The importance of autism research

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Abstract

This editorial discusses the importance of autism research, noting areas of progress and ongoing challenges and focusing on studies of the etiology, pathophysiology, and treatment of autism spectrum disorders.

Autism is one of a spectrum of behaviorally defined "pervasive developmental disorders,"[1] which are commonly referred to as autism spectrum disorder (ASD). The deficits in social communication and presence of restricted interests and repetitive behaviors result in lifelong impairments and disability. ASD has been reported to affect as many as 1 in 88 children in the US.[2] Reported prevalence rates have risen dramatically in the last two decades, though little is understood about the increase. Epidemiologic surveys of adult populations suggest that the apparent rise in numbers of affected children may not represent a true increase in prevalence rates.[3] Nevertheless, there is speculation that broadened definitions, growing awareness, and diagnostic substitution may be contributing to the apparent rise.[1,4] Regardless of the cause, the current prevalence estimates suggest that there are more than 2 million individuals in the US with ASD. To date, no preventive strategies have demonstrated consistent benefits and no treatments have proven widely efficacious in treating the core symptoms of ASD. Consequently, ASD causes lifelong disabilities for affected individuals and significant burdens on their families, schools, and society.[5]

Research on autism lags behind that of other psychiatric disorders and medical conditions. Part of the delay may be traced to the flawed constructs of autism that followed identification of the disorder in 1943. Most prominent of these was the speculation that autism was caused by parenting failures of "refrigerator mothers." Perhaps the greatest success story in autism research is the work of Dr Bernard Rimland and colleagues in the 1970s, which demonstrated that autism was actually a failure of neurodevelopment, with behavioral interventions providing potential benefits.[6] That research, in combination with an emerging basic science literature, led to our current understanding of autism as a brain-based disorder with specific (if as yet undetermined) abnormalities of brain structure and/or function. The paradigm shift also opened new avenues for research, which are producing increasing yields in terms of understanding the etiology, pathogenesis, and treatment of ASD.

For the past two decades, autism research has depended on a combination of public and private funding sources. Coordination of these efforts is one responsibility of the US Federal Government's Interagency Autism Coordinating Committee (IACC), which has responsibility for ensuring optimal utilization of federal funds and providing guidance to private funders. To facilitate these efforts, the IACC depends on the Strategic Plan for Autism Research, initiated in 2009 and updated annually.[7] The document purposefully uses plain language to summarize research directions, in order to fully reflect the various views of the "stakeholders" in autism research. Research directions are posed as questions requiring answers and range from "When should I be concerned?" through "What caused this to happen and can it be prevented?" and "Where can I turn for services?" The questions serve as organizing points for a wide variety of research studies, with exciting developments in many of these areas. We focus here on research into the etiology and treatment of autism, as these areas have demonstrated the most interest and promise in recent years.

The etiology of ASD is generally believed to involve a complex interaction of genetic abnor-

malities and environmental forces. The impact of environmental factors is suggested to be modified by the timing of the exposure,[8] such that individuals might be "protected" against an environmental hazard, if they have already passed through the developmentally sensitive period of risk. Conversely, exposures during the vulnerable period might have greater "epistatic" impact on individuals with a genetic predisposition to ASD.[9] The complex interaction of genes, environment, and developmental sensitivities has made research into the etiology of ASD more complex than that of other disorders.

Genetic abnormalities can currently be detected in a small, but significant fraction of individuals with ASD. The percentage of gene-related cases will likely increase as gene sequencing technology advances[10] and the number of genes associated with autism moves into the hundreds.[11] Specific genetic defects are often noted in ASD, such as copy number variations in 16p11.2 and 15q13.2q13.3.[12] In addition, several well-known genetic disorders may present with symptoms of autism. Two such examples are tuberous sclerosis (TSC) and Fragile X. Recent work has shown that the signaling pathways that are mechanistic in these disorders may both relate to metabotropic glutamate receptor 5 (MGLUR), but in opposite directions. That is, MGLUR signaling may be reduced in TSC and increased in Fragile X, and researchers have proposed that augmentation should alleviate symptoms in TSC, while inhibition may be beneficial in Fragile X.[13] These surprising and somewhat contradictory findings require further investigation, but hold promise for improving our understanding, not only of the pathophysiology of the intellectual disabilities observed in the two disorders, but also autistic symptomatology. More importantly, the research indicates that the etiology and pathophysiology of "look-alike" conditions may be quite different, and that these heterogeneities must be identified before treatments are developed for the larger class of patients with ASD and related disorders.[14]

