"Today we're going to talk about autism spectrum disorder, or ASD.

Autism is a neurodevelopmental disorder, meaning that it involves differences in how the brain develops, and those differences can affect behavior, communication, and sensory processing.

We're going to start with how autism is defined and diagnosed, then look at what we know about its causes and underlying neurobiology. Finally, we'll discuss treatment approaches, including some newer experimental treatments.

One thing I want you to keep in mind throughout this lecture is just how much variability there is among individuals with autism. That's one of the biggest challenges when we're trying to understand the neuroscience."

"Autism is characterized by two broad categories of symptoms: difficulties with social communication and interaction, and restricted or repetitive patterns of behavior.

But the word *spectrum* is really important here. Autism doesn't look the same in every person. Some individuals have substantial language difficulties, while others communicate very effectively. Some have significant sensory sensitivities, while others are less affected.

The image here illustrates that autism involves multiple dimensions, rather than a single continuum from mild to severe.

You'll also hear the term *neurodiversity*. This refers to the idea that there's natural variation in how human brains develop and function. *Neurotypical* describes people whose development is relatively typical, whereas *neurodivergent* describes people whose neurological development or functioning differs from what's considered typical.

Autism is one form of neurodivergence, but the term can also include conditions like ADHD and dyslexia."

"Autism is diagnosed based on behavior. We don't currently have a brain scan, blood test, or genetic test that can diagnose autism in everyone.

According to the DSM-5-TR, there are two major diagnostic categories.

Criterion A involves difficulties with social communication and interaction. All three components have to be present. These include social-emotional reciprocity, nonverbal communication, and the ability to develop and maintain relationships.

So, for example, someone might have difficulty with back-and-forth conversations, interpreting facial expressions, or understanding social expectations.

Criterion B involves restricted or repetitive behaviors, and at least two of the four categories have to be present. These might include repetitive movements, strong preferences for routines, highly focused interests, or unusual responses to sensory stimulation.

Symptoms also have to be present during early development and have a meaningful impact on functioning.

And importantly, the DSM includes specifiers for things like language ability, intellectual functioning, and associated medical or genetic conditions, because these can vary tremendously between individuals."

"The DSM also describes three levels of autism based on the amount of support a person requires.

Level 1 means requiring support. These individuals may communicate verbally and function independently in many areas but still experience significant difficulties with social interaction or changes in routine.

Level 2 means requiring substantial support, and Level 3 means requiring very substantial support.

Generally, as we move from Level 1 to Level 3, difficulties with communication, behavioral flexibility, and everyday functioning become more pronounced.

But these levels are not necessarily fixed throughout a person's life. Support needs can change with development, environmental demands, and access to appropriate services.

And they don't tell us everything about someone's intellectual abilities or individual strengths."

"Because autism is a neurodevelopmental disorder, signs can appear very early in life.

During the first year, some infants may show reduced eye contact, less social smiling, or limited responses when someone calls their name.

As children get older, we may see delays in gestures, pointing, language development, or shared attention.

Shared attention is especially important. For example, a typically developing toddler might point at a dog, not because they want the dog, but because they want you to look at it with them. That kind of shared social experience may be less common in some children who later receive an autism diagnosis.

By around two years of age, there may also be noticeable differences in pretend play, peer interaction, or repetitive behavior.

Autism can often be reliably diagnosed by an experienced clinician around age two, although many children aren't diagnosed until several years later.

And none of these individual signs automatically means a child has autism. What matters is the broader developmental pattern."

"This figure illustrates something we've already touched on, which is the enormous heterogeneity of autism.

Rather than thinking of autism as one disorder with exactly the same underlying biology in everyone, many researchers increasingly think of it as a collection of overlapping neurodevelopmental conditions.

Look at the three examples on the right. Each individual has a different combination of characteristics.

One person might have significant communication difficulties but relatively little sensory sensitivity. Another might have excellent verbal abilities but substantial difficulties with routines or sensory processing.

And this variability extends beyond symptoms. It also exists at the genetic, cellular, and neural circuit levels.

