Neural Networks in Health and Disease

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Glossary

Action potential A rapid depolarization of a neuron's membrane potential, and the basic unit of information. This is approximately an all-or-none event.

Ion channel A plasma membrane-spanning protein that allows the flow of a specific type of ion across the membrane. The protein contains a selectivity filter that determines which ion can flow through, and a gating mechanism that determines whether the channel is in an open or a closed configuration.

Channelopathies Diseases related to ion channel dysfunction. These can affect the brain, heart, muscles, or the endocrine system.

Synapse A structure that couples one neuron to another. It can be electrical, mediated by gap junctions, or chemical, involving the release and action of neurotransmitters.

Central pattern generators Neural circuits that drive rhythmic behaviors like chewing, walking, and breathing.

Cochlea A structure in the inner ear that converts sound vibrations to electrical signals through the action of hair cells, decoding both the frequency and amplitude of incoming sound.

Coincidence detection The determination of whether two inputs arrive at approximately the same time.

Auditory nerve phase locking A phenomenon in which the timing of action potentials in the auditory nerve matches the pattern of amplitude changes in a sound wave.

Introduction

There are approximately 86 billion cells in the human brain. Many of these are neurons that are interconnected by chemical and electrical synapses, while the remainder are glia that interact with the neurons in ways that are still being determined. This huge network of cells controls the function of the rest of the body, and somehow produces consciousness and self-awareness. Unfortunately, it is also the target of debilitating disorders. In this article, we discuss the basic elements of the neural networks that comprise the brain, as well as some of the neurological disorders that result from malfunctions at the single-cell or network levels.

Neurons

A neuron is a highly specialized cell with a spatially extended morphology that facilitates interaction with both nearby and distant cells. The cell body, or soma, contains the usual cellular organelles including the nucleus. The soma then branches off into dendrites, which can form an extensive dendritic tree. The dendrites receive most of the input from other neurons, and transmit the signals to the soma, where it is integrated to form an output signal. This travels down another extension of the cell, the axon. The axon often bifurcates into axon collaterals and interacts with other cells via synapses, which pass the neuron's output onto other neurons or

onto muscle cells. There are many excellent textbooks on neurons and neurophysiology, including (Levitan and Kaczmarek, 2015; Johnston and Wu, 1995; Hille, 2001).

Electrical Impulses or Action Potentials

Besides the specialized morphology, neurons are specialized to encode, transmit, and decode information in the form of electrical signals. The fundamental unit of information in the neuron is the electrical impulse or action potential. This is a large deflection of the voltage across the plasma membrane, called the membrane potential, due to the action of ion channels. Ion channels are large proteins that span the membrane, forming a portal from the outside of the cell to the inside. When open, an ion channel allows the flow of ions into or out of the cell, with preference typically given to a single type of ion. There are families of K^+ channels, Ca^{2+} channels, Na^+ channels, and Cl^- channels, each encoded by separate genes. Ion pumps and transporters in the plasma membrane maintain concentration gradients of the different ions between the inside and outside of the cell ($[K^+]$ is higher inside than outside, while $[Na^+]$, $[Ca^{2+}]$, and $[Cl^-]$ are higher outside), resulting in a membrane potential that is negative in a resting cell. During an action potential the depolarizing Na^+ and/or Ca^{2+} channels open, allowing the flow of positive ions into the cell and raising the voltage from the negative resting potential to a positive potential. This depolarization activates K^+ channels and inactivates the Na^+ channels, allowing the efflux of positive ions and reducing the influx of positive Na^+ ions, ultimately returning the membrane potential to its resting level. The ion channels are thus a system of proteins in the cell membrane that interact through a global variable, the cell's own membrane potential, as well as through intracellular Ca^{2+} ions, which regulate the opening of certain K^+ channels. (There are also Na^+-activated and ATP-inactivated K^+ channels, but these are less common.) Once an impulse is generated in the soma or in the initial segment of the axon, it travels down the axon without attenuation due to the presence of Na^+ and K^+ channels in the axon.

