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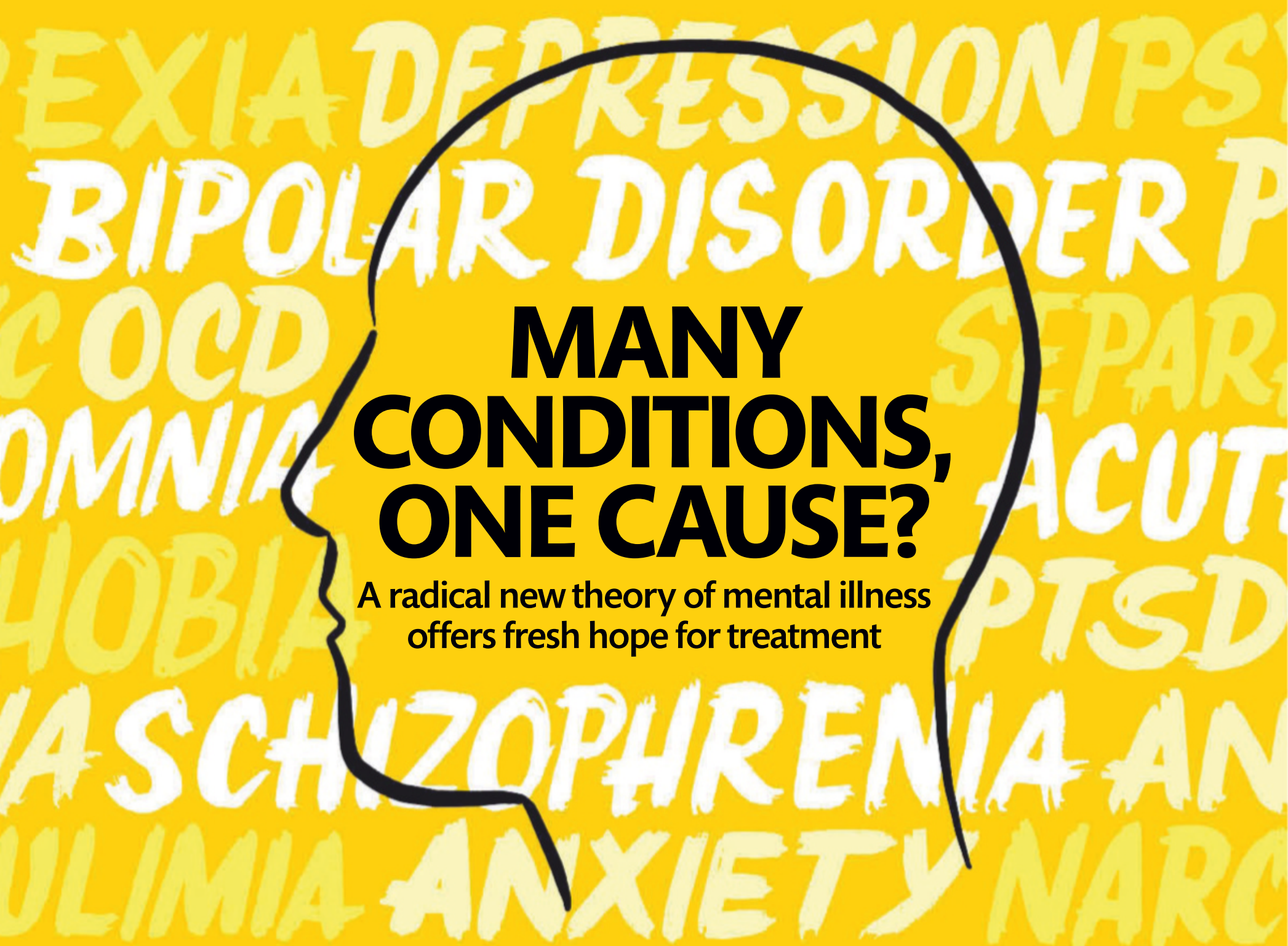

MANY CONDITIONS, ONE CAUSE?

