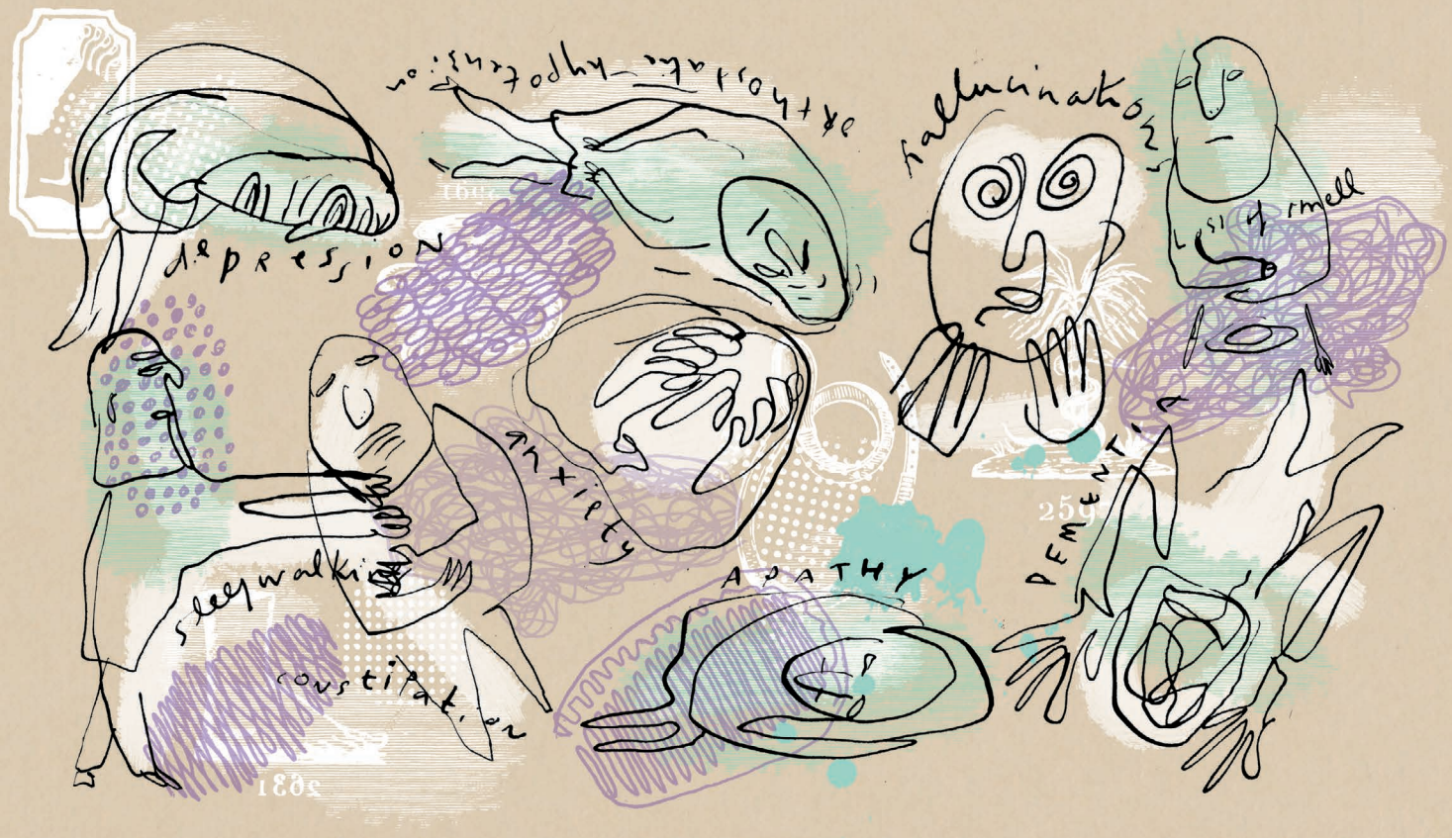


DIAGNOSIS

Warning signs

Non-motor symptoms such as sleep disorders and a poor sense of smell may hold the key to diagnosing Parkinson's disease before the characteristic tremor starts.

