attention, memory, and executive function. At the network level, seizure activity propagates through hippocampal-prefrontal and thalamocortical circuits, impairing neural connectivity and destabilizing coordinated information processing (Bernhardt et al., 2015; Keller et al., 2014). These disruptions produce both transient cognitive impairments during ictal periods and persistent deficits during interictal states (Berg et al., 2010; Kobayashi and Buckmaster, 2003). Understanding these effects provides essential context for evaluating how treatment strategies, including polytherapy, influence cognitive outcomes.

4.1 Cognitive Impairments in Epilepsy

Cognitive impairments are common in epilepsy and involve multiple domains, including attention, memory, and executive function (Helmstaedter, 2002; Aldenkamp and Arends, 2004). Attention deficits may affect sustained, selective, and divided attention, particularly in temporal and frontal lobe epilepsy, where attentional networks are disrupted (Meador et al., 2003; Hermann et al., 2006). Memory dysfunction is also prevalent. Working memory impairments reduce the ability to process and retain information, while episodic memory deficits are frequently observed due to hippocampal involvement (Bell et al., 2011; Helmstaedter et al., 2014). Procedural and spatial memory can also be affected when both cortical and subcortical networks are involved (Lah and Smith, 2012).

Executive dysfunction is another significant cognitive consequence of epilepsy. Individuals may show reduced cognitive flexibility, impaired planning and decision-making, weakened inhibitory control, and difficulty with problem-solving and multitasking (Li et al., 2019; Martin et al., 2017). These impairments are linked to dysfunction of prefrontal circuits and their interactions with hippocampal and basal ganglia networks. In addition, temporal lobe epilepsy can affect language processing and verbal communication, while chronic seizure activity is associated with impaired social cognition, including emotion recognition and theory of mind (Giovagnoli et al., 2016; Bora et al., 2016).

The severity of cognitive impairment varies across individuals and is influenced by seizure type, frequency, age of onset, and the specific brain regions involved (Bell et al., 2011; Hermann et al., 2006). These variations emphasize the need to consider individual neurobiological profiles when evaluating cognitive outcomes and treatment effects.

4.2 Brain Regions and Circuits Affected by Epileptic Activity

Epileptic activity affects specific brain regions and circuits that support cognition. The hippocampus is particularly vulnerable to seizure-related injury, resulting in deficits in episodic memory and spatial learning (Liu et al., 2013; Leite et al., 2015). At the cellular level, seizures disrupt long-term potentiation and depression, alter dendritic spine structure, and impair synaptic coordination, collectively reducing the hippocampus's ability to encode and consolidate new information (Kobayashi and Buckmaster, 2003; Cavarsan et al., 2018).

The prefrontal cortex is also affected by epilepsy, either through direct seizure propagation or through chronic network instability. Disruption of prefrontal circuits impairs executive functions such as working memory, planning, and behavioral regulation (Paz and Huguenard, 2015; Taylor et al., 2018). Similarly, abnormal synchronization within thalamocortical circuits alters sensory integration and attentional control, leading to reduced processing speed and attentional capacity (Huguenard and McCormick, 2007; Blumenfeld, 2012).

Focal epilepsies involving temporal and parietal lobes can disrupt language and visuospatial processing. These deficits arise from both localized circuit dysfunction and broader network-level reorganization (Drane et al., 2013; Bernhardt et al., 2015). Chronic epilepsy is also associated with altered connectivity between the hippocampus and neocortex, further

impairing cognitive integration (Liu et al., 2017; Vaessen et al., 2013).

4.3 Cellular and Molecular Disruption by Seizures

At the cellular and molecular level, epileptic activity disrupts neurotransmission, synaptic plasticity, and neuronal homeostasis. Hyperexcitability results from impaired balance between excitation and inhibition, weakening circuit stability and cognitive processing (Trevelyan and Schevon, 2013; Isaacson and Scanziani, 2011). Ion channel dysfunction, whether genetically determined or seizure-induced, alters voltage-gated sodium, potassium, and calcium channel activity, leading to abnormal firing patterns and increased excitability (Catterall, 2014; Zamponi et al., 2015).

Synaptic plasticity is also impaired. Seizures disrupt long-term potentiation and depression, reduce dendritic spine density, and alter receptor distribution, collectively diminishing synaptic efficiency (Kobayashi and Buckmaster, 2003; Cavarsan et al., 2018). Altered neurotrophic signaling, particularly involving brain-derived neurotrophic factor, further limits synaptic repair and activity-dependent plasticity (Binder and Scharfman, 2004; Park and Poo, 2013).

Epileptic activity also affects metabolic stability. Mitochondrial dysfunction, oxidative stress, and reduced ATP availability limit the energetic support required for sustained neuronal signaling (Kann and Kovács, 2007; Harris et al., 2012). Chronic neuroinflammation and gliosis contribute to long-term structural and functional changes by altering synaptic pruning and releasing inflammatory mediators that affect network stability (Vezzani et al., 2011; Devinsky et al., 2013).