A radical new theory of mental illness offers fresh hope for treatment

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Common cause

Genetic analyses point to a new way to think about mental health

THIS year alone, one in four people in the UK will experience a mental health condition. That includes everything from depression and anxiety to schizophrenia and phobias. Meanwhile, surveys suggest that our ability to cope with these issues is getting worse.

The personal costs of all this are huge, as are those to society. And our treatment options are limited: some conditions defy treatment, even proven interventions don't always work and many people get no treatment at all. At the same time, those who experience one condition often experience others.

But now new research into the possible causes of mental illness offers fresh hope for a better way forward (see page 34). Hundreds of distinct psychiatric conditions are currently recognised by mental health professionals, but new DNA sequencing techniques reveal that many share an underlying genetic link. Of course, experiences and environment also play a big role. But this common factor – or "p factor" as researchers call it – may help explain why some people seem more prone to mental health issues across their lifetimes. As evidence for this link grows – and the medical establishment starts to take it seriously – this understanding brings new opportunities for treatment.

"This new understanding suggests putting less emphasis on labelling conditions and more on treating symptoms"

That may start with putting less emphasis on labelling conditions and more on treating symptoms. We already know that some interventions can cross diagnostic boundaries: several drugs are effective for a number of conditions, for instance, as are talking therapies.

Some mental health professionals already use a one-size-fits-all version of cognitive behavioural therapy, called the common elements treatment approach, for people with many different conditions. If this new thinking about mental health is right, these kinds of general treatments may actually be the most useful first interventions for most people and conditions. What's more, this strategy could also increase access to treatment where resources are limited.

Perhaps then, in future, we could devote less time and money to searching for separate treatments and more time to truly helping people. ▮

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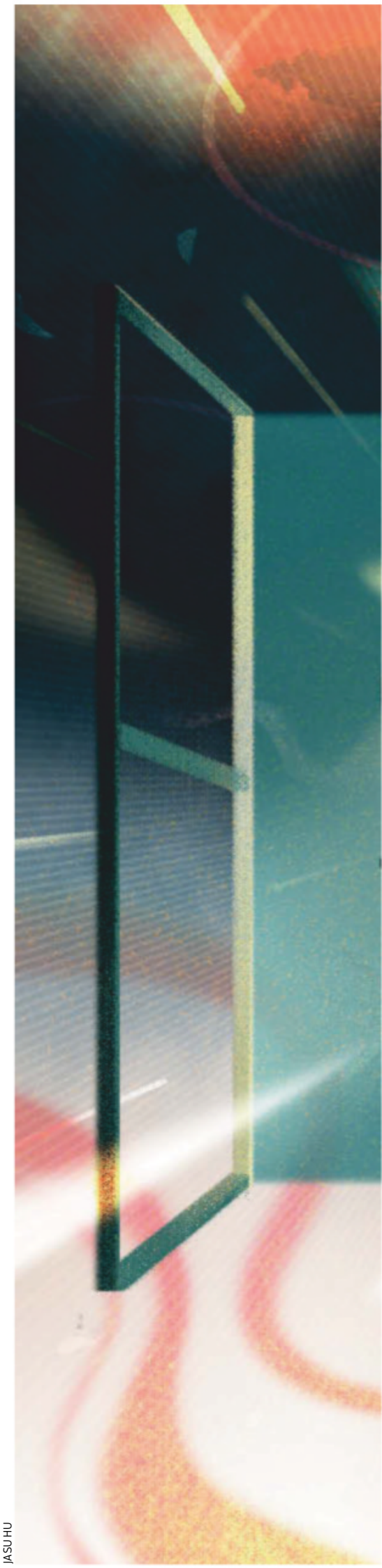
Rethinking mental health

Growing evidence that many mental health conditions share an underlying cause could transform their treatment, finds **Dan Jones**



