Summary of Advances in Autism Spectrum Disorder Research: Calendar Year 2008

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Introduction

The dramatic increase in the prevalence of autism spectrum disorders (ASD) over the past two decades has spurred research into all aspects of the disorders. Researchers are now doing critical work to understand what causes ASD, how it can be effectively treated, and how to improve the lives of those affected. ASD includes a range of developmental disorders that share common features including impaired communication skills and social interactions and restricted, repetitive, and stereotyped patterns of behavior. Currently, the Centers for Disease Control and Prevention (CDC) estimates that about 1 in 150 children in the United States has ASD.

In response to the alarming growth in autism diagnoses, Congress passed the Combating Autism Act of 2006 (P.L. 109-416), which established the Interagency Autism Coordinating Committee (IACC) to coordinate all efforts within the U.S. Department of Health and Human Services related to ASD. The Combating Autism Act requires that, in addition to several other key responsibilities, the IACC must prepare an annual summary of advances in autism research. The 2008 IACC Summary of Advances highlights 37 significant studies on autism spectrum disorder selected by members of the IACC. A bulleted overview of the major findings in 2008 is followed by a more detailed description of the scientific breakthroughs in each category. Information about funding sources and journal impact factor scores is included in a table at the end of the document.

All articles included in the summary appeared in a peer-reviewed journal during calendar year 2008 and were selected from a broad NIH Library search of biomedical literature databases (e.g., PubMed, Scopus), news sections of major journals (e.g. Science, Nature), and publications that highlight findings from scientific journals (e.g., Science News). Articles were also collected from databases of ratings and reviews of scientific publications (e.g., Faculty of 1000 Biology, Cochrane Reviews) and references from major newspapers like the New York Times and Washington Post.

Members of the IACC voted on the contents and classification of the broad article search containing 257 articles before selecting the final articles included in the 2008 Summary of Advances. A complete list of articles considered for the Summary of Advances is available at www.IACC.hhs.gov.

This year’s advances are sorted into six topic areas that correspond to six critical questions for those affected by ASD:

- **Diagnosis:** When should I be concerned?
- **Biology:** How can I understand what is happening?
- **Risk Factors:** What caused this to happen and can this be prevented?
- **Treatment:** Which treatments and interventions will help?
- **Services:** Where can I turn for services?
- **Outcomes:** What does the future hold?
The IACC Strategic Plan for ASD Research is also structured around these six questions.¹

Some topic areas contain noticeably more articles than others. This may reflect a lower level of research funding for some topic areas when compared to others. As a result, there may be fewer significant advances in some areas. Members of the committee have expressed the hope that increased funding in these areas will lead to more scientific breakthroughs in the future.

### Overview of Autism Findings in 2008

**Diagnosis: When Should I Be Concerned? (pp. 5-6)**

- High-functioning men with ASD show less activity in the brain’s cingulate cortex during social interaction. This finding suggests potential for development of new assessment tools.

- General developmental assessments do not detect many children that screen positive on autism-specific assessments. As a result, the authors recommend that all children should be screened using an autism-specific tool. The American Academy of Pediatrics issued a similar recommendation in 2006.

**Biology: How can I understand what is happening? (pp. 7-9)**

- The gene associated with Rett syndrome, a pervasive developmental disorder related to autism, is a key regulator of many genes in the hypothalamus. Scientists continue to make discoveries about the complex genetics of ASD and related disorders.

- Genes that cause tuberous sclerosis complex (TSC), a disorder that often co-occurs with autism, have been shown to impair axon formation of neurons.

- Children with autism have greater expression of genes related to the immune system’s natural-killer cells compared to typically-developing children. These elevated expression levels could serve as a potential biomarker for diagnosis and suggest the need for further research into the role of the immune system in autism.

- Levels of a specific protein (secreted amyloid precursor protein alpha) are significantly elevated in children with ASD and could also serve as a potential biomarker for the disorder.

- Mothers of children with autism were found to have antibodies in their blood that specifically bind to fetal brain proteins, suggesting that the presence of these antibodies may be associated with a higher risk for autism.

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• Measles virus is not found in the bowels of autistic children with gastrointestinal involvement, indicating that the Measles, Mumps, Rubella (MMR) vaccine is not related to autism.

**Risk Factors:** What caused this to happen and can it be prevented? (pp. 10-14)

• Several studies show that changes to the CNTNAP2 gene (Contactin associated protein-like 2), which is thought to play a role in brain cell development and the chemical signaling that enables brain cells to communicate with each other, are linked to ASD.

• Copy number variation (CNV) is emerging as a possible common genetic mechanism that may contribute to the development of autism.