Despite the rapid advances in genetics, most clinical research has not considered genetic and individual differences by conducting "genotype-up" research studies. Instead, the studies have been "phenotype-down" research in which a broad, behaviorally defined group of individuals are considered to establish a research sample. In many studies, all individuals with "autism spectrum disorders" are eligible for participation, and neuroimaging, neuropsychological tests, or other modalities are used to examine differences between subjects with ASD and those with typical development. While this has certainly been a feasible approach, phenotypic or genotypic hetereogeneity may have washed out important clues to the pathophysiology of autism, as well as rendering it impossible to find meaningful biomarkers of autism. To address this, researchers are beginning to perform "deep phenotyping" of biological and clinical variables, as well as behavioral manifestations of ASD, in order to identify subgroups of individuals with ASD that have unique and specific biological abnormalities. Finding abnormalities in basic biologic functions such as sleep[15] and default neural networks[16] among subgroups of individuals might represent new treatment targets for those individuals. Those novel therapies then could be tested in the larger ASD population for replication and generalization (or not!)

In the future, clinical studies of ASD should include not only carefully characterized, homogeneous samples of ASD subjects, but also should strive to determine the specificity of the findings to autism. Comparisons against other subjects with other neurodevelopmental disorders, intellectual disabilities, communication deficits, and other symptoms will ensure that the findings are uniquely relevant to ASD. The studies could then search for genetic and nongenetic etiologies, disease modifiers, and factors conferring risk or protection.

Medical treatment of ASD has been notoriously unsuccessful, with limited impact on the core symptoms of deficits in social reciprocity and communication and the presence of excessive restrictions of

interest or behaviors. As with research into the etiology of ASD, it is possible that treatment trials have failed because they have studied heterogeneous subject groups. It is possible that greater success might result from smaller trials of more homogeneous subject groups (such as Fragile X patients or individuals with a history of acute regression). Such studies should be of the highest priority, and directed towards the severe impairments that often accompany autism, requiring a lifetime of 1:1 supervision for many individuals.

The treatment targets in ASD are quite different from those of medical and psychiatric disorders where a new symptom has appeared and is causing impairments. In ASD, *deficits* in social and communication functioning are the focus of therapeutic interventions, making it difficult to find reliable and clinically meaningful measures of change (particularly improvement). Changing the *trajectory* of skill acquisition may be the most realistic approach for determining therapeutic effects, but this may take more time than is feasible, and it is clearly difficult to assess the "moving target" of a young child's developmental changes. Adding further complexity, many children with ASD also have intellectual and/or language impairments, making assessment of treatment effects even more challenging.

Perhaps for these reasons, the most rigorously tested psychopharmacological treatments, including the two psychotropic medications found to be efficacious in children,[17] have targeted ancillary externalizing behaviors (eg, irritability, aggression). While behavioral treatment research often targets cognitive functioning and is beginning to show promise for improving outcome areas relating to core symptoms such as language,[18] measurement issues in assessing improvements of core symptom severity must be addressed systematically before behavioral, pharmacological, or combined treatments can be rigorously tested through trials. Simultaneous to this (and noted above) is the continued search for neurochemical targets for drug intervention and biological predictors of response; and development of efficacious therapies not only for the core symptoms of autism, but also for associated morbidities, such as sleep disturbances, GI symptoms, and others.

Publication of small, underpowered clinical trials and studies with flawed research designs has made it difficult to interpret the autism literature and to judge the clinical significance of the findings, whether negative or positive. Published studies often describe "preliminary data" and statistical trends that provide false leads, obscure the true pathology of ASD, or are not generalizable beyond the small number of subjects studied. There are numerous examples of reports in which early results conflicted with findings for larger or subsequent samples,[19-21] autism-specific findings were later found to relate to a wide variety of neurodevelopmental disorders,[22] or between-site differences are as much as tenfold greater than the reported abnormalities (eg, rates of comorbid seizure disorders vary from 6% to 60%).[23] Of greatest clinical concern, in several instances, new "therapies" have been adopted by clinicians before being subjected to adequate trials, with potential harm to the individuals receiving the intervention.[24]

Autism research is important for individuals currently affected with ASD, as well as for those in whom the symptoms might be prevented. However, research on ASD is also important for understanding the larger class of neurodevelopmental disorders. Childhood disabilities are increasingly falling into the realm of behavioral/neurologic (versus physical)[25] and there are likely some commonalities in the etiologies and treatments of the conditions.