SERGE BLOCH

BY KATHERINE BOURZAC

The wild animals attacked almost every night while Mark slept. He would wake up panicked and sweating, having acted out some terrifying scenes. Mark (not his real name) went to a psychotherapist, who led him through talk therapy and psychoanalysis to try to uncover the cause of these terrible dreams. For years, nothing seemed to help. Then he consulted neurologist Brit Mollenhauer, who diagnosed him with Parkinson's disease. Sleep problems were part of Mark's condition. With her help, he finally got the right therapy.

"Everyone thinks Parkinson's disease starts with a tremor," says Mollenhauer, head of clinical research at the Paracelsus Elena Klinik in Kassel, Germany. But before there are any movement problems, she says, "it's already in the body". About half of people who have these sleep issues, known as rapid eye movement (REM) sleep behaviour disorder, will develop Parkinson's within about 15 years. REM sleep behaviour disorder causes vivid dreams and often makes people act them out, because the nervous system's mechanism for keeping the body still during sleep has deteriorated.

When asked to look back on the years leading up to their diagnosis, people with Parkinson's commonly say that they experienced sleep problems, depression and a diminishing sense of smell long before they were diagnosed. Yet, until recently, general practitioners and psychotherapists did not recognize these symptoms as early signs of Parkinson's disease. And even if Mark had been flagged as being at risk, there would have been nothing to offer him to slow the disease.

Those who study the non-motor symptoms of Parkinson's hope to change that. Clinicians are getting better at addressing these issues, and researchers hope to find broader therapies that will do more than treat the individual symptoms. Large studies are also using non-motor symptoms as signals to illuminate the origins and progression of the disease. Finding people who are still in the early stages of the disease, and tracking its development, will be central to measuring the success of new therapies. Non-motor symptoms might also help researchers to untangle the underlying pathology of Parkinson's — and show it to be more complex than previously thought.

It is not yet possible to diagnose Parkinson's until there are movement problems such as a tremor, rigidity or trouble walking. But by the time such symptoms appear, the disease has already progressed significantly. Neurologists have known about the non-movement symptoms of Parkinson's for a long time, but it took years to formally acknowledge them.

ASK THE RIGHT QUESTIONS

"Until recently it was considered a pure motor disorder," says Jaime Kulisevsky, a neurologist at Sant Pau Hospital in Barcelona, Spain. But this is because doctors had not regularly asked patients about other issues. In 2015, the International Parkinson and Movement Disorder Society added olfactory problems and the death of neurons that serve the heart as supportive diagnostic criteria for the disease. These made the cut because they can be quantified by using a 'scratch-and-sniff' test and imaging.

Most Parkinson's therapies, including deep brain stimulation and a precursor to the neurotransmitter dopamine called levodopa, ease tremors and rigidity. These symptoms are caused by the death of neurons that produce dopamine in part of the brain called the

substantia nigra (see page S10). It was only after motor problems were controlled that it became clear that Parkinson's is about much more than just movement and dopamine. Dopamine therapy does not help to relieve the non-motor symptoms of Parkinson's, which seem to be caused by the death of, or damage to, other kinds of neuron all over the body.

The cognitive and psychiatric symptoms have been underestimated partly because patients think they are not relevant to what some people believe is purely a motor disorder. Hallucinations, for example, were thought to be part of the later stages of the disease, so doctors did not routinely ask people newly diagnosed with the disease about them. "If you don't ask, patients typically don't complain about them," says Kulisevsky.

Kulisevsky is particularly interested in cognitive symptoms. As part of a larger, five-year, multicentre study in Spain called COPPADIS, he and his colleagues asked 50 patients whether they experienced hallucinations and, if so, their nature and severity. The results suggested that hallucinations occur much earlier in Parkinson's than previously thought (J. Pagonabarraga *et al. Move. Disord.* **31,** 45–52; 2015). At diagnosis, 30% of patients in the COPPADIS group reported "a sense of presence": a visual, tactile or auditory hallucination that someone or something is standing or moving nearby.

