

INTERAGENCY AUTISM COORDINATING COMMITTEE

2018

SUMMARY OF ADVANCES

in Autism Spectrum Disorder Research



OFFICE OF
AUTISM RESEARCH
COORDINATION
NATIONAL INSTITUTES OF HEALTH

INTERAGENCY AUTISM COORDINATING COMMITTEE

2018

SUMMARY OF ADVANCES

In Autism Spectrum Disorder Research



COVER DESIGN

NIH Medical Arts Branch

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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) is a federal advisory committee charged with coordinating Federal activities concerning autism spectrum disorder (ASD) and providing advice to the Secretary of Health and Human Services (HHS) on issues related to autism. The Committee was established by Congress under the *Children's Health Act of 2000*, reconstituted under the *Combating Autism Act (CAA) of 2006*, and renewed most recently under the *Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014*.

Membership of the Committee includes a wide array of federal agencies involved in ASD research and services, as well as public stakeholders, including self-advocates, family members of children and adults with ASD, advocates, service providers, and researchers, who represent a variety of perspectives from within the autism community. The IACC membership is composed to ensure that the Committee is equipped to address the wide range of issues and challenges faced by individuals and families affected by autism.

Under the CAA and subsequent reauthorizations, the IACC is required to (1) develop and annually update a strategic plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor federal activities related to ASD.

Through these and other activities, the IACC provides guidance to HHS and partners with other federal departments, federal agencies, research and advocacy organizations, and the broader autism community to accelerate research and enhance services with the goal of profoundly improving the lives of people with ASD and their families.

For more information about the IACC, see <http://www.iacc.hhs.gov>.

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INTRODUCTION

THE 2018 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

Each year, the IACC releases a list of scientific advances that represent significant progress in the field. The *2018 Summary of Advances* provides short, plain language summaries of the top research breakthroughs selected by the IACC from a pool of research articles nominated by the members. The 20 studies selected for 2018 have provided new insight into potential screening tools for autism spectrum disorder (ASD), the development of brain regions implicated in ASD symptomatology, and the prevalence of ASD in children. The advances also include studies that analyzed the degree of inclusion of children severely affected by autism in treatment studies, the effect of insurance ASD mandates on health service use, and the manifestation of ASD symptoms in adolescents and young adults. Several of the selected studies compared the genetic variations that contribute to ASD and other psychiatric disorders; studies such as these will help elucidate shared mechanisms underlying these disorders.

Articles in the *2018 IACC Summary of Advances* are grouped according to the topics represented by the seven questions of the *2016-2017 IACC Strategic Plan for ASD*. Citations for the articles selected for the *Summary of Advances*, as well as a complete listing of those nominated, are included at the end of the document.

ARTICLES SELECTED FOR THE 2018 SUMMARY OF ADVANCES

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

- EEG analytics for early detection of autism spectrum disorder: a data-driven approach
- Automatic emotion and attention analysis of young children at home: a ResearchKit autism feasibility study
- A longitudinal study of parent-reported sensory responsiveness in toddlers at-risk for autism

QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

- Neuron numbers increase in the human amygdala from birth to adulthood, but not in autism
- Complete disruption of autism-susceptibility genes by gene editing predominantly reduces functional connectivity of isogenic human neurons
- Social deficits in *Shank3*-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

- Analysis of shared heritability in common disorders of the brain
- Paternally inherited cis-regulatory structural variants are associated with autism
- Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap
- Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder
- *De novo* mutations in regulatory elements in neurodevelopmental disorders

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

- Cluster randomized trial of the classroom SCERTS intervention for elementary students with autism spectrum disorder
- Meta-analysis of parent-mediated interventions for young children with autism spectrum disorder
- Are children severely affected by autism spectrum disorder underrepresented in treatment studies? An analysis of the literature

QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

- Effects of state autism mandate age caps on health service use and spending among adolescents
- Vaccination patterns in children after autism spectrum disorder diagnosis and in their younger siblings

QUESTION 6: HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

- Autism spectrum disorder symptoms from ages 2 to 19 years: implications for diagnosing adolescents and young adults
- Psychiatric and medical conditions in transition-aged Individuals with ASD
- Understanding service usage and needs for adults with ASD: the importance of living situation

QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

- Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014.

QUESTION 1

HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach.

Bosl W], Tager-Flusberg H, Nelson CA. *Sci Rep*. 2018 May 1;8(1):6828. [PMID: 29717196]

ASD is usually diagnosed by observing behavioral symptoms in the first few years of a child's life. Because symptoms are highly variable among children, this method of diagnosis can be challenging and may result in a late diagnosis. Consequently, many researchers are interested in studying *biomarkers*— unique biological indicators of a condition or disorder – to help clinicians diagnose ASD earlier without relying on diverse behavioral symptoms that may present later in life.

In this study, researchers used EEG (electroencephalogram), a cost-effective tool used to record electrical activity in different areas of the brain. This technology can monitor atypical brain development and be used to identify potential biomarkers in children at risk for ASD. To test the effectiveness of EEG as a tool for early ASD detection, the researchers obtained EEG recordings from three groups of infants: those at high risk for ASD (determined by an older sibling diagnosed with ASD) who were subsequently determined to not have ASD, those with low risk, and those at high or low risk who ultimately received an ASD diagnosis.

The researchers gathered EEG recordings from the infants every three to six months, beginning when the children were 3 months old and ending at 36 months old. At multiple time points during the study, the children were assessed using the Autism Diagnostic Observation Schedule (ADOS), a standard ASD assessment tool. Children who met ADOS criteria at any assessment point were evaluated by a licensed clinical psychologist for ASD diagnosis.

The researchers found that EEG recordings were predictive of a clinical diagnostic outcome of ASD and estimated the severity of symptoms as early as three months of age. They noted that children who did develop ASD showed different activity patterns in certain areas of the brain compared to those in the low-risk and high-risk groups. Children who later developed ASD and children who were at high risk but did not develop ASD started with similar EEG patterns, however their patterns deviated at the 12-month interval and the high-risk group began following patterns similar to the low-risk group, although at a higher electrical frequency.

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

This study suggests that electrical activity in these brain regions may be used as biomarkers to diagnose ASD and predict symptom severity. EEG recordings present a promising method for early detection of ASD. Future research should focus on determining whether this technology can be easily administered during routine well-baby checkups to increase the likelihood of detecting ASD in infancy.

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

Automatic Emotion and Attention Analysis of Young Children at Home: A ResearchKit Autism Feasibility Study.

Egger HL, Dawson G, Hashemi J, Carpenter KLH, Espinosa S, Campbell K, Brotkin S, Schaich-Borg J, Qiu Q, Tepper M, Baker JP, Bloomfield RA, and Sapiro G. *npj Digital Medicine*. 2018 Jun 1;1(20).