So when we talk about brain differences associated with autism, we need to remember that a finding in one subgroup may not apply to everyone diagnosed with ASD."

"Autism diagnoses have increased substantially over the past several decades.

According to the CDC estimate shown here, about one in 31 eight-year-old children in the United States has been identified with autism.

Autism is also diagnosed more frequently in boys than girls, although there's increasing recognition that autism may be underidentified in girls, particularly when symptoms are less obvious or individuals develop ways of masking social difficulties.

Another important point is that autism frequently occurs alongside other conditions, including ADHD, anxiety, sleep disturbances, and intellectual disability.

But intellectual functioning varies considerably. Some individuals have intellectual disabilities, while others have average or above-average intelligence.

That's another reason why it's difficult to describe a single typical presentation of autism.

And remember that prevalence estimates depend on how we identify and diagnose the disorder."

"This figure comes from a 2023 study comparing individuals with autism to their siblings without autism.

The blue bars represent individuals with ASD, and the gray bars represent their siblings.

What stands out is that many conditions are more common in the ASD group, including ADHD, anxiety disorders, sleep disturbances, learning disabilities, and epilepsy.

This is important because autism rarely exists in complete isolation from other developmental or medical conditions.

And from a neuroscience perspective, it raises an interesting question: Are these conditions consequences of having autism, or do they share some of the same underlying genetic and neurodevelopmental mechanisms?

The answer probably depends on the particular condition. But as we'll see later, there's growing evidence that some of these disorders share biological risk factors."

"Autism has been the subject of quite a bit of controversy, both scientifically and socially.

Some debates involve how we define and diagnose the disorder. Others involve questions about its causes, how it should be treated, and even whether all aspects of autism should be considered something that needs treatment.

One important discussion concerns the neurodiversity movement, which emphasizes that neurological differences aren't necessarily deficiencies that need to be corrected.

There's also debate about representation. For example, autistic individuals who can communicate independently may have very different perspectives and priorities than families caring for individuals who require extensive lifelong support.

And then there are controversies surrounding proposed causes and treatments, some of which are based on legitimate scientific uncertainty, while others involve misinformation.

These are complicated issues, and it's important to distinguish scientific evidence from social or political opinions."

"This graph shows how dramatically autism prevalence estimates have increased over time.

Back in 2000, approximately one in 150 children was identified with autism. By 2022, that estimate had increased to one in 31.

Now, does that mean autism itself has become five times more common? Not necessarily.

One major factor is that the way we define and diagnose autism has changed.

In 2013, the DSM-5 combined several previously separate diagnoses, including autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified, into one autism spectrum disorder diagnosis.

We've also seen increased awareness, better screening, and greater recognition of autism in populations that historically went undiagnosed.

These factors explain at least part of the increase. Whether there's also been a true change in the underlying occurrence of autism is more difficult to establish.

The important distinction is that these numbers represent children *identified* with autism, not necessarily a direct measure of how frequently the underlying biological condition occurs."

"Now we're going to shift into the causes of autism.

As with many psychiatric and neurodevelopmental disorders, there's no single cause that explains every case.

Instead, autism involves a complicated interaction between genetic factors and environmental influences, particularly during development.

This figure also illustrates something important about the comorbid conditions we discussed earlier.

The same genetic or environmental factors that contribute to autism risk may also contribute to conditions like ADHD, anxiety, or intellectual disability.

So just because a condition occurs more frequently in individuals with autism doesn't necessarily mean autism caused it.

Both conditions may arise, at least partly, from overlapping underlying risk factors."

"When we talk about environmental influences on autism, we're primarily interested in exposures that occur during sensitive periods of brain development.

These include the prenatal period and early life, when neurons are developing, migrating, establishing connections, and beginning to form functional circuits.

Researchers have investigated factors such as maternal infections, immune activation, metabolic conditions, certain medications, and exposure to environmental toxins.

The graph here shows that some prenatal and postnatal exposures are more common in children with autism than in their siblings without autism.

For example, preterm birth and reduced oxygen availability around birth are among the factors researchers have investigated.

