Published in final edited form as:

Neuroscientist. 2016 June ; 22(3): 295–312. doi:10.1177/1073858415585108.

From Molecular Circuit Dysfunction to Disease: Case Studies in Epilepsy, Traumatic Brain Injury, and Alzheimer's Disease

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Abstract

Complex circuitry with feed-forward and feed-back systems regulate neuronal activity throughout the brain. Cell biological, electrical, and neurotransmitter systems enable neural networks to process and drive the entire spectrum of cognitive, behavioral, and motor functions. Simultaneous orchestration of distinct cells and interconnected neural circuits relies on hundreds, if not thousands, of unique molecular interactions. Even single molecule dysfunctions can be disrupting to neural circuit activity, leading to neurological pathology. Here, we sample our current understanding of how molecular aberrations lead to disruptions in networks using three neurological pathologies as exemplars: epilepsy, traumatic brain injury (TBI), and Alzheimer's disease (AD). Epilepsy provides a window into how total destabilization of network balance can occur. TBI is an abrupt physical disruption that manifests in both acute and chronic neurological deficits. Last, in AD progressive cell loss leads to devastating cognitive consequences. Interestingly, all three of these neurological diseases are interrelated. The goal of this review, therefore, is to identify molecular changes that may lead to network dysfunction, elaborate on how altered network activity and circuit structure can contribute to neurological disease, and suggest common threads that may lie at the heart of molecular circuit dysfunction.

Keywords

epilepsy; traumatic brain injury; Alzheimer's disease; molecular dysfunction; circuits

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Introduction

Understanding neural circuits (groups of synaptically connected neurons acting together to perform a specific function) has become a focus of neuroscience research. How does the brain orchestrate the activity of electrically and structurally diverse neurons, operating at great distances from each other? To deconstruct this question, we must first understand neural circuit structure and function. Multiple laboratories employ advanced genetic, optical, and pharmacological systems to accomplish this circuit dissection (Tye and Deisseroth 2012). These approaches involve the systematic activation and inactivation of specified neurons within a circuit and are aimed at identifying the functional roles of each neuronal subtype. While this is an elegant and forward approach, human brain disorders offer a different opportunity to understand circuit function: insight into a complex system can be gained when it is in disequilibrium, by examining what happens to it when parts of it break.

An early example of “circuit dissection” dates back to 1848, when Phineas Gage lost most of his left frontal lobe in a railroad construction accident. Gage experienced profound emotional, cognitive, and motor losses as well as posttraumatic epilepsy (Damasio and others 1994). From this grotesque beginning, a rich history of circuit dissection burgeoned using tools that were available at the time. Lesional studies of neural circuits have provided a wealth of insight into how activity in focal brain regions drives behavior (Steriade and others 1985). Studies of patients with partial focal epilepsies, brain tumors, and other focal brain pathologies have demonstrated how regionally specific disruptions of a brain circuit can manifest in unexpected ways including abrupt changes in personality, judgment, and demeanor (Mesad and others 2003; Partlow and others 1992). In the neurosurgical clinic, circuit dissection is utilized commonly. Direct electric cortical stimulation (pioneered by Penfield and Jasper) in semiconscious patients undergoing neurosurgery interrupts local circuit activity and allows mapping of eloquent brain regions that must be avoided during surgical resection (Penfield and Jasper 1954).

Recent experiments using optogenetics have advanced the field of neuronal circuit analysis immeasurably and demonstrate that activity in specific subset of neurons within a circuit can drive specific behaviors (Tischer and Weiner 2014). Optogenetics uses genetic delivery of light-sensitive ion channels (channelrhodopsins induce a depolarizing current; halorhodopsins induce a hyperpolarizing current) to specific subtypes of neurons. When channelrhodopsin-expressing neurons are exposed to light, a current is induced and the neuron’s activity is altered, allowing cell-type specific, reversible modulation of activity with high temporal resolution. Optogenetic activation of cholinergic neurons in brainstem can induce rapid eye movement sleep (Van Dort and others 2015); activation of inhibitory neurons in the hypothalamus can induce “voracious feeding behavior” (Jennings and others 2013); activation of estrogen-expressing neurons in the hypothalamus can induce fighting and sexual behaviors (Lee and others 2014). These studies validate, with exquisite specificity, the long-held idea that the activity of specific neurons within a larger circuit can have profound effects on behavior. Whether specific neurological pathologies can be explained by precise network dysfunction, however, remains a question.

To explore how molecular disruptions lead to neurological pathology via circuit dysfunction, we will utilize epilepsy, traumatic brain injury (TBI), and Alzheimer's disease (AD) as case studies. We will conceptually discuss brain circuits and molecules that contribute to circuit function. Epilepsy will be examined first as a "prototypical" network dysfunction—one in which hyperexcitability and synchrony of neuronal activity leads to episodic, complete circuit failure. TBI as a model of circuit interruption will then be discussed. Here, abrupt physical injury leads to immediate disruption of circuit activity. Last, we will explore new studies that suggest pathologies associated with AD may be caused by underlying cellular and circuit dysfunctions. To move forward, we will attempt to bring together molecular disruptions across models in order to identify universal molecular and circuit level changes associated with neurological diseases.

Neuronal Circuits: Definition and Examples

We define a neuronal circuit as a "group of synaptically connected neurons that act together to generate patterned neuronal activity." In 1937, James Papez was one of the first to theorize that a group of connected brain structures can form a circuit underlying a behavior. Papez hypothesized that the limbic circuit generated emotion based on "data derived from brain transection and stimulation experiments, developments in comparative neuroanatomy, clinical observations, and evolving neuroanatomical philosophy" (Pantel 2003). To examine how molecular changes lead to circuit-level dysfunction in our three disease case studies, we will focus on the cortico-hippocampal and thalamocortical circuits. Both are implicated in the generation and spread of seizure activity, are commonly damaged in TBI, and have significant cell loss in AD.