<http://www.nature.com/articles/s41746-018-0024-6>

Children with ASD are typically diagnosed through behavioral observation by trained professionals in a clinical setting. Professional evaluation using behavioral assessment tools is often costly, time-consuming, and depends on the availability and accessibility of qualified evaluators; these factors can delay diagnosis and intervention. Health care providers also rely heavily on caregiver reports. Although these reports are important components of the diagnostic process, they can be subjective and are influenced by the caregiver's educational background and familiarity with the questions being asked. To alleviate these problems, researchers are working to develop tools that they can use to objectively observe and measure ASD-related behavior in children in non-clinical settings.

In this study, researchers developed a mobile app for assessing children's behavior in their usual settings, such as at home or in school. They hoped that this naturalistic method of observation would provide them with firsthand evidence of children's behavior outside of a formal office or clinic setting. They also aimed to use the data from these recordings to objectively identify behavior patterns, potentially eliminating the need to rely on personal caregiver reports to screen for ASD.

The study included 1,756 caregivers of children ages 12-72 months with and without ASD. Caregivers downloaded the app to an iPhone and completed questionnaires related to their child's behavior. Caregivers also completed the Modified Checklist for Autism and Toddlers (M-CHAT), a screening tool that evaluates ASD risk. After activating the app, each caregiver's iPhone displayed short movies that were designed to elicit different patterns of attention and facial expressions while the camera in the iPhone recorded the child's responses. This allowed the researchers to quantify the child's behavioral reactions as they watched the movies. Computer vision analysis was then used to automatically code the child's facial movements and determine when the child's facial expression was positive, negative, or neutral, and whether or not the child was paying attention to the video.

The researchers found that children who were at a high risk for ASD (based on the child's M-CHAT score and the information provided by the caregiver) were more likely to react neutrally to the videos and less likely to show positive emotions, compared to low-risk children. They also found that girls at high risk for ASD were less attentive to the videos than girls at low risk for ASD. Lastly, the researchers found that the attention responses for girls at high risk for ASD were significantly lower than boys at high risk for ASD, which suggests a need for further investigation into possible sex differences in attention response that could be useful in improving screening and diagnostic tools.

This study suggests that this is a promising approach that may facilitate screening of ASD at an early age. The researchers suggest that digital phenotyping may be a valuable supplement to traditional diagnostic techniques, potentially providing clinicians with a more objective and complete picture of a child's behavior.

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

A longitudinal study of parent-reported sensory responsiveness in toddlers at-risk for autism.

Wolff JJ, Dimian AF, Botteron KN, Dager SR, Elison JT, Estes AM, Hazlett HC, Schultz RT, Zwaigenbaum L, Piven J; IBIS Network. *J Child Psychol Psychiatry*. 2018 Oct 23. [PMID: 30350375]

Children with ASD often respond differently to sensory stimuli than do typically developing children. Children with ASD may exhibit *hyperresponsivity* (overreaction to sensory stimuli), *hyporesponsivity* (underreaction to sensory stimuli), or *sensory-seeking behavior* (actively seeking out a particular stimulus). Currently, the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) broadly categorizes atypical sensory responsivity as a type of restricted and repetitive behavior (RRB). However, not much is known about the association between RRBs and the emergence of sensory responsivity symptoms in early childhood. Furthermore, there is uncertainty about the age at which atypical sensory responses can be used to determine ASD risk.

In this study, researchers sought to assess the relationship between responses to sensory stimuli and the risk for developing ASD. They administered the Sensory Experiences Questionnaire (SEQ) and the Repetitive Behavior Scale-Revised (RBS-R) to parents of infants who were at high and low risk for developing ASD at 12 months and 24 months of age. Infants were considered high risk if they had at least one older sibling with ASD. When the children reached 2 years old, they were evaluated for ASD using the Autism Diagnostic Observation Scale (ADOS), the Autism Diagnostic Interview-Revised (ADI-R), the Mullen Scales of Early Learning (MSEL), and the Vineland Adaptive Behavior Scales-II (Vineland-II). Based on their risk level and diagnosis, infants were classified as LR controls (low-risk infants who were not diagnosed with ASD), HR-neg (high-risk infants who were not subsequently diagnosed with ASD), and HR-ASD (high-risk infants who were subsequently diagnosed with ASD).

Researchers compared the children's total SEQ scores, as well as subscores for hyperresponsiveness, hyporesponsiveness, and sensory seeking behaviors. In addition, the researchers analyzed subscale scores for sensory experiences, including visual, auditory, and tactile (touch) modalities. They found that, at 12 months of age, the HR-ASD group scored higher in the hyperresponsivity and tactile modalities relative to both HR-neg and LR controls. Between 12 and 24 months, the likelihood of atypical total SEQ scores and subscores increased in the HR-ASD group and decreased in the HR-neg and LR-control groups.

The researchers also wanted to better understand the relationship between sensory responses and RRBs, so they compared the scores from the SEQ with the RBS-R and the Vineland II. They found that, at 12 and 24 months of age, HR-ASD children had SEQ scores that correlated with their scores on the RBS-R, and that the association between the two was strongest at 24 months of age. The SEQ scores at 24 months also had a negative association to the Vineland II socialization and communication scores, supporting previous research that RRBs may interfere with social-communication skills.

The results from this study support the hypothesis that these behaviors can be observed in infants who develop ASD as early as 12 months of age. Furthermore, the finding that sensory responsivity is significantly associated with RRBs supports categorizing atypical sensory responses as RRBs in the DSM-5.

QUESTION 2

WHAT IS THE BIOLOGY UNDERLYING ASD?

Neuron numbers increase in the human amygdala from birth to adulthood, but not in autism.

Avino TA, Barger N, Vargas MV, Carlson EL, Amaral DG, Bauman MD, Schumann CM. *Proc Natl Acad Sci USA*. 2018 Apr 3;115(14):3710-3715. [[PMID: 29559529](#)]

ASD is known to cause changes in global brain volume. However, little is known about the mechanisms underlying atypical brain volume in specific areas of the brain. One such area is the *amygdala*, a region of the brain that grows substantially in volume through adulthood during typical development. The amygdala plays a key role in regulating emotional behavior, and therefore is of particular interest to ASD researchers. Previous studies have suggested that individuals with ASD may have altered growth patterns in this region of the brain.

In this study, researchers compared the number of mature and immature neurons in the amygdala at different ages throughout life. Post-mortem brain samples were taken from adults and children with and without ASD who had died of other causes. The researchers found that the number of neurons in the amygdala increases with age in typically developing individuals but decreases over time in individuals with ASD. Specifically, children with ASD had more neurons in the amygdala as compared to neurotypical children. However, adults with ASD had fewer neurons in the amygdala than neurotypical adults.

Based on these results, the authors hypothesized that the age-related increase in mature neurons in neurotypical individuals is either the result of the maturation of immature neurons or the generation of new neurons after birth. In contrast, the researchers propose that the initially higher number of neurons in children with ASD could be caused by factors related to alterations in prenatal brain development. The subsequent decrease in mature neuron number over time in adults with ASD may be caused by dysregulation of the neuronal maturation process. Another possibility is that the increased number of neurons in the young amygdala leads to a hyperactivity that subsequently damages neurons. This may account for the lower number of mature amygdala neurons in adults with ASD compared to typically developed adults.