JASU HU

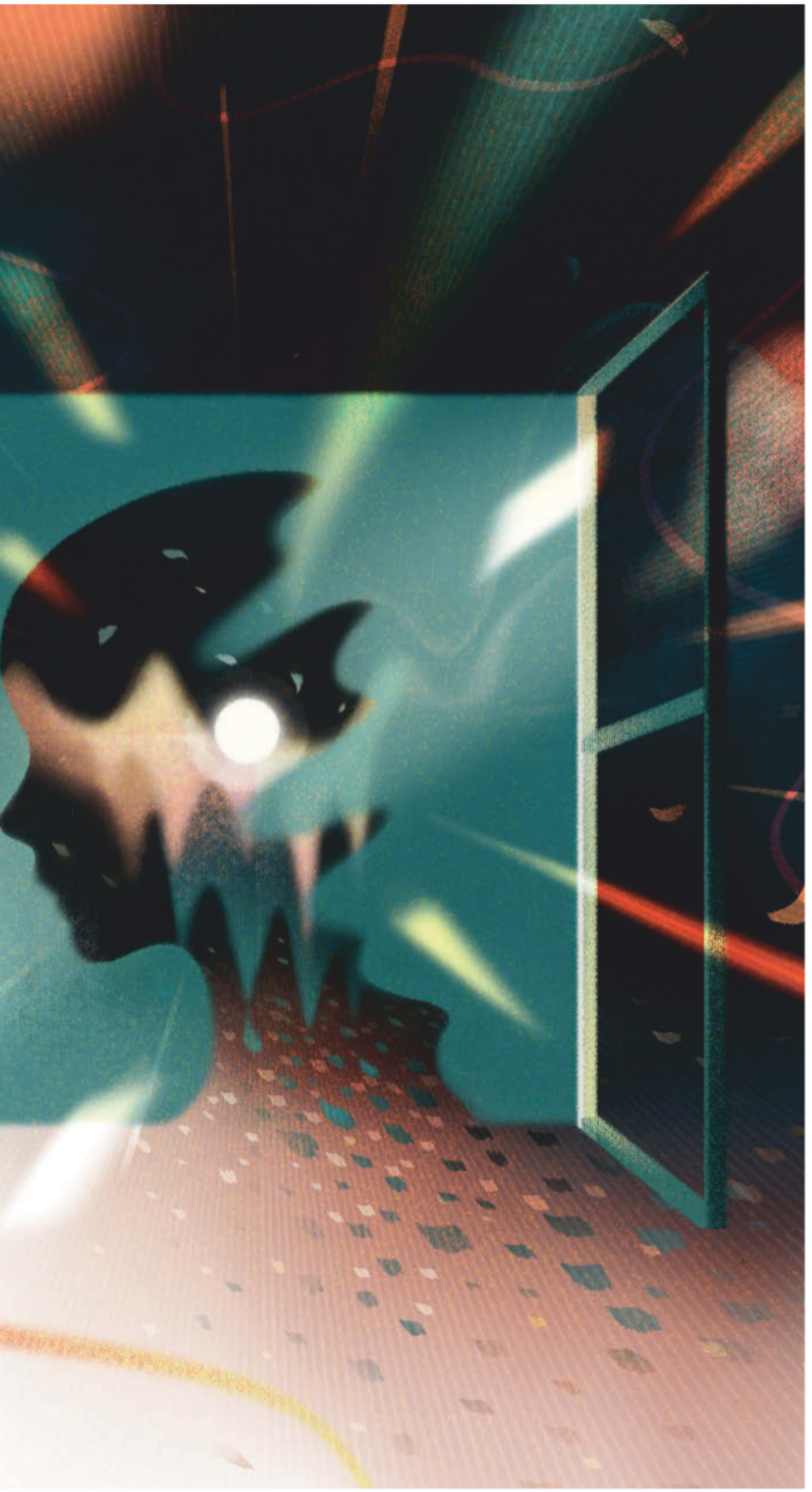
LIFE can be tough. All of us have experienced nagging worries, anxiety, sadness, low mood and paranoid thoughts. Most of the time this is short-lived. But when it persists or worsens, our lives can quickly unravel.

