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ICOSR 2011: Back to the Prenatal Environment

17 June 2011. What happens in the womb may hold clues to what causes schizophrenia, according to a symposium at the 2011 International Congress on Schizophrenia Research (ICOSR). Held on 4 April 2011 in Colorado Springs, Colorado, the session offered new data and insights into some aspects of the prenatal environment that have been fingered in schizophrenia —specifically, maternal anemia, vitamin D deficiency, birth weight, and maternal infection with herpes simplex virus. The speakers also looked beyond the environment to discuss how their findings might dovetail with other areas of schizophrenia research, such as neuroscience and genetics.

Despite all the thinking outside of the epidemiological box, a sense that environmental factors have received too little attention in schizophrenia research infused the room. Yet, epidemiology has yielded some of the biggest and most reliable effect sizes in schizophrenia research, said **John McGrath**, University of Queensland, Wacol, Australia. As the warm-up act for the talks to follow, he said that environmental factors might explain much of the unexplained apparent heritability of schizophrenia.

Ironing out schizophrenia

The first speaker, session chair **Mary Cannon**, Royal College of Surgeons in Ireland, Dublin, wants to bring the study of environmental influences in schizophrenia back into the limelight. She noted that studies have connected obstetric complications, such as malnutrition or infection in the mother, to an increased likelihood of schizophrenia in her offspring (see Clarke et al., 2006; Cannon et al., 2002; Brown, 2011). These complications may include maternal iron deficiency or anemia, a disease marked by too few red blood cells or too little iron-containing hemoglobin within those cells. To determine whether the offspring of mothers with anemia have a heightened risk for schizophrenia, Cannon and colleagues reanalyzed data from an earlier study of everyone born in Helsinki, Finland, from 1951 to 1960 (Cannon et al., 1999).

Using National Register data, the researchers identified subjects with schizophrenia and randomly chosen control subjects. They used birth records to link subjects to data on their mothers' hemoglobin levels during pregnancy, which enabled them to classify the mothers as having had moderate, severe, or no anemia. Regression analyses found a dose-response relationship between the mothers' anemia and schizophrenia in their progeny. Compared to subjects born of mothers who tested normal for hemoglobin, those whose mothers had moderate anemia had a 1.6-fold increase in risk; those born of severely anemic mothers had a threefold increase. Low ponderal index also seemed to up the risk, suggesting a benefit of baby fat.

Seeking more definitive answers, the researchers pooled their findings with those from six other studies that had results relevant to the issue of whether anemia increases the risk of schizophrenia. The subsequent meta-analysis produced remarkably consistent results that mirrored those from the Finnish study. As to what underlies the association, Cannon said that iron may play a role, but she noted that their study lacked any measure of iron levels. She explained that prenatal iron deficiency forever disrupts the building of the myelin sheath in rat studies.

Shining a light on vitamin D

The next speaker, **John McGrath**, presented an overview of findings that connect schizophrenia to vitamin D deficiency during early development, including those from his own recent work. As

SRF previously reported (see SRF related news story), he and his colleagues found an inverted U-shaped relationship between vitamin D levels at birth and the risk of developing schizophrenia. To explain the nonlinear relationship, McGrath suggested that some people may be vitamin D resistant. In any case, he and his colleagues are trying to replicate the finding in a larger Danish case-control study that will look also at single-nucleotide polymorphisms (SNPs).

According to McGrath, the brain has vitamin D receptors and "can pack its own lunch" in that neurons make their own vitamin D. Not only does the nutrient play a role in neurodevelopment, but McGrath said a lot of good evidence indicates that it protects neurons from harm. In light of these and other findings, McGrath said that epidemiology researchers should attach themselves "like Velcro" to neuroscience. He would like to see epidemiological studies crosslinked with clinical and brain studies, including those that use animal models. To address the problem that risk factors often travel in packs in obstetric epidemiological studies, he said that randomized controlled trials of interventions, such as vitamin D supplements, in at-risk groups might help tease them apart.

McGrath raised the possibility that vitamin D levels might explain a host of epidemiological phenomena in schizophrenia, such as the increased risk in subjects born in winter or spring, in dark-skinned migrants to certain nations, and in city dwellers. According to McGrath, low vitamin D might also magnify the adverse effects of exposure to stress.