But we need to distinguish correlation from causation. Just because an exposure is associated with autism doesn't mean it directly causes autism.

Some associations may reflect shared genetic vulnerabilities or other factors that influence both the exposure and developmental outcomes.

The overall idea is that environmental influences may interact with genetic susceptibility during important windows of neurodevelopment."

"Genetics plays a major role in autism. Heritability estimates suggest that a substantial proportion of variation in autism risk is related to genetic differences.

But there's not one autism gene. In fact, there are many different genetic pathways that can contribute to the disorder.

We can think about these in two broad categories.

The first involves rare genetic variants that can have relatively large effects. Examples include variants affecting genes like SHANK3 and CHD8.

Some of these variants arise *de novo*, meaning they're new mutations that weren't inherited from either parent. Others are inherited.

The second category involves common genetic variants. Individually, these have very small effects, but together they can contribute to what we call polygenic risk.

What I find particularly interesting from a neuroscience perspective is that many autism-associated genes converge on similar cellular processes.

Look at this figure. We see genes involved in synapse formation, protein synthesis, cytoskeletal organization, and regulation of gene expression.

So even though different individuals may have different genetic risk factors, those genes often affect how neurons develop, communicate, and modify their connections.

That's going to become particularly important when we discuss synaptic functioning later in the lecture."

"Before we get further into the neuroscience, I want to briefly discuss some of the problematic history surrounding autism.

One of the most damaging early explanations was the so-called refrigerator mother theory.

This theory suggested that autism was caused by mothers who were emotionally cold, distant, or insufficiently affectionate toward their children.

The idea became particularly influential during the 1950s and 1960s, largely through the work of Bruno Bettelheim and other psychoanalytically oriented clinicians.

There was never convincing scientific evidence supporting this explanation.

And of course, the consequences were terrible. Parents, especially mothers, were blamed for a neurodevelopmental condition that they hadn't caused.

The theory has been completely rejected.

It's a good example of what can happen when psychological explanations become widely accepted without adequate empirical evidence."

"Another major controversy involves vaccines.

In 1998, Andrew Wakefield and colleagues published a paper in *The Lancet* suggesting a possible relationship between the MMR vaccine and autism.

The study included only 12 children, and its conclusions were not supported by the evidence.

Subsequent investigations identified serious ethical and methodological problems, including misrepresentation of clinical information. The paper was eventually retracted, and Wakefield lost his medical license in the United Kingdom.

But by then, the idea that vaccines might cause autism had already spread widely.

Since that time, numerous large epidemiological studies involving hundreds of thousands of children have examined this question.

And the evidence is very clear: the MMR vaccine does not cause autism.

What's unfortunate is that the original claims contributed to vaccine hesitancy, which can increase the risk of preventable infectious diseases.

So this is not an area where we have two equally supported scientific explanations. The proposed causal relationship between MMR vaccination and autism has been extensively investigated and is not supported."

"After the original MMR controversy, another argument emerged involving thimerosal, a preservative that contains ethylmercury and was used in some vaccines.

The concern was that mercury exposure might interfere with brain development and contribute to autism.

But there are several problems with that explanation.

First, ethylmercury is different from methylmercury, which is the form more commonly associated with environmental mercury toxicity.

Second, thimerosal was removed from or reduced to trace amounts in most routine childhood vaccines in the United States around 2001, and autism prevalence did not subsequently decline.

And third, large studies comparing vaccinated and unvaccinated children have not found evidence that vaccination increases autism risk.

Researchers have also examined families with an older child diagnosed with autism and found that avoiding vaccination in younger siblings does not prevent autism.

So again, the evidence does not support vaccines or vaccine-associated mercury exposure as causes of autism."

"Another proposed environmental risk factor is acetaminophen, which is the active ingredient in Tylenol.

Some observational studies have reported associations between acetaminophen exposure during pregnancy and an increased likelihood of autism or other neurodevelopmental conditions.

For example, one study measured acetaminophen metabolites in umbilical cord blood and found that higher concentrations were associated with increased odds of an autism diagnosis.