Mental health conditions, including everything from depression and phobias to anorexia and schizophrenia, are shockingly common. In the UK, one in four people experience them each year, so it is likely that you, or someone you know, has sought help from a professional. That process usually begins with a diagnosis – a mental health professional evaluates your symptoms and determines which of the hundreds of conditions listed in psychiatry's classification bible, the *Diagnostic and Statistical Manual of Mental Disorders*, best fits. Then you start on a treatment tailored to your condition. It seems an obvious approach, but is it the right one? "For millennia, we've put all these psychiatric conditions in separate corners," says neuroscientist Anke Hammerschlag at Vrije University Amsterdam, the Netherlands. "But maybe that's not how it works biologically."

There is growing and compelling evidence that she is correct. Instead of being separate conditions, many mental health problems appear to share an underlying cause, something researchers now call the "p factor". This realisation could radically change how we diagnose and treat mental health conditions, putting more focus on symptoms instead of labels and offering more general treatments. It also explains puzzling patterns in the occurrence of these conditions in individuals and families. Rethinking mental health this way could be revolutionary: "I don't think there are such things as [discrete] mental disorders," says behavioural geneticist Robert Plomin at King's College London. "They're just fictions we create because of the medical model."

At first glance, the idea that different mental health conditions with distinct symptoms share an underlying cause seems counter-intuitive. The key to understanding it lies in its name. "P factor" has intentional parallels with one of the most famous concepts in psychology. More than a century ago, British psychologist Charles Spearman noted that children's performance on one kind of mental task, say verbal fluency, was correlated with their mental skill in other areas, like mathematical reasoning, spatial manipulation and logic. In other words, children who are good at one thing tend to be good at another, while those who struggle in one area tend to struggle in others. Using a statistical tool called factor analysis, Spearman showed that this is because these different mental abilities are all linked to an overarching cognitive capacity, which he named general intelligence, or the g factor.

A century on, applying the same approach to mental health diagnoses provided the first hints that something similar might be going on. There are a wide range of mental health conditions that manifest with different behavioural and psychological symptoms. Like cognitive skills, they cluster together in



individuals, either at the same time or one after another. In 2012, Benjamin Lahey at the University of Chicago and his colleagues analysed information on such diagnoses among 30,000 people studied over three years. Using factor analysis, they found that the observed patterns of illness were best explained by a general tendency towards mental health conditions.

The following year, Avshalom Caspi and Terrie Moffitt at King's College London got the same result. Their study used information from 1000 people whose health had been tracked for four decades since their birth in the early 1970s. It was Moffitt and Caspi who coined the term p factor to describe an individual's broad susceptibility to mental health problems. "Once you have any given mental disorder, it increases the likelihood that you'll have multiple other kinds of disorders," says Caspi.

Puzzling heritability

The p factor can also explain puzzling patterns of mental health conditions within families. It had long been known that these conditions have a genetic basis, and are highly heritable. Huge twin studies have estimated the heritability of schizophrenia, for example, at nearly 80 per cent, and major depression at about 45 per cent. But having a parent or sibling diagnosed with a given condition doesn't just increase the odds that you will experience it. It also increases the likelihood that you will be diagnosed with a different condition. For instance, if a parent has schizophrenia, your risk of developing bipolar disorder doubles, and vice versa. That makes sense if you inherit not just a risk for one kind of condition, but a more generalised risk: the p factor.

Indeed, the application of genetics to psychiatry in the past decade has provided key support for the existence of the p factor. In the early days, psychiatric genetics mostly entailed a hunt for individual genes conferring significant risk for developing certain conditions. But this so-called candidate gene approach hit the skids. "It was really a dead loss, but it was all we could do at the time," says Plomin. "Then SNP chips came along in the mid-2000s and changed everything."

