THOUGHT EXPERIMENT

Japanese hospitals are using near-infrared imaging to help diagnose psychiatric disorders. But critics are not sure the technique is ready for the clinic.

BY DAVID CYRANOSKI

In a room full of psychiatrists in downtown Tokyo, I prepare to have my mental health assessed. No probing questions are asked. Instead, I don an odd type of swimming cap, criss-crossed with cables and studded with red and blue knobs. At the flick of a switch, the 17 red knobs send infrared light 2 to 3 centimetres into my brain, where it is absorbed or scattered by neurons. Photoreceptors in the 16 blue knobs retrieve whatever light bounces back to the surface. Buried in the signals, say the researchers operating the system, are clues that can distinguish depression, bipolar disorder, schizophrenia and a normal state of mind.

More than 1,000 people have already been subjects of the technique, called near-infrared spectroscopy (NIRS) and developed by Masato Fukuda, a psychiatrist and neuroscientist at Gunma University Hospital in Maebashi, and the Hitachi Medical Corporation in Tokyo. Most of those were research subjects. But since April 2009, when NIRS was approved by the health ministry as an "advanced medical technology" to assist psychiatric diagnoses, more than 300 people have paid ¥13,000 (US$160) out of their own pocket to access the technique. The University of Tokyo Hospital, one of eight leading Japanese research hospitals now offering NIRS diagnostic neuroimaging, found demand for it to be so high that the hospital stopped taking appointments twice. Gunma University Hospital is fully booked to the end of March. "We've been overwhelmed by requests," says Fukuda.

The appeal of NIRS is its promise of fast, clear-cut diagnoses of psychiatric conditions which, with their messily overlapping symptoms, are frequently diagnosed wrongly or not diagnosed at all. US studies, for example, found that some 70% of bipolar patients were initially misdiagnosed[1,2]. As for patients, says Fukuda, "They want some kind of hard evidence," especially when they have to explain absences from work.

NIRS could offer an objective measure of mental health reliable and convenient enough for routine use in the clinic. Fukuda says that it can help point to a diagnosis much like a chest X-ray might be used to help diagnose pneumonia or an electrocardiogram to define a heart problem. Aside from Fukuda and a group of doctors in Japan, however, few scientists are persuaded.

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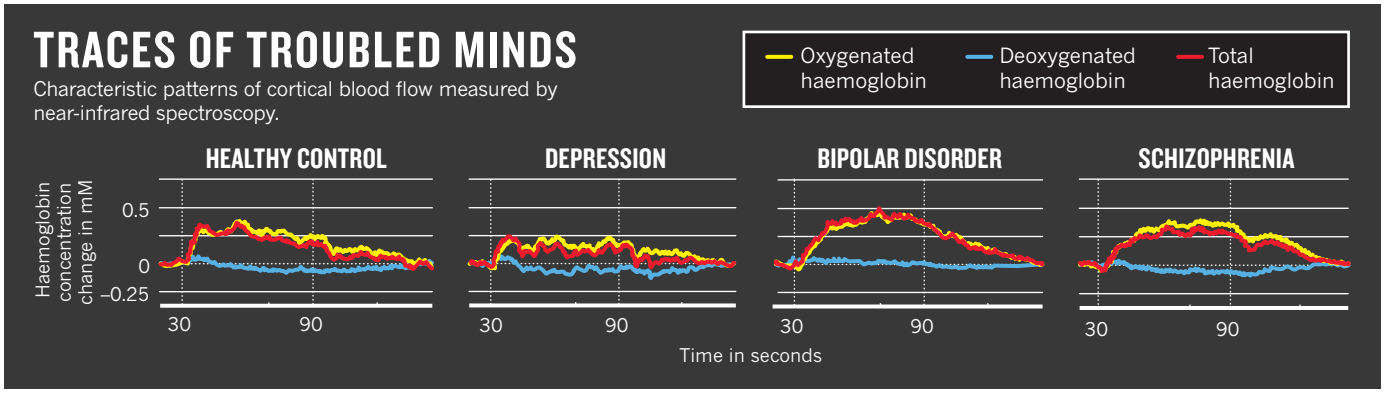
Critics charge that the studies so far have been too few, too small and too weakly designed to warrant the technique's clinical use. "It's attractive as a research topic, but the data are not convincing enough," says Masahiko Haruno, a neuroscientist at Tamagawa University in Tokyo. John Sweeney, a neuroscientist at the University of Illinois, Chicago, who has spent two decades looking for connections between various brain-monitoring techniques and diseases such as schizophrenia, says that "none has ever been validated to anyone's satisfaction". And NIRS is the least developed of them all, he says, calling it "the thinnest of ice to be treading upon. We are nowhere near ready to tell patients and families that they should have these kinds of tests."

Y. AOYAMA

NEW KID ON THE BLOCK

Sporting the knobbled cap, I stare at a screen showing Japanese phonetic characters and say aloud words beginning with each sound. The words don't come readily, particularly in front of an audience of psychiatrists and neuroscientists. Coming from all over Japan, they meet every month to discuss NIRS results and strategies.

Having entered the research scene some 15 years ago, NIRS is relatively new compared with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), but in Japan it has raced ahead to the clinic. (The two biggest suppliers of NIRS analytic devices — Hitachi and Kyoto-based Shimadzu — are both based in Japan and the country accounts for two-thirds of publications using NIRS analysis.) The technique takes advantage of the fact that compared with constituents of other tissues, haemoglobin in blood absorbs more light in the near-infrared spectrum. Blood flow to a particular brain region increases when neurons there are active. So monitoring the changes in haemoglobin concentration gives a site-specific read on blood flow and thus on neuronal activity[3]. Fukuda's NIRS device focuses on the prefrontal cortex and temporal cortex, regions that are implicated in many of the symptoms seen in psychiatric disorders; the signature pattern of blood flow associated with each disorder is used to help diagnose it. NIRS lacks the precision and depth of fMRI, which can pinpoint changes in blood flow throughout the brain and with much greater spatial resolution.