Mild cognitive impairment can also occur early. Kulisevsky often asks family members whether the patient has trouble making a meal or doing two things at once. Identifying these problems is easier now that there is a questionnaire for rating cognitive impairment that is specific to Parkinson's. The latest estimates suggest that up to 20% of people have cognitive issues at diagnosis, and these are not just older patients, says Giselle Petzinger, a neurologist at the University of Southern California in Los Angeles. After five or six years, the proportion has risen to more than 40%.

Furthermore, half of people with Parkinson's have clinically significant anxiety or depression, says Irene Richard, a neurologist at the University of Rochester Medical Center in New York. This is more than just being down about the movement issues: there is no correlation between physical disability in Parkinson's and severity of depression. "Some people don't view this as a symptom of their Parkinson's, but as a failure of will," Richard says. "I tell them: 'You wouldn't say that about your tremor'."

COMMON CAUSE

Clinicians can often treat these non-motor symptoms, such as depression and REM sleep behaviour disorder, with therapies that were designed for other diseases (see 'A whole-body disease'). But treating them individually is not ideal, says Todd Sherer, chief executive of the Michael J. Fox Foundation for Parkinson's Research. "The field is in whack-a-mole mode," Sherer says. The only thing that seems to help multiple symptoms, he says, is exercise.

Petzinger agrees with Sherer on the limits of a symptom-by-symptom understanding of Parkinson's — not only for therapeutic practice, but also for neurologists' understanding of the disease. "We silo them up, but all these non-motor symptoms in Parkinson's disease are interrelated," she says. Even motor symptoms have cognitive aspects: people must constantly make mental adjustments as they make their way through a changing environment.

Petzinger is testing the value of exercises that engage both motor and cognitive circuits in an ongoing clinical trial. People with Parkinson's still retain brain plasticity and can relearn some skills, she says. The exercises in the trial are not "just jumping jacks" or other simple aerobic activities, says Petzinger — they are Parkinson's-specific and are designed to encourage learning and multitasking. Once someone can walk with good posture at normal speed and with a good stride length, the researchers add a second challenge that requires more cognition, such as bouncing a ball while they walk. The trial will evaluate whether symptoms improve after the exercises. These activities will be compared with aerobic exercise alone and, as a control, social interaction.

DISEASE CUES

The pattern and progression of non-motor symptoms provide a window into the underlying mechanisms of Parkinson's disease. Progression seems to tally with where protein aggregates are found in the nervous system (see page S13). The protein α-synuclein forms clumps called Lewy bodies, which have been found in neurons in the parts of the brain that control movement, but also throughout the cortex and the peripheral nervous system. There are hints that Lewy bodies are associated with non-motor symptoms and with damage to parts of the nervous system that depend on neurotransmitters other than dopamine.

The presence of α-synuclein in different places in the nervous system may explain the heterogeneity of Parkinson's symptoms, says

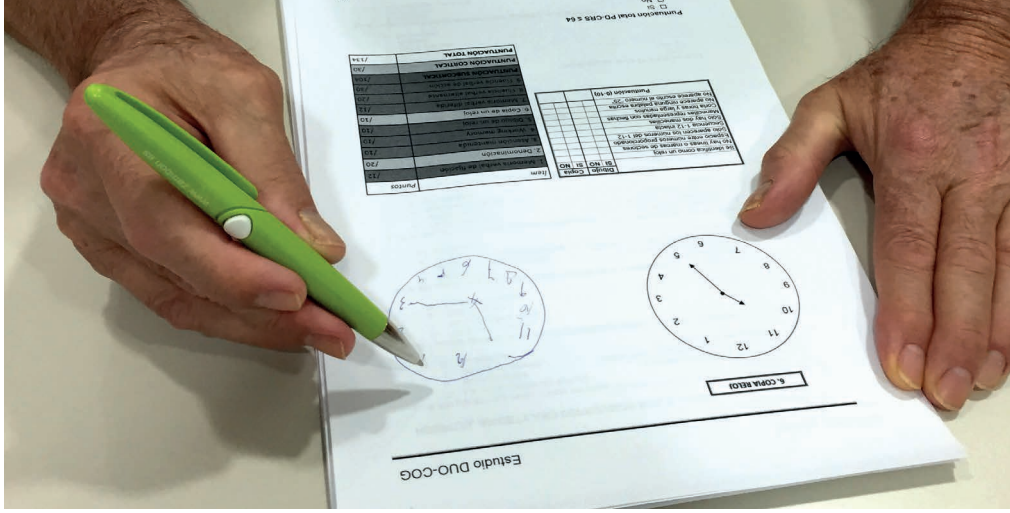
A WHOLE-BODY DISEASE

Parkinson's disease involves the degeneration of nerves around the body and causes a range of non-motor symptoms that vary from person to person. Some of the symptoms can be treated, but only on an individual level. There is currently no global therapy.

