Yes We Can! Choose Science in Autism

Catherine Lord

The most reliable diagnosis in child psychiatry, autism nonetheless remains a mystery in many ways. It has no specific biological marker, a circumstance that likely contributes to its attractiveness to advocates and zealots, as Paul Offit describes in his forceful *Autism's False Prophets*. Persons with autism spectrum disorders (ASDs) range from nonverbal individuals with severe intellectual disabilities to highly intelligent, articulate people who struggle with social expectations. This heterogeneity invites confusion. Improvements in children with the mildest ASDs are sometimes treated as "cures," as if they were transformations of the most difficult cases, whereas in fact trajectories tend to be quite predictable within levels of severity.

Offit (a vaccine researcher and pediatrician at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine) takes up the story in 1998, with the now-infamous paper by Andrew Wakefield and colleagues that proposed links between measles-mumps-rubella (MMR) vaccine and autism (*1*). He offers an easy-to-read medical thriller about the consequences of greed, hubris, and intellectual sloppiness. His account weaves together cogent comments about the dangers of teleconferences in health care decision-making and accounts of scientific-legal debates about silicone breast implants and facilitated communication in ASD. Sometimes tongue-in-cheek (chapter titles include "Mercury Rising" and "Mercury Falling"), the book vividly portrays the escalation of enthusiasm for vaccination-related hypotheses:

> So dramatic was the evidence against vaccines that a major well-respected production company was going to make a movie about it. Everything was coming together. Everything made sense.

This is a tale of heroes (parents and scientists willing to stand up to threats and accusations) and some unquestionable villains. It is also the story of lesser culprits who may not profit but who cause harm by their inconsistent application of scientific standards to their own and others' work. [A recent column (*2*) by Bernadette Healy, a former head of the U.S. National Institutes of Health, exemplifies this problem.] Sometimes Offit's comments about particular individuals seemed a bit unfair. In contrast, the financial conflicts of interest of some scientists and advocates and the failure of others to take on these conflicts are much more disturbing.

Autism's False Prophets
Bad Science, Risky Medicine, and the Search for a Cure
by Paul A. Offit
Columbia University Press, New York, 2008.
322 pp. $24.95, £14.95.
ISBN 9780231146364.

Surprisingly, Offit does not discuss the fact that human decision-making is often not rational, especially when it involves evaluating relative risks and weighing anecdotal versus empirical evidence. Anyone forced to sign a consent form acknowledging that death could be the consequence of routine dental work realizes that someone somewhere is calculating the risk of ordinary procedures. With the present ease of access to unfiltered scientific and pseudoscientific data, questions of how to help parents evaluate information about risk and make rational medical choices must go beyond consent forms.

Three types of justification have been used to argue that vaccinations (either MMR or those that contain thimerosal) cause autism: specific hypotheses about effects of mercury and the measles virus on brain function, the increasing prevalence of ASDs, and the occurrence of regression in autism. Offit carefully discusses data discounting the first two justifications but spends little time on the role of regression in explaining many parents' beliefs about vaccinations. Yet this is another area where science can contribute.

Some children who will develop autism show nonspecific abnormalities (such as motor, sleeping, or eating difficulties) early in life, but autism-specific deficits in use of eye contact, facial expressions, and simple social interactions become apparent in ASD in the second year of life (*3*). Some argue that there is a clear, specific regressive subtype of ASD. However, if most children with autism manifest ordinary socially directed behaviors at 6 months and do not show these same behaviors at 24 months, then almost all children with ASD experience a regression in social-communication skills. There are children with marked regressions and children with subtle losses. Strikingly, there is no evidence that any aspect of regression in ASD is associated with timing of vaccination or exposure to thimerosal. The loss of social-communication skills is a "red flag" for ASD and must be accounted for in explanations of the development of autistic symptoms. But rather than a "clear regressive phenotype" there is a range of patterns, none of which has been shown to be related to vaccinations (*4*).

What next? Offit's call for the application of scientific principles to these questions has

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Antivaccinationists. Demonstrators convinced of a link between MMR vaccine and autism demonstrate in London.

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already emboldened members of the media. (YouTube offers a recent striking conversation between the Today Show's Matt Lauer and a tenacious Nancy Snyderman, the show's medical analyst.) Perhaps now we can use this momentum, as Offit fiercely argues, to shift the energy and resources from the autism-vaccination debate to the need for more research about causes and the development of effective treatments and support for individuals with ASDs and their families.

References and Notes

1. A. J. Wakefield *et al.*, *Lancet* **351**, 637 (1998); retractions followed (5).
2. B. Healy, *U.S. News World Rep.* (10 April 2008).
3. S. E. Bryson *et al.*, *J. Autism Dev. Disord.* **37**, 12 (2007).
4. J. Richler *et al.*, *J. Autism Dev. Disord.* **30**, 36 (2006).
5. S. H. Murch *et al.*, *Lancet* **363**, 750 (2004).

