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Radical new approach to schizophrenia treatment begins trial in UK hospital

Evidence emerges it could be immune system disease

Trial with antibody drug normally used to treat MS

Hannah Devlin
Science correspondent

British scientists have begun testing a radically new approach to treating schizophrenia based on emerging evidence that it could be a disease of the immune system.

The first patient, a 33-year old man who developed schizophrenia after moving to London from Cameroon a decade ago, was treated at King's College Hospital in London on Thursday, marking the start of one of the most ambitious trials to date on the biology of the illness and how to treat it.

During the next two years, 30 patients will receive monthly infusions of an antibody drug currently used to treat multiple sclerosis (MS), which the team hopes will target the root causes of schizophrenia in a far more fundamental way than current therapies.

The trial builds on more than a decade's work by Oliver Howes, a professor of molecular psychiatry at the MRC London Institute of Medical Sciences and a consultant psychiatrist at the Maudsley Hospital in south London. Howes's team is one of several worldwide to have uncovered evidence that abnormalities in immune activity in the brain may lie at the heart of the illness – for some patients, at least.

"In the past, we've always thought of the mind and the body being separate, but it's just not like that," said Howes. "The mind and body interact constantly and the immune system is no different.

"It's about changing the way we think about mental illnesses."

Recent work by Howes and colleagues found that in the earliest stages of schizophrenia, people experience a surge in the number and activity of immune cells in the brain. As well as fighting infection, these cells, called microglia, have a "gardening" role, pruning unwanted connections between neurons. But in schizophrenia patients, the pruning appears to become more aggressive, leading to vital connections being lost.

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"We studied people in that [initial] phase of the illness and saw microglial changes," said Howes. "It shows that it's something [happening] very early on and seems to be driving the illness."

The most extensive pruning appears to occur in the frontal cortex, the brain's master control centre, and also the auditory regions, which could explain why patients often hear voices. The frontal cortex indirectly controls the brain's levels of dopamine – a surge in this brain chemical is thought to explain the delusions and paranoia experienced by those with schizophrenia.

Nearly all existing medications work by blocking dopamine, which can bring psychotic symptoms under control, but fail to protect the brain's basic architecture against damage.

"The current drugs are based on 1950s technology; they all still work in exactly the same way," said Howes. "They are only able to target the delusion side of things. It's like getting a sledgehammer and squashing it down."

There is a growing appreciation that other, perhaps less well-known symptoms associated with schizophrenia – memory and cognitive problems, and lack of motivation – can have an equally profound impact on patients, and existing drugs do little to help this side of the disease. "It's typically [these other] symptoms that are the most disabling," said Toby Pillinger, a psychiatrist and King's College London researcher involved in the study.

The latest trial, a collaboration between MRC scientists and King's College London, involves treating patients with a monoclonal antibody drug, called Natalizumab, that is already licensed for MS. In MS, the brain's immune cells go awry by attacking a different aspect of the brain's wiring. And although the diseases manifest in very different ways, apparent parallels in the underlying biology raise the possibility that the MS drug might help schizophrenia patients.

The drug works by targeting microglia and restricting their movement around the brain, which scientists hope could prevent the over-pruning of vital connections. In doing so, it could potentially address the disease's full spectrum of symptoms.

The first participant, Leopold Fotso, 33, received his first dose of treatment on Thursday. Fotso, who lives in south London after moving from Cameroon in 2007, was diagnosed with schizophrenia four years ago. He has been admitted to hospital several times with psychotic episodes. His illness also forced him to abandon his studies in accountancy – which he had moved to the UK to pursue – and his part-time kitchen job.

He currently has monthly injections of an antipsychotic drug, and his condition is now stable.

He feels "on the way" to being himself again and is looking to – slowly – start working again. "It's quite hard," he said.

At some time during their life about 1 in 100 people will suffer an episode of schizophrenia. In the UK, about 220,000 people are being treated for the condition by the NHS at any one time.