The results from this study help researchers understand the typical development of the amygdala, as well as identify developmental differences in children and adults with ASD. Studies such as these will continue to shed light on the biological mechanisms underlying ASD and some of its co-morbid conditions such as anxiety.

QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

Complete Disruption of Autism-Susceptibility Genes by Gene Editing Predominantly Reduces Functional Connectivity of Isogenic Human Neurons.

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. *Stem Cell Reports*. 2018 Nov 13;11(5):1211-1225. [[PMID: 30392976](#)]

Development of ASD is due in part to genetic factors. Currently, researchers are working to identify specific genes that increase the risk for ASD and to determine how each gene affects neurodevelopment. New gene-editing technology allows researchers to alter genes in *induced pluripotent stem cells* (iPSC), cultured cells taken from skin or blood that are reprogrammed into stem cells. By converting these edited iPSCs into neurons, researchers can better understand the relationship of these genes to ASD symptoms.

In this study, researchers used a gene-editing technique called CRISPR, which allows them to inactivate genes associated with ASD in cells and study the cells' activity. They selected 14 genes that are associated with an increased risk of ASD but whose functions were not well-understood. These genes are involved in various biological processes, including those that regulate cellular activity, growth, and communication. The researchers created 14 iPSC lines that each had one gene inactivated, then converted cells from each line into neurons. This allowed the researchers to study the changes in the behavior of neurons that lacked the function of the genes of interest.

The researchers found that inactivating some of the ASD-associated genes caused decreases in electrical activity in individual neurons. Neurons use electrical activity to send signals associated with biological processes, and this result suggests that the alteration of these genes changes behavior in individuals with ASD by affecting synaptic communication, which can limit the functionality of brain cells. When the researchers focused on the genes that resulted in the largest decrease in neuronal activity, they found that the loss of these genes reduced electrical activity not just in individual cells, but in populations of cells as well. They also found that some of the genes affected the way the neurons developed and formed connections with other neurons. Importantly, the researchers observed that, although these genes belonged to different functional groups, they all exhibited similarly reduced synaptic activity. These results support the idea that communication between neurons is altered in individuals with ASD, and that this change in cellular communication affects how these cells function.

This study presented a novel CRISPR strategy to isolate and analyze the expression of ASD-related genes. The researchers suggest that the next steps to understanding the relationships among these genes to ASD development should be to remove the genes in mouse models and observe behavioral changes in the animals.

QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

Social deficits in *Shank3*-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition.

Qin L, Ma K, Wang Z, Hu Z, Matas E, Wei J, Yan Z. *Nat Neurosci*. 2018 Apr;21(4):564-575. [PMID: 29531362]

Recent research demonstrates that some genes are expressed differently in individuals with ASD as compared to typically-developing individuals. In some individuals with ASD, the *Shank3* gene, which forms proteins that build and maintain the structure of synaptic connections between brain cells, is only expressed in one copy instead of two, or may be present in a mutated form. Mouse models that contain *Shank3* mutations display social deficits and repetitive behaviors similar to many individuals with ASD.

The researchers in this study sought to determine if they could correct the mutation of the *Shank3* gene by targeting enzymes — proteins that regulate cellular activities — that affect gene expression. They focused on histone deacetylase (HDAC), an enzyme that is known to suppress gene expression. The research team hoped that inhibiting HDAC could increase the expression of *Shank3*.

They compared mice with the *Shank3* mutation (a mouse model for ASD) to wildtype (normal) mice. They found that the *Shank3*-mutated mice had altered expression of several genes. They injected *Shank3* mutated mice with romidepsin, an HDAC inhibitor, and found this restored gene expression to levels similar to wildtype mice.

To understand whether correcting gene expression with romidepsin affected ASD-related behavior, the researchers observed the social behaviors of these mice. As previously demonstrated, *Shank3*-mutant mice prefer a non-social stimulus in a social interaction test, while wildtype mice prefer a social stimulus. The researchers found that romidepsin-treated mice spent more time exploring the social aspects of their environment and now behaved similarly to wildtype mice. Surprisingly, they found that this effect lasted for 21 days following the injection, suggesting the drug treatment had long-lasting effects. The researchers tested whether romidepsin had any effect on other ASD-related behaviors, but they did not observe an effect on motor function, anxiety-related behaviors, or repetitive behaviors.

In these experiments, the researchers manipulated HDAC activity using a drug, but they also wanted to better understand how HDAC activity is typically regulated without chemical intervention. They focused on a protein called β -catenin, a protein that is involved in regulating HDAC activity. In wildtype mice, β -catenin moves from the cell nucleus to the cell periphery, where it plays a role in transmitting messages from neighboring cells. The researchers determined that, in *Shank3*-mutated mice, β -catenin primarily remains in the nucleus. To better understand the role of this protein, the researchers reduced the levels of β -catenin in *Shank3*-mutant mice. They found that these mice had lower levels of HDAC and displayed higher levels of social interaction. Furthermore, the researchers identified several targets of HDAC activity that were altered in *Shank3*-mutant mice, and they were able to restore normal expression and/or activity of these targets with romidepsin treatment.

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Identification of and characterization of this molecular pathway provides insight into the underlying biology of ASD symptoms. The researchers did not observe any unintended effects as a result of treatment with romidepsin. This drug is already FDA-approved for use in cancer treatment, and the dose required for the effect seen in ASD behaviors is equivalent to about 5% of the dose used to treat cancer in humans. The researchers suggest that romidepsin may be a promising therapeutic intervention for ASD patients who have *Shank3* mutations.

QUESTION 3

WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Analysis of shared heritability in common disorders of the brain.

The Brainstorm Consortium. *Science*. 2018 Jun 22;360(6395). [PMID: 29930110]

Brain disorders can be categorized as neurologic, such as Alzheimer's disease, or psychiatric, such as attention deficit hyperactivity disorder (ADHD) or schizophrenia. In general, neurological diseases are characterized by unique, observable features of the nervous system, while psychiatric disorders are characterized by behavioral phenomena. In this study, researchers sought to determine the genetic relationships across brain disorders, specifically to determine the genetic similarities and differences between the neurologic and psychiatric categories.

To conduct this study, researchers used genome-wide association data from more than two million participants who either had a psychiatric disorder, a neurological disorder, had no known brain disorder, or had well-defined characteristics of a behavioral or cognitive trait (such as neuroticism, extraversion, or level of cognitive performance). These data were analyzed by The Brainstorm Consortium, a collection of researchers who contributed to a large database on 25 brain disorders.

The researchers found that psychiatric disorders are genetically similar to one another. In particular, schizophrenia shared common risk variants with most other psychiatric disorders, and depression shared genetic similarities with every other psychiatric disease that was tested. Interestingly, they found that ASD was relatively genetically distinct, although it did share some genetic similarities with schizophrenia. In contrast, the researchers found that neurological disorders are more genetically distinct from one another, with the exception of migraine headaches showing significant genetic similarities to ADHD, depression, and Tourette syndrome.

