Autism Spring

Autism Spring is a recent blog post by Dr. Thomas Insel. Dr. Insel is the director of the National Institute of Mental Health (NIMH) and the chair of the Interagency Autism Coordinating Committee.

As a rule, I try to not copy other articles in their entirety. As a taxpayer, I feel that work by the government is in a different category, and so I present the entire article below.

I find it very interesting to read what Dr. Insel finds important in autism research. At the same time, I think it is important to present this without much in the way of commentary (until whatever discussion unfolds, of course).

Looking back over NIMH related events these past few months, one might wonder if this has been Autism Spring. It has certainly been a busy season for autism spectrum disorder (ASD): a White House meeting, unprecedented press coverage, and the largest International Meeting for Autism Research (IMFAR) to date. But perhaps most exciting has been the early scientific harvest evident in a series of high-profile papers published over the past two months. Some of these discoveries with autism have implications for mental disorders like schizophrenia and mood disorders, which increasingly are being addressed as neurodevelopmental disorders.

While the new findings range from epidemiology to new diagnostic tests, here I will focus on new insights into the molecular basis of autism. Three studies, written up in the June issue of Neuron, based their findings on data from the Simons Simplex Collection.1,2,3 The Simons Foundation funded the collection of careful clinical descriptions and DNA from these families (a total of 1,074 children). These studies focus on DNA copy number variations (CNVs) that are more common in children with autism than in the general population.

1. M. Gerutis, et al. 2012. Neuron. 75:667-681. Identifying autism susceptibility loci: copy number variation and expression quantitative trait loci. (This study found that the 15q13.3 region is associated with autism and that the expression of a nearby gene is altered in people with autism.)

2. S. Wang, et al. 2012. Neuron. 75:682-692. Mutations in the CHD8 gene underlie autistic spectrum disorders. (This study found that mutations in the CHD8 gene are associated with autism.)

3. J. Palau, et al. 2012. Neuron. 75:693-704. Reduced copy number variation load in female autism probands. (This study found that women with autism have fewer copy number variations than men with autism.)

While these studies are exciting, they are also important because they provide new insights into the molecular basis of autism. These findings may lead to new treatments and better understanding of the disorder.
changes in the genome leading to a deletion or duplication of a segment of DNA. Many of these are de novo, meaning that the duplication or deletion is not found in the genome of either parent but develop in the DNA of germ cells (egg or sperm) over the life of one parent. Small de novo changes in DNA sequence, which occur in all of us, demonstrate that effects can be genetic without necessarily being inherited. And, of course, these germ cell changes may be the result of environmental factors, increasing with parental age.

The results are both intriguing and frustrating. Intriguing, in that children with ASD were found to have many more CNVs. These CNVs were more likely to be larger and more frequently involved specific genes than those found in unaffected siblings. But only 1 in 38 affected children had a recurrent CNV, meaning a CNV that appeared in any of the other children in the study. Of these recurrent CNVs, six genomic regions were discovered to be associated with ASD, including four duplications of the chromosome 7q11.23 region. This region is deleted in Williams-Buren syndrome, a disorder with hyper-social, hyper-verbal behavior that, in some ways, appears as the inverse of the autism phenotype. Unfortunately, the papers did not describe whether these recurrent CNVs were associated with distinct clinical characteristics.

The frustration comes from the relative rarity and complexity of these de novo CNVs. In two separate studies of the same sample using different techniques, only about 8 percent of ASD children in simplex families had CNVs. Add this number to the 8 percent with a mutation known to cause autism, such as Fragile X or tuberous sclerosis, and that still leaves more than 80 percent of ASD children with no evident genomic cause for their disorder. Traditional estimates of the heritability of ASD range as high as 90 percent. It is quite possible that these heritability estimates were too high, but even if the heritability were less, as Scharff and Zoghbi noted in an essay that accompanied these three Neuron papers, “the results are humbling.”

Of course, there are more genomic risk factors to be found, given that the CNVs identified in these studies are large (100,000 bases or greater). As the technology for genomic research improves, smaller CNVs are likely to be identified. These papers estimate that there may be 200-300 CNVs in the genome contributing to ASD. The next step in this journey will involve sequencing all the coding regions of the genome, no doubt with even more variations emerging.

But there are more questions than answers in these projections. Many CNVs are incidental (2 percent occur in unaffected siblings), many different genes may be affected by the known CNVs, and the biological significance of any of these mutations remains to be determined. Indeed, an independent paper looking at the interaction of proteins from genes implicated in ASD found networks centered on two synaptic proteins: Shank 3 and PSD95.5. A separate analysis of the genes thought to be implicated in ASD identified a network that included genes involved in synapse formation.
axon targeting, and neuronal motility. All of this suggests that, from a genomic perspective, autism is a synaptic disease.

