

News & Research

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In a Novel Theory of Mental Disorders, Parents' Genes Are in Competition

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http://www.nytimes.com/2008/11/11/health/research/11brain.html?_r=2

Two scientists, drawing on their own powers of observation and a creative reading of recent genetic findings, have published a sweeping theory of brain development that would change the way mental disorders like autism and schizophrenia are understood.

The theory emerged in part from thinking about events other than mutations that can change gene behavior. And it suggests entirely new avenues of research, which, even if they prove the theory to be flawed, are likely to provide new insights into the biology of mental disease.

At a time when the search for the genetic glitches behind brain disorders has become mired in uncertain and complex findings, the new idea provides psychiatry with perhaps its grandest working theory since Freud, and one that is grounded in work at the forefront of science. The two researchers — Bernard Crespi, a biologist at Simon Fraser University in Canada, and Christopher Badcock, a sociologist at the London School of Economics, who are both outsiders to the field of behavior genetics — have spelled out their theory in a series of recent journal articles.

“The reality, and I think both of the authors would agree, is that many of the details of their theory are going to be wrong; and it is, at this point, just a theory,” said Dr. Matthew Belmonte, a neuroscientist at Cornell University. “But the idea is plausible. And it gives researchers a great opportunity for hypothesis generation, which I think can shake up the field in good ways.”

Their idea is, in broad outline, straightforward. Dr. Crespi and Dr. Badcock propose that an evolutionary tug of war

between genes from the father's sperm and the mother's egg can, in effect, tip brain development in one of two ways. A strong bias toward the father pushes a developing brain along the autistic spectrum, toward a fascination with objects, patterns, mechanical systems, at the expense of social development. A bias toward the mother moves the growing brain along what the researchers call the psychotic spectrum, toward hypersensitivity to mood, their own and others'. This, according to the theory, increases a child's risk of developing schizophrenia later on, as well as mood problems like bipolar disorder and depression.

In short: autism and schizophrenia represent opposite ends of a spectrum that includes most, if not all, psychiatric and developmental brain disorders. The theory has no use for psychiatry's many separate categories for disorders, and it would give genetic findings an entirely new dimension.

"The empirical implications are absolutely huge," Dr. Crespi said in a phone interview. "If you get a gene linked to autism, for instance, you'd want to look at that same gene for schizophrenia; if it's a social brain gene, then it would be expected to have opposite effects on these disorders, whether gene expression was turned up or turned down."

The theory leans heavily on the work of David Haig of Harvard. It was Dr. Haig who argued in the 1990s that pregnancy was in part a biological struggle for resources between the mother and unborn child. On one side, natural selection should favor mothers who limit the nutritional costs of pregnancy and have more offspring; on the other, it should also favor fathers whose offspring maximize the nutrients they receive during gestation, setting up a direct conflict.

The evidence that this struggle is being waged at the level of individual genes is accumulating, if mostly circumstantial. For example, the fetus inherits from both parents a gene called IGF2, which promotes growth. But too much growth taxes the mother, and in normal development her IGF2 gene is chemically marked, or "imprinted," and biologically silenced. If her gene is active, it causes a disorder of overgrowth, in which the fetus's birth weight swells, on average, to 50 percent above normal.

Biologists call this gene imprinting an epigenetic, or "on-genetic," effect, meaning that it changes the behavior of the gene without altering its chemical composition. It is not a matter of turning a gene on or off, which cells do in the course of normal development. Instead it is a matter of muffling a gene, for instance, with a chemical marker that makes it hard for the cell to read the genetic code; or altering the shape of the DNA molecule, or what happens to the proteins it produces. To illustrate how such genetic reshaping can give rise to behavioral opposites — the yin and yang that their theory proposes — Dr. Crespi and Dr. Badcock point to a remarkable group of children who are just that: opposites, as different temperamentally as Snoopy and Charlie Brown, as a lively Gaugin and a brooding Goya.

Those with the genetic disorder called Angelman syndrome typically have a jerky gait, appear unusually happy and have difficulty communicating. Those born with a genetic problem known as Prader-Willi syndrome often are placid, compliant and as youngsters low maintenance.

Yet these two disorders, which turn up in about one of 10,000 newborns, stem from disruptions of the same genetic region on chromosome 15. If the father's genes dominate in this location, the child develops Angelman syndrome; if the mother's do, the result is Prader-Willi syndrome, as Dr. Haig and others have noted. The former is associated with autism, and the latter with mood problems and psychosis later on — just as the new theory

predicts.

Emotional problems like depression, anxiety and bipolar disorder, seen through this lens, appear on Mom's side of the teeter-totter, with schizophrenia, while Asperger's syndrome and other social deficits are on Dad's.

It was Dr. Badcock who noticed that some problems associated with autism, like a failure to meet another's gaze, are direct contrasts to those found in people with schizophrenia, who often believe they are being watched. Where children with autism appear blind to others' thinking and intentions, people with schizophrenia see intention and meaning everywhere, in their delusions. The idea expands on the "extreme male brain" theory of autism proposed by Dr. Simon Baron-Cohen of Cambridge.

"Think of the grandiosity in schizophrenia, how some people think that they are Jesus, or Napoleon, or omnipotent," Dr. Crespi said, "and then contrast this with the underdeveloped sense of self in autism. Autistic kids often talk about themselves in the third person."

