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Communication, interventions, and scientific advances in autism: A commentary

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ABSTRACT

Autism spectrum disorders (ASD) affect approximately 1 in 150 children across the U.S., and are characterized by abnormal social actions, language difficulties, repetitive or restrictive behaviors, and special interests. ASD include autism (autistic disorder), Asperger Syndrome, and Pervasive Developmental Disorder not otherwise specified (PDD-NOS or atypical autism). High-functioning individuals may communicate with moderate-to-high language skills, although difficulties in social skills may result in communication deficits. Low-functioning individuals may have severe deficiencies in language, resulting in poor communication between the individual and others. Behavioral intervention programs have been developed for ASD, and are frequently adjusted to accommodate specific individual needs. Many of these programs are school-based and aim to support the child in the development of their skills, for use outside the classroom with family and friends. Strides are being made in understanding the factors contributing to the development of ASD, particularly the genetic contributions that may underlie these disorders. Mutant mouse models provide powerful research tools to investigate the genetic factors associated with ASD and its co-morbid disorders. In support, the BTBR T+tf/J mouse strain incorporates ASD-like social and communication deficits and high levels of repetitive behaviors. This commentary briefly reviews the reciprocal relationship between observations made during evidence-based behavioral interventions of high- versus low-functioning children with ASD and the accumulating body of research in autism, including animal studies and basic research models. This reciprocity is one of the hallmarks of the scientific method, such that research may inform behavioral treatments, and observations made during treatment may inform subsequent research.

1. Introduction

Autism spectrum disorders (ASD) include autism (autistic disorder), Asperger Syndrome, and Pervasive Developmental Disorder not otherwise specified (PDD-NOS or Atypical Autism). ASD are highly-prevalent neurodevelopmental disorders that vary considerably in expression, and affect approximately 1 in 150 children across the U.S. [1], yielding greater prevalence than that of pediatric cancer, diabetes, and AIDS combined [2–4]. ASD are characterized by an impairment of social and communication abilities that range from very mild to severe [5,6]. The onset of ASD symptoms in at least one of the key areas must be before three years of age, while diagnosis may not occur until 6 years of age or later [7]. Individuals with ASD have life-long difficulties with novelty and environmental stressors, such as changing routines, and may suffer from co-morbid neurobiological disorders, such as seizures [8]. Few therapeutic interventions are effective, and a cure for ASD has not been found [8–10]. Although, the associated characteristics of ASD are, in many cases, detrimental, the degree of communication impairment varies widely between individuals.

Communication deficits in those with ASD can create difficulties in conversing with others, and the condition makes learning to communicate a greater challenge. Discussed below are communication difficulties, which comprise a predominant phenotype in ASD, followed by information about interventions used to improve communications among higher- and lower-functioning children and adolescents diagnosed with ASD, based upon the work of Susan DeLuke of the College of Saint Rose, Albany, NY and Myra Batista of the Kevin G. Langan School, Albany, NY, along with the work of others in the treatment of autism. Approaches in animal models that are being

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utilized to examine communicative anomalies similar to those observed in ASD, such as those used by Jacqueline Crawley, NIMH, Bethesda, MD and other researchers, are discussed in this commentary. This commentary concludes with a discussion of some of the steps that are being taken to provide outreach to those afflicted with ASD and to educate the general public regarding these pervasive disorders, such as the Center for Autism and Related Disabilities directed by Kristin Christodulu, University at Albany, State University of New York (SUNY), Albany, NY. The reciprocal relationship between behavioral observations made during evidence-based behavioral interventions and the accumulating body of research in autism, including animal studies and basic research models, is discussed.

2. Diagnostic criteria for Pervasive Developmental Disorders

According to the Diagnostic and Statistical Manual for Mental Disorders IV-TR, Pervasive Developmental Disorder (PDD) comprises autistic disorder, Asperger Syndrome, atypical autism, Rett Syndrome, and Childhood Disintegrative Disorder. The following four criteria to be met for diagnosis of autistic disorder, Asperger Syndrome or atypical autism between three and six years of age are described [5].

