# Chapter 2: Biology

*What Is the Biology Underlying Autism?*

**Aspirational Goal: Discover the roles of brain development, cognition, and physiological function in autism and its co-occurring conditions to enable the development of effective, targeted interventions and societal accommodations that promote positive outcomes across the lifespan.**

## Introduction

Current scientific evidence suggests that autism arises during early development and results in differences in brain structure, function, and connectivity. Those brain differences lead to differences in areas such as social behavior, learning, communication, sensory perception, and intellectual ability. Over the course of the last decades, research has revealed that genes and environmental influences in early development are contributing factors. The biological mechanisms by which known gene variations may lead to autism by altering the underlying neural circuitry of the brain areas of active investigation. These genetic variants are associated with several general functions in neurons (brain cells), including regulating when and how genes are expressed and the function of synapses, which are the points of connection and communication between neurons.

However, much remains to be learned about the specific biological mechanisms that lead to autism and differences in cognition (including facial processing and emotion regulation), language development and communication, motor development, and sensory processing. More research is also needed to better understand how the presentation of autism differs across sex and gender. Additionally, studies on the relationship of common co-occurring mental and physical health conditions to autism are also needed, as are longitudinal studies to better understand the developmental trajectories of autism and co-occurring conditions. Greater insight and understanding of these molecular, neurological, and developmental differences will allow for personalized, targeted interventions that can promote positive outcomes for all individuals on the autism spectrum across the lifespan.

## Molecular Mechanisms and Genes Implicated in Autism

Genetic studies over the past 20 years have identified over 100 genes that contribute to the development of autism, though many of these genes also are implicated in other mental health and developmental conditions as well.[1-3] This number is growing rapidly, and it is likely that over 1,000 genes that make smaller contributions to the development of autism will also be identified in the future.[2-14] At present, the known functions of these genes converge on biological processes that are important for neurogenesis (the development of neurons) and synapse formation and communication. However, much remains to be learned about the molecular mechanisms that may lead to observable characteristics of autism.

The discovery of gene mutations that cause single-gene disorders that often have autism as one component (such as tuberous sclerosis complex, Rett syndrome, Fragile X syndrome, and Phelan McDermid syndrome) and the large number of rare spontaneous or *de novo* mutations that contribute to autism have enabled scientists to explore the biological effects of specific proteins and molecular pathways in cellular and animal model experiments. This has led to an explosion of research examining

how these mutations alter the biology of cells and investigating their effects on neural circuitry and behavior. However, given that autism involves distinctly human characteristics, studies using animal models may not accurately reflect differences in human biology associated with changes in cognition or communication. Therefore, better preclinical models are needed to bridge the evolutionary gap between model organisms and humans.

The ability to take skin or blood cells from people on the autism spectrum, create induced pluripotent stem cells (iPSCs), and differentiate these cells into neurons have enabled the study of neural function at the cellular level. This technology allows scientists to compare how iPSCs derived from autistic individuals differ from those derived from neurotypical individuals[15, 16] and study the effects of genetic mutations in human brain cells in addition to commonly used transgenic animal models.[17] As CRISPR gene editing technology becomes more developed, more high-throughput pooled CRISPR screens[18, 19] will also be possible as a means of identifying and validating the relevance of genetic mutations to autism. However, experiments involving patient-derived iPSCs are often of small sample sizes, and variability and genetic heterogeneity in derived cells can make interpretation of results difficult. While more homogenized cell lines can mediate some of the challenges with discerning more subtle phenotypes across varied genetic backgrounds, the generalizability of these results will need further investigation and validation. A strategy for identifying relevant molecular phenotypes in iPSCs from the much more common idiopathic autism also remains a daunting task. Sample sizes for these studies are very limited, and varied methodologies across different studies make reproducibility difficult. These are challenges that need to be overcome with larger samples and better powered analyses.

iPSCs also make it possible to grow brain organoids, which are clumps of brain tissue partially organized to have some features of the human brain. These partially matured "mini-brains" can be grown in a culture dish and can be used to enable the study of the early development of brain structures that occurs *in utero*, as well as the cellular and circuit abnormalities related to autism-liked mutations.[20-24] However, these *in vitro* studies will introduce a number of variables related to culture conditions, and deliberate actions will be required to evaluate reproducibility.

Brain organoids and iPSCs cannot replace the careful structural and transcriptomic studies of postmortem tissues, which have been used to successfully identify differences in gene expression in brains of autistic individuals compared to neurotypical brains.[25-27] Future advances in single-cell RNA sequencing technology will allow for better characterization of these altered patterns of gene expression in specific brain cell types, offering the opportunity to precisely associate gene expression differences at a cellular level.[28] However, the number of available postmortem samples are limited, with a heterogeneous mix of characteristics, including sex, age, and medical history, making high-powered statistical analyses difficult. Therefore, efforts are still needed to increase the accessibility and diversity of brain tissue from well-characterized autism cases. Collaborations such as the Autism BrainNet, the Hispano-American Brain Bank of Neurodevelopmental Disorders (CENE), and the National Institutes of Health (NIH) NeuroBioBank facilitates the distribution of high-quality, well-characterized human postmortem brain tissue for the research community. Enhancing efforts to increase public awareness about the value of tissue donation for understanding autism will most effectively advance research on the biological mechanisms of autism. Additionally, performing analyses in addition to sequencing and storing samples to be used in the future as better technology becomes available can also advance our understanding of autism biology.

Another remaining challenge is to understand how the effects of hundreds of implicated genes converge to cause the common features of autism. In addition to examining rare mutations that lead to high probability of autism development, studying more common alleles that confer lower degrees of susceptibility may highlight previously undetected gene networks and molecular pathways. Studies of multiple genes in parallel and more complete gene ontology data can also help identify additional connections. Conversely, the autism genes identified so far often play multiple roles within a cell and organism, and this presents a major challenge in translating the discovery of an autism gene to viable intervention options. A better understanding of human brain development will provide valuable information on where and when to look for autism-related biological changes, which can advance needed research to determine how individual genes and their interactions in early life events explain the biological basis of the heterogeneity of autism features.

## Structure and Function of Brain Circuits in Autism

Autism is characterized by atypical patterns in physical brain connections (structure) and how regions communicate with each other (function). Brain structure in individuals with autism can be compared to typically developing children using advanced magnet resonance imaging (MRI) techniques to measure the size and shape of brain regions over time, as well as diffusion tensor imaging (DTI) to examine the structures of the major connections between brain regions. Brain circuit function can be investigated using non-invasive markers, such as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS). These studies have shown neurological differences in cognition, executive functioning, sensory processing, social communication, and language development.[29-31]

Despite a large body of work, challenges remain in fully understanding the neurobiology of autism. Current brain imaging studies often report conflicting results and suffer from reproducibility issues. The heterogeneous nature of autism presentation and technical limitations of the techniques used means large sample sizes and careful statistical analyses are often necessary to obtain truly representative and accurate results. Large collaborations and consortiums can help to increase sample size and improve rigor and reproducibility.[32-35] In addition, females on the autism spectrum, individuals of racial and ethnic minorities, minimally speaking individuals, and individuals with higher support needs are often underrepresented in brain imaging studies. Increasing the diversity of study participants will improve the data quality of brain imaging studies and produce results that are relevant to a broader swath of the autism community.

New technology can also help to overcome some of the logistical issues associated with many brain imaging techniques. For example, MRI scans require the patient to be completely still in a confined and noisy environment, which causes sensory and other issues for many on the autism spectrum and is not representative of the real-world environments. Alternatives such as high-density diffuse optical tomography (HD-DOT) are better tolerated, portable, and allow for high-density measurements in more naturalistic settings.[36, 37] Use of these techniques and developing advances to overcome tolerance and sensory issues can improve data quality in brain imaging studies.

Imaging and electrophysiology studies in model animals such as mice have provided invaluable information on the neurobiological and molecular basis of autism. As discussed in the previous section, however, because autism impacts uniquely human aspects of social-communicative behavior (such as spoken language), developing and measuring analogous phenotypes in animals has proven difficult. In

addition, because autism impacts brain regions not developed in some animal species, some neural circuitry is not readily amenable to study in model organisms. Therefore, human neuroimaging studies remain critical to understanding how autism impacts brain function and structure.

Lastly, in addition to characterizing how autistic brains differ from neurotypical brains in terms of structure and function, it is important to also ask which of these differences contribute to autism phenotypes and characteristics and which are simply correlations. For example, a recent review found that despite a correlation of between differences in functional connectivity in regions of the brain that support complex social interactions and the severity of social symptoms, whether or not these connectivity differences cause social challenges still needs to be carefully considered.[38] Teasing out these causal relationships by examining brain dynamics in the context of different tasks and situations can be helpful in developing interventions to reduce the cognitive and social difficulties associated with autism.

## Sensory and Motor Differences

The vast majority of individuals on the autism spectrum experience hypo- or hyper-sensory abnormalities, which may have negative impacts on cognitive performance,[39] social interactions and communication,[40, 41] and stress.[42, 43] The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes sensory characteristics as a diagnostic criterion for autism, highlighting the frequency with which autistic individuals experience sensory difficulties. These sensory difficulties occur across the core sensory systems, including visual, auditory, gustatory, olfactory, tactile (touch and pain), vestibular, and proprioceptive (sense of self-movement and body position) systems, and the severity and impact of these differences vary from person to person.[44] Extensive research in this area in recent years has led to a better understanding of the neurobiological differences within the central nervous system that lead to hypo- or hyper-sensitivity.[45-50]

However, more work can be done to explore how differences in peripheral nerves and organs such as the eye, nose, mouth, ear, and skin can contribute to sensory differences. Additionally, multiple stimuli can activate different sensory systems simultaneously and may lead to cognitive, social, and behavioral challenges. Research in mice has provided some information on the neurobiological mechanisms that lead to multisensory dysfunction in autism.[51] It will be important for future research to determine whether these findings are translatable to humans and develop interventions to improve the sensory experiences of individuals on the autism spectrum. Additionally, sensory challenges occur in a heterogeneous manner across the autism spectrum and across the lifespan.[52-56] Future research should continue to investigate differences in sensory processing in different subgroups within the autism community and how these change with development and across the lifespan; this will enable the development of more customizable interventions that can meet the sensory needs of individuals of all ages across the autism spectrum.

Differences in motor development and function are also common in individuals on the autism spectrum.[57] Differences in motor development in infancy can often be detected prior to and is often correlated with later development of differences in social skills.[58-60] Therefore, a better understanding of differences in motor development can lead to biomarkers that allow for earlier detection of autism. Additionally, it is not clear what the neurobiological mechanisms are behind atypical motor development and how that may contribute to other aspects of autism. Some studies indicate that improving motor function can lead to improvements in social skills, suggesting a causal relationship,

while other studies do not find the same effect.[61] Therefore, it will be important to determine the relationship between motor skills and social skills. Finally, more research is needed to understand how motor functions develop and change over time to develop interventions that can improve motor function across the lifespan so individuals on the autism spectrum can perform essential movements and physical activities.