Researchers have proposed possible mechanisms involving prostaglandin signaling, oxidative stress, and altered neural development.

However, these mechanisms are largely hypothetical in the context of typical therapeutic exposure in humans.

And there's a major methodological issue with the observational studies: people who take acetaminophen may differ from those who don't in ways that are themselves related to developmental outcomes.

For example, they may be taking it because of fever, infection, inflammation, or other medical conditions.

A large Swedish study published in 2024 addressed some of these concerns by comparing siblings within the same families.

When researchers accounted for shared familial factors, the association between prenatal acetaminophen use and autism was no longer evident.

So this is a good example of why an observed association doesn't establish causation, especially when we're studying complex developmental outcomes."

"So what's our overall conclusion about the causes of autism?

First, genetics plays a substantial role, but there are many different genetic pathways that can contribute to risk.

Second, environmental factors may influence development, particularly during prenatal and early postnatal periods, although identifying causal relationships is difficult.

Third, there's no single mechanism that explains every case of autism.

And importantly, some widely publicized proposed causes, particularly vaccines, have not held up to scientific investigation.

This figure illustrates how researchers are trying to understand the interactions among genetics, environmental exposures, immune signaling, and neural development.

The challenge is figuring out which mechanisms actually contribute to autism, which are associated with specific subgroups, and which may represent consequences rather than causes.

Now let's move from the causes of autism to what researchers have found when they actually examine the brain."

"Researchers have identified a number of structural brain differences associated with autism, although the findings aren't always consistent across studies or individuals.

Two regions that have received considerable attention are the amygdala and hippocampus.

The amygdala is especially interesting because of its role in processing emotionally and socially relevant information. Given that differences in social interaction are central to autism, researchers have investigated whether altered amygdala development might contribute to these characteristics.

Some postmortem studies have reported differences in neuronal size, density, and organization within the amygdala and hippocampus.

Another major area of interest is the cerebellum.

We've traditionally associated the cerebellum with motor coordination, but we now know that it also contributes to cognition, language, and aspects of social behavior.

One finding reported in several postmortem studies is a reduction in Purkinje cells, which are the primary output neurons of the cerebellar cortex.

Purkinje cells are GABAergic, so they provide inhibitory signaling to the deep cerebellar nuclei.

Alterations in these cells could affect cerebellar processing and communication with other brain regions.

But again, these are findings from particular studies and populations. We don't see exactly the same structural abnormalities in every individual with autism."

"This figure summarizes findings from MRI studies examining brain structure in individuals with autism.

The first thing you'll notice is that the findings are pretty complicated. Some studies report increased volume in certain brain regions, while others report reduced volume or no significant differences.

For example, researchers have reported differences in frontal and temporal cortical volume, cortical folding, the amygdala, hippocampus, and cerebellum.

Even within the cerebellum, different regions may show different patterns of structural change.

And this variability isn't necessarily surprising.

Brain development changes dramatically across childhood and adolescence, so the age of the participants can influence what researchers find.

Differences in the characteristics of the individuals being studied can also contribute to inconsistent results.

So I wouldn't try to memorize every structural finding in this figure.

The main takeaway is that autism is associated with differences in brain development across multiple regions, rather than one specific area being abnormal in every individual."

"Now we're going to look at functional differences, starting again with the cerebellum.

One reason the cerebellum is particularly interesting is that different cerebellar regions communicate with different areas of the cerebral cortex.

So the cerebellum doesn't just contribute to movement. Its connections also allow it to participate in cognitive, emotional, and social processing.

This figure illustrates how different cerebellar regions have been associated with different behavioral characteristics in autism.

For example, the anterior cerebellum is more closely associated with motor functioning, while portions of the posterior cerebellum participate in language and higher-order cognitive processing.

The posterior vermis has been associated with emotional and social processing.

And regions known as Crus I and Crus II have connections with cortical areas involved in cognition and social behavior.

So depending on which cerebellar circuits are affected, we might see different types of behavioral difficulties.

That's one possible explanation for some of the heterogeneity we've been discussing."

