# THE INFLAMED BRAIN

## Autoimmune conditions underlie some cases of psychosis. Scientists are expanding their search for patients, who often benefit from treatment

*By* **Richard Stone**

**THOMAS MÜLLER* ONCE ENJOYED** a serene life as a psychiatrist with his wife and three children in Lahr, a German town near the French border. He was also a talented artist who loved painting with his kids, and a voracious reader fond of the speculative science fiction of Philip K. Dick and the eldritch tales of H. P. Lovecraft. But in 2012, Müller fell into a profound depression. He couldn't read more than a few dozen words before losing his concentration. He began to have memory lapses. "I couldn't sleep at all, for nights at a time. I'd wander restlessly," he says. Dark thoughts crept into his mind. "I thought it would be better if I did not exist."

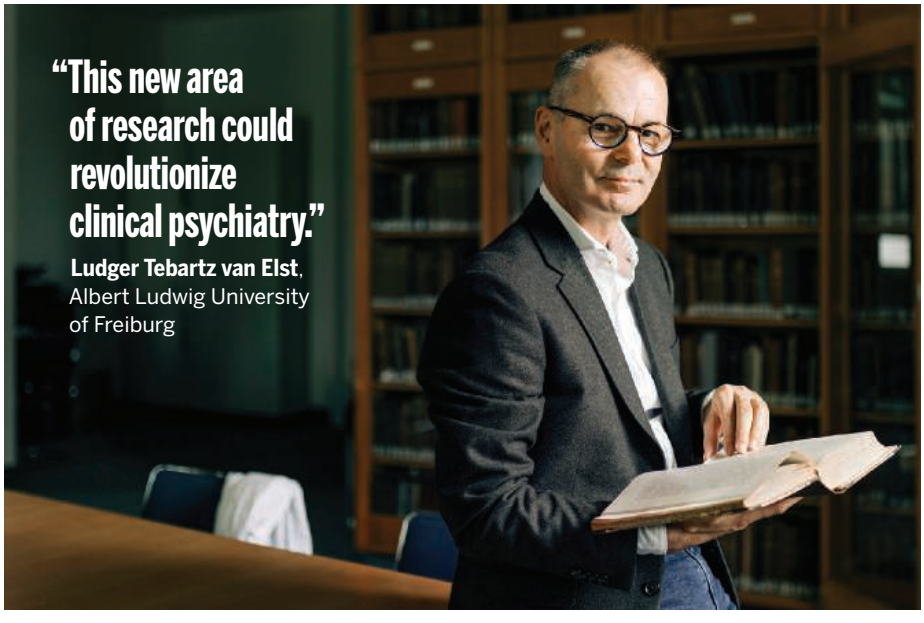
Müller quit his job in a pain clinic and received various diagnoses from different physicians, including delusional disorder and schizophrenia. He spent weeks at a stretch in psychiatric hospitals, sometimes against his will. In 2017, he developed an unquenchable thirst that compelled him to guzzle up to 15 liters of fluids a day. He moved into his parents' house, where he'd lie in bed all day, sobbing and "afraid of dying," he says. "I knew there was something terribly wrong with me."

Thomas Müller displays his artwork, some of which was inspired by his experience with psychosis brought on by autoimmune encephalitis.

PHOTO: ELENA GIOVANAZZI

Then, in 2019, Müller's aunt shared a magazine article about Ludger Tebartz van Elst, a neuropsychiatrist at the Albert Ludwig University of Freiburg who is exploring a new frontier of medicine: autoimmune conditions that trigger psychosis. Müller went to visit, and that August, Tebartz van Elst's team isolated telltale antibodies from Müller's blood serum. They signaled an autoimmune brain disease with a jawbreaker of a name: anti-leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis. The team administered high doses of intravenous cortisone, a first-line treatment for brain inflammation. "My expectations were tempered," Tebartz van Elst says. "Were we too late to help him?"

