CROSSING THE SYNAPTIC CLEFT: TREATING AUTISM SPECTRUM DISORDER

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VACCINATIONS

An infamous 1998 publication by Andrew Wakefield erroneously suggested that behavioral disorders, including autism, were linked to the MMR vaccine.[1] *The Lancet* retracted the article in 2005 after investigations revealed Wakefield's unethical methods, scientific dishonesty, and conflict of interests.[2] Since then, and as recently as 2014, scientists have been unable to find associations amongst vaccinations, autism spectrum disorder (ASD), and MMR (measles, mumps, and rubella).[3] Yet parents are still apprehensive about vaccinating their children. While 94% of parents intend to vaccinate or have already vaccinated their children with the recommended vaccines, 77% of parents have concerns about vaccines, and 30% worry that "vaccines may cause learning disabilities, such as autism."[4] The cause of autism spectrum disorder is much more complex than the anti-vaccine narrative proposes. Modern research aims to determine the exact cause of ASD and is headed in the direction of developing medical treatment for ASD.

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), autism spectrum disorder is distinguished by impaired social interactions and communications, repetitive behaviors, and preoccupations with specific stimuli. Psychiatrists diagnose individuals with autism according to symptoms that fit these criteria, which are usually recognized by the third year of life. Because the disorder varies greatly amongst individuals, it exists as a spectrum.[5]

HERITABILITY AND GENETICS

In 1943, physician Leo Kanner first identified autism as a disorder distinguished by a lack of social skills.[6] Kanner concluded that children with autism "come into the world with innate inability" to form normal relationships with other people because the children exhibited symptoms of autism at a very early age.[7] Thus, by emphasizing the innateness of the condition, his research suggested the biomedical origin of autism.[7] Yet, for the next twenty years, scientists hypothesized that bad parenting caused autism, claiming that children with apathetic and career-oriented mothers developed abnormally.[6,2] Only in the 1980s, as researchers explored the heritability of ASD, did the biomedical explanation of autism prevail over the refrigerator mother theory.[2]

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To determine whether autism spectrum disorder had a genetic cause, scientists examined concordance: the probability of two twins exhibiting the same physical or disease trait. Twin studies in 1977 revealed that autism spectrum disorder is highly heritable.[8] Concordance rates of ASD are higher amongst identical twins than fraternal twins or siblings, indicating that the likelihood of developing ASD increases as more genetic

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material is shared with an individual diagnosed with ASD.[9] But a single genetic mutation does not account for more than 1% of all ASD cases, suggesting that the genetic foundation for ASD is incredibly complex.[6] For this reason, scientists discuss the likelihood of developing ASD by referring to genetic risk factors.

In genetics, an organism's genotype refers to the genes that it carries, while its phenotype refers to the observable effects of these genes. An individual may genotypically possess the rare deleterious mutations that confer high risk for ASD but not express ASD phenotypically. The process by which an individual's genetic background modulates the phenotypic consequences of deleterious genetic variations is called genetic buffering. Individuals with high genetic buffers are more likely to alleviate the effects of high-risk mutations and lower their risk of developing ASD. On the other hand, individuals with low genetic buffers can develop ASD from a high frequency of low-risk mutations.[9]

Researchers have made significant progress in determining what constitutes a high-risk mutation. One study has identified 107 high-risk genetic mutations that occur amongst 5% of autistic subjects.[10] Both genetic factors and environmental factors account for the development of ASD, but genetic factors currently offer more potential for medical treatment. Hence, characterizing the relationship between what ASD-linked genes encode and how these genes are expressed phenotypically is the next challenge scientists face in determining how to medically treat ASD.

Figure 1. The MMR vaccine.[17] Studies indicate that some parents are still hesitant to vaccinate their children.

SYNAPTIC PLASTICITY

Many genes associated with ASD affect synaptic plasticity, the ability of synapses to adapt to changes in activity. Mutations in these genes disrupt communication amongst neurons by altering the strength of inhibitory or excitatory synaptic inputs.[9] The E/I ratio hypothesis specifically describes how this disturbance in neural networks occurs: imbalances in excitation (E) and inhibition (I).