"This figure illustrates another interesting finding involving connectivity between the cerebellum and cerebral cortex.

In this study, researchers found stronger functional connectivity between the cerebellum and cortical regions involved in sensorimotor processing in individuals with autism.

That's shown in the top portion of the figure.

But in the bottom portion, we see reduced connectivity between the cerebellum and cortical regions involved in higher-order cognitive functioning, including the prefrontal cortex.

So we're seeing both overconnectivity and underconnectivity, depending on which circuits we're examining.

One possible interpretation is that different neural systems follow different developmental trajectories.

Sensorimotor circuits develop relatively early, while circuits involved in executive functions and complex cognition continue developing over a much longer period.

Alterations in these developmental processes could produce different patterns of connectivity across the brain.

The important point is that autism doesn't simply involve too much or too little connectivity everywhere. The differences appear to depend on the specific neural circuits involved."

"Now let's talk about what researchers often refer to as the social brain network.

This isn't one anatomical structure. It's a collection of interconnected brain regions involved in perceiving, interpreting, and responding to social information.

The medial prefrontal cortex is involved in social reasoning, including thinking about other people's intentions and mental states.

The superior temporal sulcus helps us process things like eye gaze, facial movements, and biological motion.

The temporoparietal junction is particularly important for perspective-taking, or understanding that other people can have beliefs and knowledge that differ from our own.

The amygdala helps evaluate the emotional and social relevance of stimuli.

And the fusiform face area is involved in recognizing and processing faces.

When we interact socially, these regions don't operate independently. They communicate with one another to help us interpret social situations and respond appropriately.

So researchers have investigated whether differences in the functioning or connectivity of this network might help explain some of the social communication characteristics associated with autism."

"This slide compares social brain functioning in typically developing individuals and individuals with autism.

Some studies have reported reduced activation in the medial prefrontal cortex during tasks requiring people to think about someone else's mental state.

This is often called *theory of mind*, which refers to our ability to recognize that other people have their own thoughts, beliefs, and intentions.

Researchers have also observed differences in how regions like the superior temporal sulcus respond to eye movements and gaze direction.

The amygdala may respond differently to socially relevant stimuli, including unfamiliar faces.

And some studies have reported reduced activation in the fusiform face area during face-processing tasks.

But there's an important distinction here.

Different brain activation doesn't necessarily mean an individual cannot process that information. It may reflect differences in attention, experience, or the strategies being used to complete the task.

For example, if someone spends less time looking directly at faces, that can influence activation in regions involved in face processing.

So these findings suggest differences in social information processing, but they don't establish one universal neural deficit that explains autism."

"One aspect of autism that I think is particularly interesting from a neuroscience perspective is sensory processing.

Many individuals with autism experience sensory input differently.

Some are hypersensitive, meaning they respond very strongly to stimulation that other people may barely notice. For example, fluorescent lighting, background noise, certain clothing textures, or physical touch might be extremely uncomfortable.

Others may be hyposensitive, meaning they respond less strongly to certain types of sensory input.

And the same individual can be hypersensitive to one type of stimulation and hyposensitive to another.

From a neural perspective, researchers have proposed that these differences involve altered communication between sensory pathways and brain regions responsible for attention, salience, and behavioral regulation.

For example, the thalamus relays much of our sensory information to the cortex.

The insula and amygdala contribute to evaluating the significance of sensory experiences, while prefrontal regions help regulate attention and responses.

One hypothesis is that differences in bottom-up sensory signaling, combined with altered top-down regulation, can make it difficult to filter or prioritize sensory information.

So imagine trying to have a conversation in a room where every background sound seems just as important as the person talking to you.

That gives you some idea of how differences in sensory filtering could influence attention, communication, and behavior."

"Now we're going to move down to the cellular level.

We've talked about differences in brain structure and functional connectivity, but an important question is what might actually be happening at the level of individual neurons and synapses.

And this is where some of the genetic findings become particularly interesting.

Many autism-associated genes are involved in synaptic development, neurotransmission, and plasticity.