Müller showed scant improvement at first, ending up back in a psychiatric ward in early 2020. But after a second stint under Tebartz van Elst's care, his symptoms started to relent. By the fall of 2021, he was on the road to recovery.




Over the past 15 years, researchers have identified 18 different diseases, all triggered by an immune attack on the brain, that can lead to diverse neurological symptoms, and in some cases, psychosis. Like other autoimmune diseases, which include rheumatoid arthritis, psoriasis, and lupus, these autoimmune brain inflammations, or encephalitides, arise when antibodies turn against the body. These antibodies may originate in the brain or slip in from the bloodstream. They then bind to targets on the surface of neurons or in the synapses between them, altering brain function and triggering a cascade of inflammatory processes.

"These aren't new disorders," says Belinda Lennox, a psychiatrist at the University of Oxford. But before the aberrant antibodies behind autoimmune encephalitis were unmasked, many affected individuals died in intensive care units. Some languished in psychiatric wards—and a handful were even subjected to exorcisms. "You can be fine one day, and absolutely psychotic the next. And that's horrifying," says Stacey Clardy, a neuroimmunologist at the University of Utah.

When the first form of autoimmune encephalitis was discovered in 2007, psychiatrists largely ignored the revelation—or didn't think it was relevant to their patients, Lennox says. There was a "barrier to change" in the field, she acknowledges.

Many have now come around. Psychiatrists and neurologists are increasingly joining forces to find and treat patients with autoimmune psychoses. "We've been waiting for this moment, when everybody finally listened," Clardy says. Hubs for treatment and research have sprouted across Europe and in the United States. Scientists at Columbia University's newly launched Stavros Niarchos Foundation Center for Precision Psychiatry & Mental Health are planning this fall to screen for autoantibodies in patients in the New York state mental health system—14 psychiatric centers totaling 3000 beds—who may have undiagnosed autoimmune conditions.

The true rate of autoimmune encephalitis isn't known, but most researchers suspect only a small fraction of psychosis cases trace to autoantibodies. In some ways, these patients are the lucky ones. When Clardy sees a patient who has hallmark symptoms, including acute onset psychosis and seizures, and no family history of schizophrenia, "We want so desperately for it to be autoimmune. That implies we can fix it," she says. People treated with immune-modulating therapies routinely stage remarkable recoveries—a story of hope popularized by *The New York Post*'s Susannah Cahalan in her 2012 book *Brain on Fire: My Month of Madness*, which describes her hospitalization and eventual diagnosis with autoimmune encephalitis.

Now, researchers are pursuing hints that errant antibodies could play a role in other disorders once thought to lie squarely in the realm of psychiatry, including obsessive compulsive disorder and depression. "This new area of research could revolutionize clinical psychiatry," Tebartz van Elst predicts, although he cautions that more work must be done to reveal "the precise role these antibodies play in the disease process."

Indeed, some researchers warn that intriguing clues that fail to pan out will raise false hopes in patients and their families. "There's a lot of naïvete," says Josep Dalmau, a neuro-oncologist at the University of Barcelona's Hospital Clinic-IDIBAPS Research Center whose 2007 discovery of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis ignited the field. "Some ideas are very premature."

But Lennox, who is probing for autoantibodies in patients with postpartum psychosis and bipolar disorder, is confident that the pool of autoimmune mental illness is wider and deeper than many have believed. "If we find something that's a cause of illness, that's curable," she says, "for goodness' sake, we should make it available to everybody."

**HANGING ON A WALL** above a microscope in Dalmau's lab, a poster depicts rat brain slices magnified to show intricate brown staining patterns. The staining maps how various antibodies extracted from the cerebrospinal fluid (CSF) of patients bind to the rat brain tissue. One 2-centimeter-long brain slice bears the distinctive pattern of anti-NMDAR antibodies. Two decades ago, Dalmau says, detecting those autoantibodies in the CSF of several young women "was a eureka moment."