The Cortico-Hippocampal Circuit

The temporal lobe contains the cortico-hippocampal circuit, one of the most well studied circuits in the CNS (Fig. 1). This circuit consists of the entorhinal cortex (in the neocortex) and the dentate gyrus, Cornu Ammonis 3 (CA3), and CA1 (in the hippocampus) (Johnston and Amaral 2004). Activity from the entorhinal cortex is carried to the dentate gyrus granule cell layer via the perforant path. The dentate gyrus acts as a gate to filter activity moving through the circuit (Heinemann and others 1992). When salient signals activate dentate gyrus granule cells, their mossy fiber axons excite area CA3. Pyramidal cells in CA3 have recurrent collateral axons, which amplify activity coming from the dentate gyrus (Amaral and Witter 1989). CA3 cells synapse onto CA1 neurons via excitatory Schaeffer collateral axons. Excitatory axons from CA1 project back to the entorhinal cortex to complete the cortico-hippocampal circuit. Both feed-forward and feed-back inhibition, mediated by a wide variety of interneurons, shapes circuit activity at every stage.

This circuit constitutes the biological substrate for many forms of short-term memory. When both hippocampi are removed (as occurred famously in patient H.M.; Squire 2009), declarative short-term memory is lost and no new long-term memories can be formed. This circuit is also highly plastic. Long-term potentiation of synaptic efficacy from CA3 to CA1 is well studied (Martin and others 2000) and is mediated by postsynaptic changes in CA1 pyramidal neurons (Matsuzaki and others 2004). Furthermore, this circuit generates

important oscillatory activity through finely tuned action potential firing of both inhibitory and excitatory cells (Beenhakker and Huguenard 2009; Buzsaki and Moser 2013). These precise rhythmic activity patterns synchronize activity across diverse cell types and are important for facilitating memory encoding.

The Thalamocortical Circuit

The thalamocortical loop is another of the most biologically significant and rhythmic brain circuits (Fig. 1). The thalamus, a central relay station for multiple sensory modalities, is a hub for neuronal activity (Sherman and Guillery 2004). There are extensive projections from the thalamus to the cortex (thalamocortical [TC]). TC connections emanate from excitatory thalamic relay neurons and project to excitatory and inhibitory cells in the cortex. These ascending thalamocortical inputs provide an excitatory drive to both initiate (via their synaptic inputs onto excitatory neurons [Petreanu and others 2009]) and constrain (via their synaptic inputs onto inhibitory cells [Cruikshank and others 2007; Sun and others 2006]) cortical network activity. Cortical activity then propagates back to thalamus via corticothalamic (CT) projections. CT fibers arise largely from deep layer cortical pyramidal neurons and project to both thalamic relay neurons and inhibitory neurons in the thalamic reticular nucleus. Similar to TC input to the cortex, CT input to the thalamus directly activates excitatory relay cells and provides feed-forward inhibitory drive from reticular nucleus interneurons, which constrain relay cell activity (von Krosigk and others 1993; Warren and others 1994).

The controlled activity of the thalamocortical loop mediates the integration of sensory information from multiple sensory modalities that converge in the thalamus and are relayed to the cortex. This allows the coordination of activity at distal cortical locations. Interestingly, this circuit is prominently involved in the generation of sleep rhythms and the entrance and exit from various sleep states (McCormick and Bal 1997; Steriade and Contreras 1995).

Molecules That Contribute to Circuit Function

In our discussion of molecules relevant to circuit function and neurological disease, we will focus on ion channels, neurotransmitter systems, and signaling molecules that contribute to neuronal morphology. These classes of molecules give neurons unique functional properties, serve as the targets of multiple classes of pharmacotherapeutics, and are altered by disease.

Voltage-Gated Ion Channels

By definition, neurons are electrically excitable cells. This excitability is driven by the flow of ions across neuronal membranes via a diverse group of channels (Fig. 2). Voltage-gated ion channels are a large subfamily of membrane spanning proteins that open a membrane pore in response to specific changes in neuronal membrane voltage. Among the most fundamental ion channels are calcium channels (CaCh), potassium channels (KChs), and sodium channels (NaChs). Because calcium can activate a large number of intracellular processes, *CaChs* play perhaps the most diverse cellular role, mediating neurotransmitter release, kinase activation, and gene transcription (Simms and Zamponi 2014). Furthermore,

they can depolarize neurons via inward calcium currents and cause calcium spikes. *KChs* generally hyperpolarize neurons and reduce their activity. *KChs* regulate hyperpolarization following action potentials (Johnston and others 2010). *KChs* are also found in astrocytes where they mediate the inward flow of potassium, buffering it from the extracellular space following neuronal activity. *NaChs* activate at relatively depolarized membrane potentials and allow the depolarizing flow of sodium into neurons (Catterall 2014). *NaChs* are found throughout neurons and are concentrated at axon initial segments (AIS) where they initiate action potentials, and at Nodes of Ranvier, where they propagate action potentials. As *NaChs* are expressed in both excitatory and inhibitory neurons, the effects of *NaCh* dysfunction can be varied.

Neurotransmitter Systems

Molecules involved in synaptic transmission have potent effects on neuronal circuit function (Fig. 3). Although serotonergic, dopaminergic, adrenergic, cholinergic, peptidergic, and many other neurotransmitter systems are critical to brain function, they are primarily neuromodulatory and will not be discussed here. We will focus exclusively on excitatory glutamatergic and inhibitory GABAergic systems.