Why is this important? If nothing else, these humbling results beg for more exploration of the brain. And one of the most exciting studies, just out, reports that RNA expression patterns in post-mortem brains yield some surprising clues. RNA is the key intermediary for translating DNA into protein. Patterns of RNA expression define which proteins will be expressed, determining the function of each cell. In ASD brains, the expected differences in expression between different regions of the brain are less distinct, as if mature cortical patterns have not developed. While the differences in expression are complex, they converge around a few key pathways and may reflect differences in RNA splicing. For instance, with brain maturation, genes are spliced in different regions to yield different fragments of RNA and different protein products. We need much more study of this process in ASD, but this initial project of frontal and temporal cortex suggests that whatever the DNA variations in ASD may be, the RNA fragments are strikingly abnormal.

If the CNVs discovered in genomic DNA reflect a fundamental genomic instability in ASD, could there be somatic mutations (mutations found in neurons but not in blood cells) in ASD brains? Perhaps the biology of cancer, with mutations in oncogenes and tumor suppressor genes found only in the tumor, will be a useful model for the biology of ASD, with mutations found only in the cortex.

Oliver Wendell Holmes once said, “I wouldn’t give a fig for the simplicity on this side of complexity; I’d give my right arm for the simplicity on the far side of complexity.” We are, unfortunately, not near the far side of complexity of autism. These recent studies raise questions about the limits of genetics, even with the enormous power of our current techniques. Genetic signals will be complex and may not converge as we would hope around a simple developmental mechanism or pathway. Post-mortem brain analysis may be highly informative, but we have little tissue from ASD children, and comparisons with age-matched tissue continue to be a challenge.

The great uncharted territory of environmental factors remains, which might begin to explain the infrequent mutation rate and apparent increase in autism prevalence. Here, we are stymied by a different kind of complexity. Most evidence points to environmental factors acting in the second trimester, two or more years before a diagnosis of ASD. Several studies funded by NIH are looking for differences in the gestational environment of children later diagnosed with ASD. The answers — and there will be answers — will no doubt merge genetic risk and environmental exposure to help us reach the far side of the complexity of ASD.


dkmnow
July 5, 2011 at 21:15

His omissions speak far more loudly than his words: Insel, in his impenetrable ivory tower, still has not so much as one syllable to spare in the interest of improving quality of life for the countless living, breathing, hoping, feeling, loving, aspiring and toiling autistic citizens living in the real world right now.

This man is not our friend.

REPLY
“This man is not our friend.”

The question I would propose you consider is this: how can we make him our friend or, at least, our ally? I’d suggest giving him (a) the information he needs and (b) the idea that supporting autistic citizens is not only a worthwhile goal but one which has broad support.

Consider sending a polite but clear comment to the IACC. They are set to have a meeting very soon. iaccpublicinquiries@mail.nih.gov

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PeripheralPerspective  
July 5, 2011 at 22:32

“I wouldn’t give a fig for the simplicity on this side of complexity; I’d give my right arm for the simplicity on the far side of complexity.”

I found another quote in a review of “Elegance in Science” that to me says it all, since Autism, to me, exhibits profound elegance:

“elegance in science combines the dedication and intense focus of the scientist on the question to be answered, a sudden ingenious insight (often triggered by an unexpected experimental result), followed by a surprisingly simple explanation which, after its discovery, seems obvious to all.”

http://www.scimednet.org/the-beauty-of-simplicity/

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passionlessDrone  
July 6, 2011 at 02:05

Hi Sullivan –

This is more than once you’ve alerted me to a very cool posting by Mr. Insel. Thank you.

As for the content, finally, finally some common sense is starting to filter upwards. I love the complexity angle. No kidding!

Good stuff!

– pD

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sharon  
July 6, 2011 at 05:22

I found the information of interest. I am hoping someone may be able to answer a question. How do researchers determine the difference between simplex ASD children who are indeed the only ones in their family versus children who live in families where no one has been diagnosed, yet there may be a range of members who fit an ASD profile if they were screened today?

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dkmnow  
July 6, 2011 at 08:11

Sullivan,

I have considered these things at length in the past, and will go on considering them. But it’s not as if none of us have tried to get through to him, right? The autistic community has been trying to cajole Insel out of his singular immersion in “medical model” conceptions of autism, quite literally, for years. You might even say, we’ve been standing with our feet squarely rooted in “the simplicity on the far side of complexity,” and calling out to him across the “wall of silence” all along. But he hears nothing because, apparently, “Autistic” is not a language he’s able to recognize as having any worthwhile meaning. We might just as well
grunt and wail at him, for all he cares.

But it’s not just our language that Insel refuses to hear — we have another ally: the social model of disability is codified in the ADA (however crudely), but Insel persists in his tacit refusal to be guided by it, or even to sincerely consider it’s relevance. This is not acceptable, and under these circumstances, I have to ask: How long shall we be required to wait around for the unlikely event that he might creep out of his comfort zone and stumble into some sort of epiphany? Years, decades, or however long it takes to “wipe autism off the map,” would seem to be Insel’s answer.

No. The kinds of changes we should rightfully be demanding from Insel are not going to be brought about by some sprinkling of polite comments. It is unrealistic to hope that Insel himself might wake up, until and unless he is made to feel his pet interests are sufficiently threatened, in a way that cannot be brushed aside with trivializing rhetoric, as is his customary response.