The researchers also sought to determine if brain disorders were related to gene expression patterns corresponding to particular traits. They found that cognitive traits differed across psychiatric disorders with ASD, anorexia, bipolar disorder, and obsessive-compulsive disorder (OCD) showing more positive correlations with cognitive traits. Meanwhile, ADHD, anxiety disorders, depression, and Tourette syndrome showed fewer genetic correlations with cognitive traits. Among personality traits, they found that neuroticism was related to several disorders including anorexia, anxiety disorders, migraine, depression, and OCD. They also found that a low body mass index was associated with anorexia

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

nervosa, while high body mass index was related to ADHD and depression. Lastly, they compared gene expression profiles between neurological disorders and psychiatric disorders and found that neurological disorders are generally genetically different from psychiatric disorders.

The finding that psychiatric disorders are similar to each other is important because it provides evidence that those disorders may share similar symptoms. The researchers note that the relatively small sample sizes for some disorders in this population, including ASD, may account for the lower correlations between these disorders and different traits. The results of this study support a need for careful diagnostic criteria to ensure that diseases are diagnosed properly and provide a potential foundation for more personalized treatments that address overlapping conditions.

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Paternally inherited cis-regulatory structural variants are associated with autism.

Brandler WM, Antaki D, Gujral M, Kleiber ML, Whitney J, Maile MS, Hong O, Chapman TR, Tan S, Tandon P, Pang T, Tang SC, Vaux KK, Yang Y, Harrington E, Juul S, Turner DJ, Thiruvahindrapuram B, Kaur G, Wang Z, Kingsmore SF, Gleeson JG, Bisson D, Kakaradov B, Telenti A, Venter JC, Corominas R, Toma C, Cormand B, Rueda I, Guijarro S, Messer KS, Nievergelt CM, Arranz MJ, Courchesne E, Pierce K, Muotri AR, Iakoucheva LM, Hervas A, Scherer SW, Corsello C, Sebat J. *Science*. 2018 Apr 20;360(6386):327-331. [[PMID: 29674594](#)]

The genome is made up of coding regions, which give rise to RNA or protein products, and noncoding regions, which are responsible for regulating gene expression. Genetic variations can occur in either coding or noncoding regions, often leading to diseases and disorders. There are several genetic variations associated with ASD, but only a subset of these occur in protein coding regions. Thus, this study sought to better understand genetic variation in noncoding regions that are associated with ASD.

The researchers compared genetic sequences of 9,274 people, some with and some without ASD, from 2,600 families who had at least one member with ASD. By studying families, the researchers could understand how genetic variations that are associated with the development of ASD are inherited across generations. They focused on genetic variations in noncoding regions of genes (called cis-regulatory elements, or CREs) that structurally disrupt the DNA. The authors sought to identify CRE structural variants, or CRE-SVs, that are associated with ASD.

The researchers found that CRE-SVs accounted for only a small percentage of the total variation in their sample, but associations with ASD were highly significant. This suggests that CRE-SVs may account for a small portion of ASD cases whose genetic origins were previously unidentified. Furthermore, these variants exhibited specific hereditary patterns. In contrast to previous hypotheses that most genetic variations associated with ASD are inherited maternally, CRE-SVs are predominantly inherited from the father. Furthermore, SVs in coding regions were transmitted from mothers and fathers at similar rates; this suggests that mutations in coding regions are inherited differently than those in noncoding regions.

Previously, the role of noncoding genetic variations in ASD were not well-understood. The results of this study suggest that rare, inherited noncoding variants may predispose a child to ASD and that the paternal contributions of genetic variations are more important than previously appreciated. This finding furthers understanding of the underlying genetic causes of ASD and demonstrates the need for further research in genetic variation.

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap.

Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C, Schork AJ, Appadurai V, Buil A, Werge TM, Liu C, White KP; CommonMind Consortium; PsychENCODE Consortium; iPSYCH-BROAD Working Group, Horvath S, Geschwind DH. *Science*. 2018 Feb 9;359(6376):693-697. [[PMID: 29439242](#)]

Brain disorders are complex and are often caused by an accumulation of mutations occurring in multiple genes. Moreover, single or multiple variations in one gene can contribute to many different brain disorders. In this study, researchers wanted to compare gene expression profiles (a comprehensive view of which genes are expressed and at what levels) for individuals with five major psychiatric disorders. They sought to understand both the genes that are expressed normally and the genes that are expressed atypically, for individuals with ASD, schizophrenia, bipolar disorder, depression, or alcoholism. They also wanted to learn more about gene expression profiles in individuals with these conditions relative to individuals without a known psychiatric disorder.

The researchers studied the *transcriptome*, a profile of an individual's RNA molecules that reveals details about the expression of genes. By combining several computational techniques, the researchers developed an innovative methodological framework to study shared molecular pathways in brain tissue samples. This framework allowed the researchers to identify patterns of expression across the entire transcriptome.

First, the researchers analyzed published transcriptomes of 700 people with ASD, schizophrenia, bipolar disorder, depression, or alcoholism. To establish a non-neurological comparison group, they also analyzed the gene expression profiles of people with inflammatory bowel disease (IBD). They found overlap in gene expression patterns among people with ASD, schizophrenia, and bipolar disorder, and overlap in gene expression patterns among people with schizophrenia, bipolar disorder, and depression. This finding suggests that some of the same genes are involved in the development of these disorders.

To better understand the significance of commonalities in the gene expression profiles, the researchers aligned the genes with altered expression to gene modules (groups of genes that function in the same biological processes). They found that modules involved in the regulation of neurons and modules involved in some aspects of metabolism were more highly expressed and highly activated in people with ASD, bipolar disorder, and schizophrenia. Subjects with ASD showed differential expression in multiple modules involved in regulation of neurons and in the development of microglia, which are brain cells that stabilize neural connections. They also saw reduction in expression of genes that support the energy demand for neural communication in ASD. Additionally, they identified a neuron-specific module that was enriched in rare gene mutations associated with ASD and was associated with diminished neural connection. These results support previous research that suggests that disruptions in neuronal function and communication are involved in the development of ASD.

This study contributes to knowledge of the genetic associations of different brain disorders. By identifying disorders that share genetic origins, researchers and clinicians can better understand the symptoms and potential treatments for these disorders.

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder.

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; PsychENCODE Consortium, Peters MA, Gerstein M, Liu C, Iakoucheva LM, Pinto D, Geschwind DH. *Science*. 2018 Dec 14;362(6420). [PMID: 30545856]

Researchers study every element of gene expression — which involves molecules called DNA, RNA, and proteins — to understand how a gene, or a variant of a gene, results in observable traits. One way for scientists to visualize an individual's gene expression is by looking at the *transcriptome*, a genetic profile of an individual's RNA molecules. Transcriptome analyses from the brains of people with psychiatric disorders can supply valuable information about differences in gene expression relative to individuals without a known psychiatric disorder. This type of analysis is important for understanding how brain disorders are related to gene expression and related to each other.