Glutamatergic Systems—Glutamate (the primary excitatory neurotransmitter in the brain) contained within vesicles in presynaptic terminals is released when action potential-induced depolarization opens voltage-gated calcium channels. Multiple proteins are involved in the fusion and release of glutamate-filled vesicles (Sudhof 2008). Once released, glutamate diffuses within the synaptic and extrasynaptic space where it can activate ionotropic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-Methyl-D-aspartic acid (NMDA), kainate, and metabotropic glutamate receptors (mGluRs) (Traynelis and others 2010). Ionotropic glutamate receptors are excitatory, allowing the depolarizing influx of mainly sodium and/or calcium as well as a limited amount of potassium efflux. AMPA receptors are found largely in the synapse, are directly gated by glutamate, and inactivate rapidly. NMDA receptors are found in the synapse and extrasynaptically. They require co-activation by glutamate and either D-serine or glycine as well as membrane depolarization to activate, and have much slower activation and inactivation kinetics. Glutamate activation of mGluRs induces changes in neuronal properties via second messenger systems. At the same time that glutamate binds these receptors, high-affinity glutamate transporters compete to bind and transport glutamate into the intracellular compartment (Danbolt 2001). Glutamate transporters remove glutamate from the extracellular space and terminate its ability to act at receptors. The vast majority of glutamate transporters are found on astrocytic processes that contact and envelope synapses (although growing evidence suggests relevant uptake of glutamate by neurons; Petr and others 2015; Scimemi and others 2009). Once transported into the intracellular compartment of the astrocyte, glutamate is converted to glutamine and is transferred back to neurons via the glutamine/glutamate shuttle where it is converted to glutamate for rerelease in a local synaptic economy.

GABAergic Systems—GABA (the main inhibitory neurotransmitter in the brain) is synthesized from glutamate via glutamic acid decarboxylase. The synaptic release of GABA

is calcium-dependent and relies on largely the same synaptic fusion proteins. GABA receptors mediate inhibitory, chloride influx and are much more diverse than glutamate receptors (Sigel and Steinmann 2012). This receptor-level diversity allows for GABA receptors with different affinities, kinetics, trafficking, and pharmacology to be inserted in specific synapses to fine tune function. GABA_A receptors can mediate phasic inhibition via low-affinity synaptic receptors or tonic inhibition via high-affinity extrasynaptic receptors. GABA can act at metabotropic GABA_B receptors, which exert powerful inhibitory effects. GABA is bound and removed from the extracellular environment by GABA transporters (GATs) expressed on both axon terminals and on astrocytes (Roth and Draguhn 2012). Evidence supports both the direct recycling of GABA during times of relatively low GABAergic activity and reliance on glutamate/glutamine-based production of GABA when activity is increased (Liang and others 2006; Ortinski and others 2010).

Cell Biological Signaling and Neuronal Morphology

Intracellular signaling molecules and cytoskeletal components can also predispose a network to dysfunction. We will consider two basic cell biological molecules, mTOR and tau. The mammalian target of rapamycin (mTOR) is a kinase that controls cell size, proliferation, motility, and survival. Tau is a tubulin binding protein highly expressed in neurons that stabilizes axonal microtubules. These molecules are basic building blocks of cells, they affect neuronal function, and they are all implicated in epilepsy, TBI, and AD.

mTor—mTOR is serine/threonine kinase expressed in multiple cell types throughout the body (Laplanche and Sabatini 2012). It is central to multiple large signaling systems related to amino acid availability, growth factors, cytokines, protein synthesis, cell growth, and more. Downstream targets of mTOR are components of multiple signaling pathways, including S-6-Kinase, 4EBP1, eIF4a, AKT, Hif1/2, and others. This gives mTOR the ability to respond to multiple cellular signals by modulating a diverse array of cellular machinery. mTOR itself is two different protein complexes, mTORC1 and mTORC2, differentiated by the proteins they associate with and their downstream targets. Rapamycin, originally discovered as an antifungal, inhibits mTOR, and is now widely used as an immunosuppressant. Using rapamycin as a therapeutic agent has rapidly evolved to include potential applications in epilepsy, AD, TBI, cancer, drug addiction, and muscular dystrophy.

Tau—Tau is a protein most well-known for forming neurofibrillary tangles, a hallmark of AD pathology (Ballatore and others 2007). Tau stabilizes microtubules, is heavily expressed by neurons, and is commonly found in axons. Tau has very little secondary structure, is highly flexible, and stabilizes microtubules by crosslinking tubulin. The tubulin-binding function of tau arises from four repeated domains at its c-terminus end, which each can directly interact with tubulin (Brandt and others, 1993). Tau also interacts with a number of neurologically relevant molecules including NMDA receptors (Ittner and others 2010). Dysregulation of tau phosphorylation may contribute to the formation of neurofibrillary tangles, which are composed of hyperphosphorylated tau.

Epilepsy: The “Prototypical” Molecular Network Dysfunction

Epilepsy is one of the most common neurological diseases, affecting approximately 1% of people worldwide (65 million). Epilepsy is defined by recurrent spontaneous seizures and is an umbrella term covering dozens of different disorders. Brain injury, fever, genetic mutation, infection, hypoxic/ischemic insult, and brain tumors can all lead to epilepsy (Noebels and others 2012). Seizures, in general, result from the unconstrained, synchronous activation of neuronal circuitry. As brain activity is constant, it is surprising that seizures are not more common! This is because the brain has evolved numerous mechanisms to control and constrain activity. Inhibitory systems, circuits which favor desynchronization of neuronal activity, activity-dependent depression of neurotransmission, and many other mechanisms, exist to combat “runaway excitation.” When these mechanisms fail, or are disrupted, seizures occur. Interestingly, although pathologic insults can make seizures more likely, models show that anyone’s brain can seize (Jirsa and others 2014). Fortunately, the vast majority of the time endogenous antiseizure mechanisms prevent the brain from entering seizure states, even in most patients with epilepsy.