Ion Channel Composition Determines a Neuron's Output

Different neurons express different types of ion channels and at different densities. This determines the way in which the neuron responds to input coming in from the dendrites. The input-output properties of neurons are typically studied in the lab using brain slices. The neurons in the slice are kept alive in artificial cerebrospinal fluid while a neuron within the slice is patched with an electrode. The neuron's response to input is then studied by injecting either depolarizing or hyperpolarizing current into the patched cell. Fig. 1 shows examples from two different types of neurons from a brain slice of a male zebra finch. The soma and dendrites of each of these neurons reside in a part of the neural circuitry for birdsong called the HVC (proper name). In each case, responses to depolarizing current pulses (which increases the membrane potential) and hyperpolarizing current pulses (which decreases the membrane potential) are shown. The HVC neuron in panel A projects to a region in the basal ganglia called Area X (Mooney and Prather, 2005). When a sufficiently large depolarizing current is applied the neuron produces a continuous train of impulses (e.g., blue trace). When a hyperpolarizing current is applied, the voltage drops down, then slowly rises, producing what is called a sag (e.g., red trace). The HVC neuron in panel B projects down to a vocal-motor region called the RA (robust nucleus of the arcopallium) (Mooney and Prather, 2005). In response to the same 400 msec depolarizing input current pulse as in panel A the neuron produces only two impulses, following a long delay. In response to a 400 msec hyperpolarizing current pulse the voltage drops to a lower value and stays low until the termination of the pulse, after which it quickly returns to the resting potential. These two types of projection neurons clearly exhibit different electrophysiological characteristics. Although part of the brain slice, the neurons are pharmacologically isolated from other neurons by drugs that block synaptic coupling. Thus, it is the composition of ion channels expressed in the neurons that determines the different responses to input (Daou et al., 2013).
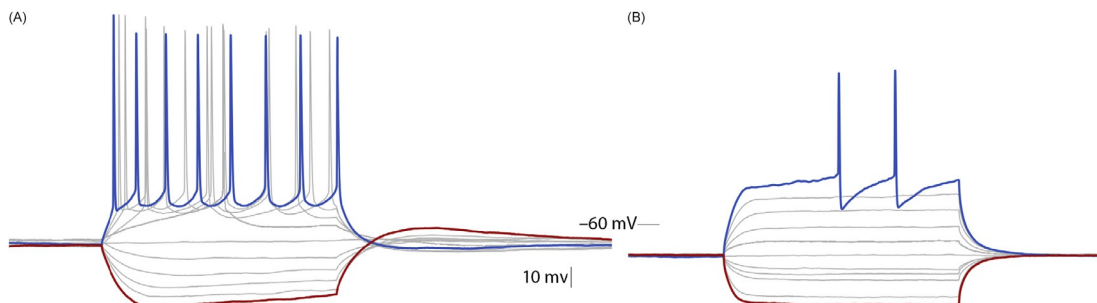

Fig. 1   (A) Responses of an HVC neuron that projects to Area X to a series of applied current pulses. The *blue* trace corresponds to a depolarizing current pulse of 250 pA, while the red corresponds to a hyperpolarizing current pulse of −250 pA. The gray traces are responses to intermediate current pulses that occur in steps of 50 pA. (B) Responses of an HVC neuron that projects to the RA.

Channelopathies

Channelopathies are diseases related to dysfunctions of ion channels (Kullmann and Waxman, 2010). These can be congenital, typically due to a genetic mutation in an ion channel gene, or acquired, such as due to an autoimmune attack on a specific type of ion channel. Because ion channels are key elements of muscles and endocrine cells, channelopathies are not restricted to the brain. Also, ion channels are expressed in some intracellular organelles, such as the endoplasmic reticulum and the sarcoplasmic reticulum (SR), where they play key roles in intracellular signaling or muscle contraction.

Febrile seizures are a common seizure disorder for children under 5 years of age associated with a spike in body temperature (Oehler and Tingle, 2012). A subset of these is due to a family of brain channelopathies known as generalized epilepsy with febrile seizures plus (GEFS+) (Scheffer and Berkovic, 1997). There are several types and subtypes of GEFS+, each due to mutation in the gene for a different ion channel or ion channel subunit. Type 1 GEFS+ involves a mutation in the gene encoding the ancillary β subunit for a Na^+ channel (Wallace et al., 1998). The second type involves a mutation in the gene encoding the primary α subunit of the Na^+ channel, and several such mutations have been identified (for example, Cossette et al., 2003). Type 3 is due to a mutation in the γ2 subunit of the receptor/channel for the neurotransmitter GABA (Baulac et al., 2001). This $GABA_A$ receptor, when activated by the binding of GABA, opens and allows the flux of Cl^- ions into the synapse. Since these are negatively charged, the effect is hyperpolarization of the synaptic membrane. Individuals with GEFS+ exhibit epileptic symptoms, including seizures, temporary confusion, and loss of consciousness or awareness (Scheffer and Berkovic, 1997).