## Cognitive and Communication Differences

Autism diagnosis is characterized by restricted, repetitive behavior and social and communication difficulties. Therefore, cognitive studies of psychological and mental processes, including memory, language production and comprehension, problem solving, decision making, and social communication, are vitally important for understanding the biology of autism.

As discussed in the previous section, research so far has highlighted the role of sensory processing in cognitive function and social communication, with multiple studies exploring how eye gaze and movement impacts facial recognition and social interactions.[62-64] In addition, we are now beginning to understand the neuronal activities that occur following verbal stimuli and conversation and during speech processing.[65-67] The role of the cerebellum and other areas of the "social brain" (including the prefrontal cortex, amygdala, hippocampus, and limbic system) in cognition and social function has also been intensely studied.[68, 69] An understanding of how differences in executive functioning affect restricted, repetitive behavior and other cognitive difficulties is beginning to emerge, with an imbalance in neural excitation and inhibition being a leading hypothesis.[70, 71] Aggressive behaviors, self-injurious behaviors, and other challenging behaviors exhibited by some individuals on the autism spectrum may be due to an attempt to relieve or communicate discomfort or pain associated with sensory difficulties or co-occurring conditions,[72] with a recent study indicating that common brain circuitry involved in emotion, motivation, cognitive processing, and decision making may be involved.[73]

However, much remains to be explored about the neurobiology underlying differences in cognition and social communication and risk and resilience factors of challenging behaviors. While some regions of the brain such as the cerebellum have been definitively shown to be altered and play a role in autism, the heterogeneity of cognitive and social phenotypes make it difficult to pinpoint the neuronal and molecular changes that cause impairments. Therefore, more studies in model systems are needed to better understand the exact nature of neurobiological differences that occur in autism. This knowledge will allow for the development of biomarkers for cognitive processes such as memory and problem solving to better identify how and what interventions may help individuals on the autism spectrum. Additionally, complex cognitive processes likely require communication between multiple brain regions, and studies of the brain at the systems level can lead to a more holistic understanding of brain networks and connections. Information at the connectome-level may allow for better predictions of cognitive and social communication outcomes in autistic individuals. It will also be important to study how cognition, social communication, and behaviors may change over time to better support individuals on the autism spectrum throughout the lifespan. In particular, research on cognitive and social adaptations of individuals on the autism spectrum can help lead to interventions that promote resilience and maximize positive outcomes.

## Immune System and Autism Development

Current evidence suggests immune differences and neuroinflammation are implicated in the severity and pathogenesis of the autism phenotype.[74] For example, recent meta-analyses found higher concentrations of pro-inflammatory cytokines in individuals on the autism spectrum compared to the control group[75] and a subset of immune-related genes were significantly associated with autistic traits.[76] Despite many studies demonstrating altered levels of immune biomarkers and abnormal immune function in both the peripheral and central nervous system in autism, it is still not clear whether the immune system plays a direct role in autism development via alteration of neurodevelopmental processes.

Several recent studies suggest that maternal immunological factors may play a role in the pathogenesis of autism during prenatal development. Maternal infection and fever, autoimmune disease, asthma, and obesity are all associated with autism development in the offspring.[74, 77] However, these results are largely based on data from peripheral blood, which may not be representative of changes that occur in the brain. Therefore, future research will need to answer whether the immunological changes observed cause differences during neurodevelopment or whether differences in neurodevelopment change the function and activity of the immune system.

Microglia are innate immune cells that reside in the central nervous system and are activated in response to infection or inflammation. Even in their so-called resting state, they perform critical homeostatic functions in the central nervous system.[78] Microglial activation has been linked to altered brain connectivity in children on the autism spectrum, and pro-inflammatory cytokines and microglial phenotypes are also seen in autistic individuals.[74] Further investigation of the role of microglia are warranted based on our emerging understanding of their role in neurotypical development and potential contribution to autism phenotypes. In addition, more studies are needed to identify the roles of molecules secreted by immune cells on brain development and function.

## Sex and Gender Differences

The most recent epidemiological data in the U.S. suggests that autism is about 4 times as prevalent in boys and men as compared to girls and women.[79, 80] Additionally, autism is more prevalent in gender-diverse individuals compared to cis-gendered individuals.[81, 82] Very little is known about the biological mechanisms that contribute to these sex and gender differences. Further work is needed to understand the phenotypic differences between males and females and gender diverse individuals on the autism spectrum and how these differences should inform the development of screening and diagnostic tools, interventions, and services that meet the needs of all autistic individuals, regardless of sex and gender.

One hypothesis for the male to female autism diagnosis ratio is the existence of the female protective effect (FPE), which posits that females would require a greater accumulation of autism-related genetic differences to reach the diagnostic threshold. Sequencing and genetic data appear to support this hypothesis, with autistic females carrying higher average numbers of rare _de novo_ mutations compared to their male counterparts,[1, 2, 83] and common and rare variants of autism genes are enriched in mothers and unaffected sisters of autistic individuals.[1, 2, 84] However, results from family- and inheritance-based studies are more conflicting. Some studies show that siblings of autistic females were more likely to receive an autism diagnosis compared to siblings of males on the autism spectrum,[85] while other results show that the relative risk of autism between maternal and paternal lineage is similar, indicating that

FPE is likely not the primary mechanism for the sex differences found in autism prevalence.[86] Additional studies are needed to determine whether the FPE exists and the extent to which such an effect contributes to the sex differences seen in autism diagnosis.

In addition to the FPE, it's possible that male-specific factors also exist which lowers the diagnostic threshold for boys and men. Previous results have shown that autistic males have more rare loss-of-function mutations on the X chromosome,[87] though it is unclear how these variants contribute to the sex difference in autism. The impact of sex chromosomes on differences in gene expression between males and females and how this may contribute to autism has been understudied in general and needs additional attention.

Sex hormones such as testosterone and estrogen may also contribute to the sex and gender difference in autism. Studies have found that estrogen may be a protective factor for autism,[88, 89] whereas excess testosterone is thought to contribute to autism development.[90, 91] Additionally, patients with polycystic ovary syndrome (PCOS) were found to have more autistic traits compared to the control group, which may be correlated with higher levels of testosterone and luteinizing hormone and lower levels of progesterone.[92] More research is needed to better understand the role that sex hormones play in autism development and what their contributions are to the sex differences seen in autism diagnosis.

Finally, more studies are needed to investigate the neurological sex differences that occur downstream of the genetic and molecular variances. Recent functional connectivity studies found sex differences in the cerebellum, which play key roles in sensorimotor, cognitive, and socio-affective processes.[93] In addition, differences in functional connectivity may explain why autistic females report more compensatory behavior ("camouflaging") compared to their male counterparts.[94] Furthermore, brain structure and anatomy also differ between males and females.[95, 96] However, these studies on the neuroanatomy of autism remain rare and limited by small sample sizes. More research is needed to better understand how differences in brain functioning and structure can lead to the sex differences seen in autism presentation and outcomes.

Girls and women with autism are often diagnosed later than autistic males and not well-represented in research studies, and research to explore the relationship between gender identity and autism development and outcomes is just beginning. Better understanding of the genetic, molecular, and neurobiological differences between males and females and cis-gendered and gender-diverse individuals on the autism spectrum can lead to the development of more accurate biomarkers and diagnostic tools, as well as more appropriate interventions and services to maximize the quality of life for individuals of all genders and sexes on the autism spectrum.

## Longitudinal Studies

Autism is a developmental disorder, and life outcomes are extremely heterogeneous. While longitudinal studies conducted so far has shown that autism diagnoses at 14 months of age are stable,[97] the strengths, challenges, and support needs associated with autism change over time.[55, 56, 98-100] Longitudinal studies have shown correlations between motor skills and later development of autism and language,[101, 102] as well as associations between autism symptoms and sleep problems.[103] Studies have also shed light on how differences and changes in the brain over time correlate with different subgroups and mental and physical health outcomes.[104-107] However, much remains to be learned about differences

in developmental trajectory and what biological factors and interventions determine better life outcomes for individuals on the autism spectrum.

The brain connectivity changes that underlie autism are not static; their manifestations appear during the dramatically dynamic period of brain development and continue to change over the lifespan of the individual. Therefore, understanding the biology of autism requires large longitudinal studies to chart the trajectory of neural circuits over time, including how they adapt to inborn differences in wiring and environmental exposures. Studies are needed that include pregnancy and follow maternal exposures and response, fetal development, and brain response to events that occur *in utero* and perinatally. More longitudinal studies that gather brain imaging data from the same set of subjects repeated over an extended study period are also needed to enhance our understanding of brain development. Furthermore, advances in human imaging technology and longitudinal study designs may provide an opportunity to better distinguish true causes from consequences of specific findings by making it possible to image brain tissue in live subjects throughout the lifespan. These kinds of studies will require standardized acquisition parameters to enable comparability across studies, and robust data sharing policies should be in place to enable expert analysis of the data by a variety of scientists. Finally, large, organized longitudinal studies across the lifespan are needed to better understand the biology, developmental trajectories, and natural history of autism, from prenatal development to early childhood and through adulthood. These studies are critical to identify the biological variables that can help autistic individuals maximize their strengths and receive the interventions, services, and supports they need to overcome challenges throughout the lifespan.

## Co-occurring Conditions

Autism is associated with a wide range of co-occurring conditions that decrease quality of life for autistic individuals. Progress has been made in recent years to better understand the prevalence and underlying biology of conditions that commonly co-occur with autism, including gastrointestinal (GI) conditions, epilepsy, sleep disorders, and psychiatric disorders. However, more research is needed on the underlying causes of these co-occurring conditions and the biological interactions with autism to facilitate interventions that can improve the health and well-being of individuals on the autism spectrum.

### *Gastrointestinal Conditions*

GI symptoms and an inflammatory mucosal pathology has been demonstrated in several studies of autism. Children with autism are more likely to experience GI symptoms compared to typically developing children or children with other developmental disabilities.[108] GI symptoms lower quality of life and can cause discomfort, distress, and pain. The presence of GI symptoms has been associated with loss of skills and language and communication ability, self-injurious behavior and aggression, sleep problems, and sensory issues.[108] It is common for individuals on the autism spectrum to eat a restricted diet, and studies have shown that the dietary patterns of autistic children differ from that of typically developing children.[109] It is unclear the extent to which this contributes to the development of GI symptoms or if the GI symptoms themselves lead to a more restricted diet. Additionally, while GI symptoms were not found to vary with age and were stable over time,[108] it is unclear if gender and sex play a role in number and severity of GI symptoms experienced and what roles sex hormones may play in the process. Most surveys also rely on parents to report symptoms, which may lead to inaccuracies.

Improvement and standardization of study tools such as questionnaires and surveys are needed to obtain more accurate results that can be compared across studies.