• DNA microdeletions and microduplications (copy number variations) to regions on several chromosomes, including chromosomes 16, 15, and 1, are associated with autism.

• Studying families where parents are related yields clues to the genetic basis of autism.

• Older parents are more likely to have children with ASD.

• Parents who have been hospitalized for a psychiatric disorder are more likely to have children with ASD.

• Births of children with autism show a seasonal pattern.

• Decreased eye contact can be used as a predictor of social impairment in two-year-old children with ASD.

**Vaccines** (pp. 14-15)

• The majority of evidence does not support a link between vaccines and autism.

• Autism rates in California continued to increase even after thimerosal was removed from nearly all childhood vaccines.

• One study found that children with autism were more likely to have Rh-negative mothers, potentially implicating a thimerosal-containing injection given to mothers with incompatible Rh-factors.

**Treatment:** Which treatments and interventions will help? (pp. 15-17)

• The drug rapamycin reduces neurological symptoms in mice with tuberous sclerosis complex, a genetic disorder that often co-occurs with autism. This finding may help to develop effective drug therapies for autism and related developmental disorders.

• A computerized training program improves the ability to process faces for people with ASD.

• Interventions to encourage joint attention and symbolic play are shown to improve language development in preschoolers with ASD.

• Some children with autism have trouble understanding the symbolic nature of pictures. This has implications for users of the Picture Exchange Communication System (PECS) and other picture-based communication.
Services and Supports: Where can I turn for services? (pp. 18-19)

- Children’s attitudes about a new classmate with autism are affected by who provides information about the disorder. This suggests that it may be helpful to engage multiple speakers to educate students about autism before mainstreaming a classmate with ASD.

- Medical expenses for children and adolescents with ASD average $3,110 to $6,200 more per year than their typically-developing peers.

- Adding to the financial strain, families of children diagnosed with ASD lose an average of $6,200 or 14 percent of their yearly income. In some cases this is due to one parent leaving the workforce to care for his or her child.

Outcomes: What does the future hold? (pp. 20-21)

- Children with relatively high intelligence, increased receptive language skills, and good verbal and motor imitation are more likely to recover from autism.

- Young autistic children’s oral- and manual-motor skills predict later speech fluency.

- Children with better joint attention skills have greater language gains as they get older.

- People with autism are more likely to die from epilepsy and infectious diseases than the general population. Thus, direct care staff could benefit from training to better manage potentially life-threatening physical illnesses that commonly affect people with ASD, in addition to accident prevention.
Correctly diagnosing children with autism spectrum disorders as early as possible is critical to receiving needed services and interventions. While the symptoms of autism arise before a child’s third birthday, some children are not diagnosed until they are much older. Currently there are no biological tests for autism; as a result, children are diagnosed based on a specific set of behavioral criteria outlined in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders). Research published in 2008 may help to develop new screening tools for ASD and refine existing diagnostic strategies.

A study investigating the neural activity of people with high-functioning autism during social interactions may lead to new assessment tools. Researchers used functional magnetic resonance imaging (fMRI) to scan the brains of 18 adolescent men with ASD while they played a social exchange game with a partner.

During the game the autistic men showed less activity in the portion of the brain that is used when imagining ‘self,’ compared to typically developing subjects. The lack of activity in this region, called the cingulate cortex, indicates that some people with high-functioning autism have an impaired ability to recognize ‘self’ during social situations.

The researchers determined that the cingulate cortex was responsible for modeling ‘self’ after performing fMRI scans on 81 typically-developing athletes visualizing themselves playing various sports. The scans showed increased blood flow (indicating increased activity) in the cingulate cortex.

After watching the exchange games, the researchers also found that the lack of ‘self’ response in the brain of the autistic subjects was related to the severity of the person’s symptoms. Subjects with more severe autistic symptoms had less activity in the cingulate cortex than did subjects with milder symptoms. This finding may be helpful in developing new diagnostic assessments for ASD.

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*Articles in bold were selected by the IACC for the 2008 Summary of Advances*
Another 2008 study identified which screening strategies are most effective for early diagnosis. Many pediatricians use a general developmental assessment for all of their patients and test specifically for autism only after a child shows developmental delays on the general assessment. However, one study found that using the general developmental screening tool, the Parents’ Evaluation of Developmental Status (PEDS), did not efficiently screen the majority of children who tested positive on the Modified Checklist for Autism in Toddlers (M-CHAT), an ASD-specific assessment.

During the study, 152 children between the ages of 18 and 30 months were screened using both the PEDS and M-CHAT tools at their well-child visit to their pediatricians. The researchers found that 16 of the 22 children (73%) who tested positive for ASD on the M-CHAT did not show any developmental concerns on the PEDS. These results suggest that the two tools assess different areas of developmental concerns and support the American Academy of Pediatrics recommendations that, in addition to regular developmental screening, children need to be systematically screened starting at 18 months of age using an ASD-specific tool.