I hold that Insel should be dealt with as a man who has HAD his chance (and then some!). The reasons must be clearly stated, of course, but even an ultimatum would not carry sufficient persuasive force to educate him. Thus, I, for one, will be calling for Dr. Thomas Insel to be replaced.

**REPLY**

**Sullivan**
July 6, 2011 at 08:32

dkmnow,

one of the best questions I heard at IMFAR was posed by Steve Silberman. He asked Dr. Insel how his perceptions of autism have changed over the years. Yes there has been change.

What I have seen in the past few years is one segment of the autism community work very hard to alienate the research community in general and Dr. Insel in specific. I feel this was a mistake on their part. I would not want to make the same mistake.

If you don’t want to work within the system, good luck to you. If you alienate the people I need, you are on your own.

**REPLY**

**dkmnow**
July 6, 2011 at 08:56

Well, I have most certainly been out of the loop for some time. If I’ve been unfair in my assessment of Insel, I’ll find out soon enough, won’t I?

Still, am I really the only one here who broke out in a cold sweat when he started talking about fractionating autistic children’s brains?

Or maybe that kind of reaction only becomes comprehensible after you’ve experienced what it’s like to hear YOURSELF being discussed as if you’re some sort of subhuman creature.

IS Insel learning, however gradually, a more humane vocabulary for discussing autistics? We’ll see…

**REPLY**

**RAJ**
July 6, 2011 at 13:41

The rapidly lowering of costs and the advancing technology in gene ‘hunting’ over the last few years now routinely includes genome testing of the parents as well as the affected child. Insel correctly notes that de novo copy number variations is associated with autism risk and that the single-gene disorders (Fragile X, Tuberous Sclerosis, owns Syndrome, Angelmans Syndrome, Prader-Willis Syndrome, Klinefelter syndrome, Rett Syndrome and more) are also associated with autism risk. Together, he states correctly that they may account for 16% of genetic risks for autism. What Insel did not say is that in the single gene disorders with the exception of Fragile X Syndrome the single-gene
mutations are de novo in the vast majority of cases. In other words, the genetic risks in copy number variations and in the single-gene disorders are not inherited at all but are the consequence of germ line reproductive errors (egg or sperm). Arthur Beaudet is one the world leading experts in the single gene mental retardation syndromes Prader-Willis and Angelman’s Syndrome and has stated: ‘In terms of potential lessons for other disorders, it should be noted that almost all of these genetic and epigenetic cases of PWS and AS are de novo as contrasted to being inherited events’.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427262/

This raises the important question of what are the causes of the de novo mutations in copy number variations and in the single gene mental retardation syndromes with high rates of co-occurring autism?

The de novo mutations in the single gene disorders and copy number variation risks for autism is a contradiction to often made claim that autism is the most heritable of the neurodevelopmental disorders wit a heritability of 90%.

These claims are based on several small European twin studies that compared simple concordance rates in twins and derived a ‘heritability’ estimate based on the different concordance rates in identical and fraternal twins.

A new twin study now casts doubts on the interpretations of the European twin studies. The California Autism Twin Study (CATS) is by far the largest population based twin study in autism ever attempted. Their conclusions raise important new questions with respect to the ‘heritability’ of autism. They found that genetic heritability is modest and that shared environmental factors are far greater than the European twin studies have suggested.

Full report can be at this link:

http://archpsyc.ama-assn.org/cgi/content/full/archgenpsychiatry.2011.76

REPLY

oakfarm
July 6, 2011 at 14:53

RAJ Do you have anything to say about the twin study published in 2006 by King’s College London, that also fund “high heritability” for “extreme autistic-like traits”. http://www.ncbi.nlm.nih.gov/pubmed/16721319.

It is obvious that you know more than me, I’m just a regular guy who has surfed a little bit on wikipedia, but the study in question involves 3,400 8-year-old twin pairs, so it cannot be dismissed for being too small, right?

REPLY

oakfarm
July 6, 2011 at 15:22

Btw, is it is worth mentioning that the California autism twin study was funded by grants from not only from the National Institute of Mental Health but also from Autism Speaks? At least what was that I read in this blog Fraternal twins with autism: Is risk in the womb?

REPLY

RAJ
July 6, 2011 at 15:49

Oakfarm:

The King’s College study was not an autism twin study but rather a study of ‘autistic traits’ in general population twins. There is no definitive boundary between disorder and normality. The twins were recruited from the The Early Developmental Study (TEDS) and were not twins diagnosed with autism but were general population twins recruited from the twin registry. The same group has also reported:

‘Around 10% of all children showed only social impairment, only communicative
difficulties or only rigid and repetitive interests and behavior, and these problems appeared to be at a level of severity comparable to that found in children with diagnosed ASD in our sample.