When seizures do occur they have diverse motor, cognitive, and emotional consequences. Seizure symptomology (as measured by seizure behavior and electroencephalography) varies based on the site of seizure initiation and the circuits through which a seizure spreads. Among seizure subtypes, temporal lobe epilepsy (TLE) is the most common. TLE occurs in the cortico-hippocampal circuit and accounts for approximately 60% of all epilepsy. Neocortical epilepsy, which involves the cortico-thalamic circuit, is also common and arises from a focal disruption in the neocortex. Many therapeutic options exist to treat seizures including pharmacotherapy, diet-based strategies, surgical resection, and multiple forms of electrical brain stimulation. Even with so many options, up to 30% of epilepsy remains refractory to treatment (Shorvon 2007). Fortunately, advances in both circuit and genetic analysis have allowed advances to be made in our understanding of the disease. Below, we will discuss specific molecular dysfunctions, taken from some recent studies, to illustrate the multiple ways in which molecular changes can lead to circuit dysfunction.

Sodium Channels and Dravet Syndrome

Voltage-dependent sodium channel antagonists are used widely as anticonvulsants as they inhibit neuronal activity. The link between sodium channel function and epilepsy, however, is not always so simple. Loss-of-function mutations in the SCN1A gene (which encodes Na_v1.1) are linked to severe developmental epilepsies including Generalized Epilepsy with Febrile Seizures plus type 2 (GEFS+2) (Claes and others 2001) and Dravet syndrome (Claes and others 2009; Escayg and others 2000; Lossin 2009). Na_v1.1 sodium channels contribute to neuronal action potential firing. How then does a loss-of-function mutation, which should decrease neuronal action potential firing, lead to seizures? The answer came when Na_v1.1 was found to be preferentially expressed in inhibitory interneurons (Yu and others 2006), in the axon initial segment (Ogiwara and others 2007), where action potentials are generated (Fig. 4). SCN1A mutant mice show a deficit in interneuron, but not pyramidal cell, excitability. Input/output relationships are altered in Na_v1.1 interneurons and the ability to generate high-frequency action potentials is diminished. Visualizing hippocampal circuit

activity using voltage-sensitive dye imaging in acute brain slices from SCN1A mutant mice showed that neuronal activity summated faster and spread more broadly (Gu and others 2014). Additionally, when the mutant Na_v1.1 channel was expressed conditionally in interneurons, but not excitatory neurons, the epilepsy phenotype persisted (Cheah and others 2012). Interrupting the ability of interneurons to respond to excitation and to produce inhibitory output compromises the control of excitatory activity, leads to aberrant circuit activity, and predisposes circuits to seize. These studies show a clear example of how a loss-of-function mutation in a molecule critical to regulating neuronal excitability leads to circuit and neurological dysfunction.

Shaping Synchrony: Oscillations and Absence Epilepsy

The thalamocortical circuit is involved in absence epilepsy, a form of epilepsy characterized by spike-wave discharges and momentary loss of consciousness (Blumenfeld 2005). In the thalamocortical circuit, multiple preclinical studies have underscored the importance of the recurrent connectivity in the TC-CT circuit, and also within the thalamic circuitry itself (Fig. 5). Because thalamic neurons express t-type calcium channels, which are inactivated at resting potentials and de-inactivate when neurons are hyperpolarized, they are able to fire calcium rebound bursts following inhibitory barrages from nRT interneurons (Llinas 1988). Increased t-type calcium currents in the thalamus enhance rebound bursting in TC neurons. This increases hypersynchronization within thalamic circuitry and leads to absence epilepsy phenotypes (Talley and others 2000). Ethosuximide, a commonly used anticonvulsant, inhibits t-type calcium channels to attenuate pathological oscillatory activity (Coulter and others 1989; Zhang and others 2004). A number of different mechanisms can drive this hyperactivation of thalamic relay neurons. Lack of a specific glutamate receptor, Gria4, at the CT-nRT synapse decreases feed-forward inhibition of thalamic relay neurons (Paz and others 2011). This allows direct activation of CT neurons via unbalanced TC excitation and initiates hypersynchronization throughout the thalamocortical circuit. Under different circumstances, decreased efficiency of GABA transport can overactivate GABA_B receptors, decreasing t-type calcium channel inactivation, elevating rebound firing, and hypersynchronizing neurons (Beenhakker and Huguenard 2010). Although there is disagreement in the field regarding how spike-wave epilepsy is initiated, it is clear that hypersynchronization of the thalamic relay neuron-nRT circuit plays an important role (Paz and Huguenard 2015). When large groups of CT cells become synchronized, this activity can rapidly spread through the thalamocortical circuit and disrupt consciousness.