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NEUROSCIENCE

The Emerging Nature of Nurture

Mriganka Sur

Our minds prefer to deal in dichotomies. We like to see the world as black or white, if only to sharpen issues that demand a decision. The opposite ways in which we frame the world are the stuff of pop psychology as well as of deep dialectics. Thus, Joan Stiles starts *The Fundamentals of Brain Development* by explaining how developmental psychologists have viewed cognitive development as shaped by either nature or nurture. As the subtitle, *Integrating Nature and Nurture*, indicates, she aims to bridge this divide. At the outset, she courageously asserts that an understanding of brain development is critical for her project—courageously, because she is a cognitive scientist (at the University of California, San Diego), not an expert in developmental neuroscience. She ends up taking readers through a surprisingly detailed exposition of brain development and constructing a scholarly synthesis that will inform not only developmental psychology but even all of neuroscience and cognitive science.

Halfway through the book, I was wondering whom it was written for. The preface suggests the book is intended for students of cognitive development, and indeed they will find it highly informative. But the heart of the book is really an extended review of the recent literature on brain development. Stiles starts with the gastrulation and neurulation stages of embryogenesis and continues through the formation of the neural tube; patterning of the neural axis; production, migration, and differentiation of neurons; formation of cortical connections; and shaping of cortical circuits by experience and electrical activity. Stiles precedes this material with a description of the gene—what it is and is not and how our ideas about gene regulation and expression are evolving rapidly. Indeed, still-newer findings (on epigenetics and RNA regulation, for example) render even more complex the nature of the gene and even richer the ways in which extrinsic influences shape gene function. The author weaves her description of brain development as a process of progressive commitment of neural elements into a masterful synthesis of innateness, inheritance, development, and plasticity. I learned a great deal from the book, and I suspect other practicing neuroscientists will, too.

The Fundamentals of Brain Development
Integrating Nature and Nurture
by Joan Stiles
Harvard University Press, Cambridge, MA, 2008. 433 pp. $49.95, £32.95, €37.50. ISBN 9780674026742.

Stiles correctly points out that among developmental neuroscientists the debate between nature and nurture has become outmoded. We now know that there is no such thing as a gene that acts in isolation and that every gene needs an environment—whether the environment is the presence of molecules made by other genes, signals generated internally within the developing nervous system, or electrical activity transduced from the external world. Thus, the discussion within the field has moved from nature versus nurture to the integration of nature and nurture and even beyond, to the nature of nurture—which kinds of environmental influences can affect gene expression at specific time points of development.

The nature of such environmental influences is a focus of much current research. At the earliest stages of brain development, the mere presence of certain molecules or signals may be sufficient: permissive influences likely suffice to shape gene and protein expression and thus influence brain development. Later on, the influence of the environment may be instructive, so that the specific pattern of signals or of electrical activity shapes brain networks and function.

This is where I suspect the divide that Stiles tries to bridge will likely persist. Nativists will argue that that the real issue is not whether an environment is required for brain development but what exactly is required. Indeed, we need to resolve the specific role of learning in development. When and under what conditions is the exact timing of spikes (as postulated by "spike timing dependent plasticity") used by the developing brain? Perhaps the earliest stages of brain development simply require the presence of external signals, and only later, as the neural machinery develops, is the pattern or structure of external information important.

Another dilemma arises from the nature of biological investigation itself. The search for mechanisms of brain development has been illuminated by selective manipulations that alter development. But the changes imposed by such a manipulation may not recapitulate the process of normal development. In the visual cortex, for example, it now appears that the pattern of projections from the two eyes is set up by the targeted early ingrowth of axons from the visual thalamus. Manipulating development by altering activity in one eye alters the pattern of projections, such that the deprived eye occupies less territory while the nondeprived eye occupies more. This plasticity, however, is a response of the system to altering the balance of activity, not a process that is necessarily used during development to settle cortical territories. Thus, the processes of plasticity, although available during development, may not be identical to the processes of development per se.

At places, the book is not an easy read. It abounds in sentences such as: "Interestingly, the introduction of Fgf8 into posterior regions where it is not normally expressed creates anomalously placed regions that express anterior identity." This is the language of developmental neurobiologists. But it is a mark of the level of engagement that Stiles brings and the way she leads readers into the material that we find such conclusions arising naturally in a discussion of cortical patterning (the way in which the developing cerebral cortex gets divided into its constituent areas).

The dichotomies of biology—nature and nurture, constancy and variation, limits and potential—while useful as artifice, are in fact inseparable from one another. As Stiles's comprehensive overview reminds us, nowhere is this more evident than in human brain development. Fundamentally derived through natural selection, the genes of brain development are impressively environment- and experience-dependent.

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