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Changes to several genes have been linked to autism spectrum disorders. Better understanding of the biology of these genes and their functions can provide insight into how they contribute to ASD and related disorders.

One gene of interest is MeCP2 (methyl CpG binding protein 2), known to produce a protein essential to normal brain development. Previous studies suggest that MeCP2 is involved in forming connections between brain cells at the synapse -- the junction where communication between neurons occurs. Mutations to the gene can cause Rett Syndrome, a pervasive developmental disorder related to autism, in addition to other disorders of the brain. \(^{12}\)

Recent studies have shown that MeCP2 plays a critical role in activating and repressing genes that direct the activities of neurons in the hypothalamus. \(^{13}\) After looking at patterns of gene expression in mice that lack MeCP2 and those that overproduce its protein, researchers made an unexpected finding -- MeCP2 activated about 85 percent of the genes of the hypothalamus. These findings show that MeCP2 is a key regulator for many genes in this region of the brain.

Another important finding involved the two genes that cause tuberous sclerosis complex (TSC), TSC1 and TSC2. Tuberous sclerosis complex is a disorder that causes tumor growth and many with the disorder are also diagnosed with epilepsy, mental retardation, and autism. A 2008 study found that the two genes that cause TSC impair the formation of axons, \(^{14}\) the neuronal projections from the cell body that carry electrical impulses to other cells. The process of axon formation is fundamental to brain development and function. When TSC1 and TSC2 proteins are overexpressed, they suppress axon formation and when lacking, the axon develops abnormally. Understanding how TSC1 and TSC2 regulate the growth of neurons may help scientists understand TSC and related disorders like autism.

A recent study also noted specific genes that were expressed at higher levels by children with classic autism when compared to typically developing children. The 11 genes that were identified are linked to natural-killer cells, \(^{15}\) immune cells necessary for mounting the body’s defenses against infecting organisms and foreign agents. These findings suggest that certain white blood cell abnormalities seen in children with autism could contribute to the risk of developing the disorder. Researchers also found different patterns of gene expression for children with regressive forms of autism compared to early onset autism, showing that the two


may be distinct subtypes of the disorder. There were no genetic differences between children with ASD who had less severe symptoms and typically-developing controls.

Currently there is no single molecular marker that can be used to diagnose autism, but a recent study has found encouraging evidence of a potential biomarker. Researchers found that levels of secreted amyloid precursor protein alpha (sAPP-alpha) were significantly elevated in 60 percent of the children with autism tested. The study, which included 25 autistic children and 25 age-matched controls, found elevated sAPP-alpha levels in children with the ASD. They also found significantly elevated levels of sAPP-alpha in 10 of 150 samples of human umbilical cord blood, showing that elevated sAPP-alpha levels could be measured at birth. Though more research is needed, measuring sAPP-alpha levels in serum and cord blood shows promise for developing an early diagnostic test for ASD.

New findings on the biology of autism also shed light on how reactions of a mother’s immune system may contribute to the disorder. A recent study found that mothers of children with autism have immune molecules called antibodies in their circulation that bind to fetal brain proteins in laboratory tests, while mothers of typically developing children do not have similarly-behaving antibodies. The finding of antibodies that bind fetal brain proteins was most common in mothers of children with the regressive form of autism, whose children lose the social and language skills they previously developed. This suggests that the presence of these specific antibodies in the mother’s blood confers an elevated risk for having a child with autism.

Researchers isolated antibodies in 61 mothers with autistic children and 62 mothers of typically developing children. Exposing the antibodies to an array of fetal brain proteins revealed that antibodies from seven of the 61 mothers with autistic children reacted with two specific clusters of fetal brain proteins. None of the samples from the mothers in the control group exhibited a response. There was no similar reaction when maternal antibodies were exposed to adult brain proteins, suggesting that these antibodies are specifically targeted toward proteins that are present during fetal development. While outside the scope of this study, the authors hypothesized that these antibodies to fetal brain proteins may somehow be interfering in normal fetal brain development, increasing the risk for autism.