A heavy genetic burden

The third speaker, **Jaana Suvisaari**, National Institute for Health and Welfare, Helsinki, Finland, presented findings from a study of the suspected link between birth weight and the later development of schizophrenia. Research supports a robust association between schizophrenia and low birth weight, but also implicates high birth weight, Suvisaari said. She and her colleagues thought that family characteristics associated with abnormal growth might be confounding the results. They reasoned that genes that predispose people to schizophrenia might also predispose them to adverse effects from environmental exposures early in development.

To test the hypothesis that low—and maybe high—birth weight interact with genetic risk to foster schizophrenia, Suvisaari and colleagues turned to a study started in 1998 in Finland. That study enrolled families thought to carry a high genetic risk for schizophrenia, either because they included at least two siblings with the disease or because they came from a genetically isolated, schizophrenia-prone region. Piggybacking on that study, the new one analyzed data on 1,051 subjects from 315 high-risk families. Based on information from birth records, the researchers divided birth weight into four categories, including the usual cutoff of less than 2,500 grams for the featherweight group.

In regression analyses, high but not low birth weight predicted increased risk for schizophrenia—not exactly what the researchers predicted. In any case, the results did not back a link between birth weight and psychotic disorders other than schizophrenia. As to why the findings contradict the weight of evidence supporting a link between low birth weight and schizophrenia, Suvisaari suggested that her study's efforts to control shared familial influences on birth weight might have made the difference.

Thinking that gestational diabetes might explain why the heaviest babies were most likely to develop schizophrenia, Suvisaari and colleagues decided to investigate; however, they had to settle for a proxy measure of gestational diabetes—namely, diabetes in the mother. They found that maternal diabetes upped the risk for schizophrenia, but did so independently of birth weight. It could not explain the extra risk in the biggest babies.

When G and E look alike

The last speaker of the session, **Preben Mortensen**, Aarhus University, Aarhus, Denmark, talked about the challenge of untangling genetic and environmental factors, which may interact or correlate with each other or reflect unknown risk factors. While researchers have used family history to index genetic liability for schizophrenia, Mortensen said that psychiatric family history

may also reflect environmental exposures and gene-environment interactions. In a new study, he and his colleagues found that variation in SNPs across the genome failed to explain the added risk of schizophrenia that comes with having a mentally ill parent. This supports Mortensen's view that family history controls poorly for genetic liability.

A recent study by Mortensen and colleagues underscores the need to tease apart confounding and interacting variables (Mortensen et al., 2010). It used data from the Danish National Registers and the Newborn Biobank, which enabled them to check for antibodies that would reveal maternal infection with herpes simplex virus type 2 (HSV2). Analyses showed that the offspring of mothers with high levels of these antibodies were at heightened risk for developing schizophrenia (relative risk = 1.56). Adjusting for family history, particularly fathers' mental illness, lessened the risk slightly. This hints that paternal psychiatric history played a confounding role, but whether that reflected the effects of genes or environment remains unclear.

Currently, Mortensen and colleagues are exploring the role of genetic variables in the excess schizophrenia risk that seems to come with having a mother infected with HSV2. Using a two-stage design, they first tested SNPs genomewide for associations with exposure to infection in healthy controls, and then followed up with case-control comparisons. Although they tied some SNPs to HSV2 antibody levels in controls, the SNPs did not account for the virus-schizophrenia connection. Now, the researchers are investigating whether interactions between genetic variants and inflammation might play a role.

Looking ahead, Mortensen said that each future study should include as wide a range of genetic and environmental variables as possible. He warned that confounding from gene-environment associations poses as much risk to genetic association studies as to their epidemiological cousins. According to Mortensen, "If we do not face the challenge of integrating epidemiology with genetics, we will likely miss central elements of schizophrenia etiology."—Victoria L. Wilcox.