Signaling Molecules: “TORopathies” and Epilepsy

Changes in neuronal morphology can also alter circuit function via changes in neuronal connectivity. Multiple studies show that overactive mTOR signaling is associated with epilepsy (Wong and Crino 2012) and is known to alter neuronal morphology. Tuberous sclerosis complex (TSC) is a form of epilepsy characterized by cortical malformations, known as tubers (Crino and others 2006). TSC is caused over 85% of the time by mutations in the *TSC1* and *TSC2* genes, both negative regulators of mTOR signaling. Histochemical analysis of brain tissue from TSC patients reveals large-scale cortical disorganization, the presence of large undifferentiated balloon cells, and hyperactivated mTOR signaling molecules (Crino 2011; Crino and others 2006). In model systems, loss of TSC1/2 leads to

ectopic axons, and overexpression of TSC1/2 can cause axon loss (Choi and others 2008). This suggests that overactive mTOR alters neuronal morphology and migration, perhaps by its known effects on cytoskeletal dynamics, response to growth factors, and cell-cell adhesions (Guertin and Sabatini 2007). Consistent with this hypothesis, axonal abnormalities and laminar disruptions are seen in the cortex of patients with TSC. Loss of PTEN, a negative regulator of mTOR, has also been shown to alter neuronal migration, morphology, and axon outgrowth (Pun and others 2012). Mutations in STRADA, another negative regulator of mTOR, cause Pretzel syndrome, a development epilepsy disorder common in the Old Order Mennonite population. Loss of STRADA leads to overactivation of mTOR, reduces neurite outgrowth, and neuron motility in culture (Parker and others 2013). Disrupted cortical circuit structure is thought to underlie seizure generation in patients with Pretzel syndrome. Like TSC, this is likely due to altered neuronal migration, neurite outgrowth, and adhesion. In fact, many “TORopathies” lead to focal cortical malformations (disruptions in local circuitry, connectivity, and cellular composition). Importantly, both preclinical and clinical studies, in the case of Pretzel syndrome, show that using rapamycin, an inhibitor of mTOR, can reverse many of the pathologies and dramatically improve patient quality of life.

mTOR signaling controls an enormous number of downstream gene targets, besides its effects on cellular and neurite motility. Loss of TSC1 can also decrease the expression of the main glutamate transporter in the adult brain, GLT1, leading to increased extracellular glutamate signaling and enhanced neuronal activation (Wong and others 2003). GLT1 levels have been reported to be decreased and glutamate levels increased in resected human epileptic foci (Rakhade and Loeb 2008). Additionally, the uptake of glutamate by astrocytes is critical to maintaining production of both glutamate (Tani and others 2014) and GABA (Ortinski and others 2010). When GLT1 is lost in the astrocyte-specific TSC1 knockout animals, increasing GLT1 with ceftriaxone decreased extracellular glutamate levels, neuronal cell death, and seizures (Zeng and others 2008).

For Further Consideration

Control of inhibitory systems including GABA receptor expression, trafficking, and function are especially relevant to circuit disruption and epilepsy (Grabenstatter and others 2012; Grabenstatter and others 2014; Maguire and others 2005; Wyeth and others 2010). Additionally, astrocyte control of extracellular glutamate levels may be a common mechanism to a number of different molecular disruptions (Armbruster and others 2014; Robel and others 2015). Recent findings also suggest a critical role for astrocyte potassium buffering in human epilepsy (Bedner and others 2015). Finally, the link between gain or loss-of-function mutation and epilepsy is not always clear; even when mutations should logically lead to circuit abnormality, they do not cause epilepsy in every patient (Klassen and others 2011). Clearly, more research is needed to understand how changes in a single molecule can lead to circuit dysfunction and disease (Staley 2015).

Traumatic Brain Injury: The Most Acute Disruption of Network Activity

Traumatic brain injury is one of the leading causes of death worldwide and arises from a vast array of physical insults. TBI induces disruptions in white matter, can cause widespread cell loss, and decreases cortical, hippocampal, and whole brain volume (Bigler and others 1997; Goddeyne and others 2015; Trivedi and others 2007). In severe TBI, direct injury can ablate neuronal tissue. More common, however, are diffuse axon injuries (DAI) caused by the rapid acceleration/deceleration and rotation forces that cause brain movement and pressure waves within the skull. Neuronal injury also occurs in phases following TBI. Following acute changes, direct damage, and DAI, extensive secondary changes occur (Lowenstein 2009). In general, there is a direct relationship between the brain regions damaged and the circuit-level dysfunction (Kasahara and others 2010; Mayer and others 2011). Disrupted circuitry commonly includes the default mode network (the brain regions active when a person is aware but quietly at rest), the saliency network (the brain regions activated when a person is attending to behaviorally relevant events), and general long-range interactions between brain regions.

TBI is linked with a number of other neurological disorders. Posttraumatic epilepsy occurs following TBI with the severity of injury directly linked to the likelihood of developing seizures (Annegers and Coan 2000). Multiple head injuries are known to substantially increase the risk for development of AD, chronic traumatic encephalopathy, and associated dementias (Moretti and others 2012; Smith and others 2013). Dementias related to head injuries are becoming an important health concern. For example, in the National Football League (NFL), up to 20% of players report to have suffered from multiple concussions (Maroon and Bost 2011). A 2009 study commissioned by the NFL reported that Alzheimer's disease and memory-related disorders have been diagnosed in former players at a rate 19 times the normal rate for men ages 30 through 49 (Stone 2011). Many recent advances in understanding the neurobiology of TBI have been made that will hopefully lead to novel prevention and treatment strategies. Here, we will examine how tau, an important cytoskeletal molecule involved in microtubule stabilization, engenders axons with unique physical properties making them prone to injury, how that injury leads to network dysfunction, and how neurotransmitter systems are involved in TBI.

