A new cause of mental disease?

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Images from silent film showing a total of fifteen frames, 10 depicting institutionalized patients, and 5 with text only, defining schizophrenia and some of the symptoms associated with the disorder. Date 4 September 2013, 12:53:32. Credit: Courtesy of the National Library of Medicine. Images from the History of Medicine (IHM)

Astrocytes, the cells that make the background of the brain and support neurons, might be behind mental disorders such as depression and schizophrenia, according to new research by a Portuguese team from the

ICVS at the University of Minho. The study, in this month Molecular Psychiatry, shows how a simple reduction of astrocytes in the prefrontal cortex (which is linked to cognition) can kill its neurons and lead to the cognitive deficits that characterise several mental diseases. Although malfunctioning astrocytes have been found in psychiatric patients before, it was not clear if they were a cause or a consequence of the disease.

"This is the first time that cognitive deficits of a psychiatric illness can be mimicked by solely affecting astrocytes" - says the team leader, João Filipe Oliveira – "opening a whole new range of possibilities, both on the causes and potential treatments for these disorders." The research by Ana Raquel Lima, João Filipe Oliveira and colleagues is particularly significant when we look at the heavy burden in human suffering and financial cost of mental diseases. In the US and Europe about 1 in 4 adults are affected in every given year (this is about 26% of the populations), while depression alone uses almost 5% of the total world health budget. And a new player behind a disease offers also potential new and maybe more effective treatments.

So what are astrocytes? These star-shaped cells are part of the so called "glial population" - non-neuron cells that form the brain background and that for a long time were considered mere "housekeepers" of the real players - the neurons. In fact, traditionally, brain function is the result of electrical impulses passing between neurons, transmitting the information necessary for all those extraordinary abilities of this brains ours, from memory storage and motor control to personality quirks.

But astrocytes, even if believed to be "the help", have always been the subject of much curiosity since it was claimed by some (and denied by others) that one of the few uniqueness of Einstein's brain was larger and more complex astrocytes within its cerebral cortex than "normal" individuals. Equally curious, was the fact that these are the most

numerous cells in the mammalian brain, because keeping cells alive costs energy, which is always in short supply, and astrocytes were not even part of the of main action/brain activity. Or so it was thought.

In fact, the last decade has seen our ideas on astrocytes (and glial cells in general) change radically; we now known they perform highly complex jobs, including several previously associated with neurons. They are, for example, important for synapses (the specialised structures that do the contact between different neurons and through which the electrical signal is transmitted), where astrocytes detect and modulate activity, so effectively controlling the transmission of information in the brain.

Supporting their importance in the brain several studies have shown that patients with mental diseases - such as depression, bipolar disorder and schizophrenia – have lower than normal astrocyte density in the brain, especially in the prefrontal cortex. This can be improved, though, with anti-psychotic drugs.

This not only supports the importance of astrocytes in normal brain function, but also suggests they could play a role in mental disorders. And in fact, in one study killing astrocytes in the prefrontal cortex of rats seemed to cause a depression-like behaviour. But even if faulty astrocytes and mental diseases were often seen together, it was not possible to be sure, at least in psychiatric patients, that these cells were behind the disorder.

It is in this state of affairs that Lima and colleagues, in the work now published, decided to design a simple but very effective experiment to understand what was happening.

They start by injecting rats in the prefrontal cortex with a toxin that specifically kills astrocytes in a very localized way, and then tested the animals' cognitive abilities correlating these with the animals' (changed?)

brain structure. The prefrontal cortex was chosen because it controls cognitive abilities such as planning, reasoning and problem solving, which are affected not only in the most common mental diseases, but also on age-related neurodegenerative illnesses like Alzheimer's.

As expected toxin-injected animals developed the cognitive deficits typical of mental disorders where the prefrontal cortex is affected. But what was really interesting, were the brain changes found - not only the prefrontal cortex's astrocytes had died with the toxin (as expected) but, as time passed, also did its neurons. Control animals injected with a solution free of toxin had no changes, either in behaviour or brain structure.

So even if faulty astrocytes have been found before in mental patients, the Portuguese researchers' results give robust support to the idea that astrocyte breakdown can be a primordial cause for these disorders (and not a result of them), and also suggests how it occurs.

"Until now, we have blamed the poorer performance of the prefrontal cortex in these diseases on the surrounding astrocyte pathology" - says Oliveira – "but this study now supports the view that astrocytes, targeted in a pathological process, may actually lead to neurodegeneration in a specific brain region. Psychiatric disease can be mimicked by simply affecting astrocytes!"

This is a totally new perspective on how these diseases can develop, and consequently on how to treat them. For now, while we do not test other brain areas, Oliveira's results are specially relevant for mood disorders diseases - depression, schizophrenia and bipolarity - which we know to have both loss of cognitive functions, and abnormalities in the astrocytes of the prefrontal cortex.

But Oliveira and his team's findings are also important challenging the

still too present view of the brain as a simple network of neurons, clearly showing that we need to see it instead as an interdependent circuit of neural and glial cells (in particular astrocytes) both in health and disease.

The new work also makes us also wonder if the claims on the importance of the astrocytes in Einstein's brain were that crazy after all…

More information: "Astrocyte pathology in the prefrontal cortex impairs the cognitive function of rats." A Lima, V M Sardinha, A F Oliveira, M Reis, C Mota, M A Silva, F Marques, J J Cerqueira, L Pinto, N Sousa and J F Oliveira. *Molecular Psychiatry* 19, 834-841 (July 2014) | DOI: 10.1038/mp.2013.182

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