Another study investigating the causation of ASD was unable to show a relationship between the vaccine for measles, mumps, and rubella (MMR) and the onset of autism, as had previously been reported in a 1998 study. The 1998 study had incited public concern after it was reported


that autistic children with gastrointestinal (GI) disturbances had measles RNA present in their bowels.¹⁹

The 2008 study looked at 25 autistic children and 13 typically developing children, all of whom experienced GI disturbances including recurrent abdominal pain, gastroesophageal reflux, vomiting and food allergies. Both groups of children were, on average, five years of age and had received their first MMR vaccination at about 15 months old. The majority of the children in the study had not yet received their second dose of the vaccine. Researchers examined bowel biopsies from the children in the study and found no difference between those with autism and those without -- one of the autistic subjects and one of the controls showed slight levels of measles virus in their sample. The majority of the children had no trace of measles RNA in their bowels, dispelling the idea that the presence of measles RNA caused either the children’s autism or their GI disturbances.

The authors noted that children with autism and GI issues were more likely to exhibit regressive tendencies, such as the loss of previously acquired social and language skills, and may represent a distinct autism subtype.

Risk Factors: What caused this to happen and can it be prevented?

New research has provided more insight into potential genetic and environmental risk factors for ASD. By looking at genome-wide scans of people on the autism spectrum and comparing them with typically developing individuals, researchers can identify changes to specific genes that may contribute to ASD. These genetic variants result from deletions and duplications in DNA, many of which have only recently been identified. While specific genetic variants account for only a small percentage of cases, researchers are making headway in understanding the complex genetic underpinnings of the autism spectrum disorders.

Recent research has indicated that several genes involved in the formation and function of synapses are linked to ASD. One particular variant of interest is CNTNAP2 (Contactin associated protein-like 2).20 21 Located on chromosome 7, the gene has been found to be enriched in regions of the brain critical for language development and was shown in one study to be related to when boys with autism say their first word. 22 Another study found that a mutated version of a gene called neurexin 1, which is in the same family as CNTNAP2, was present in two subjects with ASD.23 The father of one of the subjects with the neurexin 1 variant has the same chromosomal abnormality but did not have ASD, showing that other factors must also contribute for the disorder to occur.

Several complete genomic scans have found scores of distinct microdeletions and microduplications – tiny subtractions or additions to the chromosome not apparent using standard microscopic analysis – that are unique to people with autism. These microdeletions and microduplications are also known as copy number variants (CNV) and are believed to cause gene dosage imbalances that can contribute to health conditions and disorders. One study found 51 microdeletions and microduplications that occurred in about 12 percent of the subjects with ASD.24 Of the 51 CNV, 44 were inherited from a parent, while 7 arose spontaneously. Researchers identified three separate microduplications that were passed from mother to child.

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located in a region on chromosome 15. Another study found 277 variants in 44 percent of the subjects with ASD.\textsuperscript{25}

Studies have also focused on a region on chromosome 16 that contains genes involved in both brain development and immune system function.\textsuperscript{26} A DNA scan of 1,441 children with ASD showed that five of the children carried microdeletions in chromosome 16, while seven children had microduplications in the same region.\textsuperscript{27} In a very small percentage of people in the study, changes to this region of chromosome 16 were also linked to developmental disorders other than autism including attention deficit hyperactivity disorder (ADHD) and schizophrenia.

Abnormalities on other chromosomes have also been implicated in ASD. One study identified microdeletions and microduplications on chromosome 1 that are associated with autism, mental retardation, and congenital anomalies.\textsuperscript{28} Overall, these studies suggest that copy number variation may be a common mechanism contributing to the development of autism by causing gene dosage imbalances, and that genes identified through these studies may be worthy of closer examination in future research.

While there seem to be a variety of genes which contribute to the development of autism, researchers found a common biological link between several identified in one study of families with shared ancestry.\textsuperscript{29} The study examined 88 families with autistic children where parents were first or second cousins. Nineteen of the families studied had two or more cases of autism. Related parents are more likely to have genetic similarities, so studying them increases the likelihood of finding rare recessive genetic traits that are contributing to the family history of autism.

The researchers were able to identify several genes that may contribute to familial autism, including some that contained large inherited deletions and smaller deletions, as well as some changes in non-coding DNA, which may influence the proper expression and dosage of critical genes. Many of the genes identified are regulated by neuronal activity and mutations in these genes may interfere with the brain’s ability to create the synaptic connections that are formed in relation to a child’s early experiences. These connections are a critical foundation for further brain development. The authors hypothesize that changes in genes that regulate the formation of these connections may contribute to development of autism.


Other risk factors point strongly to a heritable component to autism. Recent studies showed that the age of a child’s mother or father contributes to the risk of autism. Mothers who are 35 years of age or older and fathers 40 years of age or older are significantly more likely to have a child on the autism spectrum.\textsuperscript{30} Researchers looked at information about the parents of 1,251 children with autism spectrum disorder and found that having an older mother and/or father was a risk factor for autism. After controlling for other factors, the study found that mothers 35 or older were 30 percent more likely to have a child with ASD than 25- to 29-year-old mothers. Fathers aged 40 or older were 40 percent more likely when compared to fathers 25- to 29-years-old. When both parents were older, their first child was three times as likely to be on the spectrum than a child with two or more older siblings born to younger parents.