1. Reciprocal social actions are uniformly abnormal in some way, including: lack of eye contact, joint attention, and empathy problems [5,11–19]. These interactions are fundamental components to everyday social interactions, and include: initiating, maintaining, shifting, and/or terminating conversation, bridging topics, monitoring and/or demonstrating interest, and paying attention to multiple cues. Social barriers can be formed when difficulties in conversation are present. Some examples include difficulties understanding social cues, sensing the feelings or reactions of others, reading/caring about boredom that others may feel, interpreting another's perspective, as well as carrying on one-sided conversations and focusing on unusual interests [20].
2. Language delays that occur in beginning language as well as in interactive conversation. However, Asperger Syndrome does not include a delay in the acquisition of language. The individual lacks subtleties of language such as: the jokes, sarcasm, humor, and possibly the melodies and rhythms of language, as well as interpretation of facial expressions, body language, and connotations behind questions [5,11–19].
3. Repetitive or restrictive behaviors, and special interests, often consisting of hand flapping, toe walking, or repeatedly engaging in the same choice behavior (doing the same jigsaw puzzle, watching the same scene out of a movie) [5,11–19]. As a result, a wall is formed between the child and his/her surroundings that can exacerbate communication difficulties. The child focuses on narrow or restricted interests, such that he/she begin to lose perspective of the world around them. Emphasis is usually placed on categorizing, such as statistics of sports, rock collecting, or a skill involving mathematics. In this way, skills can be more pronounced and allow those with ASD to excel in a specific area. This is particularly true for savants, who can master skills in math or music, which may be due to expression of extraordinary abilities and encouragement of their development early on. However, expression of these skills is infrequent and striking, especially when compared to their lack of other skills and interests. Narrowed interests, repetitive actions, and prominent problems with communications, are classic examples of how the outside world can be a difficult environment for a child with ASD to socialize and thrive in.
4. Diagnosis only occurs if behaviors are not better accounted for by Rett Disorder or another Childhood Disintegrative Disorder [5,11–19]. Those with autism may be diagnosed co-morbidly with other disorders, as one diagnosis sometimes does not encompass the range of deficits associated with ASD [21]. Described below are some of the various ways ASD can be expressed, and interventions used for treatment, of higher- and lower-functioning persons diagnosed with ASD. Higher-functioning individuals diagnosed with ASD are those who have minor issues with communication and sociability and score of more than 70 on the non-verbal intelligence test (NVIQ) [22]. Lower-functioning individuals are those who have communication and/or sociability issues to an extent that it impairs their ability to convey basic needs and/or wants to caregivers, and an NVIQ score of less than 70 [22]. Thus there are distinct differences between high- and low-functioning individuals and different interventions may be used to improve behaviors.

3. Speech/language deficits and subsequent communication problems among high-level functioning persons with ASD

Communication is an important factor when working with those diagnosed with ASD. About one-third to one-half of individuals with ASD do not develop enough natural speech to meet their daily communication needs [23]. Lower-functioning individuals can experience severe problems in socialization and every day activities due to their lack of normal social interactions [23]. High-functioning individuals diagnosed with ASD demonstrate better language skills, and perform better in tests involving spelling and vocabulary than their low-level functioning counterparts. However, both high- and low-functioning groups fail at complex language tasks involving figurative language, comprehension and inferences [24]. For example, central coherence, known as the ability to process information in context to grasp a higher level of meaning at the expense of memory, is a main problem both groups encounter [25].

High-functioning individuals with ASD have a higher IQ and generally less difficulties with language than those exhibiting higher expression of circumscribed interests, repetitive behaviors or social dysfunction. Although they typically have adequate vocabulary, their comprehension is generally behind their neurotypical peers. In contrast, those individuals diagnosed with Asperger Syndrome do not have a delay in the acquisition of language [5]. High-functioning individuals use less emotional content in speech and are less able to interpret non-verbal cues, such as when listeners are bored or distracted compared to Asperger Syndrome individuals [20,26,27]. In addition, high-functioning individuals are also similar to Asperger Syndrome in some aspects. For example, Barbaro and Dissanayake found groups did not differ on their use or understanding of self-presentational display rules, and both used less compared to typically developing children [28]. Others have argued the differentiation between the two disorders is unnecessary as there are few differences between high-functioning autism and Asperger Syndrome [29]. Though levels of understanding and using language in communication differ between individuals who have higher versus reduced expression of ASD, methods of teaching language can improve effective communication in both groups.

Those who work with high-functioning individuals will recognize there may be some consistent “autistic” personalities, which vary in how afflicted individuals approach and initiate interactions. First, there is the commonly known “aloof” personality, wherein the child avoids physical contact and eye contact. There is the “passive” personality, in which the individual does not avoid physical contact, but does not initiate interactions with others. The third, known as the “Socially Extremely Awkward Person”, is less common, and described as an individual who initiates interactions with others, but is often socially awkward resulting in others reacting inappropriately [30].

4. Social skills deficits and effects upon communication

The core problem that underlies the numerous difficulties seen in social interactions is the lack of joint attention in children with ASD. Joint attention involves actively sharing attention rather than

passively looking at what others are attending to. The critical point is "sharing awareness" or "sharing an attitude toward a thing or event" [31]. Joint attention is a struggle for individuals with ASD, although there are individual variations. Villalobos et al. demonstrated that high-functioning autistic men may have reduced functional connectivity along the dorsal stream, which is consistent with a mirror neuron defect observed in autism [32]. The mirror neuron system is comprised of neurons which respond to motor, visual and auditory stimuli, and may include the dorsal premotor, somatosensory, cerebellar and posterior temporal cortex, as well as the ventral premotor, inferior frontal gyrus and inferior parietal lobule [38]. Further, recent brain research supports a close relationship between attention and theory of mind, given that the same areas are activated during mental-state attribution and joint attention tasks [33]. Thus theory of mind in children with ASD varies across the spectrum and may be related to the mirror neuron system.

