Cellular disharmony

More than 300 genetic and functional alterations are now associated with schizophrenia

Ricardo Zorzetto

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In 1911, Swiss psychiatrist Eugen Bleuler shook the thinking of his day when he proposed the term "schizophrenia" to designate mental illnesses characterized by acute difficulties in structuring thought and establishing emotional ties. For Bleuler, emotional fragility lay at the origin of schizophrenia, until then seen as a problem caused by biology alone. Since these ideas were put forward, the explanation for how and why schizophrenia appears has gone through other changes. After swinging between extremes, opinions today – one hundred years later – seem to have found a middle ground that reconciles the psychological and biological views. It is believed that this illness, present in 1% of the population, is the result of the improper development – and thus improper functioning – of brain cells, aggravated or ameliorated by an individual's emotional characteristics or by social and environmental factors. There are now indications that the processing of blood sugar is altered in schizophrenia, which may be why diabetes is more common among schizophrenics than the rest of the population.

Brazilian researchers working both at home and abroad are taking part in this conceptual revision by analyzing gene activity and protein production in different areas of the brain and other parts of the body. Their identification of alterations in brain cell structure and function has contributed to a more comprehensive understanding of the origin of schizophrenia. In conjunction with work by foreign groups, these findings make it ever more apparent that, as with other mental illnesses, a number of biological factors influence susceptibility to schizophrenia and development of this disease, which leaves people feeling a deep emotional void and provokes delirium and hallucinations. And as research advances, more elements emerge.

Psychiatrist Wagner Farid Gattaz, of the University of São Paulo (USP), and his group have detected some 300 genetic changes that may jeopardize brain performance and characterize schizophrenia; 25% of these genes are tied to the production of energy and 20%, to cell growth. "These data make our understanding of schizophrenia more realistic," states Gattaz.

Perhaps the identification of so many biological factors should have been expected. The severity of schizophrenia varies, with clinical signs ranging from disorganized thinking, the conviction that the schizophrenic is being persecuted, and visual and auditory hallucinations to complete paralysis (catatonia). Many things can go wrong from the time the cells that will make up the brain start forming in the embryo to the moment they become specialized in, for example, conveying

Mental fragmentation, one of the signs of schizophrenia

and storing information, as neurons do. Genetic alterations inherited from parents or occurring by chance – in combination with social factors, like migration, or environmental factors, such as violence and abuse suffered during childhood – can interfere with the production of the proteins that are essential to the proper functioning of neurons and other cells that form the brain and other central nervous system organs.

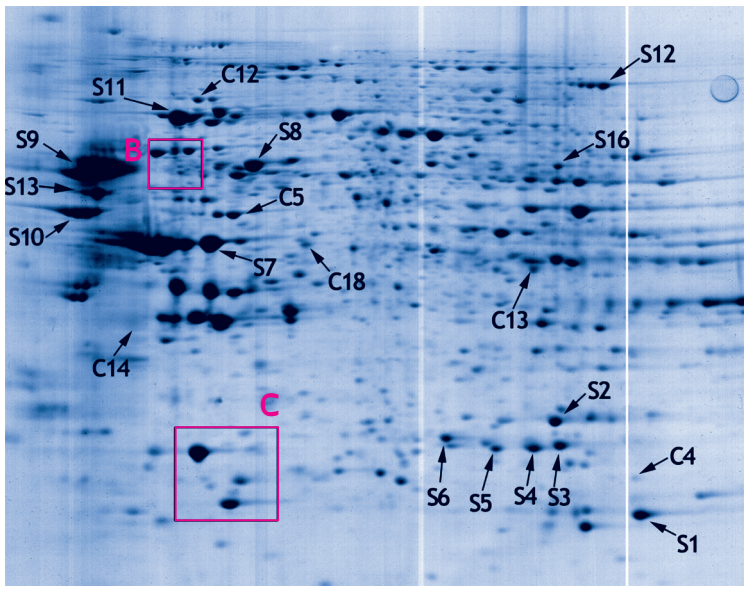
One difference between the brain cells of healthy people and those of schizophrenics is the consistency of the outer neuronal membrane, made up of a double layer of lipids. While working at Gattaz's laboratory, German researcher Gunter Eckert performed postmortem analysis of the malleability of neural membranes in schizophrenics and non-schizophrenics. The surface of cells in the prefrontal cortex, the area that coordinates rational thought and whose functioning is altered in schizophrenia, was more fluid than normal. "Increased membrane fluidity may alter cell function," explains Evelin Schaeffer, psychopharmacologist on Gattaz's team.

This finding helps to explain some anatomical and physiological changes recently observed in imaging tests on the brains of schizophrenics. And it seems to derive from an effect observed nearly 30 years ago by Gattaz when he was doing his doctorate at Heidelberg University in Germany. At that time he ascertained that the phospholipase A2 enzyme, responsible for recycling membrane lipids, is more active than normal in the neurons of schizophrenics. Phospholipase hyperactivity can alter membrane composition and help to make it more flexible, thereby allowing it to hold a higher concentration of D2 receptors, a protein that draws the chemical messenger dopamine from the extracellular medium.

