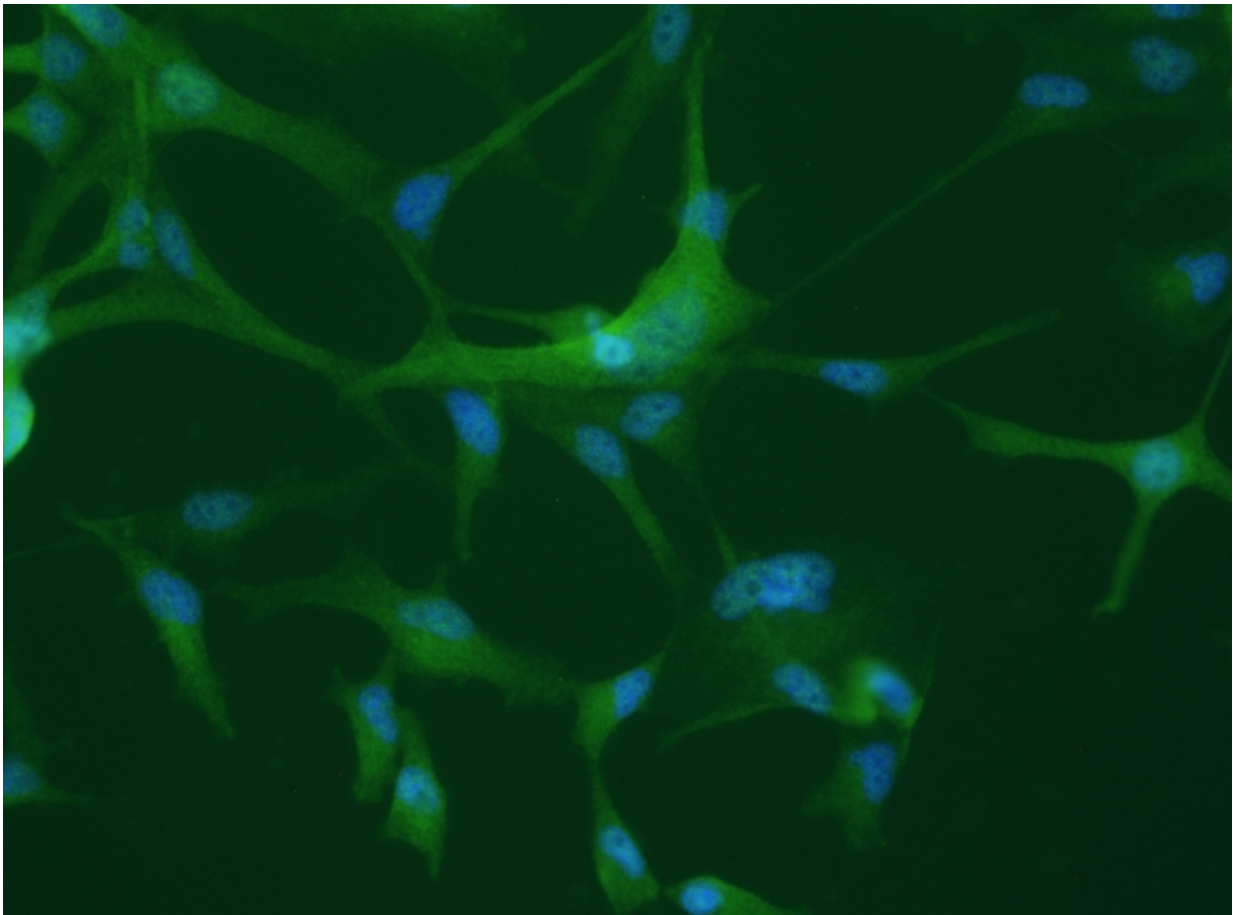


Study associates schizophrenia with defective processing of messenger RNA in cells

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Confocal microscope image of cultured human oligodendrocytes. The differential expression of hnRNPs may lead to dysfunction of oligodendrocytes, glial cells that produce myelin and are important for neuronal activity. Credit: Daniel Martins-de-Souza, University of Campinas

Schizophrenia affects approximately 1 percent of the world's population and is the main cause of psychiatric incapacitation. Despite its high prevalence and the severity of its symptoms, little is known about the biochemical mechanisms involved in its development or progression.