The role of the gut-brain axis and the microbiome in neurophysiology has been under intense study in recent years. The microbiome within the gut plays important roles not only in gut health and metabolism but also in immune activation and neuromodulation.[110] Given the prevalence of GI co-morbidities in autistic individuals, it is hypothesized that the microbiome may play a role in autism development, and studies of fecal DNA have found certain bacterial clusters overrepresented in children on the autism spectrum compared to neurotypical children.[110] Additionally, some studies have found interventions designed to normalize the gut microbiome improved both GI and autism symptoms.[111-113] However, a recent metagenomics study did not find any association between autism and the gut microbiome,[114] instead positing that the differences in microbiome may be due to dietary preferences. Therefore, more work is still needed to determine what role, if any, the gut microbiome plays in autism development.

### Epilepsy
Epilepsy occurs in 5-46% of individuals on the autism spectrum, and approximately 30% of children with epilepsy also have autism.[115] Studies have shown that many of the genetic factors for epilepsy and autism overlap,[115, 116] suggesting that autism and epilepsy may share a common etiology. In addition, differences in EEG patterns and perturbations in the neuronal excitatory/inhibitory equilibrium are seen in both epilepsy and autism.[117] Despite these connections, it is unclear what the causal relationship is between autism and epilepsy. For example, epilepsy could be a causal factor in autism development, or the neurodevelopmental differences that lead to autism could contribute to the occurrence of epileptic seizures. Alternatively, epilepsy and autism may occur on a developmental spectrum in which the specific outcome depends upon other factors. A better understanding of the biological underpinnings of both epilepsy and autism and the relationship between the two will lead to more targeted and effective medical interventions that improve the health and well-being of individuals on the autism spectrum who have co-occurring epilepsy.

### Sleep Disorders
Autism is frequently accompanied by a variety of sleep problems that cause worsened aggression, self-injurious behavior, anxiety, hyperactivity, and inattention during the daytime.[118] Studies indicate the prevalence of sleep problems in autism are as high as 50-80%, with initiating and maintaining sleep being one of the most common co-occurring clinical disorders.[119, 120] Several neurotransmitters, including serotonin, melatonin, and gamma-aminobutyric acid (GABA) play vital roles in the maintenance of sleep-wake cycles, and abnormal levels of these neurotransmitters have been described in autism. Model animals have improved our understanding of how genetic changes that lead to autism may also cause sleep disturbances.[121] In the future, it will be important to explore if genes that regulate sleep may also contribute to autism development. Additionally, more research is needed on how confounding variables such as potential sensory issues and GI symptoms may be contributing to disrupted sleep to better design interventions that improve sleep quality.

### Ehlers-Danlos Syndromes and Dysautonomia
Ehlers-Danlos syndromes (EDS) are a group of disorders characterized by hypermobility of the joints, skin hyperflexibility, and tissue fragility. EDS patients report chronic pain, fatigue, social withdrawal, and anxiety in their daily life.[122] Co-occurrence of EDS and autism has been described in the literature since

the 1980s.[123] More recent studies have shown that children on the autism spectrum have greater joint flexibility compared to age- and gender-matched peers[124] and generalized joint hypermobility and EDS are associated with both autism and attention-deficit/hyperactivity disorder (ADHD).[125-127] Many co-occurring conditions are also shared in both autism and EDS.[128] However, it is unclear what the exact connection is between EDS and autism and if they share common genetic factors. More research is needed on the biological mechanisms and interactions of EDS and autism to facilitate interventions for both conditions that can improve health and well-being.

Dysautonomia is caused by dysfunction of the autonomic nervous system, which regulates nonvoluntary bodily functions such as heart rate, blood pressure, breathing, digestion, and perspiration. Symptoms of dysautonomia are varied and can include nausea and vomiting, balance problems, dizziness, weakness, and visual disturbances. Postural orthostatic tachycardia syndrome or POTS is a form of dysautonomia and is characterized by reduced blood volume upon standing leading to lightheadedness and fainting. Recent research indicates higher prevalence of dysautonomia in autistic and neurodivergent populations and strong associations with EDS.[129, 130] However, like with EDS, it is still unclear what the biological connection is between autism and dysautonomia. Research is needed to understand the mechanisms of dysautonomia and how the disorder may manifest differently in individuals on the autism spectrum to develop interventions that can alleviate symptoms and maximize quality of life.

### Mental Health and Psychiatric Conditions

It has been estimated that approximately 70% of people on the autism spectrum have one or more co-occurring psychiatric disorder.[131] The most common of these conditions are anxiety and mood disorders, obsessive compulsive disorder (OCD), ADHD, and oppositional defiant disorder. In addition, depression, bipolar disorder, schizophrenia, eating disorders, and suicidal ideation and death by suicide have been reported at higher rates in individuals on the autism spectrum compared to the general population. Recent studies have also noted that autism is associated with an increased vulnerability for substance use disorders.[132-135] Many autistic individuals may simultaneously experience multiple co-occurring conditions. Current research indicates that these co-occurring conditions may share common genetic, epigenetic, and neurological variations.[136-139] However, additional research is needed to establish clear causal links. In addition, research is needed to better characterize the manifestation of these mental health conditions in the context of autism and vice versa to develop improved diagnostic tools and interventions to treat co-occurring conditions, in particular depression and suicide. Studies on co-occurring mental health conditions should also explore the role of sex and gender, intellectual ability, and age to determine if these factors mediate the severity of symptoms and provide more information on what interventions may be most appropriate for people of all genders and abilities across the lifespan.

Individual and intergenerational trauma also needs to be considered in mental health research of autistic individuals. Current data indicates that adverse childhood experiences (ACEs) are associated with autism;[140] caregivers of autistic youth also experienced higher rates of ACEs compared to caregivers of non-autistic youth.[141] Brain imaging studies indicate that ACEs may lead to changes in neurological functioning, some of which are already known to be associated with autism.[142-144] ACEs and other traumatic experiences greatly impact mental and emotional well-being, leading to suicidal ideation and emotional distress and impacting development into adulthood.[145] More research is needed with larger studies to understand how different traumas may differently affect diverse individuals and the

differences in how acute versus chronic trauma impacts life outcomes for individuals on the autism spectrum. Research is also needed on resilience factors, which may include places of refuge and identity,[145] that may protect individuals from the effects of adverse experiences to better develop interventions that can improve health and well-being.

## Research Policy Issues

A major challenge for the biological sciences is to utilize the most sophisticated technologies that produce ever-enlarging data sets while still ensuring the rigor and quality of research. Moving forward, the field should embrace policies that promote collaborations and enhance the reproducibility of findings and promote transparent reporting of experimental methods, use of common data elements, and sharing of data and analysis. Follow-up validation studies are a necessary part of this process, and data sharing should be integrated into the design of studies from the beginning. The National Institute of Mental Health Data Archive (NDA) platform is a valuable repository for high-quality autism data, tools, and methodologies that researchers should leverage to enable re-analysis of data and facilitate collaboration to accelerate research progress.

Larger sequencing, brain imaging, and longitudinal studies require coordination among research centers and a shift toward team science across multiple disciplines. Large-scale science initiatives and collaborations such as the Autism Biomarkers Consortium for Clinical Trials (ABC-CT), SPARK, the All of Us Research Program, and ENIGMA can contribute greatly to our understanding of the biology underlying autism. The coordinated collection and analysis of valuable imaging, behavioral, genetic, and phenotypic data can also be enhanced by the recruitment of a research workforce that includes not only neuroscientists, immunologists, and psychiatrists, but also experts in bioinformatics, machine learning, and biomedical engineers.

Community participatory research and the inclusion of people across the autism spectrum and across the lifespan in research development, implementation, and dissemination is crucial to identifying practical applications for promoting positive outcomes for autistic individuals and their families. The inclusion of autistic people in research validates the unique lived experiences of individuals on the autism spectrum and empowers them to contribute to important research on autism. When planning studies with human subjects, researchers must ensure that the privacy of participants are safeguarded and the data is stored and shared in a secure manner. In addition, researchers must also make certain that participants know what data is being collected and how that data will be used. In longitudinal studies with participants who start as children, informed consent needs to be established as the participants age into adulthood. The results of the study should also be made available to all participants in an accessible and timely manner. The dignity, rights, and welfare of the participants should be kept in mind throughout the research process. Lastly, the inclusion of individuals of underrepresented minority groups as both researchers and study participants will lead to study findings that are more accurate, applicable, and representative of the entire autism community.

## Summary

Significant progress in understanding the biological basis of autism has been made, but considerable challenges remain. Though there is a desire to demonstrate the impact of interventions on brain function, fundamental research that will allow us to fully understand the importance of alterations in brain function and development is still needed. Basic science research on the underlying biology of

autism continues to be critical to provide the foundation for translational advances that will lead to effective interventions to maximize positive outcomes for autistic individuals across the spectrum and across the lifespan.

## Recommendations

**RECOMMENDATION 1: Foster research to better understand the processes of early development, molecular and neurodevelopmental mechanisms, and brain circuitry that contribute to the structural and functional basis of autism.**

*Examples:*

- Identify neurological differences that occur in significant groups of individuals on the autism spectrum.
- Understand the differences in cognitive development and communication in individuals on the autism spectrum.
- Understand the role of the immune system and metabolic processes in autism.
- Understand how atypical sensory and motor functions arise and the role they play in autism.

**RECOMMENDATION 2: Support research to understand the underlying biology of co-occurring conditions in autism and to understand the relationship of these conditions to autism.**

*Examples:*

- Determine the molecular basis of epilepsy in autism.
- Determine how GI dysfunction impacts autism-related characteristics.
- Determine how sleep disorders impacts autism-related characteristics.
- Determine the relationship of co-occurring psychiatric conditions to autism and their impact on the health and well-being of people on the autism spectrum.

**RECOMMENDATION 3: Support large-scale longitudinal studies to answer questions about the development of autism from pregnancy throughout adulthood and the natural history of autism across the lifespan.**

*Examples:*

- Support the creation of large and diverse cohorts, characterized both phenotypically and genetically through the collection of autism-relevant exposure data and medical data on the parents and child from the prenatal period to adulthood.
- Support research on how the neurobiology of autistic individuals change throughout the lifespan and into older adulthood.