SNP (pronounced "snip") chips, which look a bit like the memory card in a digital camera, allow scientists to use a small DNA sample to scan someone's genome and discover which genetic variants they carry. Everyone has millions of single-letter differences in DNA's ›

four-letter code: where one person has a T, for example, another might have a G (and someone else could have A or C). More than 10 million of these single-nucleotide polymorphisms (SNPs) have been identified, and a single SNP chip can detect a million or more of them in one go.

The breakthrough for the p factor idea came a few years before Moffitt and Caspi coined the term. In 2009, the International Schizophrenia Consortium used SNP chips to genetically analyse more than 3000 people diagnosed with the condition. Instead of pulling out one or a few genetic variants with big impacts on schizophrenia susceptibility, the analysis found the condition was linked to thousands of variants, each having a small effect. Intriguingly, these same variants also increased the risk of bipolar disorder.

Shared genes

Later, this kind of analysis was extended. In 2013, an international group called the Psychiatric Genomics Consortium completed a landmark study. Scientists analysed genomic data from more than 30,000 people diagnosed with conditions including bipolar disorder, major depression or schizophrenia. Again, genetic risk variants cut across the traditional diagnostic boundaries of psychiatry. "It's the opposite of what was expected," says Mike Gandal at the University of California, Los Angeles. "Until recently, it was thought that genetic studies would reveal more biological specificity for each disorder, but instead we're seeing all this shared genetics."

Tellingly, the story is very different for neurological conditions, which affect the nervous system itself, such as Alzheimer's, Parkinson's, Huntington's and multiple sclerosis. A 2018 study from the Brainstorm Consortium based at Harvard University examined genetic data from more than 265,000 people with one of 25 psychiatric and neurological conditions. This revealed that neurological conditions have little or nothing genetically in common with each other or with psychiatric conditions, making them a much better fit for the classical medical model.

For neurological conditions in which single genes play a big role, people can be divided into two groups: those who carry the risk variant and those who don't. The picture is much messier for mental health conditions. The thousands of SNPs underlying them follow a bell-shaped distribution, meaning that a small percentage of people have very few risk variants, a small percentage have a lot, and most people fall somewhere in between, with symptom severity roughly tracking this curve. "There's no break point at which the number of variants suddenly leads to a diagnosable psychiatric disorder," says Plomin.

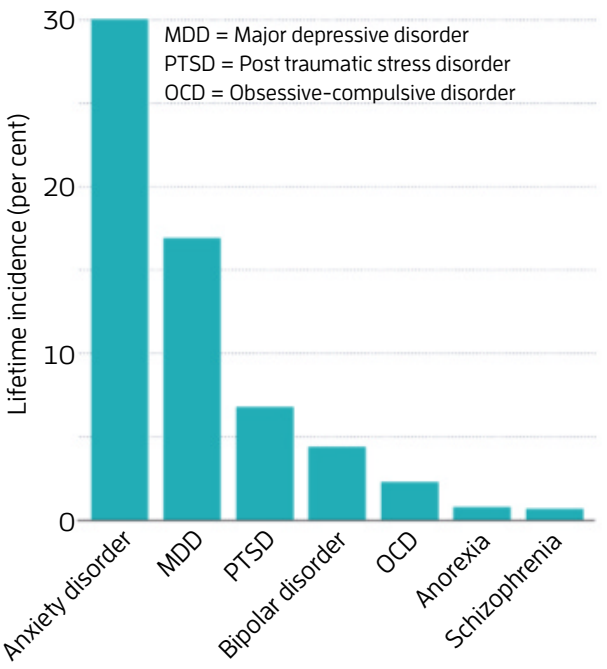
It gets messier. Researchers are now discovering some SNPs associated with individual conditions. "There's this huge genetic overlap between psychiatric disorders, but there are also some specific genetic factors that make people differ in their symptoms," says Christel Middeldorp, who studies psychiatric genetics at the University of Queensland, Australia. "The p factor doesn't explain everything."