A second brain channelopathy is episodic ataxia (EA) (Jen et al., 2007). The ataxia, or severe discoordination, is often brought on by heavy exercise or stress. It is typically due to misfiring of Purkinje cells, neurons of the cerebellum with extensive dendritic trees that receive and integrate input from many neurons and are the output neurons of the cerebellum. There are several types of EA, one of which (EA1) is due to mutation in a gene for the $K_v1.1$ type of K^+ ion channel (Adelman et al., 1995; Zerr et al., 1998). These channels are expressed in the basket cells and interneurons that provide inhibitory input to Purkinje cells through GABAergic synapses (synapses that release the GABA neurotransmitter). The gene mutation causes a decrease in the number of open K^+ channels, and thus a decrease in the hyperpolarizing current. As a result, the electrical activity of these inhibitory neurons is abnormally high, causing an inhibition of the Purkinje cell electrical activity. In a second type of episodic ataxia, EA2, the ataxia and other symptoms are due to a mutation of a gene encoding the P/Q-type Ca^{2+} channel $Ca_v2.1$ (Wan et al., 2005; Guida et al., 2001). The symptoms of EA2, which include ataxia, vertigo, and visual disturbances, tend to last longer (hours to days) than those of EA1 (seconds to minutes), and can be brought on by coffee or alcohol.

Channelopathies of the heart can be particularly dangerous. One such channelopathy, catecholaminergic polymorphic ventricular tachycardia (CPVT), is often due to a genetic mutation in the gene encoding ryanodine receptors in the SR of muscle cells (Lieve et al., 2016). This receptor is a Ca^{2+} channel, allowing the release of a great deal of Ca^{2+} from the SR into the myoplasm when stimulated. This Ca^{2+} evokes muscle contraction, and the mutation of the channel can cause ventricular tachycardia or ventricular fibrillation. These life-threatening patterns of cardiac muscle activity typically occur during exercise or emotional stress, and can lead to blackouts and even sudden death.

Our final example in our sampling from a long list of channelopathies causes cystic fibrosis. A genetic mutation in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) is the cause of this disorder (Bobadilla et al., 2002; O'Sullivan and Freedman, 2009). The CFTR is a Cl^- ion channel found in many organs, including the lungs, pancreas, liver, kidneys, and intestines, and in most cases the genetic mutation causes a misfolding of the channel protein so that it does not get inserted into the plasma membrane. Loss of function of this ion channel can result in difficulty breathing, poor growth and abnormally low weight gain during development, high blood pressure, diabetes, and infertility in most men and some women (O'Sullivan and Freedman, 2009).

Synapses

Synapses couple neurons together into networks. Two types of synapses exist: electrical synapses form junctions that allow direct current flow between coupled neurons, while chemical synapses transduce the electrical signal from the presynaptic neuron into a chemical signal via neurotransmitter release, and then this is converted back into an electrical signal at the postsynaptic neuron. The latter are much more prevalent in the brain, are primarily unidirectional, and are highly plastic.

Electrical Synapses

Gap junctions are found in most or all tissue, and in the brain they are called electrical synapses. They connect the cytoplasm of one cell to that of an adjacent cell and allow the flow of small molecules, ions, and electrical impulses directly between cells. A gap junction is formed by two connexons, each of which is composed of a ring of six connexin proteins (Maeda et al., 2009). Because the current flow between neurons is direct, without the need for transduction, this communication is very fast. In fact, neurons that are electrically coupled tend to have nearly synchronous electrical activity, so that the cell population acts as a syncytium. Examples of electrically excitable cells coupled by gap junctions are dopamine neurons of the arcuate nucleus in the hypothalamus (Lyons et al., 2010), cardiac muscle fibers (van Veen et al., 2001), and the endocrine cells within pancreatic islets of Langerhans (Zhang et al., 2008).