4.4 Long-Term Structural and Functional Consequences

Recurrent seizures lead to lasting structural and functional changes that contribute to progressive cognitive decline. Neuronal loss occurs in regions such as the hippocampus, cortex, and thalamus due to excitotoxic mechanisms driven by excessive glutamatergic activity (Fujikawa, 1996; Meldrum, 1993). This loss disrupts local circuit stability and reduces the brain's capacity for compensatory reorganization.

Seizures also induce maladaptive network reorganization, including aberrant axonal sprouting and synaptic rearrangement, which further impair circuit function (Sutula and Dudek, 2007; Morgan and Soltesz, 2008). Reactive gliosis alters extracellular ionic balance and neurotransmitter clearance, increasing neuronal hyperexcitability and reinforcing pathological network dynamics (Engel et al., 2013; Vezzani et al., 2011). These combined effects contribute to persistent impairments in memory, attention, and executive function.

4.5 Implications for Treatment and Cognitive Outcomes

Epilepsy alters the biological context in which treatments act, shaping both therapeutic efficacy and side-effect profiles. By disrupting neurotransmission, plasticity, and network communication, epilepsy increases cognitive vulnerability. Some antiepileptic drugs can improve cognition indirectly by reducing seizure burden and restoring network stability (Meador, 2002; Loring et al., 2007). However, other drugs, particularly in combination, may worsen cognitive performance by slowing processing speed or impairing attention and memory (Mula and Trimble, 2009; Aldenkamp and Arends, 2004).

Surgical interventions provide an alternative treatment approach by removing seizure-generating regions. Cognitive outcomes following surgery depend on the resected areas and pre-existing network damage. Successful seizure control can lead to improvements in cognitive function and quality of life, although specific deficits may occur depending on the surgical site (Helmstaedter et al., 2008; Baxendale et al., 2012).

5. When and Why Polytherapy is Used

Understanding how epilepsy disrupts cognition provides a framework for evaluating treatment strategies. Antiepileptic therapies target many of the same cellular and molecular mechanisms altered by seizures, including neurotransmission, synaptic plasticity, and metabolic regulation. As a result, treatment decisions must consider both seizure control and cognitive impact.

5.1 Principles of Antiseizure Therapy

The primary goal of antiseizure treatment is complete seizure control with minimal cognitive and physiological side effects. Monotherapy is preferred because it simplifies pharmacokinetic management, reduces drug interactions, and minimizes cognitive burden (Brodie and Kwan, 2012; Perucca, 2005). Approximately two-thirds of patients achieve sustained seizure control with appropriately selected monotherapy, often with minimal cognitive disruption.

When monotherapy is effective, patients typically report stable attention, memory, and executive function. Polytherapy is therefore reserved for cases in which monotherapy fails, particularly in drug-resistant epilepsy, where seizure suppression requires combined pharmacological mechanisms.

5.2 When Polytherapy Becomes Necessary

Polytherapy is often required in patients with mixed seizure types or refractory epilepsy. Combining drugs with complementary mechanisms can enhance seizure suppression while allowing lower doses of individual medications. This approach, known as rational polytherapy, aims to reduce seizure frequency while limiting adverse effects (Ryvlin et al., 2014; Mula and Trimble, 2009).

However, polytherapy increases the risk of pharmacokinetic and pharmacodynamic interactions. Combined drug exposure can intensify side effects, disrupt metabolic processing, and increase cognitive fatigue. The altered cellular environment in drug-resistant epilepsy, including changes in receptor expression and network excitability, further contributes to variable treatment responses (Löscher and Schmidt, 2011; Noebels, 2015).

6. Conclusion

Epilepsy is a complex neurological disorder that extends beyond recurrent seizures to include persistent cognitive and psychosocial consequences. Disruptions in excitatory and inhibitory balance, synaptic plasticity, neurotrophic signaling, metabolic stability, and large-scale neural networks contribute to impairments in attention, memory, executive function, and processing speed. These mechanisms form the biological foundation through which epileptic activity alters cognition.

Polytherapy remains an essential treatment strategy for individuals with drug-resistant epilepsy when monotherapy fails to provide adequate seizure control. By combining antiepileptic drugs with complementary mechanisms of action, polytherapy can reduce seizure frequency and stabilize hyperexcitable networks. However, because antiepileptic drugs act on the same cellular and molecular systems that support cognitive function, combined pharmacological exposure may also increase cognitive burden through additive effects on neurotransmission, plasticity, metabolic regulation, and network coordination.

The cognitive outcome of polytherapy is therefore shaped by a balance between seizure suppression and drug-related effects. In some patients, improved seizure control may support cognitive stability, while in others, increased pharmacological load may exacerbate existing cognitive vulnerabilities. Factors such as seizure type, age of onset, brain regions involved, developmental stage, and individual neurobiological variability play a critical role in determining these outcomes.

Understanding the cellular and molecular mechanisms linking epilepsy, cognition, and polytherapy is essential for guiding rational treatment decisions. Careful drug selection, dose optimization, and ongoing cognitive monitoring are necessary to minimize adverse effects while maintaining seizure control. Future research should focus on clarifying how specific drug combinations influence synaptic plasticity, neurotrophic signaling, and network dynamics, with the aim of developing treatment strategies that preserve cognitive function alongside effective seizure management.