Dalmau's path to discovery was circuitous. He grew up in rural Catalonia, where as a child his parents had to scrimp and save to buy the four-volume set of anatomy textbooks he now keeps on a shelf in his office. As a medical student at the Hospital de Sant Pau in Barcelona, Dalmau became entranced by the neurological complications of cancer and cancer treatments. He was offered a postdoctoral position at the Memorial Sloan Kettering Cancer Center just as his wife, Martha, fell ill with metastatic cancer, and he put his career on hold to care for her until her death in 1988.

Dalmau arrived at Sloan Kettering several months later. His English was "very poor," his lab chops weak, and looking back, he says, "I was probably clinically depressed."

PHOTO: LENA GIOVANAZZI

He persevered, met his current wife, neurologist Myrna Rosenfeld, and in 2002 followed her to the University of Pennsylvania, where she was hired to run clinical trials on brain tumors. He studied rare neurological conditions in cancer patients usually caused by T cells, another immune system warrior, attacking the nervous system.

One day, he was called in to consult on the case of a 26-year-old woman admitted to the intensive care unit in a Philadelphia hospital. Her initial symptoms included inappropriate laughing, paranoia, and combative behavior. Antipsychotic medications and antibiotics failed to help; eventually, she could no longer recognize family members, developed severe facial twitches, then lapsed into a coma and was intubated after having trouble breathing. Her only physical abnormalities, it seemed, were mild brain inflammation and a teratoma—a rare kind of germ cell tumor—in her ovary. "We were totally lost," Dalmau says.

Then, the case took a surprising turn. After ruling out a viral infection, physicians put the woman on steroids to try to tamp down the brain inflammation. She steadily improved and within a year got a clean bill of health. It dawned on Dalmau that three other young women with similar symptoms referred to him in previous months also had benign ovarian teratomas. He suspected that antibodies their immune systems generated to attack the teratomas were mistakenly taking aim at proteins in their brains as well.

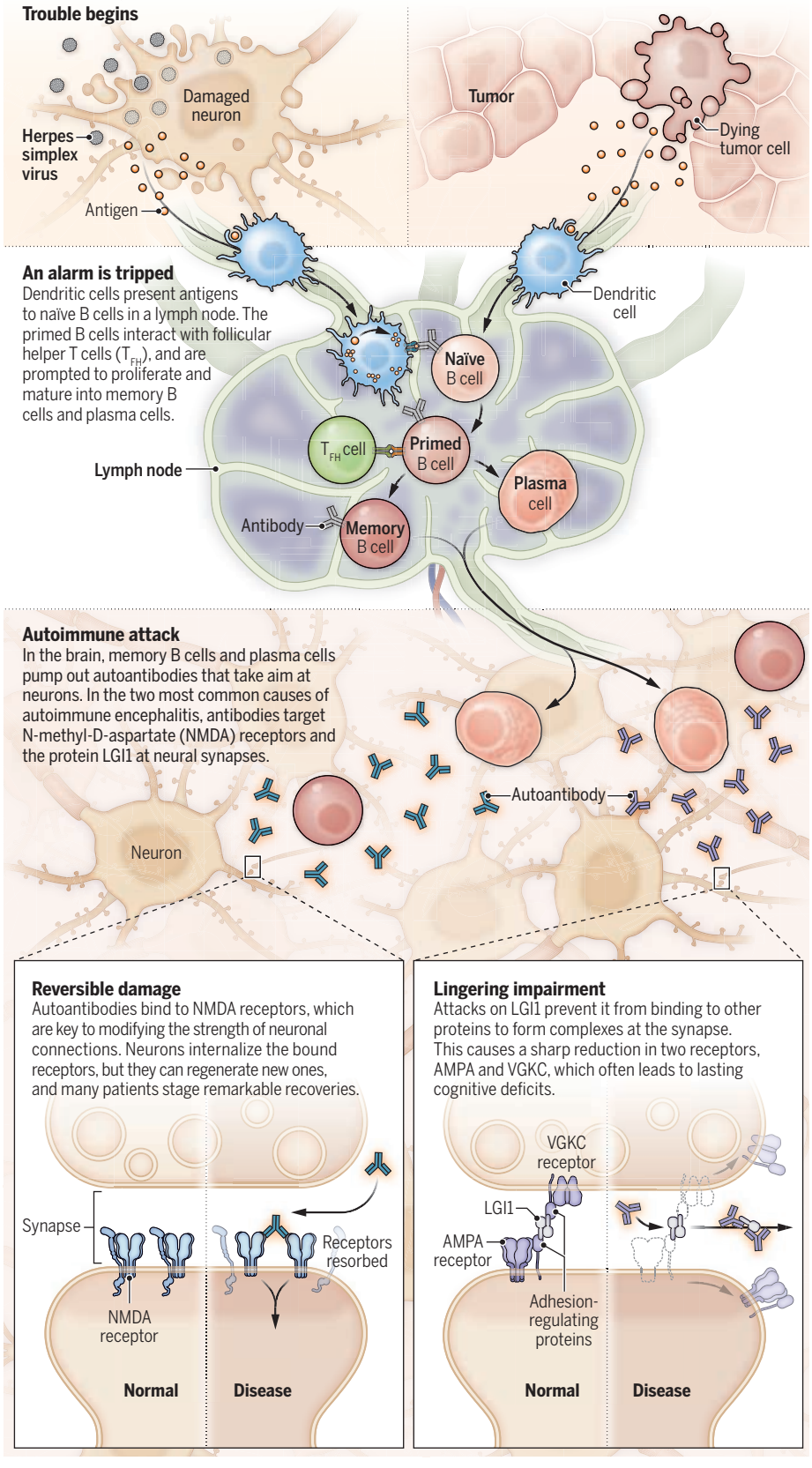
"I changed my strategy to search for new kinds of antibodies," Dalmau says, and this "act of faith" paid off. The women's CSF contained never-before-seen antibodies targeting brain tissue. This was a new kind of autoimmune disease.