A Swedish study also found that people who had been hospitalized for a psychiatric disorder were more likely to have a child with autism than parents of typically developing children.\textsuperscript{31} Mothers and fathers diagnosed with schizophrenia were nearly twice as likely to have a child with ASD compared to the general public. Mothers of children with ASD were more likely to have been diagnosed with depression and personality disorders. The same was not true for fathers of autistic children.

Some have also theorized that early umbilical cord clamping may be a risk factor for autism due to possible impact of oxygen deprivation, lower blood volume and other effects. Researchers recently undertook a review of results from eleven randomized controlled trial studies to determine possible risks and benefits of early versus late cord clamping after birth. While the study did not directly measure the relationship between cord clamping and autism, it did show that children who had their cords clamped after one minute had greater iron levels than those clamped earlier because the extra time prior to clamping allows for transfer of more fetal blood from the placenta to the newborn. Higher levels of iron are associated with better health outcomes, including reduced risk for anemia.\textsuperscript{32} However, infants who had later clamping were also more likely to have jaundice that needed to be treated with phototherapy, caused by the inefficiency of the newborn’s liver in processing bilirubin in the blood, which can be exacerbated by the increased blood volume associated with later clamping. Policies on clamping vary – some doctors clamp within a minute after birth while others wait longer or until cord pulsation stops. The study concluded that cord clamping either early or late carries both risks and benefits.

Other birth factors have been linked to autism. Children with the ASD are more likely to be born in certain seasons, according to a new study.\textsuperscript{33} After looking at the birth pattern of children with

autism, researchers found that April, June, and October were peak months for single births. Peaks occurred 2 to 4 weeks later for multiples with autism. Multiple births of boys with ASD were most frequent in March, May, and September. While the artificial cut-off of months or seasons may hide trends or enhance them, overall this study suggests that non-inherited factors may play a role in the development of autism.

Once a child is born, other factors may predict the likelihood of developing autism. Looking into another person’s eyes conveys meaning and is an important part of social interaction. At an early age, typically developing infants show a preference for looking at a person’s eyes compared to other parts of the face. Now, new research has found that autistic toddlers show decreased levels of eye contact and increased fixation on mouths by the age of 2 years old, when compared to typically developing children. Additionally, less eye contact predicted greater levels of social disability. These findings could prove useful for diagnosing autism earlier and measuring symptom severity.

**Vaccines**

Several studies published in 2008 investigated the relationship between thimerosal and the onset of autism. Researchers found that autism rates in California continued to increase even after thimerosal was removed from nearly all childhood vaccines by 2001. If thimerosal was a primary cause of autism, new diagnoses would be expected to decline significantly as exposure decreased. The study examined the rates of autism in children 3 to 12 years old that were reported to the California Department of Developmental Services (CDDS) from January 1995 to March 2007, and instead, found a steady increase in prevalence. Since 2004, the increase in California’s autism rates has been greater than that for other developmental disabilities, as a whole.

Dr. Eric Fombonne argues against the involvement of either thimerosal or the MMR vaccine in the development of ASD in his commentary, “Thimerosal Disappears but Autism Remains.” He notes that while different investigators have conducted large-scale studies using a variety of designs, the overwhelming majority have failed to show any evidence of a link between autism and immunization. Studies have also failed to find significant evidence of mercury poisoning or the persistence of measles virus in children with autism. Several studies have been conducted that failed to show an increased susceptibility to injury from exposure to mercury or the MMR

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vaccine in a specific subgroup of autistic children. Fombonne cited the CDDS study described above, as well as studies conducted in Canada and Denmark, which describe a continued rise in rates of ASD diagnoses, even after the removal of thimerosal from childhood vaccines.

However, one 2008 study did purport to find evidence of an association between thimerosal and neurodevelopmental disorders in children. At 28 weeks of pregnancy, Rhesus factor (Rh)-negative mothers who are carrying Rh-positive children are given a preparation of immune globulins in order to prevent a potentially dangerous immune response in both the mother and child at the time of delivery. Until its removal in 2002, the immune globulin injection contained the mercury-based preservative thimerosal. The researchers hypothesized that if prenatal exposure to the immune globulin was a risk factor for neurodevelopmental disorders, more mothers of children with these disorders would be Rh-negative when compared to a control group. After examining 298 children with a range of neurodevelopmental disorders, the study found that children with ASD born before 2002 were significantly more likely to have Rh-negative mothers than the control population. They found no difference in the prevalence of Rh-negative mothers after 2002, leading the authors to conclude that thimerosal contributed to the children’s risk for developing neurodevelopmental disorders.