## References

1. Sanders Stephan J, He X, Willsey AJ, Ercan-Sencicek AG, Samocha Kaitlin E, Cicek AE, Murtha Michael T, Bal Vanessa H, Bishop Somer L, Dong S, Goldberg Arthur P, Jinlu C, Keaney John F, Klei L, Mandell Jeffrey D, Moreno-De-Luca D, Poultney Christopher S, Robinson Elise B, Smith L, Solli-Nowlan T, Su Mack Y, Teran Nicole A, Walker Michael F, Werling Donna M, Beaudet Arthur L, Cantor Rita M, Fombonne E, Geschwind DH, Grice Dorothy E, Lord C, Lowe Jennifer K, Mane Shrikant M, Martin Donna M, Morrow Eric M, Talkowski Michael E, Sutcliffe James S, Walsh Christopher A, Yu Timothy W, Ledbetter David H, Martin Christa L, Cook Edwin H, Buxbaum Joseph D, Daly Mark J, Devlin B, Roeder K, State Matthew W. Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci. Neuron. 2015 Sep 23;87(6):1215-1233. [PMID: 26402605]

2. Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An J-Y, Peng M, Collins R, Grove J, Klei L, Stevens C, Reichert J, Mulhern MS, Artomov M, Gerges S, Sheppard B, Xu X, Bhaduri A, Norman U, Brand H, Schwartz G, Nguyen R, Guerrero EE, Dias C, Betancur C, Cook EH, Gallagher L, Gill M, Sutcliffe JS, Thurm A, Zwick ME, Børglum AD, State MW, Cicek AE, Talkowski ME, Cutler DJ, Devlin B, Sanders SJ, Roeder K, Daly MJ, Buxbaum JD, Aleksic B, Anney R, Barbosa M, Bishop S, Brusco A, Bybjerg-Grauholm J, Carracedo A, Chan MCY, Chiocchetti AG, Chung BHY, Coon H, Cuccaro ML, Currò A, Dalla Bernardina B, Doan R, Domenici E, Dong S, Fallerini C, Fernández-Prieto M, Ferrero GB, Freitag CM, Fromer M, Gargus JJ, Geschwind D, Giorgio E, González-Peñas J, Guter S, Halpern D, Hansen-Kiss E, He X, Herman GE, Hertz-Picciotto I, Hougaard DM, Hultman CM, Ionita-Laza I, Jacob S, Jamison J, Jugessur A, Kaartinen M, Knudsen GP, Kolevzon A, Kushima I, Lee SL, Lehtimäki T, Lim ET, Lintas C, Lipkin WI, Lopergolo D, Lopes F, Ludena Y, Maciel P, Magnus P, Mahjani B, Maltman N, Manoach DS, Meiri G, Menashe I, Miller J, Minshew N, Montenegro EMS, Moreira D, Morrow EM, Mors O, Mortensen PB, Mosconi M, Muglia P, Neale BM, Nordentoft M, Ozaki N, Palotie A, Parellada M, Passos-Bueno MR, Pericak-Vance M, Persico AM, Pessah I, Puura K, Reichenberg A, Renieri A, Riberi E, Robinson EB, Samocha KE, Sandin S, Santangelo SL, Schellenberg G, Scherer SW, Schlitt S, Schmidt R, Schmitt L, Silva IMW, Singh T, Siper PM, Smith M, Soares G, Stoltenberg C, Suren P, Susser E, Sweeney J, Szatmari P, Tang L, Tassone F, Teufel K, Trabetti E, Trelles MDP, Walsh CA, Weiss LA, Werge T, Werling DM, Wigdor EM, Wilkinson E, Willsey AJ, Yu TW, Yu MHC, Yuen R, Zachi E, Agerbo E, Als TD, Appadurai V, Bækvad-Hansen M, Belliveau R, Buil A, Carey CE, Cerrato F, Chambert K, Churchhouse C, Dalsgaard S, Demontis D, Dumont A, Goldstein J, Hansen CS, Hauberg ME, Hollegaard MV, Howrigan DP, Huang H, Maller J, Martin AR, Martin J, Mattheisen M, Moran J, Pallesen J, Palmer DS, Pedersen CB, Pedersen MG, Poterba T, Poulsen JB, Ripke S, Schork AJ, Thompson WK, Turley P, Walters RK. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell. 2020 Feb 6;180(3):568-584.e23. [PMID: 31981491]

3. Willsey HR, Willsey AJ, Wang B, State MW. Genomics, convergent neuroscience and progress in understanding autism spectrum disorder. Nature Reviews Neuroscience. 2022 Jun;23(6):323-341. [PMID: 35440779]

4. Gibitova EA, Dobrynin PV, Pomerantseva EA, Musatova EV, Kostareva A, Evsyukov I, Rychkov SY, Zhukova OV, Naumova OY, Grigorenko EL. A Study of the Genomic Variations Associated with Autistic Spectrum Disorders in a Russian Cohort of Patients Using Whole-Exome Sequencing. Genes. 2022 May 20;13(5):920. [PMID: 35627305]

5. Liu J, Wang H, Sun W, Liu Y. Prioritizing Autism Risk Genes Using Personalized Graphical Models Estimated From Single-Cell RNA-seq Data. Journal of the American Statistical Association. 2022;117(537):38-51. [PMID: 35529781]

6.    Qin Y, Cao L, Zhang J, Zhang H, Cai S, Guo B, Wu F, Zhao L, Li W, Ni L, Liu L, Wang X, Chen Y, Huang C. Whole-Transcriptome Analysis of Serum L1CAM-Captured Extracellular Vesicles Reveals Neural and Glycosylation Changes in Autism Spectrum Disorder. Journal of Molecular Neuroscience. 2022 Jun. [PMID: 35412111]

7.    Marques AR, Santos JX, Martiniano H, Vilela J, Rasga C, Romão L, Vicente AM. Gene Variants Involved in Nonsense-Mediated mRNA Decay Suggest a Role in Autism Spectrum Disorder. Biomedicines. 2022 Mar 13;10(3):665. [PMID: 35327467]

8.    Mpoulimari I, Zintzaras E. Identification of Chromosomal Regions Linked to Autism-Spectrum Disorders: A Meta-Analysis of Genome-Wide Linkage Scans. Genet Test Mol Biomarkers. 2022 Feb;26(2):59-69. [PMID: 35225680]

9.    Almandil NB, Alsulaiman A, Aldakeel SA, Alkuroud DN, Aljofi HE, Alzahrani S, Al-Mana A, Alfuraih AA, Alabdali M, Alkhamis FA, Abdulazeez S, Borgio JF. Integration of Transcriptome and Exome Genotyping Identifies Significant Variants with Autism Spectrum Disorder. Pharmaceuticals. 2022 Jan 27;15(2):158. [PMID: 35215271]

10.   Woodbury-Smith M, Lamoureux S, Begum G, Nassir N, Akter H, O'Rielly DD, Rahman P, Wintle RF, Scherer SW, Uddin M. Mutational Landscape of Autism Spectrum Disorder Brain Tissue. Genes. 2022 Jan 24;13(2):207. [PMID: 35205252]

11.   Gerges P, Bitar T, Laumonnier F, Marouillat S, Nemer G, Andres CR, Hleihel W. Identification of Novel Gene Variants for Autism Spectrum Disorders in the Lebanese Population Using Whole-Exome Sequencing. Genes. 2022 Jan 21;13(2):186. [PMID: 35205231]

12.   Tuncay IO, Parmalee NL, Khalil R, Kaur K, Kumar A, Jimale M, Howe JL, Goodspeed K, Evans P, Alzghoul L, Xing C, Scherer SW, Chahrour MH. Analysis of recent shared ancestry in a familial cohort identifies coding and noncoding autism spectrum disorder variants. NPJ Genomic Medicine. 2022 Feb 21;7(1):13. [PMID: 35190550]

13.   Hughes HK, Rowland ME, Onore CE, Rogers S, Ciernia AV, Ashwood P. Dysregulated gene expression associated with inflammatory and translation pathways in activated monocytes from children with autism spectrum disorder. Translational Psychiatry. 2022 Jan 26;12(1). [PMID: 35082275]

14.   Rodin RE, Dou Y, Kwon M, Sherman MA, D'Gama AM, Doan RN, Rento LM, Girskis KM, Bohrson CL, Kim SN, Nadig A, Luquette LJ, Gulhan DC, Walsh CA, Ganz J, Woodworth MB, Li P, Rodin RE, Hill RS, Bizzotto S, Zhou Z, Lee EA, Barton AR, D'Gama AM, Galor A, Bohrson CL, Kwon D, Gulhan DC, Lim ET, Cortes IC, Luquette LJ, Sherman MA, Coulter ME, Lodato MA, Park PJ, Monroy RB, Kim SN, Dou Y, Chess A, Gulyás-Kovács A, Rosenbluh C, Akbarian S, Ben L, Thorpe J, Pevsner J, Cho S, Jaffe AE, Paquola A, Weinberger DR, Erwin JA, Shin JH, Straub RE, Narurkar R, Abyzov AS, Bae T, Addington A, Panchision D, Meinecke D, Senthil G, Bingaman L, Dutka T, Lehner T, Saucedo-Cuevas L, Conniff T, Daily K, Peters M, Gage FH, Wang M, Reed PJ, Linker SB, Urban AE, Zhou B, Zhu X, Serres A, Juan D, Povolotskaya I, Lobón I, Solis-Moruno M, García-Pérez R, Marquès-Bonet T, Mathern GW, Courchesne E, Gu J, Gleeson JG, Ball LL, George RD, Pramparo T, Flasch DA, Frisbie TJ, Kidd JM, Moldovan JB, Moran JV, Kwan KY, Mills RE, Emery SB, Zhou W, Wang Y, Ratan A, McConnell MJ, Vaccarino FM, Coppola G, Lennington JB, Fasching L, Sestan N, Pochareddy S, Park PJ, Walsh CA. The landscape of somatic mutation in cerebral cortex of autistic and neurotypical individuals revealed by ultra-deep whole-genome sequencing. Nature Neuroscience. 2021 Feb;24(2):176-185. [PMID: 33432195]

15.   Marchetto MC, Belinson H, Tian Y, Freitas BC, Fu C, Vadodaria KC, Beltrao-Braga PC, Trujillo CA, Mendes APD, Padmanabhan K, Nunez Y, Ou J, Ghosh H, Wright R, Brennand KJ, Pierce K, Eichenfield L, Pramparo T, Eyler LT, Barnes CC, Courchesne E, Geschwind DH, Gage FH,

Wynshaw-Boris A, Muotri AR. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. Molecular Psychiatry. 2017 Jun;22(6):820-835. [PMID: 27378147]

16. Adhya D, Swarup V, Nagy R, Dutan L, Shum C, Valencia-Alarcón EP, Jozwik KM, Mendez MA, Horder J, Loth E, Nowosiad P, Lee I, Skuse D, Flinter FA, Murphy D, McAlonan G, Geschwind DH, Price J, Carroll J, Srivastava DP, Baron-Cohen S. Atypical Neurogenesis in Induced Pluripotent Stem Cells From Autistic Individuals. Biological Psychiatry. 2021 Mar 1;89(5):486-496. [PMID: 32826066]

17. Deneault E, White SH, Rodrigues DC, Ross PJ, Faheem M, Zaslavsky K, Wang Z, Alexandrova R, Pellecchia G, Wei W, Piekna A, Kaur G, Howe JL, Kwan V, Thiruvahindrapuram B, Walker S, Lionel AC, Pasceri P, Merico D, Yuen RKC, Singh KK, Ellis J, Scherer SW. Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons. Stem Cell Reports. 2018 Nov 13;11(5):1211-1225. [PMID: 30392976]

18. Zhou Y, Fu Q, Shi H, Zhou G. CRISPR Guide RNA Library Screens in Human Induced Pluripotent Stem Cells. Methods Mol Biol. 2022;2549(233-257. [PMID: 35347694]

19. van Essen M, Riepsaame J, Jacob J. CRISPR-Cas Gene Perturbation and Editing in Human Induced Pluripotent Stem Cells. The CRISPR Journal. 2021 Oct;4(5):634-655. [PMID: 34582693]