While 10% of all children may have what is ambiguously described as ‘autistic-like traits’ or the ‘broader autism phenotype’, but their study implies that around 10% of all children are on the autism spectrum, and that is, in my view, an absurdity. That doesn’t mean that genetic influences underlying normal personality traits may be associated with autism risk, but the risk is rather small and may involve the synergy between neuroanatomical alterations and the independent genetic influences underlying ‘autistic-like’ traits that follows a developmental trajectory towards an autism diagnosis rather than a developmental trajectory that leads to other non-autism developmental disorders with the same genetic or environmental risk factors.

Sir Michael Rutter has proposed a two-hit hypothesis which states that the genetic influences underlying ‘autistic-like’ traits are not the same as the genetic (Rhett Syndrome) and environmental (Rubella autism) risk factors associated with risk for a disruption of early brain development and that it is the neuroanatomical alterations that may distinguish affected from unaffected family members who may share similar traits but not similar outcomes.

In his book ‘Genes and Behavior: Nature and Nurture Interplay Explained’ he wrote:

“In other words, what is required for autism ‘proper’ to develop are the susceptibility genes and some other risk factor that could be either genetic or environmental in origin. The implication, if it is a two hit process is that the genes underlying the broader autism phenotype may not be exactly the same as those involved in the transition to the handicapping disorder.”


This 4 minute video by Sir Michael Rutter explains in part his two hit hypothesis:

The lead author of CATS twin study, Joachim Hallmayer, is a behavioral geneticist at Stanford University whose academic and research credentials in the field of autism is impeccable and he must have been surprised at the unexpected results of his twin study.

REPLY

PeripheralPerspective
July 6, 2011 at 16:53

Hi Raj, I’m wondering why you switched out “moderate” with “modest” heritability from the study? I assume that was a simple honest mistake but it does make a bit of a difference.

I think I am of the personal belief, maybe along with Sharon’s question, that there is substantial heritability. But I also feel there is a much more substantial impact from the environment. Genes are just the groundwork. But really, to me, environment lead to the inherited traits anyway, typically how we evolve in combination of random yes, but as we grew complex genetic mutations became mostly purposely and useful inherited functions, so it’s tough for me, in my mind,
to truly ever separate them. We constantly attempt to adapt and make the most of our exposures. The question in my mind... when does that lead to maladaptation? What are we screwing up that maybe served a purpose for millennia?

So what I try to do is make the distinction between traits and dysfunction and sometimes that’s a very narrow margin and many times they overlap to a great deal. But when is this overlap acceptable and to be expected and where/when is that balance thrown completely out of acceptable balance. Sometimes this is obvious and sometimes not. Depends on the individual and the system, but most diagnosable with ASD are most certainly walking that constant tight-rope if not constantly falling of that tight-rope with information over-load and “stressed out” functioning.

I think many people make the mistake of thinking heritability with merely the single gene issues that co-exist with Autism. Even though there are multiple gene causes what we’re actually still stuck saying is there may be multiple causes but we’re still separating them out into single isolated causes, just can’t get away from that hard-wired logic. And yes some people still want to continue to see genetics separate from environment and that is what I think this article by Insel is further clarifying that even these “single causes” aren’t true single causes, the environment still is a big, much bigger player than expected. We are very hard-wired to think in terms of single causes. And sometimes the opposite bounce over to thinking they’ll find lots of single multiple environmental causes, and that's problematic too.

Instead what I think of as genetic susceptibility of Autistic-like traits of information processing that's reflected in genetic make-up and neurobiological correlates, creating susceptibility and more malleability in their environments. More likely to be in dysfunctional states of info-overload, over and under functioning if in an environment not conducive to neural growth.

In regards to genome search, there is, if not a small call, to evolve to researching the teleome. And this speaks to me, as I like to know not just HOW they work but WHY they work and exist, not just each separate gene but what those combinations did in the first place and how they interact with each other, what was the reason behind them, what benefits did they have. What was the purpose and how might that purpose create susceptibility?

In search of the Teleome

I don’t like to have personal opinions about scientific leaders, they move at their own pace and must verify what they know and share, I think it’s a huge responsibility. So being yelled at by people to change may inspire him to look, but he still needs evidence and to follow with careful consideration all aspects of the issue at hand. I don’t know of the issues dkmon speaks of, but I’ve like Insel since the first article I read that he was trying to push from a categorical to dimensional view of mental disorders. so i have a bit of an isolated opinion. I liked that he knew that there were and are major changes at work to how we view mental illness. And that mental illness is found in roughly 25% of the population. This may seem insignificant but it’s huge in that it changes the way we must think of all of these disorders being separate, but connected and how profuse they have become. Sounds small but Insel promoting that says to me that we have to change the entire logical framework (single cause single outcome) and changing that thinking, re-thinking everything we thought we knew. This will take time because we have this other logic so hard-wired into our brains we have to prevent jumping to conclusions or letting assumptions and implanted stigmas/stereotypes from taking over. It’s a lot of programmed “if this – than that” hardwired thinking to overcome.

That’s how I see it anyway.