In an earlier study ("Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap," summarized on page 14), the researchers developed a methodological framework to compare transcriptomes of people with psychiatric diseases to those of neurotypical people. In this study, the researchers expanded upon their previous work to look at differences in expression of the transcriptomes corresponding to individual genes, groups of genes, and *isoforms*. Isoforms are RNA variants of the same gene that are formed by assembling different coding regions of the gene together. These isoforms thus result in different proteins with different functions.

When the researchers analyzed the expression profiles of people with ASD, schizophrenia, and bipolar disorder, they found that thousands of individual genes were expressed at either higher or lower levels, relative to unaffected controls. Moreover, they found that many differentially expressed genes were common across all three psychiatric disorders, and more than 25% of genes represented in the transcriptome analysis were differentially expressed in at least one disorder. These results suggest that different alterations to shared molecular pathways may contribute to these disorders.

The researchers identified 767, 3,803, and 248 genes with differential transcript expression associated with ASD, schizophrenia, and bipolar disorder, respectively. There was less overlap of isoforms among these three psychiatric disorders, and the researchers speculate that the use of different isoforms may contribute to the differences among these disorders. The researchers also identified non-coding RNA transcripts that were differentially expressed in ASD, schizophrenia, and bipolar disorder. Non-coding RNAs are not translated into proteins, but they often directly bind DNA and modify how genes are expressed. Lastly, the researchers identified several gene modules that are expressed differentially in ASD, schizophrenia, and bipolar disorder, five of which are common among the three disorders.

The novel techniques developed in these two studies provide researchers with a more complete picture of multiple levels of genetic differences in individuals with psychiatric disorders, including ASD. Together, these results reveal additional genetic contributions to the development of these disorders, and explain these disorders share some of the same features. The large number of genes and gene variants involved in these processes may explain how the same disease can manifest very distinctly in different people.

QUESTION 3: WHAT CAUSES ASD, AND CAN DISABLING ASPECTS OF ASD BE PREVENTED OR PREEMPTED?

De novo mutations in regulatory elements in neurodevelopmental disorders.

Short PJ, McRae JF, Gallone G, Sifrim A, Won H, Geschwind DH, Wright CF, Firth HV, FitzPatrick DR, Barrett JC, Hurles ME. *Nature*. 2018 Mar 29;555(7698):611-616. [PMID: 29562236]

Genes are made up of regions that are involved in making proteins (coding regions) and regions that are involved in regulating the gene's expression (regulatory or noncoding regions). In the past, research on the genetic roots of neurodevelopmental disorders such as ASD has focused on coding regions, but more recent studies have highlighted the importance of variations in the regulatory regions.

The goal of this study was to identify mutations in gene regulatory regions that are related to neurodevelopmental disorders and understand their role in brain development. The researchers focused on *de novo* mutations, which are "new" gene mutations present in an individual but absent in his/her parents.

The participants of this study were individuals who had a severe, undiagnosed neurodevelopmental disorder and their parents. The researchers analyzed each individual's genetic profile to identify *de novo* mutations in regulatory regions, including those associated with genes that are known to be involved in neurodevelopmental disorders.

The researchers identified a large number of mutations that were enriched in genes involved in fetal brain development. The majority of these mutations were found in genes that are evolutionarily conserved and are therefore very likely to be critical for development. However, compared to *de novo* mutations found in coding regions, the mutations identified in this study are *pathogenic* (causing or contributing to a disorder) in only a small percentage of cases. The researchers estimated that *de novo* mutations in noncoding regions may account for only 1 - 3% of undiagnosed individuals for whom a mutation was not found in a coding region.

They also found that the majority of these variants in non-coding regions do not have a dominant pattern of inheritance, meaning that they are not guaranteed to be expressed in offspring even if they are passed down and exist in the child's genetic code. This is different from pathogenic mutations that are found in coding regions, which typically have a dominant pattern of inheritance.

The results of this study help researchers understand the genetic causes of neurodevelopmental diseases, such as ASD, which can help clinicians with diagnosis. Since the majority of these genetic variants are not dominantly pathogenic, it suggests that the variants identified in this study may account for only a small percentage of developmental disorders.

QUESTION 4

WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Cluster randomized trial of the classroom SCERTS intervention for elementary students with autism spectrum disorder.

Morgan L, Hooker JL, Sparapani N, Reinhardt VP, Schatschneider C, Wetherby AM. *J Consult Clin Psychol*. 2018 Jul;86(7):631-644. [[PMID: 29939056](#)]

Nearly half a million school-aged children in the United States are estimated to have ASD, therefore it is critical to identify and optimize interventions that will improve their school experiences. While several classroom-based interventions have been developed, researchers have faced several obstacles in assessing the efficacy of these interventions. Additionally, staffing challenges, availability of resources, and teachers' time constraints pose significant barriers to the high-fidelity implementation of the interventions.

The researchers in this study therefore sought to evaluate the effectiveness of the recently-developed Classroom Social Communication, Emotional Regulation, and Transactional Support (SCERTS) Intervention (CSI). CSI is a teacher-implemented intervention in which the teacher develops individualized goals for each child with ASD to foster healthy social interactions and learning. This intervention model seeks to build students' competence in the domains of social communication and emotional regulation, as well as provide transactional supports to address the needs and interests of each student. CSI also seeks to increase students' *active engagement* in the classroom by addressing the social and learning challenges that children with ASD may face. This study was conducted over three years, from 2011 to 2014, in general and special education classrooms across 60 elementary schools in California, Florida, and Georgia. For eight months (one school year), teachers were assigned to receive either CSI or Autism Training Modules (ATM) as a control. Teachers in the ATM group had access to online training in evidence-based practices, but they were not required to complete the training or implement the practices.

To measure and compare the effectiveness of the two treatments, the researchers assessed active engagement using the Classroom Measure of Active Engagement (CMAE), which measures emotional regulation, productivity, social connectedness, directed communication, generative language production, and academic independence. Researchers used video recordings to evaluate changes in the CMAE from the beginning to the end of the study

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

period. In addition to the CMAE, researchers measured changes in the children's language skills and analyzed parent and teacher reports of the children's skills and behavior. The researchers also measured the fidelity of implementation, or the degree to which teachers implemented the intervention as intended.

The researchers found that the children who received CSI scored higher in measures of social interaction at the end of treatment, relative to ATM. They also showed greater improvement in social skills and executive functioning, and their teachers reported a larger decrease in the children's problematic behaviors. Parents reported that children in the CSI group significantly improved on the Vineland Communication Scale compared to students who received ATM. However, there was no difference in parent-reported measures of daily living skills and socialization between the two groups. The researchers also found that 70 percent of teachers trained in CSI implemented the intervention with fidelity, indicating a commitment to delivering all of the techniques detailed in the CSI.