The theory of mind-mind blindness is relevant for ASD. The ability to consider our own, and another person's, thoughts, needs, emotions, beliefs, prior experiences, motives, intentions and recognize differences between self and others is of undeniable importance when managing communication and socialization. First, one must figure out what another knows, which may occur in individuals as early as four to five years old [34]. Second is false belief testing, consisting of determining what one individual thinks of another, beginning about six years of age and continuing throughout life [34]. Typically, children with ASD will not excel in these tests, but those at the higher end of the spectrum have a higher probability of success. Typically individuals who do not excel earlier, will usually improve at a later age, or if they have been allowed more time to consider the answer. For example, 40% of high-functioning children with autism aged 6–13 years passed false belief testing compared to age-matched primary school (95%) and preschool (39%) comparison groups [35]. However, many with ASD will continue to have difficulty understanding abstract thoughts of others, especially those related to social expectation or motivations [36]. Further, the mirror neuron system has also been related to theory of mind in children with ASD and alterations in this system may be related to intentional self–other comparison and empathy [37].

Obstacles faced by an individual with ASD are: problems understanding and appreciating the thoughts and feelings of others, determining the intentions of others, and understanding how one's own behavior impacts others. Other issues include taking the perspective of others and difficulty respecting the perspective of others. This can result in the impression to others that the individual may be impolite or may perceive themselves as the director in a given situation. Individuals with Asperger Syndrome often desire social interaction, but struggle with the necessary social skills. Often parents of newly diagnosed individuals with ASD are urged to enroll their children in social skills programs that focus on teaching core skills and applying skills across social contexts. Intervention systems with higher-functioning children will be discussed below, as well as how these systems and lessons benefit a child with ASD.

5. Learning to communicate and socialize

Individuals with ASD may see their world in black and white, resulting in inflexible thought processes which could inhibit learning. Educators seek to understand how children with ASD learn and adjust their teaching methods accordingly. The need to teach social skills to youngsters with ASD is often overlooked in educational settings. Some programs, such as that conducted at the College of St. Rose in Albany, NY, include social skills development.

The primary focus of Social Skills Development Programs is to help children with ASD develop improved awareness and understanding of other perspectives in order to improve conversation skills, develop relationships with peers, play cooperatively, mediate conflict, develop self regulation skills, and problem-solve. Typically, the individual needs of those with ASD are considered so that groups may be formed based upon similar abilities in language, cognition, and social awareness, as well as age. The social skills sessions are highly structured and begin with an assessment and conclude with brief progress reports. Methods such as role-playing and simulation are also used. Activity-based lessons are often incorporated in order to focus on the teachable moments when real-life dilemmas occur. Repetition is also an essential technique, as new lessons and concepts often build one upon past lessons and social learning unfolds with all its complexity and subtlety. Learning to play together, share, negotiate and compromise are crucial skills that should be supported through a combination of explicit teaching and real-life experiences. Offering choices and avoiding power struggles are a major concern, particularly if the individual is resistant to change. The educators are trained to manage difficulties while being empathetic and making their lessons clear. In addition, agreeing to disagree may be the best solution for a given situation, and is a universal lesson for all children, so that they may learn to accept differences in opinion with their peers.

Social skills and activity-based lessons are based on assessment information used to evaluate each individual child's needs based upon checklists and feedback from the home and school. Many commercial resources are now available to guide the teaching process but lessons are typically modified to meet the individual needs of children within a group. For example, compared to elementary groups, adolescent groups address "adolescent perspectives" rather than "adult perspectives of adolescent issues". Participants in adolescent-skill-groups are limited to those who do not have delays in communication and cognition, unlike the elementary group. Group size can vary from 3 to 5 at the elementary level and from 6 to 8 at the middle- and high-school levels. Motivational systems are important in these lessons, as well, given that many individuals may find the social demands of the group challenging; as the children get older this appears to be less necessary. Other studies have also examined the effectiveness of programs to improve symptoms related to ASD in high-functioning autism. Wood et al. demonstrated that cognitive behavioral therapy improved parent-reported autism symptoms in children with ASD and an anxiety disorder aged 7–11 years [39]. Generalization of question asking was improved in adolescent high-functioning individuals when practiced in small-group training [40]. A classroom-based program using an A–B–A–B withdrawal design examined the success of picture activity schedule. Bryan and Gast found results that indicate the picture activity schedule improved on-task and on-schedule behaviors of high-functioning individuals and this generalized to novel activities [41]. Lopata et al. found a summer social-treatment program improved social skills and problem behaviors, but there were no differences in face emotion recognition [42]. However, a computer-based program improved recognition of affect in high-functioning and Asperger Syndrome individuals [43]. These results demonstrate that structure and goal-oriented programs in a school setting may be helpful to high-functioning children with ASD. Low-functioning children with ASD may require different behavioral interventions compared to high-functioning children with ASD to improve behaviors and skills.