Symptom	Description	Pathology	Treatment
Orthostatic hypotension	Sudden drop in blood pressure on standing	Death of neurons that serve the heart	Behavioural therapy (such as standing up slowly)
REM sleep behaviour disorder	Sleepwalking and acting out dreams, which may be unusually vivid	Degeneration of the autonomic nervous system	Benzodiazepines, although these can worsen balance problems and delirium
Anosmia/ hyposmia	Loss, or partial loss, of smell	Unknown, but degeneration of the brain's olfactory bulb is suggested to be an initial stage of disease	None
Hallucinations	Early stages: benign apparitions and a sense of presence; later stages: more disturbing	In early-stage disease, may be linked to degeneration in parts of the brain related to the visual system	None
Depression	Similar to other forms of depression	Unknown	SSRIs, SNRIs, cognitive behavioural and talk therapy, and lifestyle changes
Anxiety	Similar to general anxiety, but may also be associated with motor problems such as freezing	Unknown	Benzodiazepines (see above); a clinical trial is planned for buspirone, which is from a different drug class
Apathy	Lack of desire to do anything, but not caused by depression	Unknown; seems to be associated with mild cognitive impairment	None
Constipation	Similar to generic constipation	Thought to be linked to degeneration of nerves that regulate the gastrointestinal tract	Changes to diet, fibre supplements, probiotics and exercise
Mild cognitive impairment	Difficulty with multitasking and working memory that does not interfere with function	May be due to damage to non-motor areas of the brain earlier in disease	An ongoing clinical trial is evaluating whether exercise improves symptoms
Dementia	Difficulty with function, memory and language, and emotional problems	Significant neural degeneration beyond the motor areas of the brain, into the cortex during end stages	Alzheimer's drugs can provide limited benefits

REM, rapid eye movement; SNRIs, serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

SAÚL MARTÍNEZ-HORTA



The clock-copying test can determine whether a person with Parkinson's also has cognitive deterioration.

John Trojanowski, who studies protein aggregations in neurodegenerative diseases at the University of Pennsylvania in Philadelphia. He compares this diversity of symptoms to the variety of effects from a stroke. "A stroke in the cerebellum might not cause any memory problems, but the tiniest stroke in the hippocampus will," he says. People with Parkinson's develop a core of motor problems, plus a hotch-potch of non-motor symptoms that reflect where the other damage has occurred.

Heiko Braak, an anatomist at Goethe University in Frankfurt, Germany, has proposed that Parkinson's disease proceeds in a series of stages, progressing from non-motor to motor symptoms, which correlate with the distribution of Lewy bodies in the nervous system. The first stage is in the olfactory system, accounting for early degradation of the sense of smell, closely followed by the lower brainstem, which can induce sleep disorders. Braak proposes that motor problems emerge only in the third and fourth stages. In the final stages, when Lewy bodies have reached the cortex, cognitive problems culminate in dementia.

Unfortunately, hypotheses such as Braak staging are difficult to study in living people because there are no imaging agents for α-synuclein, says Trojanowski. The only way to connect α-synuclein distribution with symptoms is to observe the symptoms while patients are alive, and then look for Lewy bodies during an autopsy, which provides only a snapshot. Scientists can also look for the protein in the cerebrospinal fluid of living patients, but the test cannot pinpoint its origins.

The best researchers can do at the moment is image the neurons that are richest in dopamine. In the 1990s, David Goldstein, a neurocardiologist at the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, developed a radiotracer called fluorodopamine to visualize dopamine neurons with a positron emission tomography scan, which led to an unexpected discovery. About half of people with Parkinson's have orthostatic hypotension: when they stand up, their blood pressure drops. Goldstein showed that this effect is correlated with the death of dopaminergic neurons in the heart (D. S. Goldstein *et al. Neurology* **58,** 1247–1255; 2002). "This was the first clear evidence for a mechanism of a non-motor aspect of Parkinson's disease," he says.