**Treatment:** Which treatments and interventions will help?

In 2008, progress was made in several different types of treatments and interventions for ASD, four of which are described in this section.

Recently, scientists discovered that the drug rapamycin, an immunosuppressant drug normally used to prevent organ rejection after transplant, reduces neurological symptoms in mice with tuberous sclerosis complex (TSC), a rare genetic disorder that often co-occurs with mental retardation, epilepsy, and autism. Researchers were able to reverse learning and memory deficits in mice carrying the genetic mutation which causes TSC by injecting rapamycin. The results suggest that cognitive deficits resulting from TSC are caused by reversible changes in brain function rather than permanent damage to the developing brain. These findings could be the first step in discovering effective drug therapies for autism and related developmental disorders. Currently, there are few pharmacologic treatment options for people with ASD.

Another study investigating ASD interventions found that computerized training has shown promise in helping people with autism process facial expressions. Many people with ASD have trouble recognizing and remembering faces because they process the information differently than typically developing people. They often focus on the outer portions of the face instead of the more important central features such as the eyes and nose. Typically developing people are able to recognize faces by processing the face as a whole and paying attention to the specific configuration between features.

The 2008 study suggests that facial processing can be improved through training. Five high-functioning autistic men were shown black and white photos of faces on a computer screen and given specific instructions about how their eyes should navigate the pictures. They then practiced matching similar faces and classifying faces into categories such as “young” and “old.” Subjects were told to pay attention to the central facial features and were given tasks where only cropped portions of the faces were visible.

After their training, the subjects showed more sensitivity to facial configuration than five men with ASD who had not been trained. However, the training did not improve the men’s ability to process the face as a whole; rather they continued to focus on individual features.

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In 2008 intervention studies, two different play interventions showed the ability to improve language development in preschool children with autism.\(^{45}\) Three- and four-year-old children with autism worked with an instructor to improve either their joint attention (the ability to share in a common experience with another person; i.e., ‘Look at the big dog!’) or their symbolic play (the ability to create pretend roles and imagined scene; i.e., ‘You’re going to play the mom’). The children attended the same day treatment program but had varying levels of developmental abilities.

After receiving the play interventions for 30 minutes a day for five to six weeks, both the joint attention and the symbolic play groups showed greater degrees of expressive language 12 months later when compared to a control group. Children who had previously exhibited the lowest language abilities, showed greatest gains from the joint play intervention. These findings suggest that honing joint attention and symbolic play skills can lead to improved language skills.

Finally, another intervention study provided insight into how low-functioning children with autism learn to associate pictures, words and real-world objects. Forms of augmentative and alternative communication such as the Picture Exchange Communication System (PECS) use pictures to represent real actions and objects. However, research shows that children with autism may not be able to comprehend the symbolic nature of pictures,\(^ {46}\) a concept that typically-developing children generally demonstrate by two years of age.

Twenty-two children with autism were taught a new word, such as “whisk,” and trained to pair it with a novel picture of a whisk. Half the children in the study were PECS-users, while the other half were not. The children were then shown an actual whisk (having never seen one before) alongside a picture of the whisk and asked to indicate which one was the whisk. The majority of the children with autism associated the word with the picture rather than the object, unlike their typically developing peers with similar receptive language skills. The researchers confirmed that these results were not due to the children’s preference for selecting pictures, or their tendency to perseverate on a previous correct response. Autistic children who used PECS were much more likely to point to the picture than non-PECS users.

These results indicate that children with autism are learning picture-word and word-object pairings through association rather than grasping the symbolic nature of pictures. Children who were non-verbal and/or who were PECS users were particularly likely to associate a word with the picture rather than the real object.


Services and Supports: Which treatments and interventions will help?

Major scientific advances were made during 2008 in three areas related to services and supports for people with autism. Recent studies investigated the influence of information sources on school children’s attitudes towards autism, medical costs for children and adolescents with ASD, and the effects of ASD on household income.

Children with autism benefit in many ways by being included in a classroom with their typically developing peers. However, when entering the mainstream classroom, children with ASD may face negative attitudes from other children. A study published in 2008 may have implications for shaping school-aged children’s attitudes about autism. The study reports that children’s attitudes about a new classmate with autism are affected based on who provides information about the disorder.