REPLY

RAJ
July 6, 2011 at 17:37

Oakfarm:
I ried to post a response but it never showed up. Forgive me if this a duplicate
The twin study you referenced was not an autism twin study. It was a study of twins recruited from The Early Developmental Study (TEDS) twin registry and involved general population twins. The authors used questionnaires that scored the level of what they describe as ‘autistic-like’ traits in general population twins. There is no definitive boundary between disorder and common normal characteristic human traits. The same authors reported that “Around 10% of all children showed only social impairment, only communicative difficulties or only rigid and repetitive interests and behavior, and these problems appeared to be at a level of severity comparable to that found in children with diagnosed ASD in our sample”. Their implication that 10% of all children may be on the Autism Spectrum, in my view, is an absurdity.

A far as the CATS twin study is concerned, you are right, this project has been funded by the NIMH and Autism Speaks and the project began in 2003. It is by far the most meticulous population based autism twin study ever conducted. That they found moderate genetic heritability and a substantial shared twin environmental component had to be a surprising and unexpected result for the lead investigator Joachim Hallmayer. Hallmayer is a behavioral geneticist whose academic and institutional credentials at Stanford University are impeccable and he also serves as an editorial board member of the science journal Psychiatric Genetics. His primary area is in autism research and he is a member of several consortium’s, including the Autism Genome Consortium, that are searching for autism ‘susceptibility’ genes.

The CATS twin study is a contradiction to the smaller European twin studies which are always referenced in the genetic studies and where the claim is that autism is the most heritable of the developmental disorders with a ‘heritability’ estimate of 90%. Heritability estimates in classical twin study design are simplistic, comparing the difference in concordance rates in identical twins and fraternal twins and calculating a heritability estimate. While it has been claimed that autism is the most heritable of the developmental disorders, its not true. Based on concordance rates in identical and fraternal twins and calculating a heritability estimate, Downs Syndrome has to be the most heritable of the developmental disorders. The concordance rate for Downs Syndrome in identical twins is 98% and the concordance rate for Downs Syndrome in fraternal twins is 2%, making Downs Syndrome the most heritable of the developmental disorders. The problem of course is that Downs Syndrome isn’t heritable at all. 99% of all Downs Syndrome cases are caused by a de novo germ line reproductive error (egg or sperm) and the mutation is not present in either parent and therefore Downs Syndrome is not heritable at all even though simplistic calculations of heritability estimates suggest that it is.

Does that mean that what has been labeled by the behavioral geneticists as ‘autistic-like traits’, ‘subthreshold autistic-like traits’ or the ‘broad autism phenotype’ is not related to autism risk? Not at all. Sir Michael Rutter has proposed what he calls a ‘two-hit’ hypotheses:

“In other words, what is required for autism ‘proper’ to develop are the susceptibility genes and some other risk factor that could be either genetic or environmental in origin. The implication, if it is a two hit process is that the genes underlying the broader autism phenotype may not be exactly the same as those involved in the transition to the handicapping disorder.” M. Rutter in Genes and Behavior: Nature-Nurture Interplay explained (page 136).

The ‘two-hit’ hypothesis also implies a synergy between two independent component parts, the common genetic influences that cluster within families with a history of autism but also extend very broadly throughout the general population and the genetic (Downs Syndrome) and environmental (Congenital Rubella Syndrome) risks involved in the disruption of early brain development and the transition to the handicapping disorder.

Here is a 4 minute video by Michael Rutter on the ‘two-hit’ hypothesis:
The CATS twin study in my view may represent a paradigm shift in understanding the complexity of autism which is a complex multifactorial disorder, and encourage research into the causes of de novo genetic mutations and environmental pathogens which may eventually lead to prevention measures.

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**Sullivan**  
July 6, 2011 at 21:44

RAJ,

You've been rightly enthusiastic about this study for some time. But, when you mention a paradigm shift, that happened last year. It's unfortunate for the Stanford/UCSF team, but they were scooped on this.


Both the Columbia group (discussed in the post above) and the Wisconsin group (http://www.ncbi.nlm.nih.gov/pubmed/20410716) which I mentioned somewhere here, but can't find right now, pointed to a lower heritability for autism.

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**PeripheralPerspective**  
July 6, 2011 at 23:01

Raj, I'm really confused by maybe your definition of heritable? Can you define your use of the term. (it appears you're using it as "purely genetic with no environmental influences" and that's a bit confusing to me, if you clarify maybe I'll understand better).

Here is wikipedia:

“Heritability measures the fraction of phenotype variability that can be attributed to genetic variation. This is not the same as saying that this fraction of an individual phenotype is caused by genetics. In addition, heritability can change without any genetic change occurring. For example, if both genes and environment have the potential to influence intelligence, but if a given sample of individuals shows very little genetic variation and a great deal of environmental variation, then the contribution of genetic variability to phenotype variability in that sample will be lower than if the sample showed greater genetic variability. Because of this it can be seen that heritability is specific to a particular population in a particular environment.”