Cytoskeletal Proteins and Diffuse Axon Injury

Diffuse axon injury is caused by mechanical stress on delicate axon fibers (Fig. 6). DAI is caused by the rapid acceleration and deceleration of the brain during TBI (Smith and others 1999; Tang-Schomer and others 2010). DAI induces microtubules fracture, inward flow of Ca^{2+} ions (Wolf and others 2001), and proteolytic cleavage of voltage-gated sodium channels resulting in their inability to inactivate (Iwata and others 2004). All of these changes impair the physical and electrical stability of the injured axons and are associated with axonal retraction or degeneration (Chen and others 2009). Why are axons, not cell bodies or dendrites, so susceptible to TBI-induced pathology? Recent studies suggest that tau, which is highly enriched in axons, may be the key. Tau crosslinks microtubules giving them the stable structure they require to span from point to point. A recent modeling study suggests biophysical properties of tau increase the susceptibility of axons to damage

following TBI (Ahmadzadeh and others 2014). They report that tau cross-linked microtubules are capable of a high degree of flexibility when mechanical strain put on the brain is slow, as would occur during normal biological movement of the brain and body (Smith and others 1999). When the brain undergoes rapid mechanical strain, however, those same biophysical properties of tau-cross-linked microtubules lead to their fracture. This simple, but important, property of microtubule flexibility caused by tau provides insight into why axons may be such a mechanically sensitive neuronal structure. Once axons are damaged, axonal transport is disrupted, hyperphosphorylated tau aggregates, and a cascade of multiple pathological events occurs leading to axon retraction and even cell death (for a more complete review, see Blennow and others 2012). Of specific functional importance, axons disrupted by these mechanisms tend to lose connectivity with their postsynaptic targets.

Circuit-Level Dysfunction in TBI

From this local, physical disruption to axonal integrity, large-scale changes begin to occur throughout the brain (Sharp and others 2014). Axons degrade and retract and neurons die. In the normal brain, highly connected local circuits carry out specific functions appropriate to their location in cortex. These circuits also act as nodes, a connection or redistribution point to other circuits (Fig. 6). Not all circuits, or nodes, are connected to every other circuit, but any given circuit connects with most other circuits via only a few nodes in the human brain. This model of brain functional connectivity is known as the “small-world” model (He and others 2007). “Small-world connectivity” allows for flexibility in brain circuit function because different combinations of activity states (communication via different nodal pathways) can result in the same output of a circuit. Many examples of such networks exist including the default mode network, the salience network, and the central executive network (the brain areas activated during complex decision making) (Sharp and others 2011). The balanced activity of these networks allows distinct patterns of brain activity and cognitive states. After severe TBI, nodes within these networks can be directly injured. More commonly, however, connections between nodes are disrupted by DAI (Mayer and others 2011). Imaging studies support the hypothesis that DAI leads to inefficient flow of activity through networks, which requires larger brain regions required to perform tasks normally handled by smaller areas (Shumskaya and others 2012). Following TBI and DAI, flexibility associated with small-world connectivity is often lost; more limited options exist within a network to rapidly switch activation and subsequent cognitive states. A growing body of research shows that functional losses post-TBI may be partially due to decreased efficiency in brain network activation and transition caused by DAI.

Neurotransmitter Systems and TBI

Glutamatergic systems are altered by TBI. Acute loss of the astrocytic glutamate transporter GLT1 occurs immediately following TBI (Yi and others 2005). This may be related to increased glutamate levels seen in human CSF (Chamoun and others 2010). As in epilepsy, increasing glutamate transport using ceftriaxone can be protective following TBI (Goodrich and others 2013). Studies examining glutamate receptors suggest acute decreases in NMDA receptor expression (Park and others 2013). Studies examining AMPA receptors show more variability (Atkins and others 2006; Spaethling and others 2008). GABAergic systems are

also compromised due to cell loss (Cantu and others 2014), changes in receptor expression (Drexel and others 2015; Raible and others 2012), and function (Faria and others 2012; Jin and others 2011; Ma and Prince 2012).

For Further Consideration

Literally dozens of other important molecular changes play a role in altering neuronal, and thus circuit-level function following TBI (Blennow and others 2012). mTOR signaling is increased following TBI and therefore could cause increased neurite outgrowth and other downstream effects. Alteration of neuronal adhesion and synaptic organization is known to occur both in humans and in animal models of TBI (Park and Biederer 2013). Microglial activation and neuro-inflammation also play a significant role in the molecular pathophysiology of TBI (Davalos and others 2005; Shitaka and others 2011; Ziebell and Morganti-Kossmann 2010). Interestingly, A β plaques seen in AD are also found in the human brain following TBI (Ikonomic and others 2004; Roberts and others 1994).

Alzheimer's Disease: Slow, Progressive Circuit Destruction

Alzheimer's disease is the most common form of dementia. According to the Centers for Disease Control, in 2013 there were $\approx$ 5 million Americans living with AD, projected to rise to 14 million by the year 2050. The progression of AD includes memory impairment, neuronal cell loss, dementia, and death (Huang and Mucke 2012). As memory impairments are common, the cortico-hippocampal circuit is thought to be involved in AD. Indeed, there is significant loss of hippocampal volume in advanced-stage AD. Cell loss occurs throughout the brain, however, potentially implicating many other brain circuits. There is currently no cure for AD, and several existing drugs on the market show only modest efficacy. Thus, there is an urgent need to understand the synaptic and circuit abnormalities that lead to AD pathophysiology.

Tangles and Plaques in AD

The histopathology of AD is characterized by neurofibrillary tangles and "senile" plaques. Neurofibrillary tangles are formed by misfolded, hyperphosphorylated, and ubiquitinated tau protein. In this state, tau dissociates from microtubules and aggregates, creating fibrillary structures (Alonso and others 1996; Grundke-Iqbal and others 1986; Gustke and others 1992). Two important AD pathologies, the loss of synapses and cell death, are both thought to be downstream of disruptions in tau (Roberson and others 2011). The second major hallmark of AD is amyloid- β (A β) peptide pathology. A β peptides are generated from amyloid precursor protein (APP), a transmembrane protein ubiquitously expressed in all tissues. APP is metabolized by two mutually independent pathways: alpha, or beta and gamma secretases (Huang and Mucke 2012). Alpha secretase cleavage results in the generation of non-pathogenic peptides, which do not produce A β peptides. Sequential cleavage by beta and gamma secretases, however, generates A β monomers, which may be directly pathogenic (Selkoe 2008). These monomers form oligomers and aggregate to form extracellular plaques in the brain and periphery (Hardy and Selkoe 2002). A β plaques are located in areas of cellular dysfunction, cell loss, and network dysfunction. Interestingly,

many of the pathological effects of A β plaques are thought to be mediated by tau, as they are lost when tau is experimentally removed.