6. Communication in low-functioning children with autism

Any type of verbalizations, approximations, gestures, or use of sign language, (considered "total communication"), are encouraged in an academic setting. To teach core and effective communication skills, children afflicted with ASD often use an augmentative communication system. One low-tech and effective means of improving communication in this population is the Picture Exchange Communication System (PECS). PECS can be used everywhere and facilitates communication learning inside and outside of the classroom. This system of communication is also easy to teach and use, and is affordable. PECS contains

several steps and initially focuses on teaching children the steps involved in communication initiation. Picture symbols are used to represent items that the student wants and the student is taught to request them. This system requires children to work for interaction which helps motivate students and reinforces their efforts in learning to initiate communication, make requests, respond to questions, make academic gains, and expand their vocabulary. Picture symbols are kept in books where pages can be organized by categories in order to maximize utility. Initially, a child starting may have a few picture symbols of favored items, present one, touch it and then receive the item as a response from the communication partner. Once the child understands that they must present a picture symbol to receive a response from their communication partner, the program focuses on the use of picture symbols in several interactions they may have outside of the program, including travel with the PECS book, symbol/word discrimination, and communicative interaction.

Large strides in communication can be achieved with PECS via the use of "sentence strips" that begin with icons that display words such as "I want". Children can place the "I want" icon on the sentence strip and add picture symbols from their book in order to convey a need or want to a communication partner. This begins the use of communication phrases in a typical language format. Communication abilities and language can be substantially improved by use of PECS when verbal expression is lacking. Through time, prompting, and repetition, children learn to readily access the picture symbols within the PECS books, engage in longer communication exchanges, and frequently begin using actual verbalizations to communicate.

In addition to specific items a child may indicate with PECS, there are universal concepts utilized that can be conveyed, such as "Help", which can be used in any situation where a child may need assistance. Further, each child has a book of picture symbols that are unique and can be used to offer a sense of familiarity and improve ease of understanding communication. The effectiveness of the PECS system was reviewed by Preston and Carter [44] and of the twenty-seven studies they evaluated, it was suggested that the system may have positive effects on social-communicative and challenging behaviors, but effects on speech development are unclear. Other interventions to build communication skills include picture books, visual schedules and signing, have also proven to be effective [45–47]. Given that difficulties in translation of objects to pictures can be a difficult concept for lower-functioning individuals, it is important to utilize methods to overcome these difficulties in order to maximize learning, communication, and verbalization outside the classroom.

The counterpart to the PECS book is an electronic (voice output) device, known as a DynaVox or DynaMate [48]. Similar to a small laptop with a touch screen, these devices can have pre-formatted pages to adapt to the interests of a student. The device can have pages focused on commands, attributes, downloaded images, photos of exact items, or a keyboard for typing out statements. For use during academic activities, the devices can be programmed specifically for certain classroom activities so that the necessary vocabulary is readily available for instruction and communication. For instance, if math or social studies comprise the in-class lessons, resources, such as PowerPoint™ (Microsoft Co., Seattle, WA, USA) presentations, can be transferred to the unit. Thus, advances in behavioral compensation over the communicative obstacles that ASD presents are being utilized in classroom settings for individuals of all levels of function. In addition to the development of behavioral treatment intervention programs, identification of the etiology of these pervasive disorders is a major focus of ASD research.

7. Epidemiology

Although ASD onset may not appear until after a period of "normal" development, the epidemiology of these disorders has informed investigators of several key aspects that may yield insight into its causes and/or mechanisms. Boys are reported to be affected with ASD more frequently than are girls with an average male-to-female ratio of 4.3:1.0 [59]. Albeit, the gender ratio is modified substantially by cognitive impairment; among cases without mental retardation the gender ratio may be more than 5.5:1.0, whereas among those with mental retardation the gender ratio may be closer to 2.0:1.0 [60]. The gender ratio is also influenced by the presence of dysmorphic features of the ear and/or the nose, with lower male-to-female ratios and greater frequency of cognitive impairment reported among cases who have six or more minor dysmorphic features [60,61]. The evidence suggesting that ASD may be related to genetic contributions comes from reports of the 4.3:1.0 frequency ratio of boys:girls, and a very high concordance in monozygotic twins [62]. If one identical twin has ASD, there is up to a 90% chance that the remaining twin will also have ASD [11,63]. This ratio is among the highest detected in biological research and is as high as juvenile diabetes and many kinds of cancers, and is also higher than any other major illness [2–4]. This is compared to a concordance of 5–10% between fraternal non-identical twins, or between siblings [53]. The frequency that ASD occurs is 0.6% in the general population [64]. These data lend strong support to a genetic component in the etiology of ASD.

