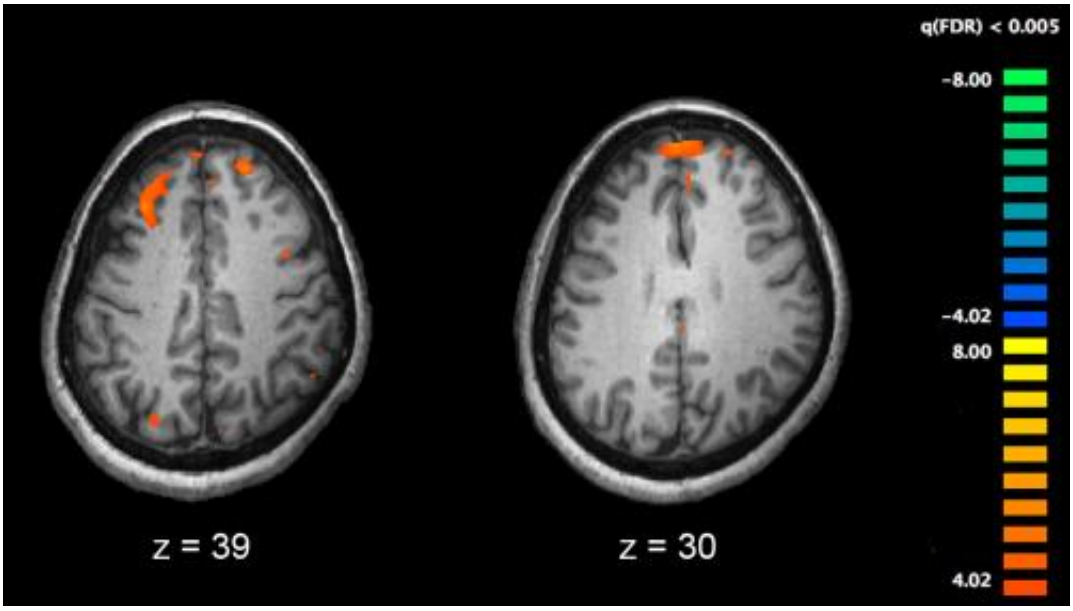
Looking for the origins of schizophrenia

February 23 2018



Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Schizophrenia may be related to neurodevelopmental changes, including brain's inability to generate an appropriate vascular system, according to new study resulted from a partnership between the D"Or Institute for Research and Education, the University of Chile and the Federal University of Rio de Janeiro (UFRJ). The results broaden the

understanding about the causes of this severe and disabling disorder, which affects about 1 percent of the world's population.

"A partnership between Brazilian and Chilean groups allowed us to create this singular study, combining expertise on neurodevelopment and formation of blood vessels to investigate schizophrenia," says neuroscientist Stevens Rehen, a researcher at D"Or Institute and UFRJ and one of the study's coordinators. Veronica Palma, from University of Chile, led the study with Rehen and highlights the combined approaches allowed the creation of an environment that mimics the one during embryonic brain development. The study was published on February 22nd in the journal *Translational Psychiatry*.

Characterized by episodes of hallucinations, confused thoughts and delusions, schizophrenia has no cure and the available treatment is only partially effective. Investigating causes of the disease can bring new therapeutic solutions and early diagnosis tools.

Previous studies on post-mortem brains and blood samples from patients with schizophrenia indicated that their brains show differences in terms of vascularization. It is also known that the interaction between blood vessels and neurons is essential for the correct development of the brain, as it allows the correct supply of oxygen and nutrients to neural cells and remove potentially harmful molecules.

The group investigated the ability of human neural cells to aid the formation of blood vessels during brain development. They used human induced pluripotent stem (iPS) cells created at D"Or Institute from the skin cells of three patients with schizophrenia and three people without the disorder. These cells were transformed into neural stem cells, which give rise to nerve cells. In addition, the scientists also used neurospheres - three-dimensional clusters of neural stem cells that begin to transform into neurons.

The cells were cultured in a suitable medium and the researchers checked the molecules they produced, in particular the pro-angiogenic ones, that is, molecules that nurture the production of new blood vessels. The experiment showed that neural cells originating from schizophrenic patients produced a smaller amount of these substances. Neurospheres from these patients also showed impairment of the ability to create new vessels, with low concentration of VEGFA, one of the most important angiogenesis regulatory molecules, and increased concentration of TIMP-1, an antiangiogenic protein.

"This is the first demonstration of the profile of angiogenic molecules expression using neural stem cells derived from patients with schizophrenia, which shows they have a less angiogenic profile when compared to controls," says Palma. "Indeed, this model of cell culture may reproduce what happens under physiological conditions."

To test the hypothesis that angiogenesis was compromised in the cells of patients with schizophrenia, a second experiment was performed. It consisted in exposing human umbilical cord epithelial cells to the substances produced by the nerve cells of the previous experiment. The same was done with chicken eggs, which served as in vivo model.

The umbilical cord epithelial cells have great capacity to form blood vessels, as well as the membrane just beneath the eggshell. Therefore, those were chosen to test whether the molecules produced by the neural stem cells of patients alter the angiogenic capacity of the cells. The results confirmed the results - substances produced by schizophrenia patients' nerve cells can hold back the angiogenic capacity of the epithelial cells.

"Advances on this subject bring new perspectives for the treatment and diagnosis of schizophrenia," Rehen says. Soon, he and his team plan to evaluate new biomarkers - that is, biological indicators, such as

molecules that suggest the presence of the disease - that can identify the disorder regardless of symptoms. "This is a completely new approach on neuro-vascular mechanisms in mental disorders," he concludes.

More information: Bárbara S. Casas et al, hiPSC-derived neural stem cells from patients with schizophrenia induce an impaired angiogenesis, *Translational Psychiatry* (2018). DOI: 10.1038/s41398-018-0095-9

Provided by D'Or Institute for Research and Education