EARLY WARNINGS

Goldstein is now using his imaging tracer to find signs of Parkinson's earlier in the course of the disease. Current trials are hindered by the fact that it is only possible to enrol patients in the later stages of disease. This is because a Parkinson's diagnosis can be made only once motor symptoms appear, by which time about half of a patient's dopamine neurons have already died, says Sherer.

To do better clinical trials, researchers must find participants earlier and track the progression of the disease. They must also identify the right mix of risk signals, including non-motor symptoms. The difficulty here is that the symptoms are so diverse, and each seems to correlate only weakly with the risk of developing Parkinson's disease. About 95% of people with Parkinson's gradually lose their sense of smell, but so do many people with Alzheimer's and schizophrenia.

Several groups are trying to eliminate these uncertainties by combining non-motor risk signals with biomarkers and imaging. Kenneth Marek, president of the Institute for Neurodegenerative Disorders in New Haven, Connecticut, is involved in the Parkinson's Associated Risk Study (PARS), which is exploring whether the loss of smell can be combined with imaging to help detect the disease earlier. PARS leaders sent standardized scratch-and-sniff tests to thousands of people who had been pre-screened online, and received 5,000 tests back. The researchers selected the respondents with the worst sense of smell in their gender and age groups for further study. Of these, 203 were given extensive clinical tests and dopamine-imaging studies; 23 were found to have both a poor sense of smell and abnormally low dopamine levels, so were considered to be at high risk of developing Parkinson's. Of these, 14 (61%) went on to develop the disease over four years of study (data from a poster by D. Jennings *et al.* at the 18th International Congress of Parkinson's Disease and Movement Disorders, 2014).

"If you have lost these neurons, it's not a matter of risk — you have the disease."

Meanwhile, Goldstein is leading a US National Institutes of Health (NIH) study called PD Risk that looks at the correlation between nerve loss in the heart and neurotransmitter levels, measured in both the spinal fluid and in imaging scans. Goldstein presented preliminary results at the World Parkinson's Congress in Portland, Oregon, in September. In the trial, NIH researchers started with 3,176 individuals, from whom they identified 22 who had three or more risk factors, such as diminished sense of smell and REM sleep behavioural disorder. They imaged this group using three different tracers for dopamine and related metabolites. After 3 years, 4 of the 22 had developed Parkinson's, and 2 were diagnosed with a related disease called Lewy body dementia. All those who developed Parkinson's had low levels of dopamine on imaging tests, which Goldstein said suggests that the test can identify high-risk patients. "If you have lost these neurons, it's not a matter of risk — you have the disease. It's a matter of time," says Goldstein.

To measure progress in a clinical trial, not only do researchers need to identify people in the earlier stages of disease, but they also need to find reliable, quantitative biomarkers that can track disease progression (see page S4). "We treat heart disease by bringing blood pressure down, we treat viral load to prevent AIDS, because these things are strongly correlated," says Marek. When these numbers change, pharmaceutical companies and doctors know a drug is working. Marek hopes to find the Parkinson's equivalents.

Marek and Mollenhauer hope the criteria for the early identification of people at high risk of the disease will be sharpened by a large, international study called the Parkinson's Progression Marker Initiative (PPMI). The PPMI, which has recruited 100 people at high risk of disease, 400 recently diagnosed patients and 200 healthy controls, is designed to find correlations between clinical signs such as a diminishing sense of smell and biomarkers such as levels of neurotransmitters in the spinal fluid, and imaging and blood biomarkers. Because of its size and scope, the PPMI could identify the right mix of signals that warn of early onset, as well as mark progression.

Neurologists know that the severity of non-motor symptoms determines the quality of life for people with Parkinson's. Now they hope that these symptoms will help them to diagnose the disease before movement problems begin. "People who are at risk, but don't have it yet, are the ideal group to try to slow the degenerative process," says Goldstein. Non-motor symptoms may be the best guides in the search for treatments that can slow Parkinson's disease or even stop it in its tracks. ■

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