Chemical Synapses

These are much more prevalent than electrical synapses (the adult human brain contains hundreds of trillion of chemical synapses Tang et al., 2001), and much more versatile and plastic. A chemical synapse, often simply referred to as a synapse, consists of a presynaptic terminal from which neurotransmitter molecules are released, and a postsynaptic density that contains receptors for the neurotransmitters. The small separation between the two ($\sim$20 nm) is the synaptic cleft. The neurotransmitters are stored in spherical membrane structures called vesicles, and when stimulated a vesicle can fuse with the plasma membrane, releasing the neurotransmitter into the cleft in a process called exocytosis. Stimulation occurs when an action potential reaches the terminal and opens voltage-dependent Ca^{2+} channels; the Ca^{2+} that enters the terminal through these channels can bind to proteins that are part of the so-called SNARE complex and initiate the exocytosis (Jahn and Fasshauer, 2012). Once released from the cleft, the neurotransmitters diffuse over to the postsynaptic membrane where they can bind to receptors that are specific to that neurotransmitter. The effect of the neurotransmitter depends on the transmitter and the postsynaptic receptor. Neurotransmitters such as glutamate and acetylcholine are typically stimulatory, while GABA, glycine, and serotonin are typically inhibitory. Others, like dopamine can be either. The ionotropic neurotransmitter receptors are ion channels that when activated by the binding of neurotransmitter open and allow one or more ionic species to flow into/out of the cell. Other receptors are metabotropic, and activation of the receptor initiates a signal through an intracellular signaling pathway that ultimately results in the opening or closing of ion channels and can have other actions inside the cell.

Unlike electrical synapses, information flow through a chemical synapse is mostly unidirectional, from the presynaptic neuron to the postsynaptic neuron or muscle cell (in the case of a neuromuscular junction). Also, unlike electrical synapses, chemical synapses exhibit both presynaptic and postsynaptic plasticity. Such plasticity can last for hundreds of milliseconds to seconds (short-term plasticity), and long-term plasticity can last hours to a lifetime. These various forms of synaptic plasticity can be expressed as an increase or decrease in synaptic strength (Regehr, 2012). Long-term plasticity involves gene expression of neurotransmitter receptors and insertion of these receptors into the postsynaptic membrane and remodeling of the postsynaptic morphology, and is a primary mechanism for learning and memory (Takeuchi et al., 2014). However, changes in the distribution of ion channels in neurons can also be part of the learning process, and is referred to as intrinsic plasticity (Alkon et al., 1982).

Diseases Involving Synapses

Dysfunctions in synaptic transmission or plasticity are the basis of many neurological diseases, a few of which we describe here. Schizophrenia is a mental disorder characterized by abnormal social behavior, distorted thoughts, hallucinations, and paranoia. This is often coupled with other mental health problems, such as anxiety, depression, and substance abuse. The molecular basis for schizophrenia is not clear. One hypothesis is that it is due to excessive signaling at dopaminergic synapses (Seeman et al., 1976), due to excessive activation of the D_2 dopamine receptors (Abi-Dargham et al., 2000). Indeed, all antipsychotic drugs for schizophrenia patients target these receptors. Another hypothesis is that one type of receptor for the glutamate neurotransmitter, the NMDA receptor, is expressed at abnormally low levels (Coyle, 2012). It is likely that schizophrenia involves the combination of a number of factors, and different combinations lead to different symptoms.

Dopamine is also a primary factor in Parkinson's disease. For reasons still under investigation, the dopaminergic neurons located in the substantia nigra pars compacta within the basal ganglia die off in Parkinson's patients (Fearnley and Lees, 1991; Surmeier et al., 2010). The basal ganglia are a group of brain nuclei that are strongly connected with the cerebral cortex, thalamus, and the brainstem, and are involved in voluntary movement. Loss of the inhibitory dopamine neurons causes disruption in the motor pathways regulated by the basal ganglia, and results in symptoms including rigidity, shaking, difficulty with walking, and slowness of movement.