A study published in *Molecular Neuropsychiatry* suggests that many of the brain alterations found in patients with schizophrenia may be rooted in the dysfunctional participation of the so-called spliceosome, a [protein](#) complex directly involved in the process of protein synthesis.

"Our study is the first to link the spliceosome with the disease," says Daniel Martins-de-Souza, a professor in the Biology Institute of the University of Campinas (IB-UNICAMP), São Paulo State, and principal investigator for the project, which receive support from the São Paulo Research Foundation (FAPESP)

At the cell level, proteins are synthesized through a process in which DNA information is transcribed by messenger RNA and then spliced by the spliceosome, whose role is to unite the codifying parts of the genetic code to the precursor molecule, therefore shaping the protein to its functional form.

According to Verônica Saia-Cereda, Unicamp doctoral student and first author of the article, malfunctioning of the messenger RNA processing machinery could mean that certain proteins are not translated correctly and that their expression is altered throughout the organism with unknown consequences.

On a post-mortem brain tissue comparative analysis between 12 [schizophrenia patients](#) and 8 healthy individuals, Martins-de-Souza group detected a high amount of proteins with modified expression at two brain regions that previous research has shown to be morphologically and functionally altered in patients with schizophrenia,

the anterior temporal lobe and the [corpus callosum](#).

"The anterior temporal lobe is involved in auditory and visual processing, so it's closely linked to symptoms such as psychosis and hallucinations. The corpus callosum is the brain region that contains the most glial cells [such as astrocytes, microglia, and oligodendrocytes]," Martins-de-Souza said.

Oligodendrocytes are crucial for synapses, as they produce a fatty substance called myelin. Propagation of electric impulses among neurons is impaired in the absence of an insulating myelin sheath.

With the aid of a mass spectrometer, the scientists could map all the proteins found in the nuclei of the cells in these two [brain regions](#) and isolating them for analysis, excluding proteins found in other organelles and in the cytoplasm. In the corpus callosum, they found 119 differentially expressed proteins, 24 of which were nuclear proteins. According to Saia-Cereda, most are involved in calcium-mediated cellular signaling, which is important both to the metabolism of mitochondria (organelles that produce energy for the cell) and to the removal of surplus amounts of the neurotransmitter dopamine from the synaptic vesicle (where information exchange between neurons occurs).

"Alterations in dopamine levels in the brain are associated with the most characteristic symptoms of schizophrenia, such as delirium and hallucinations," Saia-Cereda said.

In the anterior temporal lobe, they found 224 differentially expressed proteins; 76 were nuclear proteins. Eight of these nuclear proteins are involved in the functioning of the spliceosome—including those that are part of the heterogeneous nuclear ribonucleoprotein (hnRNP) family, produced by oligodendrocytes. In 2005, Martins-de-Souza's group found that the expression of hnRNP proteins was also altered in schizophrenia

patients.

"Subsequent studies performed by other groups on the basis of our findings showed in animal and cellular models that alterations in hnRNPs do indeed interfere in the neuron myelination process and may impair cerebral connectivity," said Martins-de-Souza. "Therefore, this may be the genesis of the myelination dysfunctions associated with schizophrenia."

In another study, postdoctoral student Mariana Fioramonte is working to identify the proteins that partner with hnRNPs to process messenger RNA. Martins-de-Souza, her supervisor for the project, explained that the aim is to determine whether the proteins that associate with hnRNPs for this function are different in patients with [schizophrenia](#) and people without mental disorders. "The next step will be to try to modulate the expression of these molecules in the laboratory and observe how the spliceosome functions when some of them are inhibited," he said. "The idea is to try to find the cause of this dysregulation of the spliceosome. Depending on the results, it's possible that some of these proteins can be tested as therapeutic targets."

More information: Verônica M. Saia-Cereda et al. The Nuclear Proteome of White and Gray Matter from Schizophrenia Postmortem Brains, *Molecular Neuropsychiatry* (2017). [DOI: 10.1159/000477299](https://doi.org/10.1159/000477299)

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