And here is an article on the “3 laws of Behavioral Genetics”: http://teammccallum.wordpress.com/3-laws-of-behaviour-genetics/

““All traits are heritable” is a bit of an exaggeration, but not by much. Concrete behavioral traits that patently depend on content provided by the home or culture are, of course, not heritable at all; which language you speak, which religion you worship in, which political party you belong to. But behavioral traits that reflect the underlying talents and temperaments are heritable: how proficient with language you are, how religious, how liberal or conservative. General intelligence is heritable, and so are the five major ways in which personality can
vary … openness to experience, conscientiousness, extroversion-introversion, antagonism-agreeableness, and neuroticism. And traits that are surprisingly specific turn out to be heritable, too, such as dependence on nicotine or alcohol, number of hours of television watched, and likelihood of divorcing.’

Dr. Michael Krasny of San Francisco radio station KQED devoted an hour-long program to the recent ASD twin study this morning. The guests were Drs. Joachim Hallmayer (the first author on the paper), Neil Risch (the senior author of the study), and Daniel Coury (identified as the medical director of the Autism Treatment Network for Autism Speaks).

I heard a couple of points that interested me, which can be roughly paraphrased:

The broader definition of ASD used in the research was not as broad as that definition used in clinical practice, so concordance as determined in the study is likely lower than might be obtained using current clinical definitions.

The authors noted that the most interesting finding was the unexpectedly high concordance in dizygotic twin pairs, which they attribute to a shared uterine environment ‘looking back to the earliest beginnings of life.’ They clearly believe that the effects are due to prenatal influences, and they noted that even in early infancy twins encounter increasingly varying environments.

The authors thoroughly discounted any role for vaccines in the development of ASD: ‘for a long time there has been evidence from the scientific community that there is no link.’

Regarding possible environmental concerns: The effect of parental age is ‘really robust’ and indicates that de novo mutations are associated with father’s age; in autism paternal and maternal age are linked independently.

The response to the question of ‘where does this study suggest we go?’ was ‘More twin studies and especially studies of gene-environmental interaction; most important is to better understand environmental and genetic factors; the more we understand the genetics the better we can understand the environmental factors.’

I didn’t catch any discussion of a crucial topic related to this paper: Since multiple births increase the risk of ASD, how much of the risk for ASD revealed by twin studies is due to the ‘environmental’ factor of simply being a twin (e.g., placental blood supply issues, often early delivery)?

Hi Brian –

I didn’t catch any discussion of a crucial topic related to this paper: Since multiple births increase the risk of ASD, how much of the risk for ASD revealed by twin studies is due to the ‘environmental’ factor of simply being a twin (e.g., placental blood supply issues, often early delivery)?

Indeed. There have been a few papers that looked at this with varying findings. Personally, I sort of liked the presumed mechanism of a more stressful prenatal environment, but the data seemed inconclusive. Familiar territory.

Here are a few links I ran into when I was poking into this a while ago.

Relationships between multiple births and autism spectrum disorders, cerebral palsy, and intellectual disabilities: autism and developmental disabilities monitoring (ADDM) network-2002 surveillance year — found no increased risk of ‘twinning’

On the twin risk in autism, — again, a negative study

Here are a few that seemed to indicate that twinning was a risk factor.

Excess of twins among affected sibling pairs with autism: implications for the
I'm not sure what, if anything, can be made of this mishmash.
– pD

PeripheralPerspective
July 7, 2011 at 00:38

Brian: I didn’t catch any discussion of a crucial topic related to this paper: Since multiple births increase the risk of ASD, how much of the risk for ASD revealed by twin studies is due to the ‘environmental’ factor of simply being a twin (e.g., placental blood supply issues, often early delivery)?

That would certainly be interesting.

As for the rest, again, what I think of the perinatal environment I think is important. If we are looking at oxidative stress plus genetic susceptibilities, then even if we say the maternal/paternal age or diet or traumas play a role which then leads to the womb factors (conditioning and downregulation) to be more influential, it still won’t for me negate other “out there” during toddler and even adolescent of other environmental factors playing a role in the balancing of information processing. Which is why I think we see other late-age disorders, like schizophrenia, on the same spectrum. Does schizophrenia come from the womb environment? Maybe partially as suggested (in Vitamin D studies etc). But I think I feel that sometimes the genetic/womb agenda is a little too vaccine-eliminating in their goals. It’s fine if it’s eliminated, but if we do look at the OxStress/adaptation angle and multiple influences degrading the condition in which we respond and recover from stressors, we have a lot of avenues to look into. How the womb sets up our reactions to stress, may still leave vaccinations at that critical time a stressor that pushes past Ox capacity in some. If we do what we can to balance out those early life influences vaccines may become less of a stress or more a “good” stress. If they are involved at all.

There are genes that regulation endocrine function and neurotransmitter function that make certain populations, and traits, more susceptible and maleable to stressors.. I hope they’re considering these.

RAJ
July 7, 2011 at 01:36

Sullivan wrote:
RAJ,
You’ve been rightly enthusiastic about this study for some time.