In addition, as Caspi is quick to stress, there is more to the story than genes. "The genetic work is exciting, but what's really remarkable about most psychiatric disorders is that they share the same environmental and psychosocial risk factors as well," he says. "Child abuse of any kind, for example, predicts every condition under the sun." The same is true for drug and alcohol abuse, and traumatic experiences during childhood such as being displaced by warfare.

"There's a huge genetic overlap between mental health conditions"

How common are mental health conditions?

Around a quarter of people in the UK experience mental health problems each year, with anxiety and depression being by far the most prevalent diagnoses



SOURCES: CDC, HARVARD MEDICAL SCHOOL doi.org/gd4b88, doi.org/dzvqfw

Plomin and his colleagues recently attempted to quantify the genetic component of the p factor. Drawing on information from more than 7000 pairs of twins, they estimated its heritability at around 55 per cent. This means that genetic differences explain just over half of the variation between people's general susceptibility to mental health problems, with the rest being driven by non-genetic factors. The study also showed that the p factor is stable across a person's lifetime.

Despite these complications, there is growing recognition that mental health conditions have a shared genetic basis, and the search is on to find out how this manifests biologically. In 2018, Gandal and his colleague Dan Geschwind led a team to do just that. They analysed gene expression in the cerebral cortex – the brain's outer layer where higher cognition occurs – from 700 post-mortems of people diagnosed with mental health conditions. "We found that disorders that share the most genetic risk factors, like schizophrenia and bipolar disorder, look very similar in the gene-expression patterns as well," says Gandal. Many of the genes involved controlled activity at synapses, the junctions between neurons.

A recent study led by Hammerschlag backs this up. Her team investigated more than 7000 sets of genes involved in a wide range of biological pathways, and then looked at which contained genes with variants linked to five common mental health conditions. Only 14 fit the bill. "Almost all of these gene sets have a function in neurons, and most play a role in the synapse," she says. In other words, the p factor seems to have something to do with communication between brain cells.

The latest research is even more enlightening. Maxime Taquet at the University of Oxford and his colleagues believe they have identified a "vulnerability network" in the brains of children at high genetic risk of developing mental health conditions. Comparing their brain scans with those of children with a low genetic susceptibility, the team found large differences in three key areas: a structure called the default network that is active while the brain is at rest, a second structure involved in planning and control, and the part of the brain that processes vision. In a similar study, Caspi and Moffitt found that people with a higher p factor have differences in a brain

circuit crucial for monitoring and processing information so it can be used in higher cortical functions such as regulating emotions, thoughts and behaviours.

It is still something of a mystery how having a brain with these sorts of features might influence an individual's psychology. Caspi and Moffitt think that a high p factor probably manifests as a combination of disordered thinking, difficulties regulating emotions and a tendency towards negative feelings. However, even if these links aren't yet clear, the p factor idea may be useful for diagnosing and treating mental health conditions.

Already, many drugs are known to be beneficial in supposedly distinct diagnoses. "In practice, we often use the same treatment for different disorders," says psychiatrist Tova Fuller at the University of California, San Francisco. "Antipsychotics, for example, are useful not only in psychosis, but also in mania, delirium, agitation and other conditions." The p factor makes sense of these "transdiagnostic" therapies. Yet they weren't developed with it in mind. "If we can figure out the biology of the p factor, then it might be possible to target the mechanisms involved and develop therapies that work better across disorders," says Gandal. "These could be given to a large number of patients, rather than treating each person based on their specific pattern of symptoms."

Talk-based treatments, such as cognitive behavioural therapy (CBT), also have transdiagnostic value. "There are always lessons for the patient on how to reframe stressful experiences and look on the bright side, how to identify triggers that set off their symptoms, and guidance on life skills," says Moffitt. Currently, there are separate therapeutic guidelines for specific conditions. However, the p factor idea lends support to clinicians advocating a one-size-fits-all version of CBT called the common elements treatment approach in an attempt to ensure that more people globally get the treatment they need.