A group of 296 children in third, fourth, and fifth grade were given information about an unfamiliar autistic student by their teacher, a video, or an actor portraying the new child’s mother, father, or physician. The children were given information about autism by the different sources, then shown a short videotaped clip of a 12-year-old male actor who is identified as “Robby.” In the video, Robby displays typically autistic behavior by rocking his body, making stereotypic hand movements, and averting his gaze. A narrator describes the similarities between Robby and the children viewing the video.

The study showed that certain age groups responded more favorably to different sources by measuring the children’s cognitive and behavioral attitudes toward Robby after receiving information about autism from the various sources. Cognitive attitudes are beliefs that the child holds about people with autism while behavioral attitudes reflect how the child intends to interact with the person. Fifth-graders showed more favorable cognitive and behavioral attitudes toward Robby when receiving information about autism from a teacher or doctor rather than the child’s parent, whereas the third-graders’ attitudes were more influenced by Robby’s mother.

These findings suggest that when introducing children on the autism spectrum into mainstream classrooms, the entire class would benefit from receiving education about ASD from multiple sources.

Another 2008 study confirmed what parents of children with ASD already knew -- medical expenses related to care of individuals with ASD are costly. A national study of 1.2 million privately-insured children with an ASD diagnosis found that children and adolescents with ASD incur medical expenses that average $3,110 to $6,200 greater per year than for typically

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developing children.\textsuperscript{48} This represents an average cost increase of 4.1 to 6.2 percent. The difference in medical costs was greatest for children with ASD from one to four years of age.

Medical costs were calculated using the total amount of reimbursements or out-of-pocket expenses incurred, though did not include the cost of complementary and alternative therapies, which are rarely covered by insurance.

The findings of this study build on previous studies that have illustrated the heavy burden of medical costs associated with ASD. In 2007, another study calculated that during the first five years of life, a child with ASD will average $35,000 in direct medical costs per year.\textsuperscript{49} These costs begin to decline when the child reaches eight years of age, to approximately $6,000 annually, and continue to decline over the lifespan.

Adding to the financial strain, families with children on the spectrum have been shown to lose a significant portion of household income -- sometimes as a result of one parent leaving the workforce to care for his or her child. One study found that a family with an autistic child lost an average of $6200 or 14 percent of their yearly income.\textsuperscript{50} This, combined with the additional out-of-pocket medical expenses, represents a significant burden for families of children with ASD.

The study surveyed parents of 11,684 children who were currently in kindergarten to eighth grade and identified 131 children who had been diagnosed with ASD. Researchers then compared reported household income for families of children with ASD to families of similar demographic and educational characteristics with typically developing children. Families of children with ASD were significantly less likely to live in a higher income household after controlling for the parent’s level of education, type of family, location, and other variables. These families also reported incomes that averaged $6,200 less than other similar families without an autistic child.


Outcomes: What does the future hold?

In 2008, there were a number of important advances in understanding what the future holds for people with ASD.

In one study, researchers reviewed outcome studies of children who had reportedly “recovered” from autism, meaning they had initially been diagnosed with the disorder but now showed a normal trajectory of development. Some researchers and clinicians are skeptical that “recovery” from autism can occur. However, the study authors evaluated evidence that between 3 and 25 percent of children lose their ASD diagnosis.51

Certain factors may contribute to whether a child will lose their ASD diagnosis. After analyzing the results of other recovery studies, the review found that relatively high intelligence, verbal and motor imitation and receptive language predicted which children had lost their diagnosis. Children diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) were more likely to report recovery, as were those who had been diagnosed and treated for autism at an earlier age. Overall symptom severity did not predict which children would lose their ASD diagnosis, nor did measures of head growth. Children with seizures, mental retardation and genetic disorders were less likely to report recovery. Losing the ASD diagnosis did not mean that children were problem-free. Many children reportedly had remaining problems such as tics, depression, phobias, and ADHD.

What brings about recovery? The review suggested several hypotheses about possible mechanisms for future research, including the idea that early interventions provide enriched environments for the children to overcome their symptoms or that the extreme repetition of intensive early interventions lead to some sort of neural reorganization. Other potential factors that may have contributed to recovery include reinforcing the value of social stimuli, repeatedly practicing weak skills, and reducing stress. While there is no evidence that biomedical interventions alone will result in recovery from autism, the authors conclude that good nutrition and sleep quality is beneficial to all children with ASD.

Two important studies in 2008 investigated the early predictors of later language development. One study found that two types of motor skills, oral and manual, could be used to predict speech fluency later in life.52 Speaking requires the complex coordination of oral-motor skills such as pursing the lips and thrusting the tongue. Oral-motor skills are also closely tied with manual-motor skills (i.e., hand and finger movements) in typically developing children.