Drug addiction also has a strong synaptic basis. The reward areas of the brain, in particular the VTA (ventral tegmental area) and nucleus accumbens, are the primary targets of drugs of addiction including alcohol, heroin, cocaine, opiates, nicotine, cannabinoids, and amphetamine (Oliva and Wanat, 2016). The VTA again consists of dopamine neurons. Use of a drug of addiction can cause a synaptic plasticity and reorganization that generates the drug dependency (Lüscher and Malenka, 2011). Opiates cause a decrease in dendritic spines (Liao et al., 2005), which are protrusions of the dendrites that make many of the synaptic contacts. In contrast, stimulants such as cocaine, amphetamine, and methylphenidate increase the dendritic complexity and spine density. Chronic exposure to cocaine also results in a reorganization of postsynaptic NMDA and AMPA glutamate receptors (Russo et al., 2010). Alcohol abuse leads to many changes in synaptic structure throughout the brain, as well as changes in the expression level of NMDA and $GABA_A$ neurotransmitter receptors, some ion channels, and intracellular signaling molecules (Alfonso-Loeches and Guerri, 2011).

Neural Networks

While the component parts of the brain, the neurons, synapses, and glia, are all quite complex biological systems in themselves, the real power of the nervous system comes from the coupling of the neurons into networks. Neural networks can be as small as several interconnected neurons and as large as millions of interconnected cells. In this section we discuss two examples, starting with a simple invertebrate central pattern generator, and then discussing two much more complex vertebrate neural systems.

Central Pattern Generators

The simplest neural networks are found in invertebrates, where the total number of neurons is so small that they can be counted and given labels. Because of this simplicity, invertebrates have been the target of much research on neural circuits and learning and memory (Kandel et al., 2014). Central pattern generators (CPGs) form a particularly interesting class of neural circuits that has received a great deal of attention by neuroscientists. These are neural networks that exhibit a rhythmic pattern of electrical activity, and this rhythm can underlie behaviors such as walking, chewing, flying, or swimming (Marder and Bucher, 2001).

As an example, we discuss the stomatogastric ganglion in decapod crustaceans, which controls the motion of the gut. Like other CPGs, this neural system remains active in vitro, facilitating its study (Marder and Bucher, 2001; Selverston, 2004). It contains about 30 neurons that form two separate CPGs: the pyloric and the gastric mill CPG. The pyloric CPG produces a fast three-phase rhythm that acts on muscles of the pyloric region of the stomach, resulting in three-phase muscle contractions that moves food through the gut. The gastric mill CPG produces a slower rhythm that controls muscles responsible for chewing by three gastric mill ossicles or teeth. Fig. 2A shows an illustration of the gastric mill neural network, which is remarkably simple, composed of only 10 neurons (Zhu et al., 2017). The network is primarily a composition of mutually inhibitory neurons, with additional electrical coupling between gastric mill (GM) and lateral gastric (LG) and medial gastric (MG) neurons. The activity of the projection neurons is illustrated in Fig. 2B. Each rectangle represents a burst of electrical impulses. The MG neuron fires first, followed shortly after by the GM and LG neurons. This almost-synchronous activity is due to the electrical coupling among the three cell types, which acts to keep the membrane potential the same across the gap junctions. Other neurons are active later in the cycle: lateral posterior gastric neurons are the next to burst, followed by the dorsal gastric neuron. Notice that neurons that have mutual inhibitory coupling, such as the LG and DG neurons, burst at different times in the cycle. This network, like other invertebrate CPGs, is simple enough that its activity can be accurately reproduced with mathematical network models (Marder et al., 1993; Rowat and Selverston, 1993).

Sensory Processing

From the above, it is clear that two key features of the neural circuit—synapses and the intrinsic properties of the component neurons—both contribute to determining the output of a neural circuit. Accordingly, the brain has evolved specializations both in synaptic structure and intrinsic features to optimize any given circuit for its specific function. To exemplify this optimization, in this section we explore a subset of specializations in the processing of auditory information. Many of these examples come from studies of the avian auditory system. Birds, like other terrestrial animals, must extract information from airborne sounds. Birds provide an experimental advantage over most mammalian model systems because of the relative simplicity of their brain stem circuitry. This allows detailed analyses of the cells and synaptic connections in the neural networks responsible for auditory processing. Additionally, like humans, birds hear lower frequency sounds than typical laboratory animals such as mice and rats. Neural networks use information in low frequency sounds to determine the location of a sound source and to identify communication signals (i.e., human speech or bird song) in a noisy background.