There appears to be a relationship between ASD and various indicators of socioeconomic status. Investigators have long suspected this association to be the result of ascertainment bias, which is the differential identification of cases based on criterion other than signs/symptoms, in this case socioeconomic status. Individuals with higher socioeconomic status may have more access to medical care than individuals with lower socioeconomic status, due to health care insurance availability or utilization, and consequently have a greater opportunity to receive a diagnosis of ASD. A study based in Atlanta found higher social class was associated with autism without mental retardation, but not autism with mental retardation. Subanalyses demonstrated that these factors associated with social class varied by ascertainment source, since children with ASD were identified only in school (which provides universal access to services) [65]. A report from Denmark, where access to health care is universal, found no association between ASD and parental wealth or education [66]. Thus, the prevalence of ASD may or may not be related to socioeconomic status.

A contributing factor to cross-study heterogeneity could be variation by expression of ASD. Reports on the relationship between maternal age and ASD prevalence have been inconsistent; some studies show increasing risk with increased maternal age, whereas others find no association [66–71]. One recent report found that maternal age at birth was positively associated with cognitive impairment in cases of ASD [72]. Others have conjectured that maternal age serves as a proxy for another true actual risk factor, paternal age, and have shown positive associations between paternal age and ASD prevalence after adjustment for maternal age [60]. The heterogeneity in parental age observed may indicate a role for genetic interactions with environmental factors that could influence the onset of these disorders.

8. Genetic heterogeneity

Previously, it has been indicated that sex differences in ASD may be related to genetic factors that mitigate the expression of ASD [49–58]. New information indicating cross-study heterogeneity may inform investigations using behavioral genetic techniques to elucidate candidate targets within the human genome that may convey risk for ASD. ASD has a strong genetic basis, yet, it is unclear whether ASD is explained more by multi-gene interactions or by rare mutations with major effects [73]. Early studies of monozygotic twins estimated the heritability of ASD to be more than 90%, and that 90% of the variance between ASD and non-ASD individuals is due to genetic effects [74,75].

By identifying genetic markers inherited with ASD in family studies, numerous candidate genes have been identified in a general chromosomal locus; most of these are thought to encode proteins

involved in neural development and function [76,77]. However, for most of the candidate genes, the mutations that increase the risk for ASD have not been identified. There is some support for the notion that genetic perturbations that underlie ASD may result from copy number variations (CNVs), spontaneous alterations in the genetic material during meiosis that delete or duplicate genetic material [78]. Sporadic, non-inherited, cases have been examined to identify candidate genetic loci involved in ASD. Using array comparative genomic hybridization, a technique for detecting CNVs, one study reported such aberrations in 10% of families with one autistic child in 1% of controls [79]. Some of the altered loci had been identified in previous studies of inherited ASD; many were unique to the sporadic cases of ASD examined in this study, compared to patients with ASD who had an affected first-degree relative and controls. Hence the mutation that may cause ASD may not be present in the parental genome.

The Autism Genome Project database contains genetic linkage and CNV data that connect ASD to genetic loci and suggest that every human chromosome may be involved [80]. It may be that using diagnoses related to ASD, such as other disorders of PDD, instead of the diagnosis of ASD will be more useful in identifying susceptible loci [81].

Though genetic factors associated with ASD explain most of the risk surrounding the disorder, they do not explain all of it. A common hypothesis is that ASD is caused by the interaction of a genetic predisposition and an early environmental insult [82]. Several theories based on environmental factors have been proposed to address the remaining risk. Some of these theories focus on prenatal environmental factors, such as agents that cause birth defects; others focus on the environment after birth, such as children's diets. All known teratogens related to the risk of ASD, such as maternal rubella infection, ethanol, thalidomide, valproic acid, and misoprostol, appear to act during the first eight weeks from conception, and there is strong evidence that ASD arises very early in development [83]. Although evidence for other environmental causes has not been confirmed by reliable studies, extensive searches are underway [84,85]. A link between fetal testosterone exposure and the expression of autism has been suggested, given that when fetal testosterone levels are higher, children also perform higher on tests measuring autistic traits [86–88]. Further, those with ASD have lower 2D:4D digit ratios than controls, which has been suggested is related to prenatal testosterone exposure [87]. The frequent occurrence of co-morbid conditions with ASD and the search for the correct gene candidates are discussed below.

