Question 2: What Is the Biology Underlying Autism?

Aspirational Goal: Discover the roles of brain development, cognition, and physiological function in autism to enable the development of effective, targeted interventions and societal accommodations that improve quality of life across the lifespan.

Introduction

Current scientific evidence suggests that autism results from subtle changes during brain development that affect brain structure, function, and connectivity. Over the course of the last decades, several studies have revealed the role of prenatal or perinatal stressors and genetic contributors in autism, possibly acting through changes in early development. The biological mechanisms by which known gene mutations may lead to autism by altering the underlying neural circuitry of the brain are under intense study. These genetic variants are associated with the remodeling of genetic material, RNA regulation, and changes to synaptic structure and function (which are the basis for neuronal function and communication). Taken together, this research suggests there may be shared features of the underlying biology across the autism spectrum.

However, our knowledge of the specific biological mechanisms that lead to autism and differences in cognition, communication, and sensory processing remain incomplete. More research is also needed to better understand how sex and gender impacts autism development and presentation. Additionally, studies on the relationship of common co-occurring conditions to autism and how they can affect autism presentation are still necessary, 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 improve the quality of life for people 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 contribute to a lower degree to 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 and synapse formation and communication. However, much remains to be learned about the molecular mechanisms that may lead to autism development.

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.

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 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. 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 the science. 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 need 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 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 this changes 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]

However, much remains to be explored about the neurobiology underlying cognition and social communication. While some regions of the brain such as the cerebellum has 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. Lastly, it will be important to study how cognition and social communication may change over time to better support individuals on the autism spectrum throughout the lifespan.

Immune System and Autism Development

Current evidence suggests immune differences and neuroinflammation are implicated in the severity and pathogenesis of the autism phenotype.[72] For example, recent meta-analyses found higher concentrations of pro-inflammatory cytokines in individuals on the autism spectrum compared to the control group[73] and a subset of immune-related genes were significantly associated with autistic traits.[74] 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.[72, 75] 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.[76] Microglial activation has been linked to abnormal brain connectivity in children on the autism spectrum, and pro-inflammatory cytokines and microglial phenotypes are also seen in autistic individuals.[72] Further investigation of the role of microglia are warranted based on our emerging understanding of their role in normal 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.[77, 78] Additionally, autism is more prevalent in gender-diverse individuals compared to cis-gendered individuals.[79, 80] 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 ration 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, 81] and common and rare variants of autism genes are enriched in mothers and unaffected sisters of autistic individuals.[1, 2, 82] 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,[83] 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.[84] 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,[85] 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,[86, 87] whereas excess testosterone is thought to contribute to autism development.[88, 89] 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.[90] 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.[91] In addition, differences in functional connectivity may explain why autistic females report more compensatory behavior ("camouflaging") compared to their male counterparts.[92] Furthermore, brain structure and anatomy also differ between males and females.[93, 94] 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 we are just beginning to explore the relationship between gender identity and autism development and outcomes. 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,[95] the strengths, challenges, and support needs associated with autism change over time.[55, 56, 96-98] Longitudinal studies have shown correlations between motor skills and later development of autism and language,[99, 100] as well as associations between autism symptoms and sleep problems.[101] Longitudinal 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.[102-105] 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.[106] 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, language and communication ability, self-injurious behavior and aggression, sleep problems, and sensory issues.[106] 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.[107] 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,[106] 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.[108] 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.[108] Additionally, some studies have found interventions designed to normalize the gut microbiome improved both GI and autism symptoms.[109-111] However, a recent metagenomics study did not find any association between autism and the gut microbiome,[112] 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.[113] Studies have shown that many of the gene factors for epilepsy and autism overlap,[113, 114] 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.[115] 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 quality of life for people 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. 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.[116] 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.[117] 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

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.[118] Co-occurrence of EDS and autism has been described in the literature since the 1980s.[119] More recent studies have shown that children on the autism spectrum have greater joint flexibility compared to age- and gender-matched peers[120] and generalized joint hypermobility and EDS are associated with both autism and attention-deficit/hyperactivity disorder (ADHD).[121-123] Many co-occurring conditions are also shared in both autism and EDS.[124] 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.

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.[125] 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.[126-129] Many autistic individuals may also simultaneously experience multiple co-occurring conditions. Current research indicates that these co-occurring conditions may share common genetic, epigenetic, and neurological variations.[130-133] 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.

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.

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 improving the quality of life for autistic individuals and their families. 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 ensure that participants know what data is being collected and how that data will be used. 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 ensure that study findings are more accurate and 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 on the underlying biology of autism continues to be critical to provide the foundation for translational advances that will lead to effective interventions to improve the quality of life for autistic individuals across the spectrum and across the lifespan.

Objectives

Objective 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.

Objective 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.

Objective 3: Support large-scale longitudinal studies that can 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.

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