Such observations and biological evidence are hardly enough to overturn current thinking about disorders as distinct as autism and schizophrenia, experts agree. "I think his work is often brilliant," Dr. Stephen Scherer, of the University of Toronto and the Hospital for Sick Children, said by e-mail message of Dr. Crespi. At the same time, Dr. Scherer added, "For autism there will not be one unifying theory but perhaps for a proportion of families there are underlying common variants" of genes that together cause the disorder.

The theory also does not fit all of the various quirks of autism and schizophrenia on flip sides of the same behavioral coin. The father of biological psychiatry, Emil Kraepelin, in the late 1800s made a distinction between mood problems, like depression and bipolar disorder, and the thought distortions of schizophrenia — a distinction that, to most psychiatrists, still holds up. Many people with schizophrenia, moreover, show little emotion; they would seem to be off the psychosis spectrum altogether, as the new theory describes it.

But experts familiar with their theory say that the two scientists have, at minimum, infused the field with a shot of needed imagination and demonstrated the power of thinking outside the gene. For just as a gene can carry a mark from its parent of origin, so it can be imprinted by that parent's own experience.

The study of such markers should have a "significant impact on our understanding of mental health conditions," said Dr. Bhismadev Chakrabarti, of the Autism Research Center at the University of Cambridge, "as, in some ways, they represent the first environmental influence on the expression of the genes."

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Study of Learning Disabled Mice Shows Balance in the Brain is Key

ScienceDaily (Nov. 3, 2008) — A new study in the October 31st issue of *Cell* has revealed the molecular and cellular underpinnings of one of the most common, single gene causes for learning disability in humans. The findings made in learning disabled mice offer new insight into what happens in the brain when we learn and remember.

While most previous studies have focused on the role of brain cells that excite other brain cells in the process of learning, the current results suggest that inhibitory neurons and a careful balance between excitatory and inhibitory signals may be just as essential, according to the researchers. They liken the role of those inhibitory and excitatory signals in the brain to the role of red and green stoplights in directing traffic.

"The significance of these findings is two-fold," said Alcino Silva of the University of California, Los Angeles. "First, we have in great detail the exact mechanism for one of the most common single gene causes for learning disability known. It's also a beachhead in our understanding of the balance between excitation and inhibition critical for learning."

Learning disabilities are estimated to affect one in five people worldwide. "It's a huge problem and there is little known about their causes," Silva said.

To begin to chip away at those underlying causes for conditions that often have complex causes, Silva's team began a hunt several years ago to unravel the mechanisms responsible for a couple of single gene disorders that lead to learning disability.

In the new study, they examined mice with learning disabilities resulting from a condition called neurofibromatosis type 1. The condition stems from a defect in the *Nf1* gene encoding a protein called neurofibromin. Earlier studies showed that neurofibromin controls a "Ras/Erk" signal that is involved in long-term potentiation (LTP) and learning in mice. LTP is a process that strengthens the connections between neurons in the brain—the cellular basis for learning and memory.

Now, the researchers have found that the deficits in spatial learning experienced by mice with an abnormal version of the *Nf1* gene stem from an increased release by inhibitory neurons of a chemical nerve messenger (or neurotransmitter) called GABA. GABA is the chief inhibitory neurotransmitter in the central nervous systems of mammals.

That rise in GABA leads to deficits in the plasticity of neurons required for learning and memory. Importantly, they also show that the learning deficits in the mice can be reversed with treatments that reign GABA levels back in. They also show that GABA levels normally swell when mice learn, suggesting that a balance of GABA is the key. Silva's team notes another recent study implicating changes in GABA inhibition in the learning deficits exhibited by an animal model of Down's syndrome. Although learning disability—characterized by profound changes in one part of brain function—differs widely from mental retardation, that finding together with the new study suggest there may nevertheless be a common thread, Silva said.

Ultimately, these insights could lead to new ways to treat learning disabilities, although reaching that goal won't be a simple proposition.



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" It won't be a single step from the mechanism to finding a drug," Silva said. As with other complex disorders like cancer, he said, it will likely take years of exploration to turn scientific advances into medical applications. Nevertheless, "the more insight we have into the mechanisms responsible, the more likely it is that our treatment efforts will be effective. "

The new study is also representative of the exciting advances in the study of neuroscience more broadly.

" We are at the beginning of a wonderful journey into how the human mind works," Silva said. "We are developing a highly detailed view of what goes on in the brain when we learn and remember. There is nothing more inspiring; it's what makes us who we are."

The researchers include Yijun Cui, University of California, Los Angeles, Los Angeles, CA; Rui M. Costa, University of California, Los Angeles, Los Angeles, CA, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD; Geoffrey G. Murphy, University of California, Los Angeles, Los Angeles, CA, University of Michigan, Ann Arbor, MI; Ype Elgersma, University of California, Los Angeles, Los Angeles, CA; Erasmus MC, Rotterdam, The Netherlands; Yuan Zhu, University of Michigan Medical School, Ann Arbor, MI; David H. Gutmann, Washington University School of Medicine, St. Louis, MO; Luis F. Parada, University of Texas Southwestern Medical Center, Dallas, TX; Istvan Mody, University of California, Los Angeles, Los Angeles, CA; and Alcino J. Silva, University of California, Los Angeles, Los Angeles, CA.

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