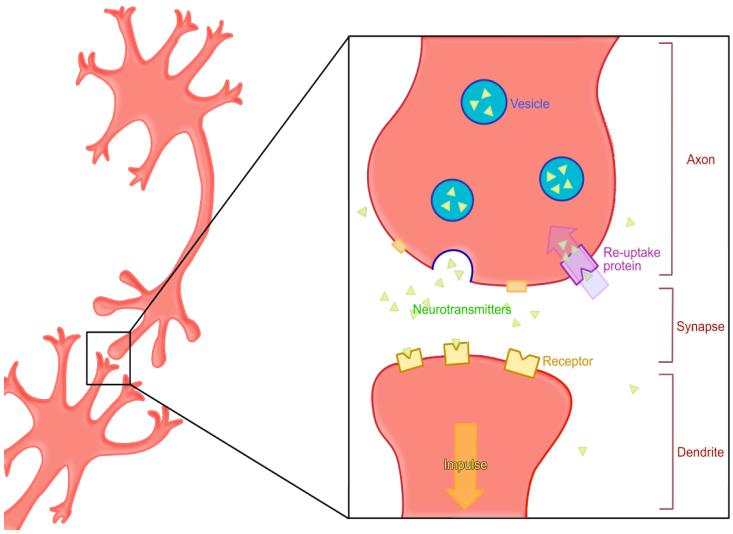

Figure 2. Synaptic function.[18] Synapses regulate communication between neurons through chemicals called neurotransmitters. At the synapse, neurotransmitters from an axon terminal of a presynaptic neuron—the neuron sending the message—travel to dendrites of a postsynaptic neuron—the neuron receiving the message. The message received by the postsynaptic neuron, the synaptic input, can be excitatory or inhibitory. While excitatory synaptic inputs increase the likelihood of an action potential, inhibitory synaptic inputs decrease the likelihood of an action potential. An action potential occurs when a flow of ions moves across the axon of a nerve cell, permitting a neuron to communicate with the next neuron. Altering the behavior of synapses impacts how an organism processes external stimuli by influencing the likelihood of an action potential.

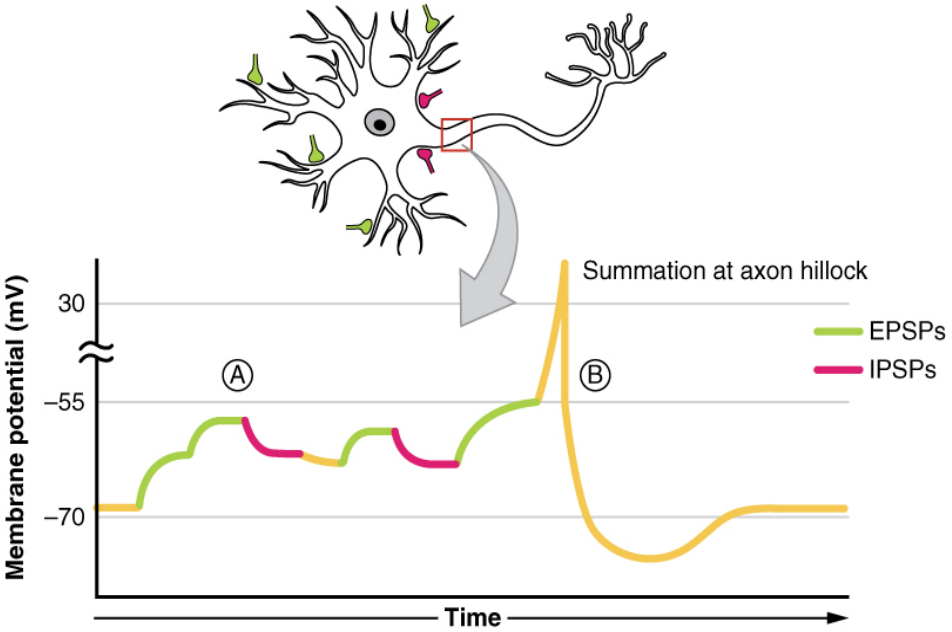

Figure 3. Excitation and inhibition.[19] Excitation and inhibition ratios determine how excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) influence the membrane potential of a neuron. The neuron fires an action potential if its membrane potential passes a critical threshold. Action potentials follow an all-or-none principle. Part A of the figure depicts EPSPs and IPSPs, while Part B portrays the action potential that ensues after an EPSP crosses the critical threshold.

What is the E/I ratio hypothesis? Many researchers predict that mutations in ASD-linked genes lead to fewer functional PV-interneurons.[14] By inhibiting action potentials, PV-interneurons decrease local neuronal activity, expressing a protein called parvalbumin (PV) in order to regulate their firing rates.[11] Thus, if there are fewer functional PV-interneurons, excitatory cells receive less inhibitory synaptic neurotransmission, causing a decrease in inhibition relative to excitation.[11] This imbalance of the E/I ratio is thought to generate an excess of activity in the brain, which impedes normal information processing and ultimately results in cognitive impairments.[12,13]

Neurons have homeostatic mechanisms that prevent too much or too little spiking activity. Synaptic homeostasis adjusts synaptic strength to stabilize firing rates, which can counter the effects of deleterious mutations.[9] But for individuals with ASD, neither genetic buffering nor synaptic homeostasis is enough to offset the effect of the mutations.[9]

Scientists have tested potential therapeutic interventions based on the E/I ratio hypothesis. For example, drugs can alleviate at least some of the symptoms of ASD in mice by targeting the synapses of PV-interneurons to restore normal levels of inhibition.[16] Likewise, optogenetic techniques (the use of light to control genetically modified cells) can increase spike rates of PV-interneurons in mice to compensate for the reduction in inhibition.[15] Though these strategies have rescued some behavioral function in mouse models, neurobiologists must investigate whether the same can be done for humans.[15,16]

From establishing the heritability of ASD to anticipating the implications of E/I imbalances, research regarding ASD has made significant progress in the last fifty years. Though no medical treatment for ASD exists today, advances in implicated fields, such as genetics, psychology, and neurobiology, encourage scientists to explore potential options. It is possible that the next generation of researchers will successfully discover medical treatment for ASD in humans. In the meantime, the existing scientific literature can at least quell fears regarding vaccinations.

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IMAGE REFERENCES

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