9. Modern advances in identification of genetic markers in ASD

A very important feature is the considerable co-morbidity between ASD and many other developmental disorders. In some cases, a proportion of individuals with a neurodevelopmental disorder known to be caused by a single gene mutation are also diagnosed with ASD and/or PDD-related disorders [89]. Genetic disorders with which ASD are commonly diagnosed (i.e. about 10% to 30% of these people also meet the criteria of the diagnosis for PDD) include Angleman syndrome, Fragile X (the most common type of inherited mental retardation in males), Smith–Lemli–Opitz cholesterol metabolism syndrome, and Rett's Disorder, which is a type of mental retardation associated with the *Mecp2* gene [90–92]. Some diseases in which ASD are co-morbid are Timothy syndrome (an autosomal disorder characterized by physical and neurodevelopmental defects) and tuberous sclerosis [93]. However, the relationship between these genetic disorders and the expression of ASD is not clear.

There are now large consortia looking for genes related to the expression of ASD, and though the field is still very young, there is a huge ongoing search. Some of these consist of family pedigree studies that are using linkage analysis, which have identified chromosome loci and gene polymorphisms, including chromosomes 2q, 7q, 15q, 16q and 17q, and neuroligin-4 (*Nlgn4*) [51,52,58,80,94–106]. There are also large association studies and whole genome scans that have identified candidate gene mutations for ASD. Some of these variations are single gene polymorphisms that occur in families and some are *de novo* mutations that occur in that particular individual [107]. Examples of some of the candidates that have shown up, each in a few individuals, include the GABA receptor gene found in the lymphatic system [108–110]. *Pten*, Engrailed 2, and contactin, which are developmental genes [111,112], have been identified as potentially important to the etiology of ASD. There have also been cases of neuroligin and shank synaptic developmental genes and transcription factors that have appeared in a few autistic individuals [113]. Thus, there are several candidate genes that are being investigated in those with ASD.

The field of autism research is still in its very early stages of finding genes that truly may be strong candidates, and at the moment there is no gene that is ubiquitous, or even one that shows itself in a very large number of individuals with ASD. Copy number variants (CNVs) may be involved in neuronal cell-adhesion or ubiquitin degradation, genomic deletions or duplications, and epigenetic factors such as methylation abnormalities in some phenotypes of ASD [114–117]. In addition, because the concordance rate between genetically identical twins never reaches 100%, environmental factors are likely to play a role.

10. Mouse models of ASD

Mouse models are developed to test hypotheses about causes of disease, and potential treatments. Mouse models with mutations in candidate genes that have been identified in people diagnosed with ASD provide useful tools to address different aspects of the genetic factors which may contribute to expression of ASD in both the human and potentially animal model. Briefly, human candidate mutations of the GABA receptor β 3 subunit, the serotonin transporter short polymorphism, and tyrosine kinase, which is found in the lymphatic system are introduced into the mouse genome [108–110]. Mutant mice are then characterized for their phenotypes that are analogous to the symptoms of autism (face validity). This process is time-consuming and labor-intensive. Finding the appropriate assays, and conducting the right controls to avoid artifacts present major challenges for modeling the symptoms of ASD in mice. In the area of social abnormalities, there are ways to measure social approach and reciprocal social interactions in juvenile and adult mice. Impairments in communication in mice may be investigated by tests analyzing responses to social cues, or ultrasonic vocalizations made by mice in the presence of socially-relevant stimuli. Using this model, researchers may study communication skills of mice with genetic or behavioral phenotypes similar to ASD to better understand how changes in genes may mediate change in behaviors in humans.

Several different mouse strains which express ASD-like behaviors have been used to identify factors that may be involved in ASD. For example, some genes encoding for scaffolding proteins which map to the X chromosome, and which may be related to sex differences observed in ASD have been investigated [11,49–58]. *Nlgn4* mutations have been detected in some autistic individuals [52,113]. *Nlgn4* is a synaptic cell-adhesion protein [113,118,119]. Synapses are essential to all brain activities, such as perception, behavior, memory, and thinking. Proper function of the brain's neuronal networks depends on a delicate balance between excitatory and inhibitory electrophysiological signaling among neurons. *Nlgn4* knockout mice exhibit deficits in social interactions and communication similar to social and communication difficulties observed in humans diagnosed with ASD, such as decreased sociability and decreased communication with others. Given that *Nlgn4* plays a part in mediating the maturation and function of synapses, this model may be useful in studying disruptions

of this pathway similar to disruptions in humans diagnosed with ASD [120]. *Nlgn3* has also been implicated in ASD [52,121–123], but *Nlgn3* knockin mice have not proven to exhibit substantially different behaviors associated with sociability, cognition, and resistance to change, which constitute some of the main features of ASD, compared to wildtype littermate control mice. However, *Nlgn3* mice did show altered development, such as different rates of somatic growth, delayed righting reflexes, and faster homing reflexes in females postnatal days 2–6, as well as less vocalizations in males on postnatal day 8, compared to wildtype controls [123]. Thus, the *Nlgn3* or *Nlgn4* mutations may be related to development and/or expression of ASD.