After several months of sleuthing, Dalmau's team worked out that the culprit autoantibodies were latching onto NMDA receptors. These channels allow ions, primarily calcium, to flow into neurons and help regulate how these cells communicate with each other—a conversation that is vital for learning and memory. After publishing their findings in the *Annals of Neurology* in 2007, Dalmau says, "we were bombarded with emails from all over the world" from physicians who had encountered similar patients.

The revelation also seemed to explain puzzling cases in the medical literature. These stretch as far back as 1843, to a description in an Austrian medical journal of an 18-year-old woman who was gravely ill with seizures and catalepsy for more than a year before recovering spontaneously—the same distinctive disease course seen in anti-NMDAR encephalitis. In the early 1990s, Guillaume Sébire, a pediatric neurologist then in France, had observed a similar condition in six children who

## Turncoats in the brain

Herpes infections and tumors can both generate antigens that lead to the production of rogue antibodies that attack the brain, causing autoimmune encephalitis. Different autoantibodies have distinct effects on neurons, influencing symptoms and prognosis.




GRAPHIC: N. BURGESS/*SCIENCE*

suffered confusion and abnormal movements and lapsed into comas before rallying and recovering fully. Fifteen years later, says Sébire, who's now at McGill University, "I read Dalmau's paper, and said, 'Oh my God! That had to be the same disease.'"

Typical acute symptoms of anti-NMDAR encephalitis include seizures, involuntary movements, hypersexuality, violent outbursts, and terrifying hallucinations caused by inflammation of the amygdala, the brain's fear center. "There's nothing quite as haunting as looking in their eyes. It's primal," Clardy says. Dalmau notes that some individuals "underwent rituals of demonic expulsion." Sébire suggests the 14-year-old boy hospitalized in 1949 who inspired the 1971 horror novel *The Exorcist* may have had anti-NMDAR encephalitis.

Confronted with such cases before the discovery of autoimmune encephalitis, psychiatrists often prescribed antipsychotics such as chlorpromazine or haloperidol. But these dopamine-blocking drugs tended to make autoimmune patients even sicker. Perhaps one in five would fall into a coma and die, Tebartz van Elst says. Others would recover but face neurological deficits for the rest of their lives.