In vertebrates, sound pressure waves enter the ear and, through the action of a variety of non-neural structures, result in the release of neurotransmitter from sensory mechanoreceptor cells called hair cells. From this spatial and temporal pattern of chemical release, the nervous system is able to extract key features from the acoustic stimulus that ultimately allow the organism to identify the sound and determine the direction of the sound source so as to respond appropriately. Understanding how the auditory system extracts and codes sound features has led to optimization of cochlear implant technology for the hearing impaired and is leading to greater understanding of central auditory disorders such as tinnitus and hyperacusis.

The first stage of feature extraction is to analyze the timing and intensity of sounds at different frequencies. This appears to be performed by parallel pathways containing neurons and synaptic connections that are optimized for each task (Carr and Soares,
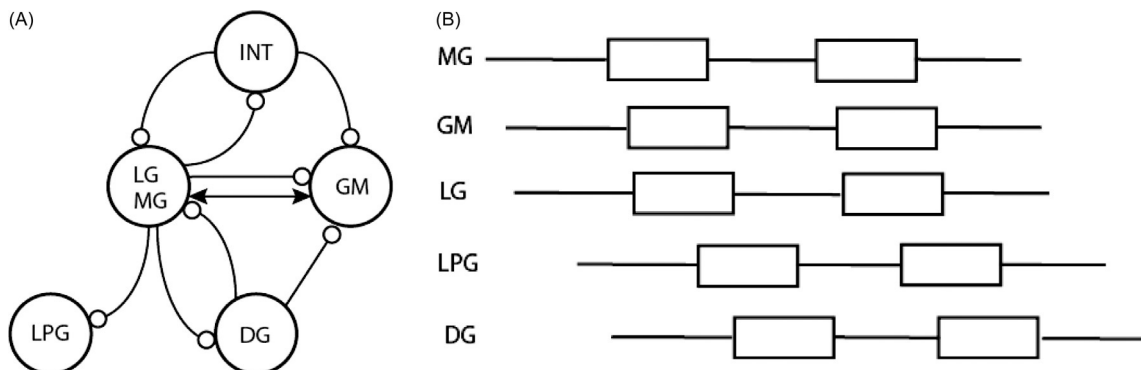

Fig. 2 (A) Simplified network diagram for the gastric mill CPG. *Curves with open ends* represent inhibitory coupling. The *line with double arrow heads* represents electrical coupling. Each *circle* represents a neuron or small group of neurons. INT = interneuron, GM = gastric mill (4 neurons), DG = dorsal gastric, LG = lateral gastric, MG = medial gastric, LPG = lateral posterior gastric (2 neurons). (B) Activity of neurons projecting out to muscles that control ossicles. *Line* segments represent a silent neuron, while *rectangles* represent bursts of electrical impulses.

2002; MacLeod and Carr, 2007; Takahashi et al., 1984). The cochlea can segregate sounds based on frequency and drive auditory nerve fibers at different rates depending on the intensity of the sound. Additionally, these neurons are driven in a way that preserves the temporal dynamics of the acoustic stimulus, detailed below. This frequency-specific, temporally-modulated, intensity-dependent information is carried into the brainstem by patterned action potentials in auditory nerve fibers. Each level of the auditory pathway has cells organized into a map based on the best sound frequency that drives their activity. The intensity and the temporal information of each frequency band appears to be processed in parallel by cells specialized for extracting those features. Variation in both synaptic and intrinsic properties of neurons, as early as the brain stem, essentially filter the pattern of auditory nerve input in different ways in order to extract key temporal information vs. key intensity information. For example, when different cells in the same brain stem region, called the cochlear nucleus, are stimulated with the same series of synaptic potential inputs, some cells produce an output that appears to be well-suited for extracting the timing of the onset of the stimulus, whereas others produce outputs better suited for coding the duration and the amplitude modulation of the stimulus (Brown and Hyson, 2019; Kreeger et al., 2012; Rothman and Manis, 2003).

In addition to differential filtering of the excitatory input from the auditory nerve, activity is further modulated by inhibitory pathways. Here too, variation in the intrinsic properties of inhibitory neurons can modulate the strength of their contribution resulting in cells that either fire transiently or in a sustained pattern (Carroll et al., 2018). Variation in inhibitory neurons is particularly interesting because the balance of excitation and inhibition is not only important for the processing of acoustic information in a neural circuit, but also because imbalances can lead to neuronal cell death (Carroll and Hyson, 2016). Alterations in central inhibitory pathways are also thought to be part of the underlying etiology of tinnitus and hyperacusis (Auerbach et al., 2014; Wang et al., 2009).