A collaborative, systematically identified and implemented autism strategic research plan is essential and requires a dynamic, cohesive process that streamlines research moving from bench to bedside (and back). Some of this work has already begun, with efforts such as Autism Genetics Resource Exchange, Autism Clinical Trials Network, and Simons Simplex Collection. The fruits of such efforts may be rewarding in an immediate fashion, with accelerated genetics findings and

large-scale field testing of therapies. Such high-quality autism research is not only necessary for identifying potential treatments, and testing them in autism, but is also likely to be informative for understanding basic developmental processes, and thus have applicability to a variety of other genetic and non-genetically based neurodevelopmental disorders.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed, Text Revision. Washington, DC: American Psychiatric Association; 2000.
2. CDC. Prevalence of Autism Spectrum Disorders — Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. In: *MMWR CDC Surveill Summ*. 2012:1-19.
3. Brugha TS, McManus S, Bankart J, et al. Epidemiology of autism spectrum disorders in adults in the community in England. *Arch Gen Psychiatry*. 2011;68:459-465.
4. Wazana A, Bresnahan M, Kline J. The autism epidemic: fact or artifact? *J Am Acad Child Adolesc Psychiatry*. 2007;46:721-730.
5. Amendah D, Grosse SD, Peacock G, Mandell DS. Economic costs of autism: a review. In: Amaral D, Geschwind D, Dawson G, eds. *Autism Spectrum Disorders*. New York, NY: Oxford University Press; 2011:1347-1360.
6. Silverman C, Brosco JP. Understanding autism: parents and pediatricians in historical perspective. *Arch Pediatr Adolesc Med*. 2007;161:392-398.
7. Interagency Autism Coordinating Committee. IACC Strategic Plan for Autism Spectrum Disorder Research. Available at: Department of Health and Human Services Interagency Autism Coordinating Committee website: http://iacc.hhs.gov/strategic-plan/2011/index.shtml; 2011.
8. Hornig M, Mervis R, Hoffman K, Lipkin WI. Infectious and immune factors in neurodevelopmental damage. *Mol Psychiatry*. 2002;7(suppl 2):S34-S35.
9. Rodier P. Environmental Exposure that increase the risk of autism spectrum disorders. In: Amaral DG, Dawson G, Geschwind DH, eds. *Autism Spectrum Disorders*. New York, NY: Oxford University Press; 2011:863-874.
10. Abrahams BS, Geschwind DH. Connecting genes to brain in the autism spectrum disorders. *Arch Neurol*. 2010;67:395-399.
11. Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*. 2012;485:237-241.
12. Shen Y, Dies KA, Holm IA, et al. Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics*. 2010;125:e727-735.
13. Auerbach BD, Osterweil EK, Bear MF. Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature*. 2011;480:63-68.
14. Insel TR. Experimental medicine. In: *NIMH Director's Blog*. Bethesda, MD: NIMH; 2012.
15. Buckley AW, Rodriguez AJ, Jennison K, et al. Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development. *Arch Pediatr Adolesc Med*. 2010;164:1032-1037.
16. Christakou A, Murphy CM, Chantiluke K, et al. Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with Autism. *Mol Psychiatry*. In press.
17. McPheeters ML, Warren Z, Sathe N, et al. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics*. 2011;127:e1312-e1321.
18. Dawson G, Rogers S, Munson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*. 2010;125:e17-e23.
19. Anagnostou E, Taylor MJ. Review of neuroimaging in autism spectrum disorders: what have we learned and where we go from here. *Mol Autism*. 2011;2:4.
20. Main PA, Angley MT, Thomas P, O'Doherty CE, Fenech M. Folate and methionine metabolism in autism: a systematic review. *Am J Clin Nutr*. 2010;91:1598-1620.
21. Alarcon M, Yonan AL, Gilliam TC, Cantor RM, Geschwind DH. Quantitative genome scan and Ordered-Subsets Analysis of autism endophenotypes support language QTLs. *Mol Psychiatry* 2005;10:747-757.
22. Scherer SW, Dawson G. Risk factors for autism: translating genomic discoveries into diagnostics. *Hum Genet*. 2011;130:123-148.
23. Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatr Res*. 2009;65:599-606.
24. Krishnaswami S, McPheeters ML, Veenstra-Vanderweele J. A systematic review of secretin for children with autism spectrum disorders. *Pediatrics*. 2011;127:e1322-e1325.
25. Halfon N, Houtrow A, Larson K, Newacheck PW. The changing landscape of disability in childhood. *Future Child*. 2012;22:13-42.