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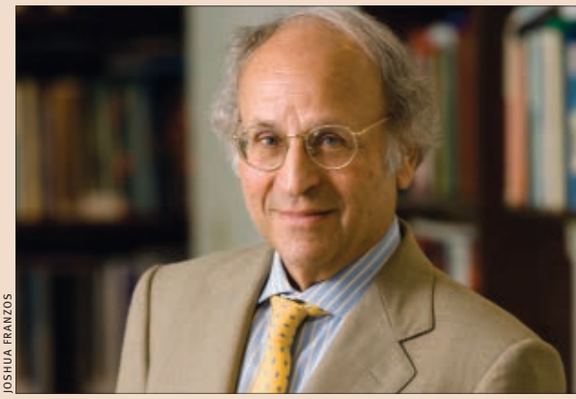
Pitt Med is published by the Office of the Dean and Senior Vice Chancellor for the Health Sciences in cooperation with the Office of University Communications. It is produced quarterly for alumni, students, staff, faculty, and friends of the School of Medicine. # 6735


JOSHUA FRANZOS

I watch the ripples change their size
But never leave the stream
Of warm impermanence and
So the days float through my eyes
But the days still seem the same
—David Bowie, "Changes"

A decade ago, a group of geneticists from around the world embarked on the largest-ever search for the genetic basis of schizophrenia. They found associations in more than a hundred disparate chromosomal areas. Surprisingly, the association that was far and away the most damning to these patients was a locus on chromosome 6 that's home to most of the known genes that govern, of all things, the immune system.

This winter, Aswin Sekar, a bright graduate student in the lab of Harvard geneticist Steven McCarroll, spent a weekend holed away on his couch in Boston, combing through data; he compared patients with schizophrenia against controls in a sample of 64,000 people from 22 countries and found a correlation between risk for schizophrenia and a variant of a gene called *C4*, which lives on chromosome 6. A protein that it encodes was known to mark cellular debris for disposal by the immune system and then discard it. This same protein, it turns out, has evolved in us to serve in another integral cleanup job—in the brain.

Adults have 40 percent fewer brain connections than newborns do. From infancy through adolescence, an elaborate pruning of synaptic connections takes place. The connections that prove most useful stay with us—a classic case of use it or lose it. A mouse model showed that a protein encoded by *C4* is what marks the synapses for pruning. The Sekar data suggest that people with schizophrenia are more likely to have *C4* expressed more often, and that probably results in runaway pruning. Although not yet proven, it has been suggested that the regions of the brain that are excessively pruned may correspond to regions thought to be involved in schizophrenia.

The finding has a certain logic, as families with a history of schizophrenia are often plagued by autoimmune diseases like rheumatoid arthritis, celiac disease, and type 1 diabetes. They also have fewer synaptic connections. Our own David Volk has shown that people with schizophrenia also show evidence of inflammatory responses in the brain.

Skin heals, the liver regenerates. Every part of us responds to injury in one way or another. But the brain and the immune system share a unique commonality: Both respond to new experiences and threats not just by patching themselves back together, but by transforming themselves at the most basic molecular levels. Notably, in addition to *C4*, genes (called *RAG*s) that promote the DNA recombination that underlies new antibody formation are also expressed in the brain and may be engaged in learning and memory.

It has been said that the ability to adapt well is a mark of intelligence; that ability could also be critical to our health.

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