Comments on News and Primary Papers

Comment by: Segundo Mesa
Submitted 24 June 2011 Posted 24 June 2011

There is increasing evidence that favors the prenatal beginning of schizophrenia (Gourion et al., 2004; Cannon and Murray, 1998; Wintour et al., 2006). This evidence points toward intrauterine environmental factors that act specifically during the second pregnancy trimester, producing direct damage of the brain of the fetus. The currently available technology doesn't allow us to observe what is happening at the cellular level, since the human brain is not available for direct analysis in that stage of life. Most of the techniques that have accumulated evidence of prenatal cerebral damage have been of low resolution and by means of indirect methods. It is necessary to have a technique with high resolution that allows for obtaining the necessary information on the brain of the fetus and of the environmental factors that surround him or her.

In 1977, we began direct research of the brain with schizophrenia with electron microscopic techniques, using the brains of deceased adult schizophrenic patients, animals experimentally inoculated with cerebrospinal fluid from schizophrenic patients, and fetuses of schizophrenic mothers. The obtained results guide toward a viral etiology of the illness, specifically by herpes simplex hominis type 1 virus (Mesa-Castillo, 2001; Mesa-Castillo, 2011). Later results of other authors using other techniques and research designs relate damage of the brain to the direct action of a virus or indirect immunologic damage (Fruntes and Limosin, 2008; Brown et al., 2004; Shi et al., 2005). The objective of our research was not only to study the brain of the fetus, but also the environment that surrounds him or her; thus, we studied both the brain of the fetus and the placenta during the second trimester of schizophrenic mothers

whose pregnancies were interrupted for medical indications.

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Comments on Related News

Related News: Research Roundup —The Tapestry of Environmental Influences in Psychosis

Comment by: John McGrath, SRF Advisor
Submitted 5 November 2010 Posted 5 November 2010

The large study from Nuevo and colleagues is very thought provoking. There was substantial between-site variation in response to various psychosis-screening items. Assuming that endorsement of these items is a mix of: 1) "true" psychotic-like experiences, 2) "true" responses that are understandable from the perspective of local cultures and beliefs, and 3) innocent misinterpretations of the questions, why is there such marked variation? For example, why do 46 percent of respondents from Nepal endorse at least one psychotic-like experience and a third report auditory hallucinations?

It seems self-evident that populations with strong religious and/or cultural beliefs related to psychotic-like experiences might endorse psychosis-screening items more readily (type 2 in the above list). But could it be feasible that these same populations might also "kindle" psychotic experiences in vulnerable people? This notion is pure speculation, but we should remain mindful that dopaminergic pathways related to psychosis are vulnerable to the process of endogenous sensitization (Laruelle, 2000).

What does it mean to be a member of a cultural group that is more "prone" to psychotic-like experiences? Tanya Luhrmann, an anthropologist based at Stanford University, has examined individuals attending evangelical churches who "hear" the voice of God during prayer

(Luhrmann et al., 2010). The vignettes suggest that some individuals reported more "hearing the voice of God" after improving their prayer skills. Practice makes perfect, but could it also kindle pathways related to schizophrenia?

Regardless of the underlying mechanisms, understanding variations in these symptoms is a fascinating topic worthy of more multidisciplinary research.

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Related News: Research Roundup —The Tapestry of Environmental Influences in Psychosis

Comment by: Tanya Luhrmann
Submitted 12 November 2010 Posted 12 November 2010

It seems to me that there may be two different patterns that show up in these large epidemiological studies: the psychotic continuum and phenomena associated with absorption. Absorption is basically a capacity for/interest in being caught up in your imagination. It is associated with hypnotizability and dissociation, but not identical to them (Tellegen and Atkinson, 1974).

In my own work on evangelical Christianity, I identify a pattern in which people report hallucination-like phenomena that are rare, brief, and not distressing (as opposed to the pattern associated with psychotic disorder, in which the hallucinations are often frequent, extended, and distressing). Those who report hearing God's voice audibly or seeing the wing of an angel are also more likely to score highly on the Tellegen absorption scale (Luhrmann et al., 2010). This relationship between unusual experiences and absorption also shows up in a significant relationship between absorption and the Posey-Loesch hearing voices scale when these scales are given to undergraduates. Among undergraduates, the rates for hallucination-like phenomena are also consistently far higher than the Nuevo paper reports, perhaps because neither the absorption scale nor the Posey-Loesch scale seems to probe for pathology (Luhrmann, forthcoming).