20. Gordon A, Yoon S-J, Tran SS, Makinson CD, Park JY, Andersen J, Valencia AM, Horvath S, Xiao X, Huguenard JR, Paşca SP, Geschwind DH. Long-term maturation of human cortical organoids matches key early postnatal transitions. Nature Neuroscience. 2021 Mar;24(3):331-342. [PMID: 33619405]

21. Amiri A, Coppola G, Scuderi S, Wu F, Roychowdhury T, Liu F, Pochareddy S, Shin Y, Safi A, Song L, Zhu Y, Sousa AMM, Gerstein M, Crawford GE, Sestan N, Abyzov A, Vaccarino FM, Akbarian S, An J-Y, Armoskus C, Ashley-Koch AE, Beach TG, Belmont J, Bendl J, Borrman T, Brown L, Brown M, Brown M, Brunetti T, Bryois J, Burke EE, Camarena A, Carlyle BC, Chae Y, Charney AW, Chen C, Cheng L, Cherskov A, Choi J, Clarke D, Collado-Torres L, Dai R, De La Torre Ubieta L, Delvalle D, Devillers O, Dracheva S, Emani PS, Evgrafov OV, Farnham PJ, Fitzgerald D, Flatow E, Francoeur N, Fullard JF, Gandal MJ, Gao T, Garrett ME, Geschwind DH, Giase G, Girdhar K, Giusti-Rodriguez P, Goes FS, Goodman T, Grennan KS, Gu M, Gürsoy G, Hadjimichael E, Hahn C-G, Haroutunian V, Hauberg ME, Hoffman GE, Huey J, Hyde TM, Ivanov NA, Jacobov R, Jaffe AE, Jiang Y, Jiang Y, Johnson GD, Kassim BS, Kefi A, Kim Y, Kitchen RR, Kleiman JE, Knowles JA, Kozlenkov A, Li M, Li Z, Lipska BK, Liu C, Liu S, Mangravite LM, Mariani J, Mattei E, Miller DJ, Moore J, Nairn AC, Navarro FCP, Park RB, Peters MA, Pinto D, Pochareddy S, Polioudakis D, Pratt H, Price AJ, Purcaro M, Ray M, Reddy TE, Rhie SK, Roussos P, Sanders SJ, Santpere G, Schreiner S, Sheppard B, Shi X, Shieh AW, Shin JH, Skarica M, Song L, Sousa AMM, Spitsyna VN, State MW, Sullivan PF, Swarup V, Szatkiewicz J, Szekely A, Tao R, Van Bakel H, Wang Y, Wang D, Warrell J, Webster MJ, Weissman S, Weng Z, Werling DM, White KP, Willsey JA, Wiseman JR, Witt H, Won H, Wray GA, Xia Y, Xu M, Yang YT, Yang M, Zandi P, Zhang J, Zharovsky E. Transcriptome and epigenome landscape of human cortical development modeled in organoids. Science. 2018 Dec 14;362(6420):eaat6720. [PMID: 30545853]

22. Trevino AE, Sinnott-Armstrong N, Andersen J, Yoon SJ, Huber N, Pritchard JK, Chang HY, Greenleaf WJ, Paşca SP. Chromatin accessibility dynamics in a model of human forebrain development. Science. 2020 Jan 24;367(6476). [PMID: 31974223]

23. Chiola S, Edgar NU, Shcheglovitov A. iPSC toolbox for understanding and repairing disrupted brain circuits in autism. Mol Psychiatry. 2022 Jan;27(1):249-258. [PMID: 34497379]

24. de Jong JO, Llapashtica C, Genestine M, Strauss K, Provenzano F, Sun Y, Zhu H, Cortese GP, Brundu F, Brigatti KW, Corneo B, Migliori B, Tomer R, Kushner SA, Kellendonk C, Javitch JA, Xu B,

Markx S. Cortical overgrowth in a preclinical forebrain organoid model of CNTNAP2-associated autism spectrum disorder. Nat Commun. 2021 Sep 1;12(1):4087. [PMID: 34471112]

25. Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, Mill J, Cantor RM, Blencowe BJ, Geschwind DH. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature. 2011 May 25;474(7351):380-4. [PMID: 21614001]

26. Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, Won H, van Bakel H, Varghese M, Wang Y, Shieh AW, Haney J, Parhami S, Belmont J, Kim M, Moran Losada P, Khan Z, Mleczko J, Xia Y, Dai R, Wang D, Yang YT, Xu M, Fish K, Hof PR, Warrell J, Fitzgerald D, White K, Jaffe AE, Peters MA, Gerstein M, Liu C, Iakoucheva LM, Pinto D, Geschwind DH. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science. 2018 Dec 14;362(6420). [PMID: 30545856]

27. Velmeshev D, Schirmer L, Jung D, Haeussler M, Perez Y, Mayer S, Bhaduri A, Goyal N, Rowitch DH, Kriegstein AR. Single-cell genomics identifies cell type-specific molecular changes in autism. Science. 2019 May 17;364(6441):685-689. [PMID: 31097668]

28. Wang D, Liu S, Warrell J, Won H, Shi X, Navarro FCP, Clarke D, Gu M, Emani P, Yang YT, Xu M, Gandal MJ, Lou S, Zhang J, Park JJ, Yan C, Rhie SK, Manakongtreecheep K, Zhou H, Nathan A, Peters M, Mattei E, Fitzgerald D, Brunetti T, Moore J, Jiang Y, Girdhar K, Hoffman GE, Kalayci S, Gümüş ZH, Crawford GE, Roussos P, Akbarian S, Jaffe AE, White KP, Weng Z, Sestan N, Geschwind DH, Knowles JA, Gerstein MB. Comprehensive functional genomic resource and integrative model for the human brain. Science. 2018 Dec 14;362(6420). [PMID: 30545857]

29. McPartland JC, Lerner MD, Bhat A, Clarkson T, Jack A, Koohsari S, Matuskey D, McQuaid GA, Su W-C, Trevisan DA. Looking Back at the Next 40 Years of ASD Neuroscience Research. Journal of Autism and Developmental Disorders. 2021 Dec;51(12):4333-4353. [PMID: 34043128]

30. Ayoub MJ, Keegan L, Tager-Flusberg H, Gill SV. Neuroimaging Techniques as Descriptive and Diagnostic Tools for Infants at Risk for Autism Spectrum Disorder: A Systematic Review. Brain Sciences. 2022 May 5;12(5):602. [PMID: 35624989]

31. Ghuman AS, van den Honert RN, Huppert TJ, Wallace GL, Martin A. Aberrant Oscillatory Synchrony Is Biased Toward Specific Frequencies and Processing Domains in the Autistic Brain. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 Apr;2(3):245-252. [PMID: 29528295]

32. van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, Busatto GF, Calderoni S, Daly E, Deruelle C, Di Martino A, Dinstein I, Duran FLS, Durston S, Ecker C, Fair D, Fedor J, Fitzgerald J, Freitag CM, Gallagher L, Gori I, Haar S, Hoekstra L, Jahanshad N, Jalbrzikowski M, Janssen J, Lerch J, Luna B, Martinho MM, McGrath J, Muratori F, Murphy CM, Murphy DGM, O'Hearn K, Oranje B, Parellada M, Retico A, Rosa P, Rubia K, Shook D, Taylor M, Thompson PM, Tosetti M, Wallace GL, Zhou F, Buitelaar JK. Cortical and Subcortical Brain Morphometry Differences Between Patients With Autism Spectrum Disorder and Healthy Individuals Across the Lifespan: Results From the ENIGMA ASD Working Group. Am J Psychiatry. 2018 Apr 1;175(4):359-369. [PMID: 29145754]

33. Sha Z, van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, Bernhardt B, Bolte S, Busatto GF, Calderoni S, Calvo R, Daly E, Deruelle C, Duan M, Duran FLS, Durston S, Ecker C, Ehrlich S, Fair D, Fedor J, Fitzgerald J, Floris DL, Franke B, Freitag CM, Gallagher L, Glahn DC, Haar S, Hoekstra L, Jahanshad N, Jalbrzikowski M, Janssen J, King JA, Lazaro L, Luna B, McGrath J, Medland SE, Muratori F, Murphy DGM, Neufeld J, O'Hearn K, Oranje B, Parellada M, Pariente JC, Postema MC, Remnelius KL, Retico A, Rosa PGP, Rubia K, Shook D, Tammimies K, Taylor MJ, Tosetti M, Wallace GL, Zhou F, Thompson PM, Fisher SE, Buitelaar JK, Francks C. Subtly altered topological asymmetry of brain structural covariance networks in autism spectrum disorder

across 43 datasets from the ENIGMA consortium. Molecular Psychiatry. 2022 Apr;27(4):2114-2125. [PMID: 35136228]

34. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, Anderson JS, Assaf M, Bookheimer SY, Dapretto M, Deen B, Delmonte S, Dinstein I, Ertl-Wagner B, Fair DA, Gallagher L, Kennedy DP, Keown CL, Keysers C, Lainhart JE, Lord C, Luna B, Menon V, Minshew NJ, Monk CS, Mueller S, Müller RA, Nebel MB, Nigg JT, O'Hearn K, Pelphrey KA, Peltier SJ, Rudie JD, Sunaert S, Thioux M, Tyszka JM, Uddin LQ, Verhoeven JS, Wenderoth N, Wiggins JL, Mostofsky SH, Milham MP. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. Mol Psychiatry. 2014 Jun;19(6):659-67. [PMID: 23774715]

35. Di Martino A, O'Connor D, Chen B, Alaerts K, Anderson JS, Assaf M, Balsters JH, Baxter L, Beggiato A, Bernaerts S, Blanken LM, Bookheimer SY, Braden BB, Byrge L, Castellanos FX, Dapretto M, Delorme R, Fair DA, Fishman I, Fitzgerald J, Gallagher L, Keehn RJ, Kennedy DP, Lainhart JE, Luna B, Mostofsky SH, Müller RA, Nebel MB, Nigg JT, O'Hearn K, Solomon M, Toro R, Vaidya CJ, Wenderoth N, White T, Craddock RC, Lord C, Leventhal B, Milham MP. Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. Sci Data. 2017 Mar 14;4(170010. [PMID: 28291247]

36. Fishell AK, Burns-Yocum TM, Bergonzi KM, Eggebrecht AT, Culver JP. Mapping brain function during naturalistic viewing using high-density diffuse optical tomography. Sci Rep. 2019 Jul 31;9(1):11115. [PMID: 31366956]

37. Ferradal SL, Liao SM, Eggebrecht AT, Shimony JS, Inder TE, Culver JP, Smyser CD. Functional Imaging of the Developing Brain at the Bedside Using Diffuse Optical Tomography. Cereb Cortex. 2016 Apr;26(4):1558-68. [PMID: 25595183]

38. Gotts SJ, Ramot M, Jasmin K, Martin A. Altered resting-state dynamics in autism spectrum disorder: Causal to the social impairment? Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2019 Mar 2;90(28-36. [PMID: 30414457]

