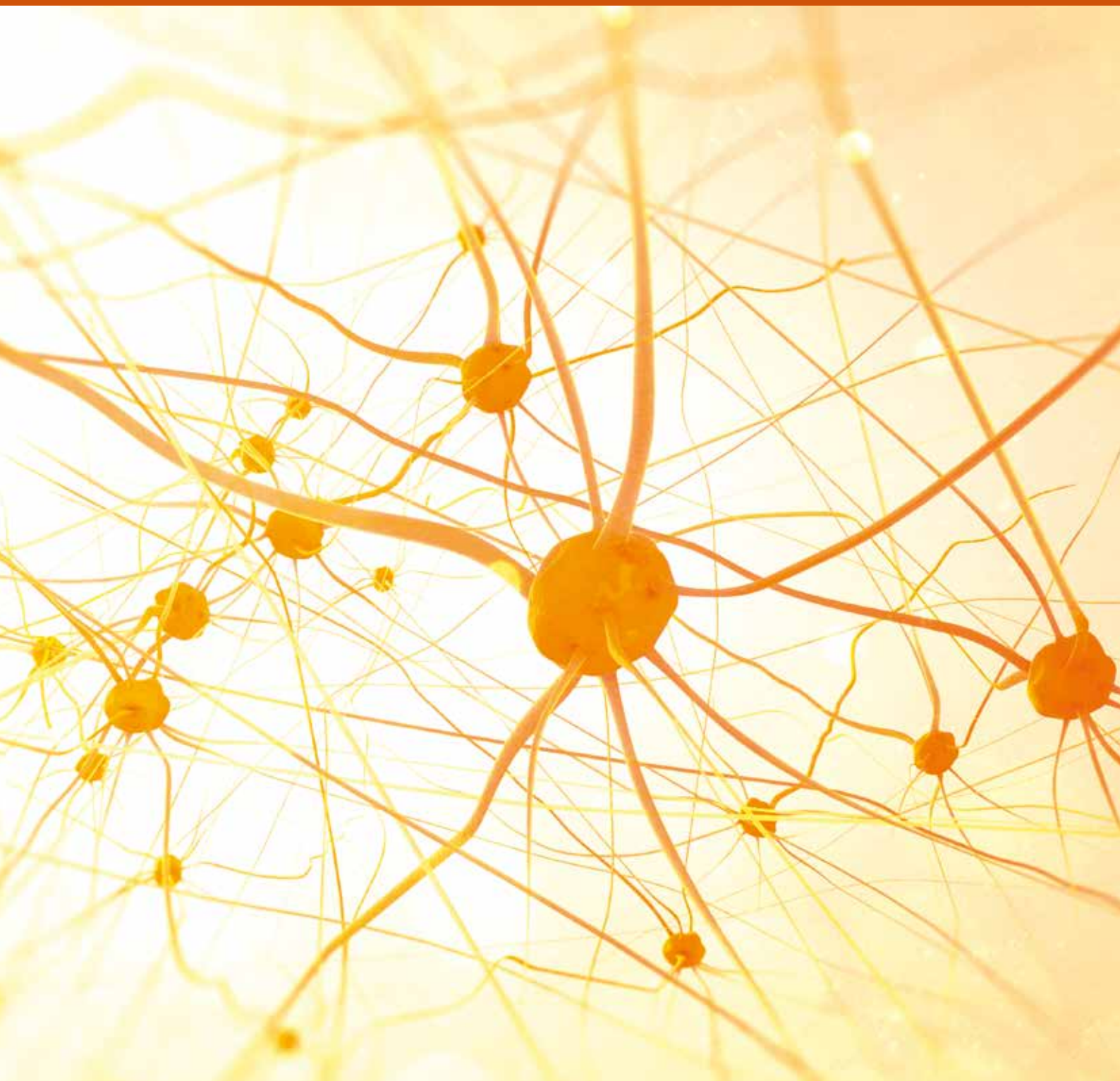
IMPACT

A CLEARER PICTURE OF MENTAL DISORDERS



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A clearer picture of mental disorders

*A lab at the **National Taiwan University College of Medicine** is using sophisticated imaging technology to reveal aspects of the brain that could be used to diagnose and treat schizophrenia more effectively and at an earlier stage*

The symptoms of schizophrenia can be as erratic as the thoughts of someone affected by the condition. They range from emotional flatness and depression through to hallucinations and delusions. While physicians are trained to recognise these symptoms, due to their subjective nature diagnosis is open to a fair degree of uncertainty. This is an issue, because contrary to popular assumption schizophrenia is not a rare condition; typically first occurring during a person's youth, the lifetime prevalence rate is around 0.7 per cent for the entire population. Medication is available, but the effects of the various drugs on offer vary greatly from person to person, which is why there is a need to establish not only whether or not a person has schizophrenia as early as possible, but also what therapy works best for them.