SOURCE: M. FUKUDA *ET AL.* IN: FUKUDA M. (ED) *NIRS AND PSYCHIATRIC DISORDERS* (NAKAYAMA SHOTEN, 2009)

Left: Headgear for probing blood flow in the brain with near-infrared light.

But NIRS is relatively cheap and mobile, and subjects can sit upright without having to endure a spell in the large, loud and sometimes nerve-wracking tube of an fMRI machine. This means that NIRS is easier to use on fidgety subjects such as children, and people with psychotic conditions or anxiety. The advantages have made infrared imaging increasingly popular with brain researchers worldwide. Devices from the largest maker in the United States, NIRx Medical Technologies of Glen Head, New York, are being used to study areas ranging from autism to brain–computer interfaces. Hitachi now offers a stripped-down version that allows the brains of four people interacting in a room to be analysed wirelessly.

Fukuda, though, has focused on applying the technology to diagnoses. Lean and grey-haired, he speaks thoughtfully and is confident in the technique and its potential to help people. He started using a basic NIRS device in 1997, when he was an associate professor at the University of Tokyo already working with EEG. Since then, he has been measuring the brain activity of people with a variety of disorders and has reported that those with depression, bipolar disorder or schizophrenia have, when averaged across groups of 10–20, a characteristic pattern of brain activation[4,5]. Fukuda boils the data down to graphs describing activity in the prefrontal and temporal cortices for the first 60 seconds or so of each task (see 'Traces of troubled minds'). He says that the NIRS test on its own classifies patients correctly 80% of the time.

These studies have not convinced other neuroscientists. Haruno says the patient numbers in the published studies are "far too small" to distinguish patterns, and that even if such patterns are found when signals are averaged across groups, this does not mean that one person's pattern can be used to assign them to a group. "What does that mean for an individual patient? It's very misleading," Haruno says.

Even Fukuda's collaborator, Andreas Fallgatter of the University of Tübingen in Germany, who has used NIRS for 14 years on about 1,000 patients and is now repeating Fukuda's language test in German, says "NIRS is still a research method." Still, he says, "Obviously, Dr Fukuda could successfully convince the Japanese authorities."

That approval came via a fast-track process instituted by the national health ministry's Advanced Medical Technology programme in 2005 in an attempt to spur the development of biomedical technologies. Teruhiko Higuchi, a clinician and researcher specializing in depression and president of the National Center of Neurology and Psychiatry, led the evaluation of NIRS. He concluded that the technology was safe, effective and fast, and could help to make critical distinctions between different mental states (major depression, bipolar disorder or schizophrenia) at an early stage, when used with other diagnostic techniques. "It is, in the end, only to assist diagnosis," he told the members of the evaluation committee, according to meeting minutes posted online. Higuchi's centre now offers the technique. Other committee members raised concerns about the small numbers of patients in the studies, and the fact that some were receiving drugs, but they did not object to its approval.

Fukuda says that a larger study involving more than 500 patients will be submitted for publication soon and will answer many of his critics. He says that doubling the number of knobs and other methodological modifications reveal a much sharper distinction between the conditions, and that controlling for medicated versus non-medicated patients showed that drugs do not obscure a patient's NIRS profile. He acknowledges the validity of criticism about using group averages to diagnose individuals: "Strictly speaking, this criticism is right." But he says the same is true for many other measurements, such as electrocardiograms and EEG, which vary from one individual to the next and thus require interpretation, but can still be clinically useful. "Clinical diagnosis and NIRS examination are complementary to each other," he says. "We stress this complementary nature to all the patients."

But in at least some cases, NIRS seems to take the lead in diagnosis. For example, when Fukuda calculates his success rates, NIRS results that match the clinical diagnosis are considered a success. If the results don't match, Fukuda says he will ask the patient and patient's family "repeatedly" whether they might have missed something — for example, whether a depressed patient whose NIRS examination suggests schizophrenia might have forgotten to mention that he was experiencing hallucinations. Andreas Meyer-Lindenberg, an expert in neuroimaging and mental health at the University of Heidelberg, Germany, says that studies of patients without an existing diagnosis or psychiatric medication would be more persuasive. "You would need a sample of unclear cases, as you would get in the clinic, classify them and then ascertain their diagnosis by following them up."

DEMAND WAS SO HIGH THAT THE HOSPITAL STOPPED TAKING APPOINTMENTS TWICE.

Fukuda and his colleagues are already moving on to NIRS studies that might aid diagnoses of a range of disorders, including those centring on panic, attention deficit and post-traumatic stress.

My own NIRS results, however, are short on clarity. Within 15 minutes, including the tests and a quick computer analysis, Fukuda is able to look at my traces and deliver a diagnosis: normal. When I later compared them to the patterns published in the literature, however, my trace seems to describe a brain somewhere between normal and bipolar.

Later, Fukuda says that my pattern is not a normal 'normal' NIRS trace, perhaps because the observers in the room made me hesitate to speak. He also says that a subset of healthy subjects has the pattern that I do in the frontal lobe and that data he measured from the temporal lobe helped him reach a diagnosis. However they are reached, I suppose I should be happy about my results. ■ SEE EDITORIAL P.132

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