Talk-based therapies are used to treat a variety of mental health conditions

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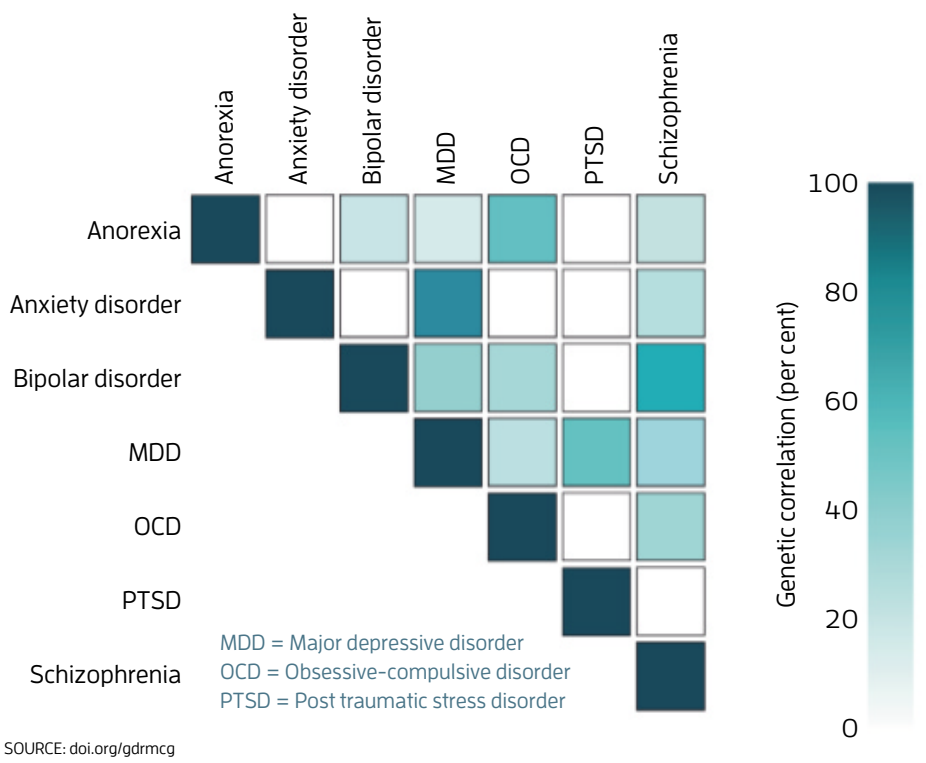
"It's a front-line cognitive therapy that can be offered to everybody who has mental distress," says Moffitt. "Then, after that, people could be referred onwards to a specialist who treats, say, only schizophrenia or panic attacks, depending on the symptoms present."

Moffitt also believes that the existence of the p factor should prompt a shift from treating conditions themselves to treating the often distressing symptoms people experience. "We tend to think: 'This person has depression today, so this is a person who is depressive and we really need to focus on depression'," she says. "We obviously need to treat their depressive symptoms, but, knowing that this patient will present with different symptoms in the future, we also need to provide them with tools and skills to cope when they arise."

Plomin goes even further. For him, the blurred biological lines between mental health conditions alongside the genetic continuity of susceptibility across populations demolish the orthodox view of mental illness. "I think these diagnostic classifications are mostly a myth," he says. That doesn't mean people don't experience mental health problems that require the help of a professional, but Plomin would be happy to see the current model of psychiatry go the way of the dodo. "It's caused a lot of harm because it implies there are mentally ill people versus 'normals'," he says. "Really we're all somewhere along a continuum." ▮

Mental health conditions are not so distinct

Psychiatric conditions have many genes in common, supporting the idea that there is an underling cause that makes individuals more or less susceptible to them



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