Molecular and Cellular Targets of AD Pathology

It has been difficult to identify the precise mechanism by which any of these pathologies lead to AD cellular pathology or circuit dysfunction. Both plaques and hyperphosphorylated tau have multiple potential molecular effectors, alter numerous cellular functions, and have broad or unknown function. Even though there are many challenges, recent work has brought to light a number of potential molecular changes in AD linked to neuronal excitability and circuit function. We will discuss recent work examining their potential role on glutamate toxicity and sodium channel dysfunction in regulating inhibition in AD.

Glutamate Toxicity

As cell loss is a component of AD, it is not surprising that glutamate, glutamate receptors, and glutamate-induced excitotoxicity have been a focus of AD (Palop and Mucke 2010; Rush and Buisson 2014; Spires-Jones and Hyman 2014). A number of studies have demonstrated that A β plaques directly increase NMDA receptor function (Larson and others 2012; Texido and others 2011) and glutamate release (Abramov and others 2009). Interestingly, synaptic activity (Cirrito and others 2005) and NMDA receptor activation regulates APP processing and the formation of A β plaques. The activation of synaptic NMDA receptors appears to favor alpha-secretase activity and decreased A β plaque formation (Hoey and others 2009). Extrasynaptic NMDA receptor activation, on the other hand, increases beta-secretase activity, leading to more formation of A β plaques (Bordji and others 2010). This creates a potentially vicious cycle in which A β leads to increased NMDA receptor activation, which in turn leads to more A β . In addition, the astrocytic removal (Li and others 2009; Masliah and others 1996) and processing of glutamate (Robinson 2001) may also be reduced in AD, leading to more activation of extrasynaptic NMDA receptors. Interestingly, as A β load increases with disease progression, excitatory synaptic systems begin to be inhibited via receptor internalization and dendritic spine loss (Mucke and others 2000; Walsh and others 2002). This leads to a global loss of synapses in the AD brain, the degree of which correlates well with decreased cognitive function (Terry and others 1991).

Based on these findings, memantine, an NMDA receptor antagonist, was developed as an AD therapeutic. Memantine is an open channel NMDA receptor blocker that attenuates NMDA-induced neurotoxicity (Chen and others 1992). Memantine acts to decrease GluN2B-containing NMDA receptor activation and inhibits A β -mediated disruptions in synaptic plasticity (Hu and others 2009). It has been shown to slow the progression of dementia in AD, but does not radically improve disease outcome (Herrmann and Gauthier 2008). Treating memory loss with an NMDA antagonist seems somewhat contradictory, as NMDA receptors are key in mediating memory formation. Current thinking on this treatment suggests memantine mediates its effect by either reducing cell loss or by restoring the excitation/inhibition balance.

Inhibition and NaChs in AD

Recent findings suggest that impaired inhibition may be involved in AD (Busche and others 2008; Palop and others 2007; Palop and Mucke 2010; Sperling and others 2009). These studies indicate that A β plaques and tau tangles can lead to decreased function of inhibitory interneurons and increased excitation in neuronal circuits. Several studies have described inhibitory cell loss in AD, particularly in hippocampal circuits (Loreth and others 2012; Ramos and others 2006). This inhibitory dysfunction can result in aberrant neuronal activity spread in the hippocampal circuit (Hazra and others 2013). On the other hand, inhibitory axonal sprouting was observed as a potential compensatory mechanism to inhibitory cell loss (Palop and others 2007). Interestingly, high levels of beta amyloid can induce epileptic activity in mouse models of AD (Palop and Mucke 2009) and loss of inhibition could also explain high incidence of seizures in human AD (Hauser and others 1986).

New evidence suggests sodium channel dysfunctions may play a significant role in AD pathology and link directly to decreased inhibitory neurotransmission. As in the previous discussion of Dravet syndrome and SCN1A mutation, sodium channel dysfunction in interneurons may lead to AD symptoms. Using the hAPP J20 model, Verret and colleagues showed a lack of Na v 1.1 in parvalbumin expressing interneurons (Verret and others 2012). This led to increased network hyperexcitation (similar to Fig. 4) and poor cognitive function. When Na v 1.1 was reintroduced into interneurons genetically, epileptiform activity was decreased and cognitive performance was enhanced. Importantly, they also showed that Na v 1.1 levels were decreased in the human AD brain. Together with previous studies, this work suggests circuit hyperexcitability as a core component of at least part of the progression of AD. In line with that hypothesis, levetiracetam, an anticonvulsant drug, has shown promise in reversing AD pathology in a mouse model (Sanchez and others 2012).

Circuit-Level Pathology in AD

To understand diseases like AD, we must understand the early functional and anatomical pathology in specific cell subtypes, circuits, and regions of interest. Memory encoding is primarily mediated by the limbic networks where the cortico-hippocampal circuitry is thought to serve as an anatomical entry gate for forming memory traces. Changes in brain rhythms may signal some of the earliest pathology of AD, prior to massive cell loss (Goutagny and Krantic 2013). Indeed, brain rhythms in cortico-hippocampal circuits are impaired in animal models of AD (Palop and others 2007). Additionally there are significant hypo-metabolisms, which correlate with regions of increased plaque density (Buckner and others 2005), in the default mode network in AD (Sperling and others 2009) (Fig. 6). Interestingly, plaques seem to accumulate in specific regions and cortical layers (Eriksen and Janus 2007) and disrupt activity locally. It is possible that “active plaques” cause the most harm if they are situated in specific points within neuronal circuits that are especially poised to generate abnormal activity.