Another mouse model that may be relevant for studying the neurobiological aspects of ASD is the *Pten* mouse. Five mutations in *Pten* gene sequencing, a lipid phosphatase disrupted in some cancers, have been implicated in patients diagnosed with ASD with a prevalence of 8.3% [111] and is important for mediation of cell size and number, although the link to ASD is currently unclear. *Pten* knockout mice display abnormal social interactions and enhanced responses to sensory stimuli, analogous to those observed in humans with ASD [124]. In humans, the tuberous sclerosis genes *Tsc1* and *Tsc2* are frequently associated with mental retardation, epilepsy and ASD [125–127]. In a mouse model, heterozygotes for the tuberous sclerosis gene *Tsc2*, display deficits in learning and memory [128]. The cognitive deficits observed in the mice are independent of neuropathology and seizures, indicating other mechanisms may be involved in these behavioral abnormalities [128]. Thus disruption in genes, such as *Pten*, *Tsc1* and *Tsc2* may be related to ASD, as observed in humans and animal models of ASD.

Another proposed model of ASD is the reelin haploinsufficient (+/−) reeler mouse (HR), which may have neural deficits similar to those observed in ASD. It has been demonstrated that HR mice have reduced expression of oxytocin receptors, particularly in the cortex and part of the hippocampus [129]. Disruptions in oxytocin or its receptor activation early in development could alter gene expression or genetic variations [129]. Reelin plays a role in the development of the oxytocin system [10,129,130]. This model may help to elucidate the role of hormonal factors, such as oxytocin, in the development and/or expression of ASD [129,130]. Thus, genetic mouse models with phenotypes similar to human expression of ASD may be useful tools in discovering the underlying neurobiological mechanisms that lead to the development and/or expression of ASD in humans.

11. Identifying a mouse model of autism by examining social abilities

Robust, easily replicable assays have been developed to quantify social behaviors relevant to ASD in mouse models. One such task is an automated three-chambered apparatus to measure social approach [131–135]. In this task, the experimental mouse is placed in the middle of two chambers to which entry is barred. Following a habituation period, the doors to the two compartments are opened, and the mouse is allowed to freely explore the entire apparatus. One compartment contains a novel object and the other compartment contains a novel mouse that the subject has never been in physical or olfactory contact with before. The novel mouse is enclosed in an inverted wire cup that allows visual, olfactory, auditory, and some tactile contact with a novel mouse, but ensures that all social approach is initiated only by the subject mouse.

Typically, the subject mouse will start in the middle, and will quickly approach the novel mouse. There are many visits to each compartment during which, beam-breaks, number of visits to each compartment, and time spent in each compartment are recorded. Most normal, inbred strains of mice that have been investigated will spend more time with the novel mouse, than with the novel object [133–135]. Time spent sniffing the novel mouse is also measured. Strong correlations are observed between time spent in the chamber and time spent sniffing the conspecific mouse. In all probability, this single automated parameter is sufficient to capture true social behaviors.

Extensive validation of the automated three-chambered test was conducted by Jacqueline Crawley's group, using standard inbred strains of mice [132–134]. They observed that an experimental B6 mouse would respond to novel mice of several strains (B6, A/J, or 129/ImJ) with high sociability [134]. These data support the notion that this task assesses the traits of the experimental subject, and not of the novel partner. Utilizing this paradigm, one inbred strain of mouse, in particular, was observed to demonstrate a social phenotype reminiscent of ASD, the BTBR T+tf/J (BTBR) mouse. McFarlane et al. characterized multiple behavioral phenotypes relevant to all three diagnostic symptoms of autism in the inbred BTBR mouse strain [132]. This BTBR mouse strain has been designed as an animal model that may yield insights into the etiological factors of ASD [134,136–138].

12. Validity of using animal models to study communication

Communication skills and styles are vastly different between animals and humans. Perhaps, one important aspect comparing communication in animal models versus a human disorder is the purpose that communication serves and its effectiveness within the species. As highlighted in this commentary, those with ASD typically present with one or more social communication deficits, such as understanding and appreciating thoughts and feelings of others, difficulty in determining intentions of others, and difficulty understanding how their behavior may impact others [139–141]. Thus, social communication may be studied in an animal model based upon the effectiveness of communication within the species.

There are several factors to consider when choosing and testing an animal model of human symptoms, such as those observed in ASD. The 'face validity' of a test is determined by its ability to measure what it is intended to measure. For example, if assessment of communication is the goal, then the different types and styles of communication should be determined by the test being used. 'Construct validity' is the similarity between the underlying causes of ASD, such as genetic mutations. Chromosomal loci and genetic polymorphisms may underlie ASD and are investigated in humans and animal models [142]. Those with ASD seem to exhibit very different communication skills and may have genetic mutations compared to those not diagnosed with ASD. In human studies, sociability and/or communication of individuals with ASD are compared to the social and/or communication skills and abilities of those who are not diagnosed with ASD. Similarly, animal models of sociability and/or communication of animals that exhibit ASD-like behaviors, such as the BTBR mouse strain, are compared to other inbred mouse strains that do not exhibit social and/or communication deficits [132–134]. 'Predictive validity' is the anticipated response of animal models to treatments used to manage ASD in humans [142]. Several intervention programs have been developed to improve behaviors relevant to ASD in animal models. In fact, it has been found that continuous environmental enrichment 8 days prior to training improves learning and memory of BTBR mice in the object recognition task compared to B6 mice [143]. The BTBR mouse model may be valid and useful for determining whether specific genes predict social and/or communication skills and/or style and expression of ASD [144]. Genetic alterations in the BTBR mouse strain that are also present in populations of ASD may help researchers and clinicians gain some insight into development and/or expression of ASD in humans using this animal model.