This is one of the largest studies to measure the effect of school-based active engagement intervention in children with ASD. Due to the study's broad sample, the results suggest that the effects of CSI are generalizable to students of diverse ethnicity, location, cognitive level, and symptom severity. Direct observation of the students through video recordings also provided an advantage over relying on teacher and/or parent reports. The researchers concluded that the results of this study show promise for teacher-implemented interventions focusing on active engagement for improving outcomes for children with ASD.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Meta-analysis of parent-mediated interventions for young children with autism spectrum disorder.

Nevill RE, Lecavalier L, Stratis EA. *Autism*. 2018 Feb;22(2):84-98. [PMID: 29490483]

Numerous studies have shown that children with ASD benefit from early behavioral intervention. It is recommended that children engage in at least 25 hours weekly of targeted intervention to improve social skills and reduce attention deficits; however, such intensive levels of intervention can be difficult to implement outside the home. Parents are in an ideal position to provide such intervention, and studies show that parents feel more confident and less stressed when they are trained and involved in their child's treatment.

There have been several studies evaluating the effectiveness of parent-implemented interventions, but it has been difficult to compare multiple studies at a time due to differences in the methods used and the outcome measures. Thus, the purpose of this study was to analyze the current state of research on parent-mediated interventions for children between one and six years old. The researchers reviewed 19 randomized controlled trials that were conducted in the United States, United Kingdom, Australia, Canada, Asia, or the Netherlands between 2000 and 2015. They assessed the results of each study for changes in ASD symptom severity, socialization, communication-language, daily living skills, and cognitive functioning as a result of the interventions. They also gathered data on the association between parent training and child outcomes.

They found that, in general, parent-mediated interventions resulted in small but significant improvements to children's ASD symptom severity, socialization, and cognition, but smaller improvements in communication-language skills. In studies where parents received fewer than 20 hours of training, children were reported to have made significant improvements in communication-language skills and socialization. Meanwhile, in studies where parents received 20 or more hours of training, children were reported to have made significant improvements in socialization skills and cognition. The researchers also found that parent-rated measures were more likely to report significant improvements to the child's communication and language skills but not their socialization skills, while clinician-reported measures found that the child's socialization improved but not their communication and language skills.

The researchers concluded that parent-mediated intervention has only modest effects on outcomes for children. They speculate that this may be due to differences in parent training and program methodology, such as differences in hours of intervention delivered to the child and categorization of outcomes.

QUESTION 4: WHICH TREATMENTS AND INTERVENTIONS WILL HELP?

Are Children Severely Affected by Autism Spectrum Disorder Underrepresented in Treatment Studies? An Analysis of the Literature.

Stedman A, Taylor B, Erard M, Peura C, Siegel M. *J Autism Dev Disord*. 2018 Dec 10. [PMID: 30536112]

The field of ASD research has expanded over the past several years, however some experts are concerned that there is a lack of research on individuals severely affected by ASD. This research imbalance could have far-reaching implications, including a focus on the development of medical and behavioral interventions that may not address the most significant concerns of those with severe disabilities. To determine whether research on interventions and outcomes are representative of the entire ASD spectrum, the authors conducted a critical analysis of ASD treatment-related research published between 1990 and 2013. In addition to determining how much of the existing research focuses on individuals severely affected by ASD, the researchers also sought to examine the ways that ASD severity is classified in the literature. They used three factors to evaluate whether ASD severity was assessed in a given study: cognitive functioning, communication ability, and adaptive functioning (e.g., communication, daily living skills, and socialization).

From an initial library of 9,408 ASD research articles, the authors focused on 367 studies that involved treatment studies in children. Most of these studies included both male and female children with ASD, with average ages between 1.5 and 16 years old. Importantly, about half of these studies included individuals severely affected by ASD. The other studies either explicitly stated that severely affected individuals were not included, or inclusion was unable to be determined. Studies that assessed drug-related treatments were three times more likely to include severe ASD populations. Excluding studies in which the severity of ASD was undetermined, nearly all studies of early intervention or parent- and home-based interventions included severely affected populations.

The most common factor used to report ASD severity was cognitive function, which was used in nearly two-thirds of studies. Communication ability was used in about half of the studies, and adaptive function was the least frequently reported. Most studies only used one factor to assess severity and only 45 studies reported on all three severity domains. Between the years 1990 and 2013, inclusion of children severely affected by ASD decreased overall by 16.5 percent. Across the studies, cognitive function and communication ability was measured using 30 different scales, while only 7 different scales were used to measure adaptive function.

Though this study was limited in that it only included analysis of treatment-related research of the pediatric ASD population, the results indicate a clear decline over time in the number of studies involving those severely affected by ASD. The authors attributed this to the increased rate of diagnosis of individuals less severely affected by ASD. The researchers also note that the variability in measures used to rate severity reflects the need for the research community to assign standard rating instruments. Analyses such as this will hopefully guide the research community in its efforts to be more inclusive of the entire autism spectrum.

QUESTION 5

WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

Effects of State Autism Mandate Age Caps on Health Service Use and Spending Among Adolescents.

Kennedy-Hendricks A, Epstein AJ, Mandell DS, Candon MK, Marcus SC, Xie M, Barry CL, et al. *J Am Acad Child Adolesc Psychiatry*. 2018 Feb;57(2):125-131. [PMID: 29413145]

ASD is a lifelong condition, and many people require ASD-related health care into adulthood. Many states have addressed these needs by requiring insurance companies to provide coverage for health services specific to ASD needs. However, these mandates often include age caps that allow insurers to end ASD-related service coverage for individuals who have reached adolescence. In this study, researchers considered how age caps affect use and spending of ASD-specific services among adolescents who have aged out of coverage. They hypothesized that when insurance companies stop covering outpatient services, outpatient service use will decrease, and will result in increased use of inpatient services and psychotropic medication.

The researchers gathered data on individuals aged 10 to 21 between 2008-2012 from three major commercial insurers. Using these data, researchers identified 7,845 individuals in the 11 states where mandated autism insurance coverage ended in adolescence (14 to 18 years old). Researchers compared outpatient and inpatient health service use and spending among individuals below and above the age cap to individuals in matching age groups that were ineligible for the mandated coverage in their respective states.

The researchers found that adolescents who had aged out of state mandated coverage were 4.2 percent less likely to use any ASD-specific health services and spent \$69 less per month on ASD-specific services than those who were never subject to mandate provisions. They found similar results for outpatient service use, determining that individuals who exceeded the age cap were 4.1 percent less likely to use ASD-related outpatient services than the comparison group who were never subject to the age cap. However, mandated age caps were not significantly associated with increased use of ASD-related inpatient services or increased use of psychotropic medication. Although the researchers did not find that age caps significantly lowered the probability of overall health care service use, they did find that adolescents who had aged out of mandated services spent an average of \$99 less per month on all health care services combined.

QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?

These findings suggest that state mandated age caps set in adolescence may significantly decrease health service usage and spending among transition-aged youth. Although these individuals may require additional services and supports as they progress towards and through adulthood, insurance age caps may lead to disruptions in continuity of care and engagement with health care systems.