This result favors the oldest and most widespread hypothesis for explaining the clinical signs of schizophrenia, according to which apathy and dulled emotions or psychotic breaks

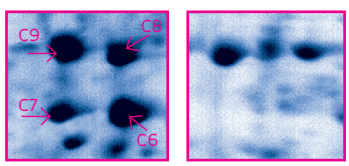
The footprints of schizophrenia

As células do cérebro, quando alteradas, produzem
When altered, brain cells produce greater or fewer numbers of proteins than normal



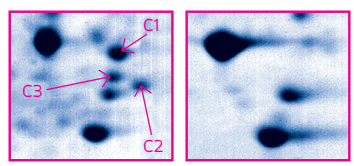
Each dot in the image represents a clump of equal proteins (separated in a gel according to mass and electrical charge) from a region of a schizophrenic brain.
Non-schizophrenics make more of the proteins identified by the letter C (control), while schizophrenics produce more S (schizophrenia).

B



Above, signs of intense expression of the proteins alpha tubulin 1 (C6 and C7) and beta tubulin 5 (C8 and C9), less abundant in schizophrenics (right).

C



Above, three proteins from the control group (C1, breast cancer metastasis suppressor; C2, tropomyosin 3; and C3, heterogeneous ribonucleoproteins), produced more intensely than in schizophrenics (right).

are the result of alterations in dopamine levels in the space between cells, which disrupt communication between neurons. Excess intercellular dopamine, which schizophrenia drugs try to reverse, is thought to decrease the activity of brain regions like the prefrontal cortex, located at the very front of the brain, just above the eyes, responsible for complex thought, verbal expression and decision making.

There is growing evidence that it is not just information transfer from cell to cell that is jeopardized in schizophrenia. Cell function is apparently compromised too, according to the proteomic studies of biologist Daniel Martins-de-Souza, currently at the Max Planck Institute of Psychiatry in Germany. Martins-de-Souza compared the brain function of schizophrenics and non-schizophrenics and ascertained that some brain regions associated with the disease apparently do not correctly process blood sugar, the brain's prime energy source. "Proteomics allows us not only to see what is different in protein production, but also how [the proteins] act together to affect related biochemical pathways," he says.

Martins-de-Souza has described potential alterations in the metabolism of blood sugar in prefrontal cortex cells, in the thalamus (the brain region where sensory information is incorporated into consciousness) and in Wernicke's area, linked to the comprehension of written language. He has almost always detected altered levels – higher or lower than normal – of the enzymes involved in the first stage of converting glucose into energy. "All metabolism in these regions may be slower," suspects Martins-de-Souza, who initiated proteomic studies as part of his doctorate at Gattaz's laboratory in 2004, under the advisorship of biologist Emmanuel Dias-Neto.

What Martins-de-Souza has so far seen in brain cells may be a characteristic of schizophrenia with broader repercussions in the body, possibly lying at the origin of a phenomenon that intrigued neurologist Frans Hieronymus Kooy a little over 90 years ago. At the hospital where he worked in the Netherlands, Kooy administered blood and urine tests to ten patients with schizophrenia, then more commonly called dementia praecox. He noticed that these people presented high blood sugar levels, or hyperglycemia, a typical sign of diabetes. In an article published in the journal *Brain* in 1919, Kooy stated that he was inclined to believe that emotions were responsible for increased blood sugar. But this begged the question: was it a cause or a consequence of the mental disorder?

Kooy's idea is now being reinterpreted in light of research into the connections between diabetes and schizophrenia found in a growing number of

IMAGE DANIEL MARTINS-DE-SOUZA / INSTITUTO MAX PLANCK. SOURCE: MARTINS-DE-SOUZA, D. *ET AL.* 2009

people. More common among those presenting this psychiatric disorder than among the rest of the population, diabetes does not appear to be the cause. Nor does it simply seem to be a side effect of some drugs that boost weight gain, since studies conducted over the past decade on people prior to treatment have also shown alterations in glucose processing. Taken together, these data show insulin resistance and diabetes as one of the manifestations of schizophrenia.