Parents of children with autism were interviewed about their child’s early development, and were asked to recall specifics about their child’s oral-motor and manual motors at key developmental


milestones. (i.e., Did he stick out his tongue on request at 24 months? Did he grab glasses off your face at six months?) Early home videos were used to corroborate parental accounts. Researchers then assessed the current language skills of 115 autistic children, who were about 8 years old on average at the time. The study found that infant and toddler oral- and manual-motor skills could predict level of speech fluency for children around eight years of age to early teens. The study also showed that early motor skills differed significantly between autistic and typically developing children.

Another language development study found that certain behaviors can predict which children will show the most language growth.53 Autistic children who respond to others’ attempts to share in observing an object or event (for example, playing with the same toy or pointing out an interesting happening) show more language growth than those who do not respond to bids for joint attention. In a study of 28 children with ASD, those who were able to coordinate their interest in external events or objects had significantly greater language gains three to four years later. During play, the parents’ responsiveness to their child’s focus of attention and ongoing activity also predicted future language development. Interestingly, these gains were independent of the child’s IQ, mental age, or initial language skills.

A long-term study of 341 Danish citizens with ASD found that the mortality rate for the participants was nearly double that of the typically developing population when matched for age and gender.54 In total, 26 of the 341 people with ASD died during the study period from 1960-2006; nearly double the 13.5 deaths that would have been expected. Mortality risk was greatest during the first fifteen years post-diagnosis, and was not affected by IQ levels.

Epilepsy and infectious diseases such as meningitis, pneumonia, and appendicitis were common causes of death for people with ASD. The high mortality from epilepsy and related issues suggests that the disorder may pose an even greater risk for people with ASD than for typically-developing individuals with epilepsy. The study also found that people with ASD may be more prone to fatal accidents. The study authors suggest that direct care staff receive training to better manage potentially life-threatening physical illnesses that commonly affect people with ASD and that additional focus on accident risks and prevention would be beneficial.

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## Articles Selected for 2008 Summary of Advances

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<tr>
<th>Journal Article</th>
<th>Funding Information</th>
<th>Journal Impact Factor (2008)*</th>
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<td>Arking, D. E., D. J. Cutler, et al. (2008). &quot;A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism.&quot; Am. J. Hum. Genet. 82(1): 160-4. Epub 2008/01/09.</td>
<td>National Institutes of Health (NIH) grants MH52708, MH39437, MH00219, and MH00980; National Health Medical Research Council grant 0034328; and by grants from the Scottish Rite, the Spunk Fund, Inc., the Rebecca and Solomon Baker Fund, the APEX Foundation, the National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD), the endowment fund of the Nancy Pritzker Laboratory (Stanford); and the Autism Society of America, and the Janet M. Grace Pervasive Developmental Disorders Fund</td>
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<td>Hornig, M., T. Briese, et al. (2008). &quot;Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study.&quot; PLoS ONE 3(9): e3140.</td>
<td>CDC grant U50 CCU522351 to AAP and by National Institutes of Health awards AI57158 (Northeast Biodefense Center-Lipkin), HL083850, and NS47537</td>
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<td>Marshall, C. R., A. Noor, et al. (2008). &quot;Structural variation of chromosomes in autism spectrum disorder.&quot; Am. J. Hum. Genet. 82(2): 477-88. Epub 2008/02/07.</td>
<td>Genome Canada/Ontario Genomics Institute, the Canadian Institutes of Health Research (CIHR), the McLaughlin Centre for Molecular Medicine, the Canadian Institute of Advanced Research, Autism Speaks, the McMaster Children's Hospital Foundation, the Hospital for Sick Children (SickKids) Foundation, the German National Genome Research Network (NGFN), the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Netherlands Organization for Scientific Research and the Royal Netherlands Academy of Arts and Sciences, a Health Scholar award from the Alberta Heritage Foundation for Medical Research and a CIHR New Investigator award</td>
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<td>Mefford, H. C., A. J. Sharp, et al. (2008). &quot;Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes.&quot; N. Engl. J. Med. 359(16): 1685-99. Epub 2008/09/12.</td>
<td>National Institutes of Health (HD043569), the South Carolina Department of Disabilities and Special Needs, the Wellcome Trust (061183), the André &amp; Cyprien Foundation and the University Hospitals of Geneva, and the European Union (project 219250) AnEUploidy project (037627), the Health Research Board, the Dutch Foundation for Brain Research (Hersenstichting grant 2008(1) 34), the Oxford Partnership Comprehensive Biomedical Research Centre, the Cambridge Biomedical Research Centre, with funding from the United Kingdom Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme, the National Genetics Reference Laboratory (Wessex) by the United Kingdom Department of Health, the Research Foundation–Flanders, and the Howard Hughes Medical Institute</td>
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