I am not the only one to have found a significant association between unusual sensory experiences and absorption. Aleman and Laroi (2008) report that a handful of other researchers have also found significant correlations between hallucination scales and the absorption scale. As a result of this work, I think that there may be different pathways to hallucination-like phenomena—some pathological, others less so.

Yet, I also wonder whether there is indeed something like "priming" psychosis, as John suggested. This would arise if there were some looseness in the relationship between psychosis and dissociation, which there appears to be. At least that's the way I interpret some of the phenomena that Romme and Escher (1993) report. If there is some kind of loose relationship, it would suggest that someone could have an absorption/dissociation response to trauma that would look psychotic; it might also suggest that an intensely absorbing negative imaginative experience (being pursued by demons, e.g.) might contribute to a vulnerable person exhibiting more psychotic-like symptoms.

How would we begin to pull this apart?

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View all comments by Tanya Luhrmann

Related News: Research Roundup —The Tapestry of Environmental Influences in Psychosis

Comment by: Mary Cannon
Submitted 15 November 2010 Posted 15 November 2010

This beautifully written piece serves to excite interest in the fascinating epidemiology of schizophrenia. In our search for the "missing heritability" of schizophrenia, we don't have to look too far for clues. There are many contained in this piece. It just requires some Sherlock Holmes-type deductive reasoning to put them all together now!

The realization that psychotic symptoms (or psychotic-like experiences) can be used as a proxy for schizophrenia risk has opened up new vistas for exploration (Kelleher and Cannon, 2010). For instance, the paper by Nuevo and colleagues will provide a fertile ground for testing ecological hypotheses on the etiology of schizophrenia—such as examining cross-national vitamin D levels (McGrath et al.) or fish oil consumption. Geneticists have yet to appreciate the potential value of studying such symptoms. Ian Kelleher, Jack Jenner, and I have argued in a recent editorial that the non-clinical psychosis phenotype provides us with a population in which to test hypotheses about the evolutionary benefit of psychosis genes (Kelleher et al., 2010; see also Nesse, 2004). This non-clinical psychosis phenotype gives rise to the possibility of moving beyond just-so stories into the realm of testable hypotheses.

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Related News: Research Roundup —The Tapestry of Environmental Influences in Psychosis

Comment by: Jean-Paul Selten
Submitted 17 November 2010 Posted 17 November 2010

☑ I recommend the Primary Papers

With interest, I read Victoria Wilcox's summary of some thought-provoking papers published this year. It seems that schizophrenia, like cancer, has many different causes. I would like to point out that three of the studies (Zammit et al., 2010; Wicks et al., 2010; Schofield et al., 2010) support the idea that social defeat and/or social exclusion increase risk. The paper by Zammit et al. showed this in an elegant way: being different from the mainstream, no matter on what account, increased the subject's risk. The next step is to show that social exclusion has an impact on an individual's dopamine function. My group is examining this in young adults with an acquired hearing impairment, using SPECT.

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View all comments by Jean-Paul Selten

Related News: Research Roundup —The Tapestry of Environmental Influences in Psychosis

Comment by: Chris Carter
Submitted 26 November 2010 Posted 26 November 2010
☑ I recommend the Primary Papers

I have been collecting diverse references for environmental risk factors in schizophrenia at Schizophrenia Risk Factors. These include many prenatal influences due to maternal infection, usually with some sort of virus, or immune activation with fever. Several animal studies have shown that infection or immune activation in mice can produce schizophrenia-like symptoms in the offspring. Toxoplasmosis has often been cited as a risk factor in adulthood.

Many of the genes implicated in schizophrenia are also involved in the life cycles of these pathogens, and interactions between genes and risk factors can together contribute to endophenotypes; for example, MICB and Herpes simplex infection have single and combined effects on grey matter volume in the prefrontal cortex.

Over 600 genes have been associated with schizophrenia. When these were pumped through a Kegg pathway analysis, the usual suspects (neuregulin, dopamine, and glutamate pathways, among others) figure highly in the list of pathways. Immune-related pathways are also highly represented, as are many pathogen entry pathways, including that for toxoplasmosis, which heads the list. Some of the more exotic pathways, for example, Chaga's disease, should be considered as generic, as well as specific.

These Kegg-generated data suggest that there are strong relationships between genes and risk factors. Perhaps stratification of GWAS data in relation to infection could take this into account.

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