What is really needed to improve both diagnosis of schizophrenia itself, and assignment of the best treatment, is a more quantitative way of looking at the condition. As it stands there are no biomarkers available that physicians can use when they are trying to establish whether or not someone is showing symptoms of schizophrenia. However, this is something that a pioneering team based in Taiwan is currently trying to change. Professor Wen-Yih Isaac Tseng leads the Advanced Biomedical MRI Lab at the National Taiwan University College of Medicine (NTUCM), and he is leveraging his extensive professional experience using advanced imaging techniques to tackle the problem of individualised schizophrenia diagnosis. 'Our recent work demonstrates that it is potentially feasible to discover imaging biomarkers for early diagnosis and prediction of treatment response in schizophrenia,' he reveals. 'It will create a brand-new field in radiology to diagnose schizophrenia or other mental disorders.'

TESTING THE TRACTS

Though schizophrenia is still a largely mysterious condition, basic research has indicated that it does have a genetic component. In particular, it has been linked with genes that control the development of glial cells in the brain, which in turn are responsible for producing the myelin sheaths that coat the outside of the axons of nerve cells, or neurons, and allow them to conduct electrical signals. This is why schizophrenia is sometimes referred to as a dysconnectivity syndrome, that is, a disorder that arises from problems with the connectivity of neurons in the brain. The white matter of the brain is the inner region, which is composed of myelinated axon bundles. Alterations in the structure of white matter are known to be prevalent in schizophrenia patients, which adds to the evidence that changes in axon myelination – resulting from disrupted glial cells – are involved in the condition's onset.

The key innovation that Tseng and his colleagues have been working on is a novel method they call tract-based automatic analysis (TBAA). To undertake this they use a technique called diffusion spectrum imaging (DSI), developed by Tseng and his then-colleague at Massachusetts General Hospital, USA, Professor Van Wedeen, back in 1999. DSI is a type of advanced diffusion magnetic resonance imaging (MRI), which enables researchers and clinicians to resolve crossing of axonal fibre tracts in the brain, enabling them to look for altered connectivity in a variety of neurological diseases or mental disorders. With this, they can examine the structure of the brain's white matter. Specifically, by looking for impairments in the tracts – or axons – the researchers are able to make accurate predictions about the onset of schizophrenia in the patient in question, as well as their response to antipsychotic medication.

PREDICTING SCHIZOPHRENIA

To demonstrate this, the NTUCM team recruited schizophrenia patients who have been diagnosed by psychiatrists using traditional, observation-based methods. They also recruited a cohort of healthy patients who not only themselves had no previous history of neurological or mental disorders, neither did their immediate family. Using TBAA to analyse the DSI and structural images that the researchers obtained from their test subjects, they built up a picture of the microstructure of tracts across the whole brain. 'With the information about tract integrity along 76 fibre tracts, we are able to examine the differences between patients and healthy subjects, or perform machine learning to determine a model that best predict disease or treatment response,' explains Tseng.

> *'Our recent work demonstrates that it is potentially feasible to discover imaging biomarkers for early diagnosis and prediction of treatment response in schizophrenia. It will create a brand-new field in radiology to diagnose schizophrenia or other mental disorders'*

The results of these experiments revealed that certain aspects of the tracts in question make them viable biomarker candidates. Some tracts, for example, appear to become impaired very early in the course of the disease, presenting a warning sign to any doctor performing these tests on a patient. Other tracts only appeared to show impairment in patients who are known to show particularly poor response to antipsychotic medication. This could mark these patients out as being suitable for different kinds of treatments, and avoid any unpleasant side effects from unhelpful drugs.

THE CHALLENGE OF VARIATION

These results are promising, but Tseng notes that they have not been easy to obtain. Working with a condition as heterogenous as schizophrenia is difficult, not least because differences between the patients can cause unpredictable variations that could confound the findings from the TBAA. 'It is almost impossible to have a group of patients with uniform clinical manifestations,' says Tseng. However, one way to standardise future experiments, according to Tseng, would be to incorporate people who have only just experienced their first schizophrenic episode into the trial. As their experience of illness is new, and they haven't undergone any courses of antipsychotic medication that could affect outcomes, these individuals might provide clearer insights into the potential tract biomarkers under scrutiny. Such measures would require extensive collaboration with other medical facilities, as first-episode schizophrenia patients only occur in the NTUCM hospital around ten times in a year. However, collaboration is nothing new to these researchers. They are used to working in an extensive team that covers both basic research and clinical work, because of course they rely on psychiatrists to recruit their patients for them. The back-and-forth between the research team and the psychiatrists is essential to the project, and reflects their commitment to making discoveries that benefit both clinicians and patients. By identifying illness at an early stage, effective treatments can be administered as soon as possible. This will ultimately mean a future in which unnecessary upset is avoided.