So one major area of research involves understanding how changes in synaptic functioning during development might eventually produce differences in neural circuits and behavior.

We're going to look at several mechanisms that have received considerable attention, including synaptic proteins, synaptic pruning, plasticity, and the balance between excitation and inhibition."

"This figure shows several proteins that are important for normal synaptic functioning and that have been implicated in autism.

Let's start with neurexins and neuroligins.

Neurexins are primarily located on the presynaptic side, while neuroligins are located on the postsynaptic side. These proteins interact across the synaptic cleft and help organize connections between neurons.

You can think of them as part of the machinery that helps neurons form and maintain appropriate synaptic connections.

Another important protein is SHANK3, which is located in the postsynaptic density of excitatory synapses.

SHANK3 is a scaffolding protein. It helps organize receptors and other signaling proteins that are necessary for normal glutamatergic transmission.

Mutations affecting SHANK3 can disrupt synaptic structure and plasticity, and they're associated with a genetic condition called Phelan-McDermid syndrome, which frequently includes autism-related characteristics.

The figure also shows genes such as MECP2, which regulate gene expression and indirectly influence synaptic development.

So these genes don't all do the same thing.

Some influence synaptic adhesion, others regulate postsynaptic organization, and others affect gene expression.

But the common theme is that they can influence how neural connections develop and function."

"Another mechanism that has received a lot of attention is synaptic pruning.

During early development, the brain produces an enormous number of synaptic connections.

But we don't keep all of them.

As neural circuits mature, some connections are strengthened and maintained, while others are eliminated through a process called synaptic pruning.

This helps refine neural circuits based on developmental processes and experience.

Some postmortem studies have reported increased dendritic spine density in individuals with autism, suggesting that synaptic pruning may be altered in at least some cases.

The illustration at the bottom gives you the general idea. On the left, we have a more extensively pruned neuron. On the right, we have a neuron with a greater number of connections.

Now, more synapses might sound like a good thing, but that's not necessarily true.

Efficient neural processing depends on having appropriately organized and regulated connections, not simply maximizing the number of synapses.

If pruning is altered, that could potentially influence neural connectivity, sensory processing, and learning.

Researchers have also investigated pathways such as mTOR, which regulates protein synthesis and cellular processes involved in synaptic development.

But I want to emphasize that reduced pruning is one proposed mechanism, not an established explanation for all cases of autism."

"Related to synaptic pruning is synaptic plasticity, which we've discussed previously in this course.

Remember that synaptic plasticity refers to the ability of synapses to strengthen or weaken in response to activity and experience.

Two important examples are long-term potentiation, or LTP, and long-term depression, or LTD.

LTP generally involves a persistent strengthening of synaptic transmission, while LTD involves a persistent weakening.

Both are important for learning and adapting to our environment.

In several animal models associated with autism, researchers have reported abnormalities in LTP, LTD, or other forms of synaptic plasticity.

The figure here illustrates how these processes depend on signaling through glutamate receptors, including NMDA and AMPA receptors, and the regulation of local protein synthesis.

One protein shown here is FMRP, which is associated with Fragile X syndrome.

FMRP normally helps regulate the translation of proteins at synapses. When FMRP is absent or dysfunctional, synaptic protein synthesis and plasticity can be altered.

This raises the possibility that differences in synaptic plasticity could contribute to some of the behavioral characteristics associated with autism, including repetitive behaviors or difficulty adapting to changing situations.

Of course, autism doesn't simply mean someone has an inability to learn. Rather, specific forms of learning or adaptation may be affected differently depending on the individual and the underlying mechanisms."

"Another major hypothesis involves the balance between excitation and inhibition in neural circuits.

As you know, glutamate is the primary excitatory neurotransmitter in the brain, while GABA is the primary inhibitory neurotransmitter.

For neural circuits to function appropriately, excitation and inhibition have to be carefully regulated.

If there's excessive excitation, reduced inhibition, or some combination of the two, the way information is processed can change.

One proposed consequence is a reduction in the signal-to-noise ratio.

Think about trying to listen to one person talking in a crowded room. You need to process the relevant signal while filtering out competing activity.

