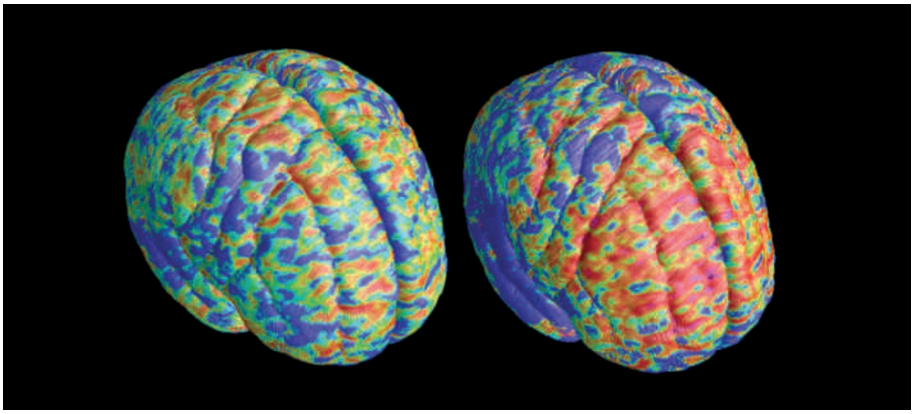

The brain of someone developing schizophrenia (right) typically shrinks more rapidly than normal (red colours indicate the highest rates of contraction).

ELSEVIER SCIENCE PUBLISHING/TYRONE CANNON

PREVENTION

Before the break

Paying attention to risk factors and warning signs could avert some cases of schizophrenia — or at least better prepare people for what's to come.

BY MICHELE SOLIS

Like any mother, Farrell Adrian worried about her child, Matt. He started off as a happy, sweet boy, but grew unusually sad at the age of five, when his father left the family. He developed problems with thinking and focus at school, and as a teenager he became depressed and addicted to drugs. Along the way, Farrell took him to see psychologists and other specialists, hoping that if they could solve what she thought was an emotional issue about his father, the old Matt would return.

When Matt was 17, he was finally diagnosed with schizophrenia. Twenty years on — after a bumpy road of hospitalization, therapy and antipsychotic medicines — Matt lives on his own in Seattle, Washington, works part-time at a football stadium, and is close to his family. Even though it took more than a decade to figure out what was wrong, Farrell says she feels lucky. "We got help sooner than most people do," she says.

Some researchers are now proposing that others could be helped much sooner, by being alert to signs that unfold during the months or even years preceding psychosis. A growing number of studies suggest that treating these early, muted signs can halve the number of people who later develop a break from reality. Researchers are also hunting for more concrete signs of risk in the brain, blood and saliva to better identify those at risk. Pre-emptive treatment could delay, or even avert, schizophrenia, and bring psychiatry into the realm of preventive medicine.

"Traditionally psychiatry offers too little too late," says Patrick McGorry, a psychiatrist at the University of Melbourne in Australia who advocates earlier intervention. "But now we see that the path to psychosis is a lot more sensitive to intervention than we used to think."

If better predictors of risk are found, and the successes of small treatment trials can be replicated on a larger scale, pre-emptive treatment could become an accepted practice in psychiatry, says Jeffrey Lieberman, a psychiatrist at Columbia University in New York and president of the American Psychiatric Association. "Then it could be a game changer and reduce the burden on people with schizophrenia, their families and society."

SEEDS OF PSYCHOSIS

Evading schizophrenia is not a new idea. Epidemiological studies have identified environmental risk factors that may contribute to errors in early brain development that are thought to underlie schizophrenia. For example, improving nutrition and avoiding infection during pregnancy may prevent some cases of the illness, and researchers are considering the possibility that getting the correct amount of vitamin D in early life could decrease the risk of schizophrenia (see 'Born at risk'). Even when schizophrenia has taken hold, early treatment after the first episode of psychosis can limit the severity of the illness and increase the chances of recovery.

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McGorry and others have taken the idea of early treatment further, proposing to intervene at the first suggestive signs of psychosis. A person might become suspicious, or start to hear a voice, but still recognize that these things are not tethered to reality. They may withdraw from friends and family, or have trouble focusing at school or work. The criteria for this 'at risk' category differ slightly between researchers, but they all require that a person is sufficiently distressed by their symptoms to seek help.

About one-third of people in this at-risk category develop psychosis within three years, and most are diagnosed with schizophrenia. A version of this at-risk category, called attenuated psychosis syndrome (APS), was considered for inclusion as a new diagnosis in the recent fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), one of the most widely used inventories of mental illnesses. But most people with APS do not actually develop full-blown psychosis, so after much discussion the syndrome was not included in *DSM-5*.

Despite these diagnostic uncertainties, people deemed at risk for psychosis based on their behaviour carry marks of their vulnerability in their brains. For example, an excess of the chemical messenger dopamine in a part of the brain called the striatum is thought to drive psychosis. A 2011 study[1] found that people at risk for psychosis had a surplus of dopamine in the striatum compared with healthy controls, and those with the highest levels were most likely to develop psychosis in the next three years. Other studies have found that the prefrontal cortex — the brain's supervisory centre — shrinks more than usual in people at risk during typical ageing, although not as much as in people with schizophrenia.

"We think we're detecting the early, leading-edge indicators of the same processes at work in schizophrenia," says Tyrone Cannon, a neuroscientist at Yale University in New Haven, Connecticut, who conducted the studies on the prefrontal cortex.

TREATMENTS ON TRIAL

So far, 11 randomized, controlled trials have found that treating people at risk results in fewer people developing psychosis within one year. Mostly small, the trials tested interventions such as low doses of antipsychotics, cognitive behavioural therapy (CBT) and omega-3 fatty acid supplements.

