Is our thinking on depression wrong?

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Scientists are looking at whether the disease originates in the immune system, not the brain. The answer could revolutionise how we treat mental health problems, writes *Anna Magee*

One in 10 of us will experience depression at some point. Just what causes this highly debilitating disease, and the best way to treat it, remain controversial: last month, Danish researchers reported that antidepressants raise the risk of suicide when taken by healthy people.

The most widely prescribed antidepressants, such as Prozac, are known as selective serotonin reuptake inhibitors (SSRIs), and work on the basis that depression is caused by low levels of the brain chemical serotonin and that it can be treated by correcting this imbalance.

For decades, we've been told that serotonin is the key culprit for mood disorders, but now a growing number of doctors are subscribing to a radical new theory of depression – that the problem, at least for some people, is in fact the result of inflammation in the body, caused by the body's immune system reacting to an infection or stress.

This is one of the hottest areas in psychiatry right now, and it may bring

One third of depressed patients have increased inflammation

welcome news to approximately half of depressed patients, who don't respond to first line treatment with SSRIs.

The serotonin question

Increasingly, experts are questioning the concept that depression is a serotonin problem. In April last year, Dr David Healy, professor of psychiatry at Bangor University, published a paper in the *British Medical Journal* called "Serotonin and Depression: The Marketing of a Myth", which concluded: "The lowered serotonin theory [of depression] took root in the public domain rather than in psychopharmacology... a piece of biobabble."

Dr Kelly Brogan, a psychiatrist in New York, concurs: "In six decades, not a single study has proven that depression is caused by a chemical imbalance in the brain. There has never been a human study that successfully links low serotonin levels and depression."

Dr Brogan explores the theories of the causes of depression and the scientific evidence that lay behind them in her new book, *A Mind of Your Own*. She, and others, believe that depression can instead be the result of our immune system working in overdrive, causing inflammation that may manifest in the brain. "Depression is often an inflammatory condition, a manifestation of irregularities in the body that can start far away from the brain and are not associated with the simplistic model of so-called 'chemical imbalances'," she says.

Such an argument challenges traditional ideas of depression as a genetic illness, suggesting instead that our experiences and environments could play more of a role than we thought.

How the immune system can make us depressed

Inflammation is part of the body's natural response when we're sick.

"The substances we produce in response to an infection such as a virus are called cytokines, and they signal the immune system to activate," says Dr Valeria Mondelli, senior clinical lecturer in psychological medicine at King's College London.

Dr Mondelli believes that high levels of inflammation can decrease the number of neurons in our brains and affect the way they communicate, leading to depression. "We've seen repeatedly that people with depression have higher levels of inflammation in their brains, and we think this could be a new theory of depression in competition to the chemical imbalance theory."

One third of depressed patients have increased inflammation, she says, and they are the same people who don't respond to SSRIs.

We've all experienced how having a cold or flu can affect mood – we become less sociable, more withdrawn and generally fed up. Perhaps this isn't just feeling sorry for yourself because you're run down, but inflammation acting on the brain, causing classic signs of depression.

More evidence for the theory comes from the fact that people with inflammatory diseases such as rheumatoid arthritis (RA) suffer from higher levels of depression than average.

In a study at the Glasgow Royal

CONTINUED FROM PAGE 21

Daily Telegraph 4.11.16

Infirmary, doctors noticed that when patients with RA (caused when the immune system attacks the joints) were given precise anti-inflammatory drugs to calm down the immune system, their mood improved. Brain scans showed the volunteers weren't just feeling happier because their pain had improved. "The brain pathways involved in mediating depression were favourably changed in people who were given immune interventions," says Prof Iain McInnes, a consultant rheumatologist who ran the study.

The role of stress

It's not just physical illnesses and infections that may trigger inflammation: cytokines are also activated in response to stress.

Dr Mondelli last year published a meta-analysis which found that people who had experienced traumatic effects in childhood had higher levels of brain inflammation in adulthood. "We found that having had severe stress during childhood predisposes you to mental health problems by increasing the levels of inflammation."

She believes that people who experienced high levels of infection or trauma as children may develop compromised immune systems. As a result, they may be more susceptible to developing depression as adults after subsequent, repeated stress or infections

Meditation stimulates anti-inflammatory genes

in adulthood. "Childhood trauma and infections can prime the immune system, and that may then become a risk factor to developing depression in adulthood," she explains. "If they then face another stressful event, they may be more likely to develop depression, because their immune system is already threatened."

The new blood test that could change everything

The inflammation theory could have major implications for how we think about, and treat, depression. Although SSRI antidepressants do provide relief for many people with depression, a significant minority do not respond, and a string of studies have shown that this same group tend to have high levels of inflammation.

In July, researchers from King's College London published a study in *The International Journal of Neuropsychopharmacology* in which depressed patients were given a blood test that focused on two biomarkers measuring inflammation in the body. Patients with high levels of inflammatory markers were the ones who didn't respond to SSRIs.

Though more research and development of the blood test is needed, the team at King's say it paves the way for more "personalised psychiatry", where treatment is guided by such blood tests, rather than the current one-size-fits-all approach.

"Patients who have blood inflammation above a certain threshold could be directed towards earlier access to more assertive antidepressant strategies, including the addition of other antidepressants or anti-inflammatory drugs," said Prof Carmine Pariente, a leading psychiatrist and senior author of the study.

It seems, then, that what was considered for centuries as a mental illness might originate – at least for some – in our physical bodies.

"Finally, we can say that depression is not always something that is only in your mind, it could be a problem in your body as well," says Dr Mondelli.

"If people start to think about depression in this way, it could be less stigmatising because we would be seeing depression as a real physical illness, much like diabetes. It could, in time, also lead to a revolution in treatments."

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