If neural circuits are excessively active or poorly regulated, distinguishing meaningful information from background activity may become more difficult.

This could potentially contribute to sensory hypersensitivity or other differences in information processing.

Researchers have identified autism-associated genes involved in GABAergic signaling, ion channel functioning, and the regulation of neuronal excitability.

Animal models have also demonstrated changes in inhibitory interneuron functioning and neural oscillations.

Now, we shouldn't interpret this as meaning that every autistic brain has too much glutamate or too little GABA.

The idea is that altered regulation of excitation and inhibition may contribute to atypical neural circuit functioning in some forms of autism."

"So let's put these cellular mechanisms together.

We started by looking at genetic variants that affect proteins involved in building and maintaining synapses.

Then we discussed changes in synaptic pruning, which could alter the number and organization of neural connections.

We also talked about differences in synaptic plasticity, which could influence how neural circuits change in response to experience.

And finally, we looked at the possibility that altered excitation and inhibition could affect how efficiently neural circuits process information.

These mechanisms aren't necessarily independent.

For example, a mutation affecting synaptic protein synthesis could also influence plasticity and ultimately change neural circuit activity.

Another area of research involves glial cells and inflammatory signaling, which we'll discuss next.

The important point is that autism-related differences in brain function may emerge from multiple interacting cellular and synaptic processes."

"Neurons aren't the only cells involved in brain development, of course.

Glial cells also play important roles, and there's increasing interest in how they might contribute to autism.

Let's start with microglia.

Microglia are the brain's resident immune cells, but they also participate in normal neural development, including synaptic pruning.

Under some conditions, altered microglial functioning could interfere with the normal refinement of neural circuits.

Researchers have reported evidence of altered microglial activity and inflammatory signaling in some individuals with autism, although the findings aren't universal.

Astrocytes are another important cell type.

As we've discussed, astrocytes help regulate the extracellular environment, including the uptake of neurotransmitters such as glutamate.

So changes in astrocyte functioning could potentially affect extracellular glutamate concentrations, neuronal excitability, and synaptic transmission.

There's also interest in maternal immune activation during pregnancy and whether inflammatory signaling during sensitive developmental periods might influence the developing nervous system.

But it's important not to oversimplify this into the claim that autism is an inflammatory disorder.

Instead, immune signaling and glial functioning are additional mechanisms that may contribute to certain forms of autism, particularly through their effects on neural development and synaptic regulation."

"Now let's move into treatments.

The first thing to understand is that autism is a lifelong neurodevelopmental condition. Treatment isn't necessarily about eliminating autism. Instead, interventions generally focus on improving communication, supporting independence, developing skills, and addressing difficulties that interfere with quality of life.

One commonly used approach is applied behavior analysis, or ABA.

ABA uses principles of learning and reinforcement to teach skills and modify behavior.

It's also somewhat controversial. Although some individuals and families report substantial benefits, critics have raised concerns about approaches that emphasize compliance or try to eliminate harmless autistic behaviors rather than focusing on meaningful functional outcomes.

Another approach is the Early Start Denver Model, which combines behavioral principles with developmentally appropriate, play-based interactions.

It's designed for very young children and focuses particularly on communication, social engagement, and learning.

Speech therapy is also important, and that doesn't always mean teaching spoken language. It may include alternative communication systems, such as tablets or other assistive technologies.

Occupational therapy can help with sensory regulation, motor coordination, and everyday activities.

Overall, the most appropriate interventions depend on the individual's abilities, challenges, goals, and support needs."

"Now, what about medications?

One important point is that we don't currently have medications that reliably treat the core social communication characteristics of autism.

Instead, medications are generally used to manage associated symptoms or co-occurring conditions.

For example, risperidone and aripiprazole are FDA-approved for treating irritability associated with autism in children and adolescents. This can include severe aggression, tantrums, or self-injurious behavior.

Both drugs act on dopamine receptors, although their pharmacology is somewhat different.

Risperidone is a D2 receptor antagonist, while aripiprazole is a partial D2 receptor agonist.