QUESTION 5: WHAT KINDS OF SERVICES AND SUPPORTS ARE NEEDED TO MAXIMIZE QUALITY OF LIFE FOR PEOPLE ON THE AUTISM SPECTRUM?**Vaccination Patterns in Children After Autism Spectrum Disorder Diagnosis and in Their Younger Siblings.**

Zerbo O, Modaresi S, Goddard K, Lewis E, Fireman BH, Daley MF, Irving SA, Jackson LA, Donahue JG, Qian L, Getahun D, DeStefano F, McNeil MM, Klein NP. *JAMA Pediatr.* 2018 Mar 26. [[PMID: 29582071](#)]

Although previous research supports no association between vaccination and the development of ASD, public concerns about this connection have led to a decrease in vaccination rates among children in the United States. Currently, there is little existing research regarding vaccination patterns among family members of children with ASD. This study sought to determine whether children with ASD and their younger siblings are receiving their vaccinations on schedule and to completion. Additionally, researchers investigated if there were differences in vaccination patterns between families of children with ASD and families with no history of ASD.

In this study, the Vaccine Safety Datalink (VSD) was used to collect data from 3,729 children with ASD, 592,907 children without ASD, and their younger siblings. The researchers found that among children 4 to 6 years old, those with ASD were significantly less likely to have completed the recommended vaccine schedule than children without ASD, but both groups were equally likely to have received their recommended vaccines for ages 11 to 12 years. Moreover, younger siblings of children with ASD were less likely to have received all recommended vaccines than younger siblings of children without ASD. This difference was the greatest for younger siblings aged 1 to 11 months, and this finding was consistent for all age groups except vaccines recommended for children aged 11 to 12 years. Finally, parents of children with ASD were more likely to limit vaccinations for their younger children during the first year of life relative to parents without a child with ASD.

These findings suggest that some parents of children with ASD perceive that vaccines were at least in part responsible for the ASD diagnosis. As a result, these parents may be less likely to vaccinate their younger children during the first year of life. The results of this study indicate that the perceived association between vaccines and ASD remains a strong factor in the health care decision-making process of many parents in the United States. Additionally, the results of this study indicate that children with ASD and their siblings are at a greater risk of developing vaccine-preventable diseases.

QUESTION 6

HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

Autism spectrum disorder symptoms from ages 2 to 19 years: Implications for diagnosing adolescents and young adults.

Bal VH, Kim SH, Fok M, Lord C. *Autism Res.* 2018 Aug 12. [PMID: 30101492]

ASD is typically diagnosed between three to four years old. Less is known about how ASD manifests throughout the lifespan, and most screening instruments for ASD are based on how symptoms present in early childhood. Consequently, it is unclear if these instruments are sensitive to older age groups. In this study, researchers were interested in how the social and communication abilities of children with ASD changed from early childhood to young adulthood and if symptom trajectories through adolescence and adulthood would affect the sensitivity of current ASD screening and diagnostic tools.

The researchers used caregiver reports of 140 children followed from 2 to 19 years old that were diagnosed with ASD during childhood. The children were grouped by social-communicative symptoms: verbal, delayed speech, or minimally verbal. They assessed overall social-communication impairments as well as three subdomains, including nonverbal communication, development and maintenance of relationships, and socioemotional reciprocity. Socioemotional reciprocity is the ability to engage in back-and-forth social interactions such as gesturing, nodding, and using facial expressions.

The researchers found that, at 2 years old, most of the children had similar levels of impairment in all three subdomains regardless of their language ability grouping, and most showed significant improvement by age 19. The verbal group of children showed the largest increase in overall social-communication skills, while the minimally verbal group of children showed slower improvements. Although minimally verbal children had greater impairments in nonverbal communication at ages 2 and 3 than children in the other ability groups, they no longer significantly differed from their peers in this subdomain at age 19. Neither the children with delayed speech nor the minimally verbal children showed significant improvements in developing and maintaining relationships over time, while the verbal children showed improvements in this subdomain between ages 2 and 3 years, which were maintained throughout the study period.

QUESTION 6. HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

All of the children's socioemotional reciprocity improved over time. However, each group showed different timing of symptom improvement, which seemed to correlate with language development for each group. The delayed speech children showed the most improvement between ages 3 and 5 years, while the verbal children improved somewhat earlier, between 2 and 3 years. The minimally verbal children showed slower and steadier improvement in socioemotional reciprocity over the 17-year study period.

At age 19, the researchers assessed the young adults for a clinical diagnosis of ASD. Of the young adults who received an ASD diagnosis, nearly 14% had caregivers reporting no symptoms in at least one of the three subdomains. These findings suggest that young adults with ASD may not exhibit the same symptom patterns as younger children. Since many ASD screening tools are based on symptomology in children, a reduction in symptoms as children age into adolescence and young adults could inhibit accurate diagnoses for these older age groups. Future research studies need to assess screening tools that will accurately capture symptoms of ASD in older populations.

Psychiatric and Medical Conditions in Transition-Aged Individuals With ASD.

Davignon MN, Qian Y, Massolo M, Croen LA. *Pediatrics*. 2018 Apr;141(Suppl 4):S335-S345. [PMID: 29610415]

Individuals with ASD are at increased risk for co-occurring medical conditions, including seizures, gastrointestinal (GI) problems, sleep disturbances, and psychiatric disorders such as anxiety and depression. These symptoms are well-documented in children with ASD, but less is known about the prevalence of these co-occurring conditions in adolescents and adults. As children with ASD grow older and begin to transition into the adult health care system, it is important to understand their health service needs.

In this study, researchers collected data from adolescents and young adults, ages 14 to 25 years, who were insured by Kaiser Permanente Northern California for at least nine months of each year between 2013 and 2015. There were 4,123 individuals with a diagnosis of ASD included in the study. The ASD group was compared to a group of peers with attention-deficit disorder (ADHD), a group of peers with diabetes mellitus, and a typical control group of peers who had none of these conditions.

The researchers found that 13% of individuals in the ASD group had a diagnosis of intellectual disability (ID). The prevalence of an ID diagnosis was higher in females than in males and increased with age. More than one-third of individuals in the ASD group had at least one co-occurring psychiatric condition, most commonly ADHD, anxiety, or depression. The ASD group was significantly more likely to have a co-occurring psychiatric disorder and a significantly higher rate of suicide or self-injurious behavior than any of the comparison groups. Yet, transition-aged individuals with ASD had lower rates of smoking and drug abuse than the comparison groups.

Medical conditions were more common in the ASD group than in the ADHD and typical control groups. However, individuals with ASD were at similar or lower risk of co-occurring medical conditions than their peers with diabetes mellitus. The most commonly reported medical conditions among the ASD group were infections, obesity, neurologic conditions, allergy and/or immunology conditions, musculoskeletal conditions, and GI conditions.