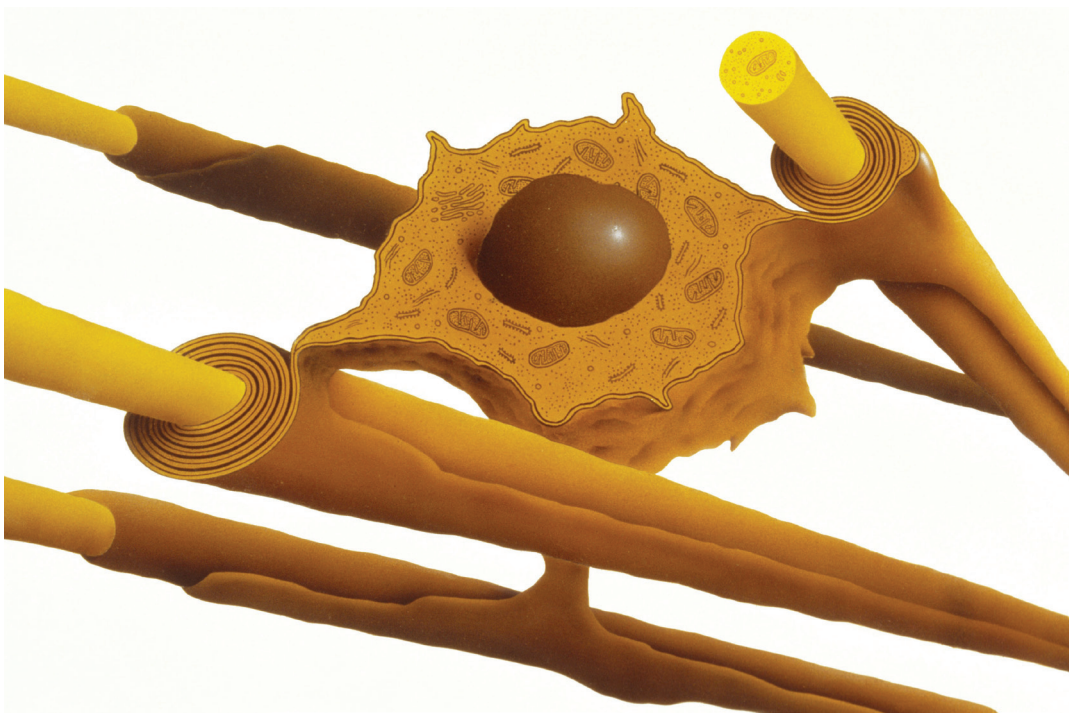
After observing changes in metabolism in different regions of the brain, Martins-de-Souza is now relying on protein analysis to investigate how glucose is processed in different types of brain cells. The suspicion is that neurons are not the only problem cells in schizophrenia. Apparently astrocytes and oligodendrocytes, two of the three types of glial cells, do not function well either. Martins-de-Souza is conducting tests with cells in culture, with the addition of the compound MK-801, which in laboratory animals triggers signs similar to those of schizophrenia.

Preliminary findings have indicated altered protein expression in astrocytes, which are cells that feed neurons and also act as defense cells, and in oligodendrocytes, which wrap around the main projection of the neuron and insulate it electrically. At a congress in Italy in April, he discovered that an old hypothesis was again gaining strength, to wit, that some degree of degeneration occurs in schizophrenia, an idea that had been discarded because imaging does not identify any anatomical changes in the brain.

"There may be some loss, and not necessarily of neurons," observes Martins-de-Souza. At the congress, Russian researcher Natalya Uranova reported on a decrease in the number of oligodendrocytes in some regions of the brains of schizophrenics. Martins-de-Souza has noted alterations in the level of proteins that are the classic markers of multiple sclerosis – a neurodegenerative disease associated with the loss of the electrical insulation promoted by oligodendrocytes – in the thalamus and the liquor. "If more evidence emerges that these cells do not function well in schizophrenia, it may become characterized as a disease of the glial cells, and not of the neurons," he says.

Nerve cell metabolism may be slower in people with schizophrenia

These findings may be relevant to an understanding of schizophrenia but, as Gattaz points out, it will not be easy to show whether they are the cause or consequence of this complex and devastating disease. ■



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An oligodendrocyte, whose membrane expands to wrap and protect the projections of neurons

PROJECTS

1. Metabolism of phospholipids in schizophrenia and Alzheimer's disease – proc. no. 1997/11083-0 (1998-2002)
2. Metabolism of phospholipids in neuropsychiatric diseases – proc. no. 2002/13633-7 (2003-2007)

GRANT MECHANISM
1. and 2. Thematic project

COORDINATOR
1. and 2. Wagner Farid Gattaz – Institute of Psychiatry, School of Medicine, USP (IPq/FMUSP)

INVESTMENTS
1. R$1,655,007.34
2. R$1,803,528.52

SCIENTIFIC ARTICLES

1. MARTINS-DE-SOUZA, D. *et al.* Proteome analysis of schizophrenia patients Wernicke's area reveals an energy metabolism dysregulation. **BMC Psychiatry.** v. 9, n. 17, 2009.
2. MARTINS-DE-SOUZA, D. *et al.* The role of energy metabolism dysfunction and oxidative stress in schizophrenia revealed by proteomics. **Antiox Redox Signal**. v. 15, n. 7, p. 2067-79, 2011.
3. ECKERT, G. P. *et al.* Increased Brain Membrane Fluidity in Schizophrenia. **Pharmacopsychiatry**. v. 44, n. 4, p. 161-62, 2001.

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