Going forward, the NTUCM researchers are gathering more evidence for the effectiveness of their biomarker-based methods. They are recruiting patients at different stages in the condition, and are supporting their image collection with analysis of neurocognitive deficits, event related potentials, genetic variants and peripheral blood biomarkers as well. Tseng and his team have been working on this problem for ten years, and have collected hundreds of DSI images in that time. Ultimately, they would like to see their work becoming standard procedure for clinicians who want to offer individualised treatment to patients with mental health disorders.

Project Insights

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Professor Wen-Yih Isaac Tseng is the Chief Director of the National Taiwan University Molecular Imaging Center, and a professor in the Institute of Medical Devices and Imaging. Prior to this he was an instructor in radiology at Massachusetts General Hospital, USA, and a postdoctoral research fellow at Harvard Medical School, USA.

Ministry of Science and Technology

Impact Objectives

- Find magnetic resonance imaging (MRI)-based biomarkers for early diagnosis and prediction of treatment response in schizophrenia
- Provide clinicians with objective laboratory examinations that can be used to diagnose schizophrenia and assign appropriate antipsychotic medication

Signs of schizophrenia

Diagnosing schizophrenia is challenging due to the variety of ways patients with it behave and react to treatments. ***Professor Wen-Yih Isaac Tseng*** *and* ***Dr Chih-Min Liu*** *are part of a team hoping to improve the situation by finding biomarkers that can be used to predict onset of the condition*

Professor Wen-Yih Isaac Tseng

Dr Chih-Min Liu

What is diffusion magnetic resonance imaging (MRI), and how does it help you understand the inner workings of the brain?

W-YIT: I have been working on advanced diffusion MRI techniques for more than 10 years. Diffusion MRI can measure cellular orderliness and orientation of the microstructures in our body. One of the most fascinating applications is using it to uncover 3D pathways of neuronal fibre tracts in the brain and quantify microstructural properties along these pathways. With this information, we can understand the wiring scheme of the brain. Specifically, we can understand how the brain is connected from region to region, and how robust those connections are. This tool is very suitable for studying white matter tract impairment in so-called dysconnectivity syndromes such as schizophrenia.

How are you trying to improve diagnosis of schizophrenia?

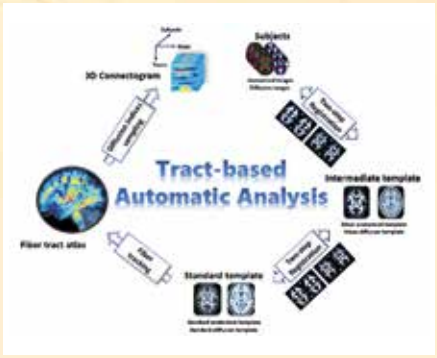
W-YIT: The goal of my research is to find MRI-based imaging biomarkers for early diagnosis and prediction of treatment response in schizophrenia. Our results show that microstructural properties as measured by diffusion MRI can be exploited to distinguish patients with schizophrenia from healthy people, as well as patients with good responses to medication from those without. Specifically, we use a machine learning approach to develop algorithms for individualised prediction of the disease and its prognosis. Currently the accuracy is around 80 per cent. We are planning to validate our method by testing the diagnostic performance in people who are in the subclinical phase of the disease, or in drug-naïve patients who are just starting to take antipsychotic medication. If these prospective studies yield positive results, our method can be considered viable to provide imaging biomarkers with clinical values

Why is there such a need for biomarkers to diagnose people with schizophrenia? Are the current methods used for diagnosis unreliable?

C-ML: Current diagnosis of schizophrenia is based on the operational criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), mainly through clinical interview. The procedures are subjective and subject to information bias. Also, schizophrenia defined by DSM-5 criteria is heterogeneous in terms of aetiology, treatment response and prognosis. Currently there is a lack of objective laboratory examinations that can be reliably used for the diagnosis of schizophrenia.

Why is assigning antipsychotic medication to patients with schizophrenia such a challenge?

C-ML: Currently, the mechanism employed by all of the antipsychotics on the market is dopamine receptor-related. The main differences between first-generation and second-generation antipsychotics are



Workflow of tract-based automatic analysis (TBAA), from top and proceeding clockwise.

the side effect profiles, and there are also differences in side effects among different classes of second-generation antipsychotics. We are still finding it hard to predict the treatment response to the specific antipsychotics we select for treatment. Therefore, it is still far away from individualised medicine. The main reason this is so challenging is that the diagnosis of schizophrenia is still so heterogeneous in terms of aetiology, treatment response and prognosis. That is why it is in dire need of purifying clinical phenotypes through reliable lab examinations.

What are the most interesting findings you have arrived at so far?

W-YIT: Our most interesting findings are that there are fibre tracts that are characteristic for the presence of schizophrenia, even at the very early stages of the disease, and there are also other fibre tracts that are characteristic for poor response to treatment. These tracts are potential imaging biomarkers to diagnose disease or predict treatment outcomes on an individual basis. This will potentially be valuable for clinicians.