Today, first-line immunotherapies include plasmapheresis, in which blood is circulated outside the body to purge plasma of antibodies, or an infusion of immunoglobulins—antibodies produced by plasma cells—which prompts the body to sop up autoantibodies. Most patients also get high doses of steroids.

Josep Dalmau discovered anti-NMDAR encephalitis in 2007 and has since unmasked 10 more varieties of autoimmune brain disease.

**AFTER DALMAU'S 2007** discovery, he and Rosenfeld decamped from Philadelphia to Barcelona to focus on antibody-mediated encephalidites. Altogether, they and Barcelona colleague Francesc Graus have uncovered 11 of the 18 known varieties: a rogue's gallery with sharply different symptoms depending on the autoantibody responsible. In one, antibodies attack a cell-surface protein on neurons called IgLON5, causing abnormal sleep patterns and a buildup of tau, the protein that forms insoluble tangles in the brains of people with Alzheimer's disease. Patients, usually stricken in middle or old age, often succumb to the disease, Dalmau says.

The other 17 autoimmune encephalitides tend to have better outcomes, but the consequences can still be profound. In anti-LGI1 encephalitis, the second most common of these diseases after anti-NMDAR encephalitis, autoantibodies glom onto and impede LGI1 protein, which is found in synapses and helps regulate the transmission of electrical signals between neurons. Patients usually recover, but with lasting deficits: memory gaps, mild seizures, and muscle twitching. "It's an iceberg phenomenon," Dalmau says: Uncharted pathology lurks below the surface.

Antonio Serra, a 74-year-old survivor of anti-LGI1 encephalitis, is physically fit 4 years after receiving treatment, with a wry smile that rarely leaves his face as he readies for his thrice-yearly overnight checkup with Dalmau at the University of Barcelona Hospital Clinic. After experiencing a perplexing, but fleeting, memory lapse one day in 2019, Serra's memory black hole formed suddenly and irrevocably in March 2020. "I woke up and didn't remember anything," he says. "I didn't remember that my parents had died," more than 10 years earlier.

Physicians initially thought he had a neurodegenerative disease before Dalmau found he had anti-LGI1 antibodies. He improved after immunotherapy, but his memory remains poor, and his personality has changed, says his wife, Montse Serra. Before his illness, he had a short temper. "His aggression has disappeared," she says. The couple has adapted to his new reality: They binge TV dramas, for example, so he can watch an entire series before he forgets earlier episodes. More vexing to Montse, her husband has lost interest in travel. "In other houses I wake up disoriented," he explains.

For Serra, like most patients, what biological match lit the autoimmune fire is a mystery. Teratomas and other tumors set off some cases. In about 5% of anti-NMDAR patients, a brain inflammation caused by a herpes simplex infection later turns into autoimmune encephalitis; researchers think neurons destroyed by the virus release molecules that prompt the production of autoantibodies (see graphic, p. 731). "We're trying to track down other triggers," Lennox says.

Regardless of their trigger, all these diseases are unicorns. Anti-NMDAR encephalitis occurs in only about 1.5 out of 1 million people each year. Still, that means there are thousands worldwide who develop a life-threatening but treatable illness, Lennox says—"not a trivial number of people who might be helped."

**IN GERMANY**, a lucky few patients find their way to Freiburg, on the edge of the Black Forest. On his university's medical campus there, dotted with towering sequoias, Tebartz van Elst established an outpatient autoimmune clinic after receiving a €400,000 gift from a private foundation for schizophrenia research. Patients whose sudden-onset symptoms lead their doctors to suspect autoimmune psychosis are referred here from across the country.

Tebartz van Elst and neurologist Kimon Runge run patients through a standard set of tests: bloodwork, electroencephalography, neurological exams, an MRI brain scan, and in many patients a spinal tap. One of the most definitive tests is the rat brain staining that Dalmau pioneered 20 years ago, which involves daubing the rodent brain slices with samples of a patient's serum or CSF to reveal the signature patterns of known autoantibodies. If the test identifies signs of autoimmunity, patients can be treated promptly.