For individuals who also experience hyperactivity or attention difficulties, clinicians may use medications such as methylphenidate or atomoxetine.

Methylphenidate increases catecholamine signaling, particularly dopamine and norepinephrine, by inhibiting their reuptake.

Atomoxetine primarily inhibits norepinephrine reuptake.

SSRIs are sometimes used for co-occurring anxiety or other symptoms, although evidence for treating repetitive behaviors in children with autism is limited.

And there are other medications, such as guanfacine or buspirone, that may be useful for particular symptoms in some individuals.

But these treatments need to be individualized because medication responses and side effects can differ considerably.

And again, the goal is symptom management, not treating autism as though it's caused by one specific neurotransmitter abnormality."

"Beyond the medications currently used in clinical practice, researchers are investigating treatments that target some of the underlying biological mechanisms we've discussed.

One approach involves trying to modify the balance between excitation and inhibition.

For example, bumetanide is a diuretic that can influence chloride regulation and potentially alter how neurons respond to GABA.

Remember that the effects of GABA depend partly on the chloride gradient across the neuronal membrane.

So theoretically, changing intracellular chloride concentrations could influence inhibitory signaling.

There was some early interest in bumetanide as a treatment for autism, although results from clinical trials have been mixed and larger studies haven't consistently demonstrated benefit.

Another approach targets the mTOR signaling pathway.

We discussed earlier how mTOR regulates protein synthesis and aspects of synaptic development.

In certain genetic conditions, including tuberous sclerosis complex, mTOR signaling is abnormally elevated.

So researchers have investigated whether mTOR inhibitors, such as rapamycin, might help address some of the downstream consequences of these mutations.

There are also experimental approaches targeting inflammatory signaling, including compounds such as sulforaphane and minocycline.

But I want to emphasize that these are experimental approaches, not established treatments for the core characteristics of autism.

And the fact that autism is so heterogeneous makes developing broadly effective biological treatments particularly challenging."

"One of the more interesting directions in autism research involves developing treatments for specific genetic forms of the disorder.

And this is where our understanding of the molecular mechanisms might eventually translate into more targeted therapies.

There are several different strategies.

One approach is to target a pathway that's disrupted by a particular mutation.

For example, tuberous sclerosis complex involves mutations affecting TSC1 or TSC2, which normally help regulate mTOR signaling.

mTOR inhibitors are already used to treat certain manifestations of tuberous sclerosis, including some forms of epilepsy.

Another approach is gene replacement therapy.

The basic idea is to deliver a functional copy of a gene when the original gene is missing or dysfunctional.

For example, researchers have been investigating SHANK3 gene replacement as a potential treatment for Phelan-McDermid syndrome.

Remember that SHANK3 encodes an important postsynaptic scaffolding protein at excitatory synapses.

So restoring SHANK3 expression might improve synaptic functioning in individuals with mutations affecting that gene.

Animal studies have shown that restoring SHANK3 expression can improve certain synaptic and behavioral abnormalities, which provides some support for this approach.

The company shown here, Jaguar Gene Therapy, has been developing a gene therapy approach targeting SHANK3-related disorders.

A third strategy involves reactivating genes that have been silenced, such as FMR1 in Fragile X syndrome.

These approaches are still being investigated, and there are major challenges involving gene delivery, appropriate expression levels, treatment timing, and safety.

But they illustrate something important: as we learn more about the genetic and cellular mechanisms underlying particular forms of autism, it may become possible to develop treatments that are much more biologically specific.

And that's particularly exciting because it moves us away from trying to develop one treatment for everyone with an autism diagnosis."

"So that's where we'll finish our discussion of autism.

The main thing I want you to take away from this lecture is that autism is an extremely heterogeneous neurodevelopmental condition.

Genetics clearly plays a major role, but many different genes and biological pathways are involved.

And although we've identified differences in brain structure, connectivity, synaptic functioning, and neural development, there's no single neural mechanism that explains every case.

Understanding that heterogeneity is going to be important for developing better interventions and, potentially, more targeted biological treatments.

And that's it for autism!"