As a specific example of how synaptic and intrinsic properties of neurons are optimized for extracting key information from the acoustic stimulus, we will use the analysis of timing information in the avian brain stem auditory system. For relatively low frequency sound waves, the ear will generate a patterned release of neurotransmitter from the hair cells such that the auditory nerve fibers will generate action potentials in a pattern that matches the period of the sound wave. This is called "phase-locking" of the auditory nerve activity and results in a well-timed pattern of activity into the brain stem (Warchol and Dallos, 1990; Oline et al., 2016). In the bird, a portion of these auditory nerve fibers will synapse in a cochlear nucleus called Nucleus Magnocellularis (NM). One of the specializations that allows for the preservation of the highly timed signal is that the synapses in this area are quite large, contacting a large portion of the nearly adendritic soma of the NM neuron (Parks, 1981). These connections, called calyceal synapses or endbulbs of Held, provide synchronous activation of a large number of postsynaptic receptors on the NM neuron. On the postsynaptic side, the NM neurons possess an unusually high concentration of low-threshold K^+ channels on their membrane, which are activated at small depolarizations (Hong et al., 2016; Reyes et al., 1994). One consequence of these channels is that NM neurons will generate only a single action potential to a prolonged depolarization. Hence the phase-locked input is preserved (and possibly enhanced) by these specializations since the cell will only respond to the largest and most synchronous synaptic events.

NM neurons send their axonal projections to another brain stem auditory nucleus called Nucleus Laminaris (NL). In chickens, NL neurons have dendrites that extend in the dorsal direction, where they receive synaptic input from NM neurons on the same side of the brain, and dendrites that extend in the ventral direction, where they receive synaptic input from NM neurons on the opposite side of the brain (Overholt et al., 1992; Young and Rubel, 1983). Here, the process of comparing information from the two ears begins by analyzing the timing differences between the two inputs from NM. This analysis of interaural time differences relies on a relatively simple neuronal network and is depicted in Fig. 3. There are two main features of this circuit: coincidence detectors and delay lines. The array of postsynaptic NL neurons act as coincidence detectors in that they respond maximally when they receive simultaneous activation to both the dorsal and ventral dendrites (Overholt et al., 1992; Joseph and Hyson, 1993). NL neurons also possess a high concentration of low-threshold K^+ channels making them sensitive to the timing of synaptic activation (Kuba et al., 2002; Reyes et al., 1996). Axons from NM neurons on the opposite side of the brain traverse the array of NL neurons sending out collaterals along the way (Young and Rubel, 1983). This sets up a systematic delay in activation of different NL neurons with medially located cells getting their input slightly before more laterally located NL neurons. In the chicken, input from the NM on the same side of the brain appears to splay out to activate all NL neurons at nearly the same time. The end result of this arrangement is that different NL neurons will receive simultaneous activation to the two dendrites depending on the timing differences of sound activating the two ears (Hyson, 2005). In this way, the differential activation of NL neurons helps determine where a sound is originating, since sounds will activate the two ears at slightly different delays depending on the angle of the source relative to the head direction.