The Freiburg clinic can be a last resort. Alina Sternberg's diagnostic odyssey began in 2005, when she was a medical student. She loved playing sports, but suddenly started putting on weight and suffering muscle pain after mild exertion. She was treated for an autoimmune disease called Hashimoto's thyroiditis, and her symptoms abated. But in 2017, she was hit with crushing fatigue and brain fog. Over the next 3 years, she visited several neurology clinics but never received a definitive diagnosis. "They said I was depressive. I told them, 'No, I can enjoy my life and I know what depression is.' It was absurd—I'm a psychiatrist!"

Sternberg deteriorated. She struggled to help her husband care for their two daughters, both of whom are autistic, and in 2021 had to close her private practice. By early 2023, she was spending most days in bed. One afternoon she lost her way to her home in Heidelberg, where she'd lived for 20 years. She forgot how to use an ATM. She developed severe muscle spasms and insomnia. "It was a catastrophe," she says.

Sternberg asked a colleague whether she might have autoimmune encephalitis. "He said that was impossible, because I wasn't psychotic." She asked him to test her for neuronal autoantibodies, but he refused, and other

PHOTO: UNIVERSITY OF BARCELONA HOSPITAL CLINIC

neurologists backed him up. "It made me sad and angry that they didn't believe me," she says. Then early last year, she came to Tebartz van Elst's clinic. Her bloodwork revealed antibodies to contactin-associated protein-like 2 (CASPR2), a membrane protein in the central nervous system that's crucial to transmission of neural signals.

The CASPR2 autoantibody levels in Sternberg's blood were borderline, but considering all the evidence, Runge says, the medical team put her on intravenous cortisone. Within days she was jogging again, for the first time in nearly a decade. In November 2023, Sternberg went back to work as a forensic psychiatrist. "It's just incredible," she says. "I got my life back."

Not every autoimmune patient responds so spectacularly, cautions Tebartz van Elst, whose clinic sees several new patients a week. They identify known autoantibodies in only about 1% of their cases—a low number, he says, because other German hospitals and clinics are proficient at catching clear-cut cases of anti-NMDAR and anti-LGI1 encephalitis. In up to 20% of patients they detect unidentified antibodies, and some of those patients also respond well to immunotherapy, he says.

Diagnosis can be tricky, Dalmau notes: All anti-NMDAR encephalitis patients have antibodies in their CSF, but not all have them in their blood, leading to false negative diagnoses if only serum is tested. On the other hand, autoantibodies can turn up in the blood of people without autoimmune disorders, leading to false positive diagnoses. Yet another wrinkle is that commonly used commercial assays, which detect the interaction of antibodies with their protein targets in cells, sometimes fail to find CASPR2 and LGI1 antibodies in the CSF of patients with these types of autoimmune encephalitis. Such diagnostic pitfalls are less likely with the more definitive confirmatory test that uses rat brain slices. But few labs are equipped to carry out such tests—which aren't mandated by current clinical guidelines.

Some experts worry less experienced practitioners are making the wrong call and giving immunotherapy to patients who will not benefit. "We're trying to get them to calm down and not overdiagnose it on a whim," Clardy says.

Immunotherapy is not risk-free, after all. Steroids suppress the immune system, leaving patients vulnerable to infection. And in rare cases, steroids can themselves induce psychiatric symptoms including catatonia, insomnia, mania, and suicidal thoughts. Given these hazards, "enthusiasm has to be very tempered" when doctors suspect autoimmune encephalitis, Clardy says. "It can take years to undo a rash decision."

If first-line therapies fail or offer only temporary relief, the drug of choice has been rituximab, a monoclonal antibody used to treat blood cancers and rheumatoid arthritis. It targets a surface protein called CD20 on B cells, which produce antibodies, tagging these cells for destruction. To test that approach, Lennox's team is heading a clinical trial that is recruiting people with psychosis who have known autoantibodies and mild illness. Half are put on immunoglobulins, followed by rituximab. The other half get a placebo. "There's a track record of false hope with new treatments in psychiatry," Lennox says. "That's why we have to be extra cautious and collect evidence that treatments work to a gold standard."