Quite right, but I was also somewhat disappointed as well. Over a year ago I asked one of the co-investigators involved in the CATS study if they were going to record chorion data and was told that they would be recording chorion data where the records were available. Apparently they were unsuccessful in recruiting a large enough sample of MZ twin with unambiguous chorion data that might have offered further insight into prenatal influences.

Chorion data in autism twin studies have never been attempted. The reason chorion data may be important is that not all MZ twins develop in the same prenatal environment (single placenta), some MZ twins depending on the timing of the zygotic split develop in separate placentas and do not share the exact same prenatal environment.

The East Flanders Prospective Twin Survey is one of the oldest and largest twin registries and is unique in that from the beginning, it is the only twin registry that has systematically examined and recorded perinatal chorion data.


The East Flanders Twin Survey has published a 2:1 ratio by chorion type based on 2,000 MZ twin pairs entered into the registry as of 2004. 66% of MZ twins
were monochorionic (single placenta) and 34% of MZ twins were dichorionic (separate placenta). The reason why this may be important is explained by examining the results of three major twin studies. The 1995 MRC British twin study, the Ian twin study and the CATS twin study.

I have been corresponding with Michael Rutter whose group published the 1995 MRC British twin study and we are in agreement in that all three of these studies are in broad agreement with respect to concordance rates in autism twin studies. About 60% of MZ twins are concordant for narrowly defined or narrowly diagnosed autism. The British twin study has been criticized because they reported a concordance rate in DZ twins of zero. That’s not entirely the case. The British twin study did report that in discordant twin pairs both MZ and DZ, the ‘unaffected’ twin usually has a history of childhood communication disorder or social impairments persisting into adulthood.

When they included discordant twins where the unaffected twin had a developmental problem not meeting strict criteria for autism the concordance rate rose to 92%. The Ian twin study also reported a 60% concordance rate in narrowly diagnosed MZ twins (same PDD Dx) in both MM and FF twin pairs (genotype concordance and phenotype concordance). When they considered MZ twins who with broad concordance, any PDD Dx but not the same PDD Dx (genotype concordance and phenotype discordance) and included both sub types they report a concordance rate of 88%. The CATS study also produced similar results.

The broad agreement between these autism twin studies have reported a 2:1 ratio between narrowly defined or diagnosed MZ twins and broadly defined or diagnosed MZ twins which is consistent with the 2:1 ratio by chorion type (MC=66%, DC=34%).


Recording concordance rates by chorion type could offer important insight into the prenatal environment influences within MZ twin pregnancies.

There is substantial evidence that MZ/MC twins are more alike than MZ/DC twins in all sorts of ways. I’ll just list two:


I agree with Hlmmayer that more twin studies are needed but I would include the recording of unambiguous chorion data as well.

REPLY

PeripheralPerspective
July 7, 2011 at 01:48

An example I think of gene-nutrition-stress, so what I feel is that the same environmental impacts have the potential to impact sub-type segments of the population differently. (Again we have to change our logic here) and (If anyone knows my theory “verbal-thinkers” are on the sert-estrogen side of the spectrum, but there’s many mixes and variations of susceptibility). Just a perspective.

A mixed polyunsaturated fatty acid diet normalizes hippocampal neurogenesis and reduces anxiety in serotonin transporter knockout rats.
http://lib.bioinfo.pl/pmid:21606840

The aim of this study was to investigate the effects of a mixed dietary intervention on behavioral symptoms in serotonin transporter knockout (5-HTT) rats modeling the human 5-HTT length polymorphic region short-allele. Twenty female 5-HTT and 19 wild-type (5-HTT) rats were fed for 3 months on a mixed polyunsaturated fatty acid (PUFA) diet comprising n-3 PUFAs, B vitamins and phospholipids, or an isocaloric control diet, and a subgroup was subsequently tested in an array of anxiety-related behavioral tests. All brains were harvested and immunostained for doublecortin, a neurogenesis marker. In addition,
hippocampal volume was measured. 5-HTT rats on the control diet displayed increased anxiety-related behavioral responses, and impaired fear extinction. These effects were completely offset by the mixed PUFA diet, whereas this diet had no behavioral effect in 5-HTT rats. In parallel, dentate gyrus doublecortin immunoreactivity was increased in 5-HTT rats fed on the control diet, which was reversed by the mixed PUFA diet. Hippocampal volume was unaffected by the mixed PUFA diet in 5-HTT subjects, whereas it increased in 5-HTT rats. We conclude that a mixed n-3 PUFA diet ameliorates anxiety-related symptoms in a genotype-dependent manner, potentially by normalizing neurogenesis. We suggest that such a mixed diet may serve as an attractive adjuvant to treat anxiety in 5-HTT length polymorphic region short-allele carriers.

Association of verbal and figural creative achievement with polymorphism in the human serotonin transporter gene.
Volf NV, Kulikov AV, Bortsov CU, Popova NK.

doi: 10.1093/hmg/6.13.2233
http://hmg.oxfordjournals.org/content/6/13/2233.full

RAJ
July 7, 2011 at 14:01

Raj, I’m really confused by maybe your definition of heritable? Can you define your use of the term. (it appears you’re using it as “purely genetic with no environmental influences” and that’s a bit confusing to me, if you clarify maybe I’ll understand better).