The earliest trials found that antipsychotics had beneficial effects, but these are no longer seen as a first line of treatment for people at risk. "There's a lot of sentiment, I think wisely so, that antipsychotics can easily do more harm than good for people who are

not actually on the verge of developing a full psychotic illness," says William Carpenter, a psychiatrist at the University of Maryland in Baltimore. Carpenter oversaw the discussion of whether to include APS in *DSM-5*.

Instead, studies in the past five years have emphasized safer treatments such as CBT, an approach that teaches people to recognize their own patterns of thinking and to reappraise situations. For example, someone with APS who jumps to conclusions about the bad intentions of others will learn from CBT to recognize this, and not to trust their first suspicions but find alternative explanations for someone's behaviour. In 2012, the largest CBT trial to date confirmed its ability to stave off psychosis in 201 people at risk: 12% of the group receiving CBT developed psychosis within 18 months, compared with 24% in the group that did not get CBT.

A more peculiar, and preliminary, finding points to beneficial effects of omega-3 fatty acid supplements in the form of fish oil. Omega-3 fatty acids are components of neuronal membranes that also dampen inflammation and oxidative stress — both suspected of contributing to schizophrenia. A 2010 study[2] led by Paul Amminger, a psychiatrist working at the Medical University of Vienna in Austria and with McGorry in Melbourne, reported that only 5% of people at risk who took four fish oil capsules a day for 12 weeks developed psychosis, compared with 28% who took a placebo. Unpublished results suggest that this regimen staves off psychosis for at least six years, and a larger trial is now seeking to replicate the finding.

"People always ask me if omega-3 fatty acids will be as good as antipsychotics, but it seems they're even better," Amminger says. Unlike the early antipsychotic trials, he notes, those taking the supplements also showed improvements in the way they functioned in daily life.

"If they replicate that study, it may be the most important thing since Thorazine," Carpenter says, referring to chlorpromazine, the first antipsychotic drug, which was introduced in the 1950s.

RECOGNIZING RISK

To get a better idea of who could benefit from treatment, researchers are looking for other risk indicators that could more precisely flag someone on the path to psychosis. One comes from a survey of cognitive abilities, which accurately predicted 91% of people who developed psychosis and 89% of those who did not[3]. Brain imaging and electroencephalography also reveal patterns that start to differentiate between those who later develop psychosis and those who do not.

Beyond the brain, levels of the stress hormone cortisol and profiles of gene expression and protein abundance in blood cells are also likely candidates. For example, research in 2013 from the North American Prodrome Longitudinal Study (NAPLS), a consortium studying the early signs of psychosis and its prevention, found higher cortisol levels in people at risk of psychosis[4] — especially those who later developed psychosis. In the future, someone with APS could be evaluated by using a computerized cognitive test, a saliva swab and a blood test. "Based on these multiple lines of information, an algorithm would spit out a number that would provide enough predictive power for a clinician to help that person," says Cannon, who directs NAPLS.

"People always ask me if omega-3 fatty acids will be as good as antipsychotics, but it seems they're even better."

Until then, increasing awareness among healthcare professionals of the early behavioural signs of psychosis risk could help a lot. Given that most mental illnesses appear between 12 and 25 years of age, McGorry has spearheaded the creation of youth mental-health centres in Australia that provide a friendly place for young people to get support for any kind of problem, not just the early stages of psychosis.

Even in the United States, where people typically have to reach a crisis point before receiving mental health care, things may be changing, thanks in part to the horror of recent gun violence carried out by people presumed to be mentally ill. Prompted by the tragic shootings in Newtown, Connecticut, in 2012, the state of Maryland has recently funded the creation of a youth mental-health programme similar to those in Australia. "I expect a mushrooming of these sorts of early identification and intervention centres," Carpenter says, "which won't wait on the science." ■

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THINKSTOCK/GETTY IMAGES

Fish oil capsules containing omega-3 fatty acids may be able to delay the onset of psychosis.

BORN AT RISK

Prevention in the womb

Schizophrenia strikes nearly 1% of the world's population, but affects certain people more than others. Someone born during the winter months, for example, has a higher risk of schizophrenia than someone born in the summer. And dark-skinned people living in northern countries are three to four times more likely to develop schizophrenia than light-skinned natives. "Those clues scream out that there must be modifiable risk factors underpinning those gradients, and we need to find out what they are," says John McGrath, an epidemiologist at the University of Queensland in Brisbane, Australia.

McGrath has been investigating the case of dark-skinned migrants, starting with the hypothesis that their increased risk may be due to a lack of vitamin D, which is important for proper brain development and is often lacking in dark-skinned people in northern countries. He found that in Denmark, abnormal levels of vitamin D at birth were associated with an increased incidence of schizophrenia. If a larger study currently underway confirms this connection, McGrath thinks it might be worth monitoring vitamin D, particularly in dark-skinned migrant populations.

Seasonal infections such as influenza could partly explain the higher risks faced by those born in winter. Pregnant women may pass these infectious agents to their unborn child, where they could affect brain development. Alan Brown, a psychiatrist at Columbia University in New York, has found that while mothers were pregnant with babies who eventually developed schizophrenia, they showed abnormally high levels of antibodies to the influenza virus in their blood.

These findings point to the importance of nutrition and avoiding infection during pregnancy, which are already prominent messages for having a healthy baby in the developed world. These guidelines may already be reducing schizophrenia incidence in developed nations, and extending them to developing countries may bring further decreases.

"Many of the big medical advances — say, in cardiovascular disease or cancer — have come through changes in our diet and behaviour," McGrath says. "There's no reason to think that mental illness would be any different." ***M.S.***