Meanwhile, a clinical trial at 40 sites around the world is vetting what could become an even more potent treatment. The ExTINGUISH trial, led by University of Utah Health and sponsored by the National Institutes of Health, is recruiting newly diagnosed anti-NMDAR patients to test inebilizumab, a monoclonal antibody used to treat another autoimmune condition. Inebilizumab targets a different antigen on B cells, CD19. Unlike CD20, it's also on the surface of young plasma cells, which means the drug tags for destruction an additional source of autoantibodies. Trial results are expected as early as 2027.

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> **Belinda Lennox**, University of Oxford

**HARALD PRÜSS** of the German Center for Neurodegenerative Diseases and the Charité University Hospital of Berlin is a close collaborator of Tebartz van Elst—and his go-to person for staining rodent brain slices for autoantibodies. Earlier this year he found that the CSF of a 21-year-old piano prodigy diagnosed with schizophrenia produced an enigmatic staining pattern. She improved greatly after immunotherapy. Prüss is now striving to identify the antibody—and perhaps unmask yet another autoimmune encephalitis.

In recent months, he has also been blazing a more provocative trail: a hunt for autoantibodies that might have a role in a wider range of psychiatric ailments. "This is a paradigm shift," he asserts. Whereas high levels of some autoantibodies cause encephalitis, Prüss posits that at lower levels, the same antibodies or others might cause chronic psychiatric illness in a much larger population. In people with depression, for instance, he and colleagues have found autoantibodies that target astrocytes, the most abundant cell in the central nervous system, they reported in *Psychiatry Research* in 2022. The same year, they published a case report in *Molecular Psychiatry* describing autoantibodies against certain cells in the hippocampus, isolated from the CSF of a young woman with obsessive-compulsive disorder.

Prüss suggests that autoimmune reactions might even shape the course of Alzheimer's disease. He points to a recent patient with memory problems who appeared to be developing Alzheimer's. The man's CSF had high levels of autoantibodies to voltage-gated potassium channels (VGKCs), proteins that are key to neuronal signaling. After he was treated with plasmapheresis and rituximab, his condition stabilized for a year before "the underlying genetic disease" began to progress again, Prüss says. This is just a single case study, he says, "but our interpretation is that the antibodies were responsible for a certain fraction of his disease."

Dalmau calls Prüss's conclusions "highly speculative" and notes that other research has failed to verify the clinical significance of VGKC autoantibodies. He adds that few centers now test for them, "due to the high frequency of diagnostic errors." More broadly, he cautions, many antibodies will prove to be red herrings that have nothing to do with disease processes. "Autoimmune psychosis is a sexy concept that sells papers—an enormous number of splashy papers," he says. Tebartz van Elst says, "I accept his skepticism," but argues it is nevertheless important to get preliminary findings in front of peers. "You collect the data and look for patterns," he adds. "And of course, treat as well as you can."

Most autoimmune encephalitis patients face a long road to recovery and never fully regain their old selves. At Tebartz van Elst's clinic, Müller, who has come in for a routine follow-up, is leafing through an album filled with prints of his artwork and mementos of his life before his downward spiral. After a second round of cortisone therapy, he regained the ability to concentrate and express himself coherently, he says. He moved out of his parents' house into his own place. But insomnia keeps him up all night at least once a week. He doesn't expect to be able to practice psychiatry again. "I miss it," he says.

Still, Müller can read books again, and "painting distracts me from my depression," he says. Every Wednesday, his teenage son comes by, and he has monthly visits with his daughters. And he's in a new relationship. "It's been so long since I could truly feel happiness or joy," Müller says. "But at least my life has some meaning again." ■

*All patients in this story have been given pseudonyms to protect their privacy.