Here is wikipedia:
“Heritability measures the fraction of phenotype variability that can be attributed to genetic variation
My definition of ‘heritable’ is transgenerational inheritance. As far as autism is concerned, most cases in the single-gene disorders and copy number variations are caused by a reproductive error (egg or sperm) and are not the consequence of transgenerational inheritance.
Classical twin study design calculates a heritability estimate based on the different concordance rates between MZ and DZ twin pairs. There is a profound logical flaw in classical twin study design in that it assumes that genetic = inheritance and that will always have a bias in vastly overstating genetic heritability and cannot apply to autism which most researchers agree that it is a complex multifactorial disorder.
Transgenerational inheritance does occur in a minority of cases in many of the named single gene disorders, for example, tuberous sclerosis, Williams Syndrome 16P mutation syndrome and transgenerational inheritance also can occur in copy number variations. The problem for the genetic determinists is that where transgenerational inheritance does occur, invariably the parent is unaffected, at least as far as autism is concerned.

PeripheralPerspective
July 7, 2011 at 14:19

So if I’m following you. And there are aspects that I would agree. If what you are saying is that many people have been mislead to think that because it is genetic it must have just been inherited. And this does occur, sort of, in single gene disorders. Although, even in those disorders there are manners in which the environment plays a sometimes very large part. So you are saying it is not genes alone.
What you are saying about the twin studies is you don’t feel they can give us accurate data about how inheritable Autism is because Autism is multifactorial disorder. But I’m not sure you have stated a case that genes aren’t a part of that
multifactorial pool just yet. And I think that is what you are trying for... am i wrong?

Now you say when it comes to Autism and the parent is unaffected, I think what many, and myself, question is– is the parent exhibiting “traits”? Some say yes, some say no. But those traits would be inherited. And in autism… are they amplified?

When you say they vastly over-estimate genes and that they can’t apply it to Autism. I don’t think I follow? I get that gene is not destiny that the environment plays a large role and there may be many people who do get stuck in those logical flaws, but I don’t understand how you come to the conclusion it needs to be thrown out all together?

It seems to me what you’re saying, is because it’s flawed by the single cause logic (which I believe it absolutely is) it therefore can’t be applied at all? And I’m not sure I would agree with you. I think it’s a parallel shift, not a 180 degree shift.

REPLY

PeripheralPerspective
July 7, 2011 at 14:31

Sorry-off topic a bit, I looked up “transgenerational epigenetics” and found this in wikipedia. I think it’s fascinating how the estrog/test and then the diets of the generation before can create changes in programming responses to the environment. From the MecP2 conversation I seemed to notice research suggesting that even though it is present mostly in females, males seem to not make it past 1 years old. And after 9/11, in the womb, it seems there were more male than female miscarriages… something about test/estr that may impact how one handles stress. Multifactorially.

Transgenerational epigenetic observations
http://en.wikipedia.org/wiki/Epigenetics#Transgenerational_epigenetic_observations

Marcus Pembrey and colleagues also observed in the Överkalix study that the paternal (but not maternal) grandsons [46] of Swedish men who were exposed during preadolescence to famine in the 19th century were less likely to die of cardiovascular disease; if food was plentiful then diabetes mortality in the grandchildren increased, suggesting that this was a transgenerational epigenetic inheritance.[47] The opposite effect was observed for females—the paternal (but not maternal) granddaughters of women who experienced famine while in the womb (and therefore while their eggs were being formed) lived shorter lives on average.[48]

46.^ A paternal grandson is the son of a grandparent’s son; a maternal grandson is the son of a grandparent’s daughter.
47.^ Pembrey ME, Bygren LO, Kaati G, et al.. Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet 2006; 14: 159-66. PMID 16391557. Robert Winston refers to this study in a lecture; see also discussion at Leeds University, here

9/11 miscarriages

Boys rett
http://jmg.bmj.com/content/40/1/e5.full

REPLY

RAJ
July 8, 2011 at 04:00

Anyone intersest in further debate and argument can follow the debate at:

REPLY
The left brain handles mathematical equations, but right brain helps out with comparisons and rough estimates. General personality traits, individual preferences, or learning style don’t translate into the notion that you’re left-brained or right-brained. Still, it’s a fact that the two sides of your brain are different, and certain areas of your brain do have specialties. The exact areas of some functions can vary a bit from person to person. I am the left brain, I work really hard ‘til my inevitable death dfgdg brain You got a job you better do it right in the right way is with the left brains might. I like oreos and pussy yah! (yes, in that order) And I cried for at least an hour after watching Toy Story 3 (Woody!) Cause I am the right brain, I have feelings, I’m a little all over the place but I’m lustful and trustful and I’m looking for somebody to love Or put my penis in. Here comes a female, here comes a female Puff your chest.