39. Mallory C, Keehn B. Implications of Sensory Processing and Attentional Differences Associated With Autism in Academic Settings: An Integrative Review. Front Psychiatry. 2021 Aug 27;12(695825. [PMID: 34512416]

40. Feldman JI, Raj S, Bowman SM, Santapuram P, Golden AJ, Daly C, Dunham K, Suzman E, Augustine AE, Garla V, Muhumuza A, Cascio CJ, Williams KL, Kirby AV, Keceli-Kaysili B, Woynaroski TG. Sensory Responsiveness Is Linked With Communication in Infant Siblings of Children With and Without Autism. J Speech Lang Hear Res. 2021 Jun 4;64(6):1964-1976. [PMID: 34003699]

41. John TS, Estes A, Begay KK, Munson J, Reiter MA, Dager SR, Kleinhans N. Characterizing Social Functioning in School-Age Children with Sensory Processing Abnormalities. J Autism Dev Disord. 2022 Mar;52(3):1361-1373. [PMID: 33956254]

42. Normansell-Mossa KM, Top DN, Jr., Russell N, Freeston M, Rodgers J, South M. Sensory Sensitivity and Intolerance of Uncertainty Influence Anxiety in Autistic Adults. Front Psychol. 2021 Nov 16;12(731753. [PMID: 34867612]

43. Matsushima K, Matsubayashi J, Toichi M, Funabiki Y, Kato T, Awaya T, Tsuchida R, Kato T. Atypical Physiological Response to Less Controllable Sensory Stimulation in Children with ASD. Res Child Adolesc Psychopathol. 2022 Apr 23. [PMID: 35460427]

44. Cheung PPP, Lau BWM. Neurobiology of sensory processing in autism spectrum disorder. Prog Mol Biol Transl Sci. 2020;173(161-181. [PMID: 32711809]

45. Tavassoli T, Brandes-Aitken A, Chu R, Porter L, Schoen S, Miller LJ, Gerdes MR, Owen J, Mukherjee P, Marco EJ. Sensory over-responsivity: parent report, direct assessment measures, and neural architecture. Mol Autism. 2019 Feb 4;10(4. [PMID: 30740199]

46. Avery JA, Ingeholm JE, Wohltjen S, Collins M, Riddell CD, Gotts SJ, Kenworthy L, Wallace GL, Simmons WK, Martin A. Neural correlates of taste reactivity in autism spectrum disorder. Neuroimage Clin. 2018 Apr 4;19(38-46. [PMID: 30035000]

47. Green SA, Hernandez L, Lawrence KE, Liu J, Tsang T, Yeargin J, Cummings K, Laugeson E, Dapretto M, Bookheimer SY. Distinct Patterns of Neural Habituation and Generalization in Children and Adolescents With Autism With Low and High Sensory Overresponsivity. Am J Psychiatry. 2019 Dec 1;176(12):1010-1020. [PMID: 31230465]

48. Cummings KK, Lawrence KE, Hernandez LM, Wood ET, Bookheimer SY, Dapretto M, Green SA. Sex Differences in Salience Network Connectivity and its Relationship to Sensory Over-Responsivity in Youth with Autism Spectrum Disorder. Autism Res. 2020 Sep;13(9):1489-1500. [PMID: 32860348]

49. Jung J, Zbozinek TD, Cummings KK, Wilhelm FH, Dapretto M, Craske MG, Bookheimer SY, Green SA. Associations between physiological and neural measures of sensory reactivity in youth with autism. J Child Psychol Psychiatry. 2021 Oct;62(10):1183-1194. [PMID: 33587311]

50. Patterson G, Cummings KK, Jung J, Okada NJ, Tottenham N, Bookheimer SY, Dapretto M, Green SA. Effects of sensory distraction and salience priming on emotion identification in autism: an fMRI study. J Neurodev Disord. 2021 Sep 23;13(1):42. [PMID: 34556059]

51. Siemann JK, Veenstra-VanderWeele J, Wallace MT. Approaches to Understanding Multisensory Dysfunction in Autism Spectrum Disorder. Autism Res. 2020 Sep;13(9):1430-1449. [PMID: 32869933]

52. Dwyer P, Ferrer E, Saron CD, Rivera SM. Exploring Sensory Subgroups in Typical Development and Autism Spectrum Development Using Factor Mixture Modelling. J Autism Dev Disord. 2021 Sep 9. [PMID: 34499275]

53. Gunderson J, Worthley E, Grzadzinski R, Burrows C, Estes A, Zwaigenbaum L, Botteron K, Dager S, Hazlett H, Schultz R, Piven J, Wolff J. Social and non-social sensory responsivity in toddlers at high-risk for autism spectrum disorder. Autism Res. 2021 Oct;14(10):2143-2155. [PMID: 34145789]

54. Dwyer P, Wang X, De Meo-Monteil R, Hsieh F, Saron CD, Rivera SM. Defining clusters of young autistic and typically developing children based on loudness-dependent auditory electrophysiological responses. Molecular Autism. 2020 Jun 15;11(1):48. [PMID: 32539866]

55. Wolff JJ, Dimian AF, Botteron KN, Dager SR, Elison JT, Estes AM, Hazlett HC, Schultz RT, Zwaigenbaum L, Piven J. A longitudinal study of parent-reported sensory responsiveness in toddlers at-risk for autism. J Child Psychol Psychiatry. 2019 Mar;60(3):314-324. [PMID: 30350375]

56. Dwyer P, Saron CD, Rivera SM. Identification of Longitudinal Sensory Subtypes in Typical Development and Autism Spectrum Development Using Growth Mixture Modelling. Research in Autism Spectrum Disorders. 2020 Oct;78(101645. [PMID: 32944065]

57. Zampella CJ, Wang LAL, Haley M, Hutchinson AG, de Marchena A. Motor Skill Differences in Autism Spectrum Disorder: a Clinically Focused Review. Current Psychiatry Reports. 2021 Aug 13;23(10):64. [PMID: 34387753]

58. Posar A, Visconti P. Early Motor Signs in Autism Spectrum Disorder. Children (Basel, Switzerland). 2022 Feb 21;9(2):294. [PMID: 35205014]

59. Ohara R, Kanejima Y, Kitamura M, Izawa KP. Association between Social Skills and Motor Skills in Individuals with Autism Spectrum Disorder: A Systematic Review. European journal of investigation in health, psychology and education. 2019 Dec 12;10(1):276-296. [PMID: 34542485]

60.  Wickstrom J, Farmer C, Green Snyder L, Mitz AR, Sanders SJ, Bishop S, Thurm A. Patterns of delay in early gross motor and expressive language milestone attainment in probands with genetic conditions versus idiopathic ASD from SFARI registries. J Child Psychol Psychiatry. 2021 Nov;62(11):1297-1307. [PMID: 34382689]

61.  Busti Ceccarelli S, Ferrante C, Gazzola E, Marzocchi GM, Nobile M, Molteni M, Crippa A. Fundamental Motor Skills Intervention for Children with Autism Spectrum Disorder: A 10-Year Narrative Review. Children (Basel, Switzerland). 2020 Nov 23;7(11):250. [PMID: 33238562]

62.  Riddiford JA, Enticott PG, Lavale A, Gurvich C. Gaze and social functioning associations in autism spectrum disorder: A systematic review and meta-analysis. Autism Research. 2022 Aug;15(8):1380-1446. [PMID: 35593039]

63.  Ramot M, Walsh C, Reimann GE, Martin A. Distinct neural mechanisms of social orienting and mentalizing revealed by independent measures of neural and eye movement typicality. Commun Biol. 2020 Jan 29;3(1):48. [PMID: 31996763]

64.  Reimann GE, Walsh C, Csumitta KD, McClure P, Pereira F, Martin A, Ramot M. Gauging facial feature viewing preference as a stable individual trait in autism spectrum disorder. Autism Res. 2021 Aug;14(8):1670-1683. [PMID: 34008916]

65.  Jasmin K, Gotts SJ, Xu Y, Liu S, Riddell CD, Ingeholm JE, Kenworthy L, Wallace GL, Braun AR, Martin A. Overt social interaction and resting state in young adult males with autism: core and contextual neural features. Brain. 2019 Mar 1;142(3):808-822. [PMID: 30698656]

66.  Crutcher J, Martin A, Wallace GL. Dissociations in the neural substrates of language and social functioning in autism spectrum disorder. Autism research : official journal of the International Society for Autism Research. 2018 Aug;11(8):1175-1186. [PMID: 30365251]

67.  Key AP, D'Ambrose Slaboch K. Speech Processing in Autism Spectrum Disorder: An Integrative Review of Auditory Neurophysiology Findings. Journal of Speech, Language, and Hearing Research. 2021 Nov 8;64(11):4192-4212. [PMID: 34570613]

68.  Mapelli L, Soda T, D'Angelo E, Prestori F. The Cerebellar Involvement in Autism Spectrum Disorders: From the Social Brain to Mouse Models. International journal of molecular sciences. 2022 Mar 31;23(7):3894. [PMID: 35409253]

69.  Maliske L, Kanske P. The Social Connectome - Moving Toward Complexity in the Study of Brain Networks and Their Interactions in Social Cognitive and Affective Neuroscience. Frontiers in psychiatry. 2022 Apr 5;13(845492-845492. [PMID: 35449570]

70.  Demetriou EA, DeMayo MM, Guastella AJ. Executive Function in Autism Spectrum Disorder: History, Theoretical Models, Empirical Findings, and Potential as an Endophenotype. Frontiers in psychiatry. 2019 Nov 11;10(753-753. [PMID: 31780959]

71.  Tian J, Gao X, Yang L. Repetitive Restricted Behaviors in Autism Spectrum Disorder: From Mechanism to Development of Therapeutics. Frontiers in neuroscience. 2022 Mar 2;16(780407. [PMID: 35310097]

72.  Edelson SM. Understanding Challenging Behaviors in Autism Spectrum Disorder: A Multi-Component, Interdisciplinary Model. Journal of Personalized Medicine. 2022 Jul 12;12(7):1127. [PMID: 35887624]

73.  Yan H, Elkaim LM, Venetucci Gouveia F, Huber JF, Germann J, Loh A, Benedetti-Isaac JC, Doshi PK, Torres CV, Segar DJ, Elias GJB, Boutet A, Cosgrove GR, Fasano A, Lozano AM, Kulkarni AV, Ibrahim GM. Deep brain stimulation for extreme behaviors associated with autism spectrum disorder converges on a common pathway: a systematic review and connectomic analysis. J Neurosurg. 2022 Jan 21:1-10. [PMID: 35061980]

74.  Robinson-Agramonte MdLA, Noris García E, Fraga Guerra J, Vega Hurtado Y, Antonucci N, Semprún-Hernández N, Schultz S, Siniscalco D. Immune Dysregulation in Autism Spectrum

Disorder: What Do We Know about It? International journal of molecular sciences. 2022 Mar 11;23(6):3033. [PMID: 35328471]

75. Saghazadeh A, Ataeinia B, Keynejad K, Abdolalizadeh A, Hirbod-Mobarakeh A, Rezaei N. A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. J Psychiatr Res. 2019 Aug;115(90-102. [PMID: 31125917]