Experiments conducted were designed to determine whether or not the auditory cues given by mice were valid forms of communication among mice which express ASD-like behaviors (BTBR mouse strain) compared to those that do not [145]. Mice vocalize at an ultrasonic level that humans cannot hear. By using Avisoft software, ten different categories of auditory calls that mouse pups emit were

identified. The pup vocalizations that are audible to humans occur when pups are separated from the nest, resulting in retrieval by the mother. Compared to standard B6 pup vocalizations, BTBR pups call much louder, and much more frequently [145]. BTBR call categories also differed from two other strains, 129 and FVB. The analysis employed 1 min audioclips from pups of each strain, to analyze properties, and design categories based upon the audio files. Investigators observed that these three strains had more similar patterns to each other than to the BTBR strain. Picker et al. have found differences in the numbers of ultrasonic vocalizations in other models of PDD, such as *Mecp2* mice, a model of Rett's Disorder [146]. Null male and heterozygous female mice demonstrated dramatic increases in vocalizations in response to social isolation as early as postnatal day 5 [146]. It is unclear whether these different patterns of calling have true communication functions in the life of the mouse but this information will be a critical component in developing a mouse model of the aforementioned second diagnostic symptom of ASD, which is difficulties with language and communication.

13. Autism awareness: beyond the individual

The most basic, yet most essential, step in being able to more effectively help those afflicted with ASD is to educate ourselves as well as the world around us. Fortunately, there are many programs that have been developed to help those who do not have ASD to better interact and communicate with those who do. Programs such as the Center for Autism and Related Disabilities (CARD; http://www.albany.edu/psy/autism) aim to provide evidence-based training and support to families and professionals on topics related to ASD [147–151]. CARD offers seminars and workshops on a variety of topics to individuals throughout New York State. CARD also provides special events and programs to children with autism and their families, including a summer picnic and a holiday party. CARD recently held a family seminar entitled "Encouraging the Development of Social Skills in Children and Young Adults with Autism Spectrum Disorders" (March 23, 2009, Courtyard Marriot, Saratoga Springs, NY), which was well-received by all who attended.

In addition to providing workshops and seminars, CARD is actively involved in ongoing research. Current areas of research at CARD include evidence-based interventions for ASDs, peer modeling, and eating and sleeping difficulties in children with disabilities. Early efforts to improve social skills in children with ASD were typically adult-directed and highly-structured; more recent research has focused on peer-initiated approaches and naturalistic settings such as classrooms.

In 2007, CARD formed partnerships with six university-affiliated programs across New York State (NYS) to establish and operate regional centers for ASD. The overarching goal of the 6 centers is to identify, disseminate, and assist in the implementation of evidence-based practice to build capacity and improve services and outcomes for children and youth with ASD. The University at Albany—SUNY currently serves as the headquarters for the statewide network, with partners at the University of Rochester, Canisius College/Summit Educational Resources, Inc., New York Medical College/Westchester Institute for Human Development, Hunter College, City University of New York (CUNY), and Queens College—CUNY. Using a regional model approach, an approach demonstrated to be a successful paradigm around the nation for providing community education and technical assistance, resources are now available to families and professionals in areas of NYS that have not had access to cost-effective services in the past. Each of the six centers provides high quality resources to individuals and families affected by autism, and to school personnel and community providers. These programs allow children all over NYS to have the opportunity to get the help they need and hopefully, this approach will begin to benefit children and their families outside of NYS as well.

14. Summary

Although there are many obstacles and complexities involved in the effort to elucidate causes and treatments for ASD, the potential for advancement is greater now than ever before due to observations and research in human and animal models. Clinicians have developed behavioral techniques to challenge and educate high- to low-functioning individuals afflicted with these disorders. Scientists have identified analogous aspects of these disorders in animal models which will be utilized to investigate pharmacological therapeutic interventions and to, ultimately, determine the etiology of ASD. As such, it is critical that investigations of these pervasive disorders continue to receive funding and public attention as they may one day yield the cure for ASD. Further, it is necessary to study communication disorders in human and animal models to inform behavioral interventions as well as future research on diagnosis, interventions, treatments, and/or causes of ASD.

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