In total, in this first trial, 60 patients will be treated for three months, attending clinic once a month for infusions – half will receive the antibody, half a placebo. The patients' symptoms will be tracked and, along with 30 healthy volunteers, they will be given a series of brain scans, cognitive assessments and tests of immune activity. The hope is that, even if symptoms do not improve, the study should also answer fundamental questions about the role of the immune system in the illness.

Belinda Lennox, senior clinical lecturer in psychiatry at the University of Oxford, whose work also focusses on the role of the immune system in schizophrenia, said the concept behind the latest study was exciting – although at a very experimental stage. "There's a lot of emerging evidence that the immune system is going wrong [in schizophrenia]," she said. "This study should start to show whether getting rid of that inflammation actually helps.

"If reducing inflammation acts to improve psychosis it will open a new range of treatment possibilities, which is very exciting for the field, and desperately needed."

Leopold Fotso receiving his first treatment at King's College Hospital, London
Photograph: Teri Pengilley

Trial figures

60

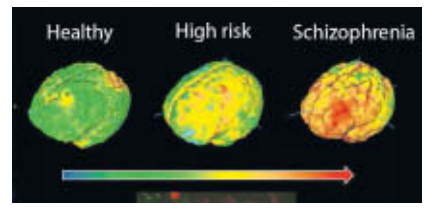
Number of schizophrenia patients on the two-year trial who will receive weekly doses of a drug first developed for MS

1

Number of people out of 100 in the population who will suffer an episode of schizophrenia at some time in their lives

220,000

Number of people in the UK who are being treated for schizophrenia by the NHS, often with drugs dating back to the 1950s



Analysis
Challenge to the notion of mind-body separation

Hannah Devlin

Descartes's notion of dualism – that the mind and body are separate entities – is wrong, but has proved surprisingly persistent, and until recently it has dominated attempts to understand mental illness. When the brain stopped working properly, a psychological origin was sought.

Undoubtedly, life's experiences and our personalities shape the way our brains function. But there is now a compelling body of evidence that brain disorders can also originate from things going awry in our basic biology.

Particularly intriguing is the discovery that the brain, once thought to be separated from the immune system by the blood-brain barrier, is powerfully influenced by immune activity.

The latest trial, focused on schizophrenia, is backed by converging evidence from several fields that immune cells in the brain, called microglia, play at least some role in this disease.

Prof Oliver Howes, the psychiatrist leading the work, discovered that these cells appear to go into overdrive in the early stages of schizophrenia. Genetic studies have linked changes in immune system genes to increased risk of schizophrenia, and anecdotal evidence also triangulates on to the immune system. For example a recent case report showed a patient developed schizophrenia after receiving a bone marrow transplant from a sibling with the illness.

"It's all challenging the idea that the brain is this separate privileged organ," said Howes.

Schizophrenia is not a special case. Scientists are showing that immune activity may play a role in a broad spectrum of mental disorders, ranging from depression to dementia.

People with diabetes, an autoimmune disease, are 65% more likely to develop dementia, according to a 2015 study. Other research has found that Alzheimer's patients who suffered regular infections, such as coughs and colds, had a fourfold greater decline in memory tests during a six-month period compared with patients with the lowest infection levels. And there is tentative evidence that some patients with treatment-resistant depression may benefit from antibody treatments.

Perhaps most striking has been the discovery of an entire network of vessels beneath the skull, linking the brain and the immune system, that had surprisingly been overlooked until very recently.

"It has been a fundamental problem that the brain and mind have been seen as somehow separate entities, and that physical and mental healthcare are separate," said Belinda Lennox, senior clinical lecturer in psychiatry at the University of Oxford.

"It has denied the psychological factors that play a vital part in all medical disorders, just as much as it has denied the importance of the biological factors in mental illness."

Whether the latest trial will yield a successful treatment is difficult to predict and psychiatry's record warns against premature optimism. However, recognising that biological factors, such as the immune system, can have a powerful influence on the brain and sometimes explain why things go wrong, will be essential to finding new and better treatments.