76. Arenella M, Cadby G, De Witte W, Jones RM, Whitehouse AJ, Moses EK, Fornito A, Bellgrove MA, Hawi Z, Johnson B, Tiego J, Buitelaar JK, Kiemeney LA, Poelmans G, Bralten J. Potential role for immune-related genes in autism spectrum disorders: Evidence from genome-wide association meta-analysis of autistic traits. Autism : the international journal of research and practice. 2022 Feb;26(2):361-372. [PMID: 34344231]

77. Han VX, Patel S, Jones HF, Dale RC. Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nature Reviews Neurology. 2021 Sep;17(9):564-579. [PMID: 34341569]

78. Rodríguez AM, Rodríguez J, Giambartolomei GH. Microglia at the Crossroads of Pathogen-Induced Neuroinflammation. ASN neuro. 2022 Jan-Dec;14(17590914221104566. [PMID: 35635133]

79. Maenner MJ, Shaw KA, Bakian AV, Bilder DA, Durkin MS, Esler A, Furnier SM, Hallas L, Hall-Lande J, Hudson A, Hughes MM, Patrick M, Pierce K, Poynter JN, Salinas A, Shenouda J, Vehorn A, Warren Z, Constantino JN, DiRienzo M, Fitzgerald RT, Grzybowski A, Spivey MH, Pettygrove S, Zahorodny W, Ali A, Andrews JG, Baroud T, Gutierrez J, Hewitt A, Lee LC, Lopez M, Mancilla KC, McArthur D, Schwenk YD, Washington A, Williams S, Cogswell ME. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. MMWR Surveill Summ. 2021 Dec 3;70(11):1-16. [PMID: 34855725]

80. Dietz PM, Rose CE, McArthur D, Maenner M. National and State Estimates of Adults with Autism Spectrum Disorder. J Autism Dev Disord. 2020 Dec;50(12):4258-4266. [PMID: 32390121]

81. Warrier V, Greenberg DM, Weir E, Buckingham C, Smith P, Lai M-C, Allison C, Baron-Cohen S. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. Nature Communications. 2020 Aug 7;11(1):3959. [PMID: 32770077]

82. Kallitsounaki A, Williams DM. Autism Spectrum Disorder and Gender Dysphoria/Incongruence. A systematic Literature Review and Meta-Analysis. Journal of Autism and Developmental Disorders. 2022 May 20. [PMID: 35596023]

83. Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, Beckmann JS, Rosenfeld JA, Eichler EE. A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet. 2014 Mar 6;94(3):415-25. [PMID: 24581740]

84. Antaki D, Guevara J, Maihofer AX, Klein M, Gujral M, Grove J, Carey CE, Hong O, Arranz MJ, Hervas A, Corsello C, Vaux KK, Muotri AR, Iakoucheva LM, Courchesne E, Pierce K, Gleeson JG, Robinson EB, Nievergelt CM, Sebat J. A phenotypic spectrum of autism is attributable to the combined effects of rare variants, polygenic risk and sex. Nat Genet. 2022 Jun 2. [PMID: 35654974]

85. Palmer N, Beam A, Agniel D, Eran A, Manrai A, Spettell C, Steinberg G, Mandl K, Fox K, Nelson SF, Kohane I. Association of Sex With Recurrence of Autism Spectrum Disorder Among Siblings. JAMA Pediatr. 2017 Nov 1;171(11):1107-1112. [PMID: 28973142]

86. Bai D, Marrus N, Yip BHK, Reichenberg A, Constantino JN, Sandin S. Inherited Risk for Autism Through Maternal and Paternal Lineage. Biol Psychiatry. 2020 Sep 15;88(6):480-487. [PMID: 32430199]

87.  Lim ET, Raychaudhuri S, Sanders SJ, Stevens C, Sabo A, MacArthur DG, Neale BM, Kirby A, Ruderfer DM, Fromer M, Lek M, Liu L, Flannick J, Ripke S, Nagaswamy U, Muzny D, Reid JG, Hawes A, Newsham I, Wu Y, Lewis L, Dinh H, Gross S, Wang LS, Lin CF, Valladares O, Gabriel SB, dePristo M, Altshuler DM, Purcell SM, State MW, Boerwinkle E, Buxbaum JD, Cook EH, Gibbs RA, Schellenberg GD, Sutcliffe JS, Devlin B, Roeder K, Daly MJ. Rare complete knockouts in humans: population distribution and significant role in autism spectrum disorders. Neuron. 2013 Jan 23;77(2):235-42. [PMID: 23352160]

88.  Willsey HR, Exner CRT, Xu Y, Everitt A, Sun N, Wang B, Dea J, Schmunk G, Zaltsman Y, Teerikorpi N, Kim A, Anderson AS, Shin D, Seyler M, Nowakowski TJ, Harland RM, Willsey AJ, State MW. Parallel in vivo analysis of large-effect autism genes implicates cortical neurogenesis and estrogen in risk and resilience. Neuron. 2021 Mar 3;109(5):788-804.e8. [PMID: 33497602]

89.  Hoffman EJ, Turner KJ, Fernandez JM, Cifuentes D, Ghosh M, Ijaz S, Jain RA, Kubo F, Bill BR, Baier H, Granato M, Barresi MJ, Wilson SW, Rihel J, State MW, Giraldez AJ. Estrogens Suppress a Behavioral Phenotype in Zebrafish Mutants of the Autism Risk Gene, CNTNAP2. Neuron. 2016 Feb 17;89(4):725-33. [PMID: 26833134]

90.  Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, Cohen AS, Chakrabarti B, Ruta L, Lombardo MV. Elevated fetal steroidogenic activity in autism. Mol Psychiatry. 2015 Mar;20(3):369-76. [PMID: 24888361]

91.  Auyeung B, Baron-Cohen S, Ashwin E, Knickmeyer R, Taylor K, Hackett G. Fetal testosterone and autistic traits. Br J Psychol. 2009 Feb;100(Pt 1):1-22. [PMID: 18547459]

92.  Jiang L, Tian L, Yuan J, Xu X, Qu F, Zhang R, Wang J. Associations Between Sex Hormone Levels and Autistic Traits in Infertile Patients With Polycystic Ovary Syndrome and Their Offspring. Front Endocrinol (Lausanne). 2022 Jan 31;12(789395. [PMID: 35173679]

93.  Smith REW, Avery JA, Wallace GL, Kenworthy L, Gotts SJ, Martin A. Sex Differences in Resting-State Functional Connectivity of the Cerebellum in Autism Spectrum Disorder. Front Hum Neurosci. 2019 Apr 5;13(104. [PMID: 31024276]

94.  Walsh MJM, Pagni B, Monahan L, Delaney S, Smith CJ, Baxter L, Braden BB. Sex-related brain connectivity correlates of compensation in adults with autism: insights into female protection. Cereb Cortex. 2022 Feb 25. [PMID: 35212373]

95.  Zhang W, Groen W, Mennes M, Greven C, Buitelaar J, Rommelse N. Revisiting subcortical brain volume correlates of autism in the ABIDE dataset: effects of age and sex. Psychol Med. 2018 Mar;48(4):654-668. [PMID: 28745267]

96.  Calderoni S. Sex/gender differences in children with autism spectrum disorder: A brief overview on epidemiology, symptom profile, and neuroanatomy. Journal of Neuroscience Research. 2022 Jan 18. [PMID: 35043482]

97.  Pierce K, Gazestani VH, Bacon E, Barnes CC, Cha D, Nalabolu S, Lopez L, Moore A, Pence-Stophaeros S, Courchesne E. Evaluation of the Diagnostic Stability of the Early Autism Spectrum Disorder Phenotype in the General Population Starting at 12 Months. JAMA Pediatr. 2019 Jun 1;173(6):578-587. [PMID: 31034004]

98.  Ly A, Heron J, Rai D, Wright C. Autism, autistic traits and multiple risk behaviours in adolescence: a longitudinal birth cohort study. Psychol Med. 2022 Apr 28:1-10. [PMID: 35481795]

99.  Iwasa M, Shimizu Y, Sasayama D, Imai M, Ohzono H, Ueda M, Hara I, Honda H. Twenty-year longitudinal birth cohort study of individuals diagnosed with autism spectrum disorder before seven years of age. J Child Psychol Psychiatry. 2022 Apr 11. [PMID: 35405770]

100. Nordahl CW, Andrews DS, Dwyer P, Waizbard-Bartov E, Restrepo B, Lee JK, Heath B, Saron C, Rivera SM, Solomon M, Ashwood P, Amaral DG. The Autism Phenome Project: Toward

Identifying Clinically Meaningful Subgroups of Autism. Frontiers in neuroscience. 2022 Jan 17;15(786220-786220. [PMID: 35110990]

101. Pant SW, Skovgaard AM, Ammitzbøll J, Holstein BE, Pedersen TP. Motor development problems in infancy predict mental disorders in childhood: a longitudinal cohort study. Eur J Pediatr. 2022 Apr 6. [PMID: 35384508]

102. Deserno MK, Fuhrmann D, Begeer S, Borsboom D, Geurts HM, Kievit RA. Longitudinal development of language and fine motor skills is correlated, but not coupled, in a childhood atypical cohort. Autism. 2022 Apr 26:13623613221086448. [PMID: 35470698]

103. Sadikova E, Dovgan K, Mazurek MO. Longitudinal Examination of Sleep Problems and Symptom Severity in Children with Autism Spectrum Disorder. J Autism Dev Disord. 2022 Apr 6. [PMID: 35384626]

104. Andrews DS, Aksman L, Kerns CM, Lee JK, Winder-Patel BM, Harvey DJ, Waizbard-Bartov E, Heath B, Solomon M, Rogers SJ, Altmann A, Nordahl CW, Amaral DG. Association of Amygdala Development With Different Forms of Anxiety in Autism Spectrum Disorder. Biological Psychiatry. 2022 Jun 1;91(11):977-987. [PMID: 35341582]

105. Gabard-Durnam LJ, Wilkinson C, Kapur K, Tager-Flusberg H, Levin AR, Nelson CA. Longitudinal EEG power in the first postnatal year differentiates autism outcomes. Nat Commun. 2019 Sep 13;10(1):4188. [PMID: 31519897]

106. Bruno JL, Romano D, Mazaika P, Lightbody AA, Hazlett HC, Piven J, Reiss AL. Longitudinal identification of clinically distinct neurophenotypes in young children with fragile X syndrome. Proc Natl Acad Sci U S A. 2017 Oct 3;114(40):10767-10772. [PMID: 28923933]

107. Prigge MBD, Lange N, Bigler ED, King JB, Dean DC, Adluru N, Alexander AL, Lainhart JE, Zielinski BA. A 16-year study of longitudinal volumetric brain development in males with autism. NeuroImage. 2021 Aug 1;236(118067. [PMID: 33878377]

108. Leader G, Abberton C, Cunningham S, Gilmartin K, Grudzien M, Higgins E, Joshi L, Whelan S, Mannion A. Gastrointestinal Symptoms in Autism Spectrum Disorder: A Systematic Review. Nutrients. 2022 Apr 1;14(7):1471. [PMID: 35406084]