References

[1] World Health Organization. *Epilepsy*. WHO Fact Sheet, 2023.
[2] Devinsky O, Vezzani A, O'Brien T, Jette N, Scheffer I, de Curtis M, Perucca P. Epilepsy. *Nature Reviews Disease Primers*. 2018; 4: 18024.
[3] Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine*. 2000;342(5):314–319.
[4] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs. *JAMA Neurology*. 2018;75(3):279–286.
[5] Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: Potential mechanisms and contributing factors. *CNS Drugs*. 2009;23(2):121–137.
[6] Lagae L. Cognitive side effects of antiepileptic drugs. *Seizure*. 2014;23(9):591–597.
[7] Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475–482.
[8] Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper. *Epilepsia*. 2017;58(4):512–521.
[9] Shorvon SD. The causes of epilepsy: Changing concepts of etiology of epilepsy over the past 150 years. *Epilepsia*. 2011;52(6):1033–1044.
[10] Hesdorffer DC, Tomson T, Benn E, et al. Combined analysis of risk factors for sudden unexpected death in epilepsy. *Epilepsia*. 2011;52(6):1150–1159.
[11] Devinsky O. Sudden, unexpected death in epilepsy. *New England Journal of Medicine*. 2011;365(19):1801–1811.
[12] Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood-onset epilepsy on brain and cognition. *Epilepsia*. 2007;48(Suppl 9):S1–S7.
[13] Holmes GL. Cognitive impairment in epilepsy: The role of network abnormalities. *Epileptic Disorders*. 2015;17(2):101–116.
[14] Bernhardt BC, Bonilha L, Gross DW. Network analysis for a network disorder: The emerging role of graph theory in the study of epilepsy. *Epilepsy & Behavior*. 2015;50:162–170.
[15] Staley K. Molecular mechanisms of epilepsy. *Nature Neuroscience*. 2015;18(3):367–372.
[16] Noebels JL. Pathway-driven discovery of epilepsy genes. *Nature Neuroscience*. 2015;18(3):344–350.
[17] Löscher W, Klein P, Schmidt D. The clinical impact of pharmacoresistance in epilepsy. *Epilepsia*. 2020;61(11):2165–2178.
[18] Bell B, Lin JJ, Seidenberg M, Hermann B. The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nature Reviews Neurology*. 2011;7(3):154–164.
[19] Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. *Principles of Neural Science*. 5th ed. New York: McGraw-Hill; 2014.
[20] Isaacson JS, Scanziani M. How inhibition shapes cortical activity. *Neuron*. 2011;72(2):231–243.
[21] Turrigiano G. Homeostatic synaptic plasticity: Local and global mechanisms for stabilizing neuronal function. *Cold Spring Harbor Perspectives in Biology*. 2012;4(1):a005736.
[22] Hille B. *Ion Channels of Excitable Membranes*. 3rd ed. Sunderland, MA: Sinauer Associates; 2001.
[23] Traynelis SF, Wollmuth LP, McBain CJ, et al. Glutamate receptor ion channels: Structure, regulation, and function. *Pharmacological Reviews*. 2010;62(3):405–496.
[24] Malenka RC, Bear MF. LTP and LTD: An embarrassment of riches. *Neuron*. 2004;44(1):5–21.
[25] Bliss TVP, Collingridge GL. Expression of NMDA receptor-dependent LTP in the hippocampus. *Nature*. 2013;361:31–39.
[26] Neves G, Cooke SF, Bliss TVP. Synaptic plasticity, memory and the hippocampus. *Nature Reviews Neuroscience*. 2008;9(1):65–75.

[27] Binder DK, Scharfman HE. Brain-derived neurotrophic factor. *Growth Factors*. 2004;22(3):123–131.
[28] Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. *Nature Reviews Neuroscience*. 2013;14(1):7–23.
[29] Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy. *Nature Reviews Neuroscience*. 2013;14(6):401–416.
[30] Kann O, Kovács R. Mitochondria and neuronal activity. *American Journal of Physiology*. 2007;292(2):C641–C657.
[31] Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. *Neuron*. 2012;75(5):762–777.
[32] O'Keefe J, Nadel L. *The Hippocampus as a Cognitive Map*. Oxford: Oxford University Press; 1978.
[33] Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*. 2001;24:167–202.
[34] Sherman SM. Thalamus plays a central role in ongoing cortical functioning. *Nature Neuroscience*. 2016;19(4):533–541.
[35] Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proceedings of the National Academy of Sciences USA*. 2001;98(2):676–682.
[36] Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network. *Annals of the New York Academy of Sciences*. 2008; 1124:1–38.
[37] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*. 1997;387(2):167–178.
[38] Tau GZ, Peterson BS. Normal development of brain circuits. *Neuropsychopharmacology*. 2010;35(1):147–168.
[39] Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development. *Proceedings of the National Academy of Sciences USA*. 2004;101(21):8174–8179.
[40] Casey BJ, Tottenham N, Liston C, Durston S. Imaging the developing brain. *Trends in Cognitive Sciences*. 2005;9(3):104–110.