From the above, it should be appreciated that a wide range of factors must come into play to develop and maintain an effective neuronal network. Axons must be guided to their targets to set up an intricate pattern of connectivity, synapses must be formed that have the appropriate strength for activating their post-synaptic targets and still maintain the fidelity of the incoming signal, and cells in the circuit must express different specific combinations of ion channels to optimize their input-output function so as to extract timing or intensity information. Perturbance of any of these features can lead to central auditory processing disorders that would not necessarily be detected by simple audiological exams but could have profound influences on perception of rapidly changing stimuli such as speech (Felix et al., 2018; Moore, 2015).
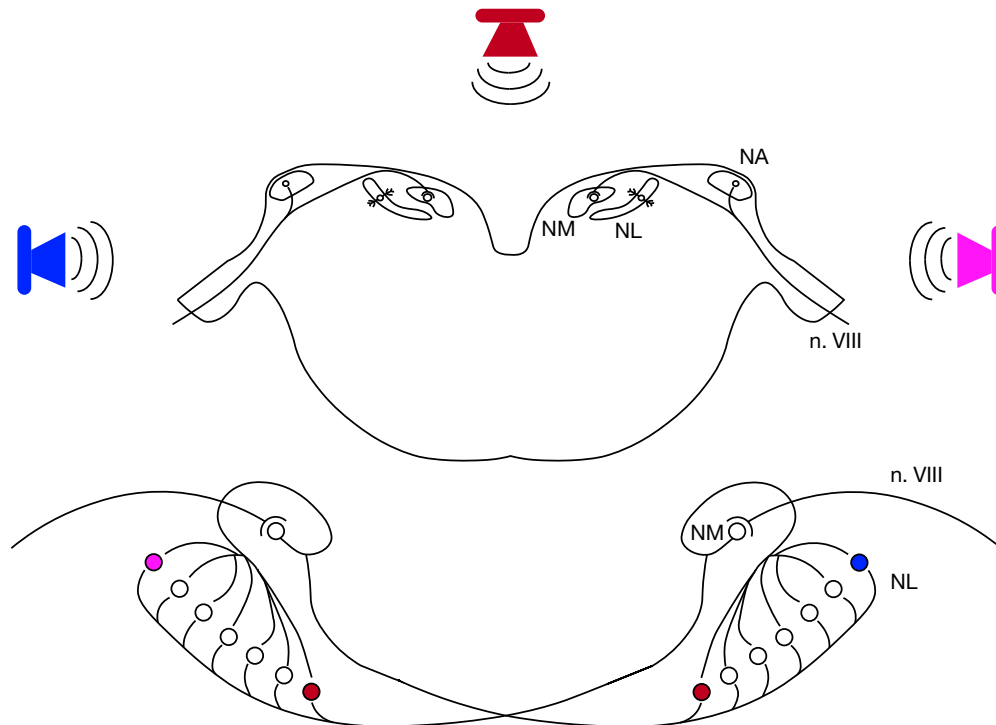
Fig. 3 Schematic illustrating sound localization circuit used for processing interaural time differences in the chicken. Top: Cross section of the brain stem of the chicken showing the location of the auditory nuclei (NM, Nucleus Magnocellularis; NA, Nucleus Angularis; NL, Nucleus Laminaris) and innervation from the auditory nerve (n. VIII). Speakers represent locations of possible sound sources relative to the bird's head. Bottom: Schematic illustration of the innervation patterns from NM to NL denoting the location of maximal activity produced by sounds from the different locations. Each NM neuron receives timed activation by the auditory nerve and sends projections to NL bilaterally. The contralateral projection sequentially activates NL neurons in the medial to lateral direction. The ipsilateral projection activates the entire array of NL neurons nearly simultaneously. Depending on the location of the sound source, only one location in NL will receive simultaneous input from both the ipsilateral and contralateral projections because sounds at different locations will activate the two ears at slightly different delays. For example, a sound at midline (*red*) will activate both ears simultaneously and this results in bilateral activation of cells in the medial-most positions of both NL. A sound located off to the left (*blue*) will activate the left ear first. This means all cells in the left NL will get activated by the left NM before any information from the right NM arrives and only the lateral-most cells in the right NL will receive simultaneous bilateral activation from the two NM. The opposite is true for sound sources located to the right side of the bird (*magenta*). These estimates were obtained by comparing physiological measurements of conduction velocities across the medial-to-lateral extent of NL (Overholt et al., 1992) to measurements of the time differences in how the ears respond to sounds at different locations (Hyson, 2005).

Conclusion

In this article, we have discussed the basic structural and functional units of the brain. The brain is a unique organ that must perform a wide array of functions, from providing the breathing rhythm to interpreting the environment, to making executive decisions. These diverse functions are accomplished through neural networks, many of which are in a cycle of continuous change. Dysfunction of the component parts, such as ion channels or synapses, can have debilitating consequences on health and well-being. Even in the absence of such dysfunctions, the networks themselves can cease to operate as intended due to, for example, the effects of hormone imbalance or drugs. Given the extremely large number of neurons and neural networks that comprise the brain, there is great room for failure, but also feedback mechanisms and redundancy to ensure that small perturbations have little or no consequences. When this fails, the consequences can be devastating.

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