109. Esteban-Figuerola P, Canals J, Fernández-Cao JC, Arija Val V. Differences in food consumption and nutritional intake between children with autism spectrum disorders and typically developing children: A meta-analysis. Autism. 2019 Jul;23(5):1079-1095. [PMID: 30345784]

110. Puricelli C, Rolla R, Gigliotti L, Boggio E, Beltrami E, Dianzani U, Keller R. The Gut-Brain-Immune Axis in Autism Spectrum Disorders: A State-of-Art Report. Frontiers in Psychiatry. 2022 Feb 3;12([PMID: 35185631]

111. Kang D-W, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, Khoruts A, Geis E, Maldonado J, McDonough-Means S, Pollard EL, Roux S, Sadowsky MJ, Lipson KS, Sullivan MB, Caporaso JG, Krajmalnik-Brown R. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017 Jan 23;5(1):10-10. [PMID: 28122648]

112. Kang D-W, Adams JB, Coleman DM, Pollard EL, Maldonado J, McDonough-Means S, Caporaso JG, Krajmalnik-Brown R. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Scientific reports. 2019 Apr 9;9(1):5821-5821. [PMID: 30967657]

113. Grimaldi R, Cela D, Swann JR, Vulevic J, Gibson GR, Tzortzis G, Costabile A. In vitro fermentation of B-GOS: impact on faecal bacterial populations and metabolic activity in autistic and non-autistic children. FEMS microbiology ecology. 2017 Feb;93(2):fiw233. [PMID: 27856622]

114. Yap CX, Henders AK, Alvares GA, Wood DLA, Krause L, Tyson GW, Restuadi R, Wallace L, McLaren T, Hansell NK, Cleary D, Grove R, Hafekost C, Harun A, Holdsworth H, Jellett R, Khan F, Lawson LP, Leslie J, Frenk ML, Masi A, Mathew NE, Muniandy M, Nothard M, Miller JL, Nunn L,

Holtmann G, Strike LT, de Zubicaray GI, Thompson PM, McMahon KL, Wright MJ, Visscher PM, Dawson PA, Dissanayake C, Eapen V, Heussler HS, McRae AF, Whitehouse AJO, Wray NR, Gratten J. Autism-related dietary preferences mediate autism-gut microbiome associations. Cell. 2021 Nov 24;184(24):5916-5931.e17. [PMID: 34767757]

115. Keller R, Basta R, Salerno L, Elia M. Autism, epilepsy, and synaptopathies: a not rare association. Neurological Sciences. 2017 Aug;38(8):1353-1361. [PMID: 28455770]

116. Specchio N, Di Micco V, Trivisano M, Ferretti A, Curatolo P. The epilepsy–autism spectrum disorder phenotype in the era of molecular genetics and precision therapy. Epilepsia. 2022 Jan;63(1):6-21. [PMID: 34741464]

117. Zahra A, Wang Y, Wang Q, Wu J. Shared Etiology in Autism Spectrum Disorder and Epilepsy with Functional Disability. Behavioural neurology. 2022 Apr 27;2022(5893519. [PMID: 35530166]

118. Han GT, Trevisan DA, Abel EA, Cummings EM, Carlos C, Bagdasarov A, Kala S, Parker T, Canapari C, McPartland JC. Associations between sleep problems and domains relevant to daytime functioning and clinical symptomatology in autism: A meta-analysis. Autism Res. 2022 Jul;15(7):1249-1260. [PMID: 35635067]

119. Johnson KP, Zarrinnegar P. Autism Spectrum Disorder and Sleep. Child and Adolescent Psychiatric Clinics of North America. 2021 Jan;30(1):195-208. [PMID: 33223062]

120. Singer EV, Niarchou M, Maxwell-Horn A, Hucks D, Johnston R, Sutcliffe JS, Davis LK, Malow BA. Characterizing sleep disorders in an autism-specific collection of electronic health records. Sleep Med. 2022 Apr;92(88-95. [PMID: 35367909]

121. Doldur-Balli F, Imamura T, Veatch OJ, Gong NN, Lim DC, Hart MP, Abel T, Kayser MS, Brodkin ES, Pack AI. Synaptic dysfunction connects autism spectrum disorder and sleep disturbances: A perspective from studies in model organisms. Sleep Medicine Reviews. 2022 Apr;62(101595. [PMID: 35158305]

122. Kennedy M, Loomba K, Ghani H, Riley B. The psychological burden associated with Ehlers-Danlos syndromes: a systematic review. Journal of Osteopathic Medicine. 2022 Apr 14;122(8):381-392. [PMID: 35420002]

123. Sieg KG. Autism and Ehlers-Danlos Syndrome. Journal of the American Academy of Child & Adolescent Psychiatry. 1992 Jan;31(1):173. [PMID: 1537777]

124. Shetreat-Klein M, Shinnar S, Rapin I. Abnormalities of joint mobility and gait in children with autism spectrum disorders. Brain and Development. 2014 Feb;36(2):91-96. [PMID: 22401670]

125. Glans MR, Thelin N, Humble MB, Elwin M, Bejerot S. The Relationship Between Generalised Joint Hypermobility and Autism Spectrum Disorder in Adults: A Large, Cross-Sectional, Case Control Comparison. Frontiers in psychiatry. 2022 Feb 8;12(803334-803334. [PMID: 35211037]

126. Kindgren E, Quiñones Perez A, Knez R. Prevalence of ADHD and Autism Spectrum Disorder in Children with Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome: A Retrospective Study. Neuropsychiatric disease and treatment. 2021 Feb 10;17(379-388. [PMID: 33603376]

127. Cederlöf M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. BMC psychiatry. 2016 Jul 4;16(207-207. [PMID: 27377649]

128. Casanova EL, Baeza-Velasco C, Buchanan CB, Casanova MF. The Relationship between Autism and Ehlers-Danlos Syndromes/Hypermobility Spectrum Disorders. Journal of personalized medicine. 2020 Dec 1;10(4):260. [PMID: 33271870]

129. Owens AP, Mathias CJ, Iodice V. Autonomic Dysfunction in Autism Spectrum Disorder. Front Integr Neurosci. 2021 Dec 30;15(787037. [PMID: 35035353]

130. Csecs JLL, Iodice V, Rae CL, Brooke A, Simmons R, Quadt L, Savage GK, Dowell NG, Prowse F, Themelis K, Mathias CJ, Critchley HD, Eccles JA. Joint Hypermobility Links Neurodivergence to Dysautonomia and Pain. Front Psychiatry. 2021 Feb 2;12(786916. [PMID: 35185636]

131. Rosen TE, Mazefsky CA, Vasa RA, Lerner MD. Co-occurring psychiatric conditions in autism spectrum disorder. International Review of Psychiatry. 2018 Feb;30(1):40-61. [PMID: 29683351]

132. Huang J-S, Yang F-C, Chien W-C, Yeh T-C, Chung C-H, Tsai C-K, Tsai S-J, Yang S-S, Tzeng N-S, Chen M-H, Liang C-S. Risk of Substance Use Disorder and Its Associations With Comorbidities and Psychotropic Agents in Patients With Autism. JAMA Pediatrics. 2021 Feb 1;175(2):e205371-e205371. [PMID: 33394019]

133. Bowri M, Hull L, Allison C, Smith P, Baron-Cohen S, Lai M-C, Mandy W. Demographic and psychological predictors of alcohol use and misuse in autistic adults. Autism. 2021 Jul;25(5):1469-1480. [PMID: 34232103]

134. Kunreuther E. Autism Spectrum Disorder and Substance Use Disorder: A Dual Diagnosis Hiding in Plain Sight. Psychiatric Clinics of North America. 2021 Mar;44(1):35-49. [PMID: 33526236]

135. Weir E, Allison C, Baron-Cohen S. Understanding the substance use of autistic adolescents and adults: a mixed-methods approach. The Lancet Psychiatry. 2021 Aug;8(8):673-685. [PMID: 34217427]

136. Ali H, Marth L, Krueger-Burg D. Neuroligin-2 as a central organizer of inhibitory synapses in health and disease. Sci Signal. 2020 Dec 22;13(663). [PMID: 33443230]

137. Tsai SJ. Role of interleukin 8 in depression and other psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 2;106(110173. [PMID: 33186640]

138. Alameda L, Trotta G, Quigley H, Rodriguez V, Gadelrab R, Dwir D, Dempster E, Wong CCY, Forti MD. Can epigenetics shine a light on the biological pathways underlying major mental disorders? Psychological Medicine. 2022 Jul:1-21. [PMID: 35193719]

139. Zinkstok JR, Boot E, Bassett AS, Hiroi N, Butcher NJ, Vingerhoets C, Vorstman JAS, van Amelsvoort T. Neurobiological perspective of 22q11.2 deletion syndrome. Lancet Psychiatry. 2019 Nov;6(11):951-960. [PMID: 31395526]

140. Zarei K, Xu G, Zimmerman B, Giannotti M, Strathearn L. Adverse Childhood Experiences Predict Common Neurodevelopmental and Behavioral Health Conditions among U.S. Children. Children (Basel). 2021 Aug 31;8(9). [PMID: 34572191]

141. Andrzejewski T, DeLucia EA, Semones O, Khan S, McDonnell CG. Adverse Childhood Experiences in Autistic Children and Their Caregivers: Examining Intergenerational Continuity. J Autism Dev Disord. 2022 Apr 12. [PMID: 35412212]

142. Kitamura S, Makinodan M, Matsuoka K, Takahashi M, Yoshikawa H, Ishida R, Kishimoto N, Yasuno F, Yasuda Y, Hashimoto R, Miyasaka T, Kichikawa K, Kishimoto T. Association of adverse childhood experiences and precuneus volume with intrusive reexperiencing in autism spectrum disorder. Autism Res. 2021 Sep;14(9):1886-1895. [PMID: 34185397]

143. Okazaki K, Ota T, Makinodan M, Kishimoto N, Yamamuro K, Ishida R, Takahashi M, Yasuda Y, Hashimoto R, Iida J, Kishimoto T. Associations of childhood experiences with event-related potentials in adults with autism spectrum disorder. Sci Rep. 2020 Aug 10;10(1):13447. [PMID: 32778726]

144. Yoshikawa H, Kitamura S, Matsuoka K, Takahashi M, Ishida R, Kishimoto N, Yasuno F, Yasuda Y, Hashimoto R, Miyasaka T, Kichikawa K, Kishimoto T, Makinodan M. Adverse Childhood Experience Is Associated With Disrupted White Matter Integrity in Autism Spectrum Disorder: A Diffusion Tensor Imaging Study. Front Psychiatry. 2022 Jan 3;12(823260. [PMID: 35046859]

145.  Heselton GA, Rempel GR, Nicholas DB. "Realizing the problem wasn't necessarily me": the meaning of childhood adversity and resilience in the lives of autistic adults. Int J Qual Stud Health Well-being. 2022 Dec;17(1):2051237. [PMID: 35297725]