Because ASD is associated with an increased risk of co-occurring diseases and disorders, the researchers suggest that clinicians' approach ASD as a chronic health condition that requires consistent health care services and supports. As transition-aged individuals with ASD age into the adult health care system, it is critical that they continue to receive regular follow-ups and routine screenings for co-occurring medical and psychiatric conditions.

QUESTION 6. HOW CAN WE MEET THE NEEDS OF PEOPLE WITH ASD AS THEY PROGRESS INTO AND THROUGH ADULTHOOD?

Understanding Service Usage and Needs for Adults with ASD: The Importance of Living Situation.

Dudley KM, Klingler MR, Meyer A, Powell P, Klingler LG. *J Autism Dev Disord.* 2018 Aug 25. [PMID: 30145735]

ASD is associated with increased usage of services. As individuals with ASD and their caregivers age, there will be an increase in the prevalence of adults who will seek ASD-related services. However, little research has been conducted to investigate the service usage and needs of adults with ASD, and how one's living situation affects service experiences.

The researchers conducting this study administered a survey to 274 caregivers of adults with ASD. Individuals with ASD were diagnosed by clinicians at the University of North Carolina TEACCH Autism Program (TEACCH) between 1969 and 2000. At the time of the current study, individuals with ASD were at least 20 years old. Each caregiver completed the TEACCH Autism in Adulthood Survey, an 87-item questionnaire that assesses ASD-related variables in adults, including factors such as demographics, service usage, current living situation, and developmental level. To assess independence in daily life, the researchers administered the Waisman Activities of Daily Living Scale (W-ADL).

The researchers determined that, within the last two years, more than one-third of caregivers reported that their adult son or daughter with ASD had used employment-related services, and about half reported usage of mental health care services, transportation services, and/or diagnostic services. However, more than half of caregivers also reported that their adult child needed more services than they actually received, typically because services were located too far away or caregivers did not know how or where to access them.

The researchers were particularly interested in the effects of living situation on service use among adults with ASD. In this study, living situations for adults with ASD were described as living independently, living with family, or living in a supported living facility (supervised housing, group home, etc.). More than half of the participants in this study lived at home with a caregiver, however, adults with ASD who lived at home were less likely to receive services and were more likely to have greater unmet needs as well as experience greater barriers to access services. The most commonly reported barriers for caregivers of adults living at home were a lack of knowledge on how to access services and an overall lack of service availability.

As more individuals with ASD enter and progress through adulthood, there is a need to increase service supports for adults with ASD. Given that those who live at home with caregivers tend to have more unmet service needs, living situation should be considered when evaluating obstacles to services.

QUESTION 7

HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014.

Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, Kurzius-Spencer M, Zahorodny W, Robinson Rosenberg C, White T, Durkin MS, Imm P, Nikolaou L, Yeargin-Allsopp M, Lee LC, Harrington R, Lopez M, Fitzgerald RT, Hewitt A, Pettygrove S, Constantino JN, Vehorn A, Shenouda J, Hall-Lande J, Van Naarden Braun K, Dowling NF. *MMWR Surveill Summ*. 2018 Apr 27;67(6):1-23. [PMID: 29701730]

One of the goals of research on ASD is to understand the prevalence, or number of people with ASD in a given population and the characteristics of those individuals. The Autism and Developmental Disabilities Monitoring (ADDM) Network is a program supported by the Centers for Disease Control and Prevention that tracks over time the number of eight-year-old children with ASD in participating sites; in this report there were 11 participating sites in the following states: Arizona, Arkansas, Colorado, Georgia, Maryland, Minnesota, Missouri, New Jersey, North Carolina, Tennessee, and Wisconsin. In this report, the authors estimated the prevalence of ASD in the ADDM Network among 8-year-old children in 2014. In particular, this report assessed prevalence rates of ASD based on diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), compared to the criteria in the updated Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

The researchers estimated prevalence by collecting data from children's health records and, in most cases, education records. Clinicians then reviewed the data and assessed ASD status based on criteria established in the DSM-IV-TR and the DSM-5. They found that the overall prevalence of ASD in 8-year-old children was 1 in 59, and it was four times higher in boys than girls. Prevalence estimates also varied by race/ethnicity, with a 7% higher prevalence in white children than black children, and a 22% higher prevalence in white children than Hispanic children. The researchers noted that the increase in diagnostic rates among black children compared to reports from previous surveillance years likely does not represent an increase in prevalence, but rather an improvement in ascertainment. Also, although the majority of parents reported having concerns about their child's development by 36 months of age, the median age of formal diagnosis was 52 months of age.

QUESTION 7: HOW DO WE CONTINUE TO BUILD, EXPAND, AND ENHANCE THE INFRASTRUCTURE SYSTEM TO MEET THE NEEDS OF THE ASD COMMUNITY?

Among the sites with data on intellectual disability, 31% of the children with ASD had IQ scores of 70 or lower (intellectual disability), 25% had IQ scores of 71-85 (borderline intellectual disability), and 44% had IQ scores higher than 85. Girls were more likely than boys to have IQ scores of 70 or less. The proportion of children with ASD and intellectual disability was similar in 2010, 2012, and 2014, but markedly lower than those reported in previous surveillance years, indicating that in recent years, more children with ASD and no intellectual disability are being identified.

In general, the researchers found that DSM-IV-TR and DSM-5 diagnosis criteria resulted in very similar measures of ASD prevalence, both overall and when specifying for demographic features, such as gender, race, ethnicity, and level of intellectual ability. When reevaluating cases based on DSM-5 criteria, the researchers found that 86% of children met criteria for both, 9% met criteria for the DSM-IV-TR only, and 5% met criteria for the DSM-5 only. The overall prevalence estimates were 4% higher using the DSM-IV-TR than the DSM-5 criteria.

These results indicate that the estimated prevalence of ASD was higher in 2014 than in previous surveillance years. The prevalence estimates continue to vary by racial and geographic groups, but some of these disparities have decreased relative to previous years. The increasing prevalence of ASD is an important public health concern, requiring significant services and resources to address the needs of this population and continued research to better understand the risk factors associated with ASD.

ARTICLES SELECTED FOR THE 2018 SUMMARY OF ADVANCES

QUESTION 1: HOW CAN I RECOGNIZE THE SIGNS OF ASD, AND WHY IS EARLY DETECTION SO IMPORTANT?

Bosl WJ, Tager-Flusberg H, Nelson CA. EEG Analytics for Early Detection of Autism Spectrum Disorder: A data-driven approach. *Sci Rep*. 2018 May 1;8(1):6828. [PMID: 29717196]

Egger HL, Dawson G, Hashemi J, Carpenter KLH, Espinosa S, Campbell K, Brotkin S, Schaich-Borg J, Qiu Q, Tepper M, Baker JP, Bloomfield RA, and Sapiro G. Automatic Emotion and Attention Analysis of Young Children at Home: A ResearchKit Autism Feasibility Study. *npj Digital Medicine*. 2018 Jun 1;1(20). <http://www.nature.com/articles/s41746-018-0024-6>

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QUESTION 2: WHAT IS THE BIOLOGY UNDERLYING ASD?

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