Other Considerations

Many other mechanisms that we did not explore are at play in AD. It has been reported that the plaques can produce reactive oxygen species (Mayes and others 2014). There are a number of other channelopathies reported in mouse models of aging and AD, including

potassium (Sachse and others 2013), calcium and calcium-dependent potassium channels (Thibault and others 2012), and muscarinic M current (Poulin and others 2010). Microglia and inflammatory signaling also play an important role (Heneka and others 2015; Johansson and others 2015). Furthermore, hyperactive mTOR signaling may be involved (Sun and others 2014). We hope that our discussion encourages readers to delve deeper into all the pathophysiological mechanisms at play in all three of the diseases discussed.

Summary

When the diverse changes that occur in epilepsy, TBI, and AD are viewed together, a few central themes emerge. Multiple molecules including neurotransmitter receptors, transporter, ion channels, and structural elements have the potential to alter neuronal function and thus circuit activity. Of particular interest are the roles of sodium channel activity in shaping inhibition within circuits, morphological changes in neuronal processes that lead to altered circuit structure, and frank cell loss, especially interneuron loss, leading to decreased circuit efficiency. Among all three diseases there appears to be a reciprocal relationship between decreased inhibition, increased excitation, and excitotoxicity. In epilepsy, both decreased inhibition and increased excitation can lead to excitotoxicity. In TBI, damage to axons can lead to uncontrolled excitatory output, downstream cell death, and loss of inhibitory interneurons. In AD, it seems harder to isolate one process from the other as protein aggregation may directly lead to increased excitation, decreased inhibition, and cell death. As we move forward, we hope a number of specific questions common to all three diseases can be addressed. Why are interneurons prone to dysfunction and death? Are there opportunities to retrain neuronal circuits to function more efficiently even when damaged? How could modulators of widely expressed molecules be delivered or utilized in new ways to restore network function? When these pathological commonalities are considered, it is not surprising that epilepsy, TBI, and AD are highly comorbid. Perhaps, if we are fortunate, treatment strategies may also be common, aiding our ability to translate therapies from one disease to another.

Acknowledgments

The authors would like to thank Lauren Andresen for her helpful commentary and critique of the review.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institute of Neurological Disorders and Stroke (NS076885).

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Figure 1.

The cortico-hippocampal and thalamocortical circuits. *Top.* Schematic of the cortico-hippocampal circuits. Excitatory pyramidal neurons, brown pyramids; inhibitory interneurons, red circles; synaptic terminals, black circles. DG = dentate gyrus; EC = entorhinal cortex. *Bottom.* Same as top. Thalamic relay cells, brown circle. Superficial and cortical layers labeled. nRT = thalamic reticular nucleus; TC = thalamocortical; CT = corticothalamic.

Figure 2.

Ion channels in microcircuits. Example two neuron microcircuit. Reciprocal connectivity between an excitatory neuron (brown pyramid) and an inhibitory interneuron (red circle). NaChs in the axon initial segment generate action potentials that drive synaptic output onto the connected cell. Calcium channels allow inward current and potassium channels allow outward current flow in the soma of both neuronal subtypes. Nearby astrocytes buffer extracellular potassium via inward flow of potassium ions (see synaptic figure for more roles of astrocytes). For all symbols and their corresponding molecules, see legend.

Molecular Glutamatergic Synapse Map

Molecular GABA Synapse Map

Figure 3.

Synaptic molecules relevant to circuit function. *Top.* Example excitatory glutamatergic synapse with molecules relevant to synapse and circuit function. *Bottom.* Example inhibitory GABAergic synapse with molecules relevant to synapse and circuit function. For all symbols and their corresponding molecules, see legend.

Interneuronal Sodium Channel Dysfunction and Seizures

Figure 4.

Interneuronal sodium channel dysfunction and seizures. Loss of NaChs in the axon initial segment of inhibitory interneurons (1) leads to decreased interneuron activity and reduced inhibition (2). This leads to unconstrained excitation (3) and seizure generation (4). This dysfunction can occur throughout the brain, but here is depicted at the CA3 to CA1 synapse (*inset*).

Figure 5. Thalamocortical circuit disruption. Multiple changes can lead to generation of pathological, seizure-inducing activity in the thalamocortical circuit. These include (1) increased t-type calcium currents in excitatory neurons, (1a) decreased corticothalamic-driven excitation of thalamic interneurons, and (1b) decreased GABA transport by thalamic astrocytes. All these changes lead to increased thalamic excitatory neuron output as depicted by (2) increased rebound bursting. Increased thalamic excitatory neuron output leads to (3) increased circuit hypersynchronization and seizures.

Figure 6.

Traumatic brain injury–induced axonal and network damage. (A) Diffuse axonal injury is induced when microtubules (red and blue circles) in the axon are fractured. The presence of the tau protein (blue oval) on microtubules make them able to bend when physical deformation occurs slowly, but makes them brittle when rapid physical strain is put on them (as occurs during TBI). Fracturing of microtubules increases both sodium and calcium influx leading to uncontrolled synaptic output and cell death. (B) Traumatic brain injury disrupts node connectivity and local activity in the brain. In the healthy brain nodes (*red circles*), or

local circuits, are connected to other nodes by their axonal projections (gray lines). This allows efficient network activation and proper local activation (*red highlighted areas*). After TBI, frank cell loss can occur (loss of red nodes) and axon injury leads to loss of node-to-node connections. This in turns leads to inefficient network activity and reduced local activity (*blue highlighted areas*).

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