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Mapping brain and body connections

In this Q&A, we speak to Andrew Zalesky, professor at the University of Melbourne, a co-leader of the Systems Lab and awardee of the prestigious Rebecca L. Cooper Fellowship that provides US$1.35 million over 5 years to study brain networks in health and disease and develop high-tech psychiatric therapies based on brain stimulation. He also led the development of the Melbourne Subcortex Atlas and is recognized for the novel tools he has developed to analyze brain networks.

Thank you for taking time to talk with us. Can you tell us a little bit about yourself. Your background is in engineering and mathematics, and I'm curious to know at which point and how you got interested in the human brain and psychiatry?
Yes, that's right. My PhD is in electrical engineering and I focused on mathematical modeling of optical telecommunications networks. At that time, I can't say that I had a deep interest in the human brain and psychiatry. In the last year of my candidature, I applied for a part-time coding job at the Melbourne Neuropsychiatry Centre, which involved coding automated pipelines to process magnetic resonance imaging (MRI) scans in people with schizophrenia. Around that time, the first human connectome was mapped, and I started to recognize how my expertise in telecommunications network modeling could potentially be used to study and map brain networks. I became excited about these parallels and established a new method to estimate brain connectivity from a person's brain scans. The following year, I was fortunate to receive a postdoctoral fellowship from the Australian Research Council to continue this research on the connectome, and so my career in neuroscience and neuropsychiatry had officially begun. As you can see, my switch to human brain networks was largely by chance. None of this would have been possible without the fantastic collaborators at the Melbourne Neuropsychiatry Centre and the support that they provided.

What do you think are the main things that connectomics and computational approaches have revealed to us about brain function and mental disorders?
Connectomics has reinforced the view that mental disorders involve disruptions across several brain regions and systems. This is not a new view though. Pioneers such as Emil Kraepelin, Eugen Bleuler and Carl Wernicke thought that schizophrenia was a disorder of abnormal brain integration. But these psychiatrists didn't have the tools to test their hypotheses. It was only with the advent of diffusion-weighted imaging and connectomics in the past two decades or so that we have been able to prove them right. I'm currently most excited about the potential for connectomics to help guide brain-based interventions for psychiatric disorders and that's a key focus of our work now.

What are you currently working on?
Our team recently developed technology to personalize brain stimulation targets for depression. The basic idea is that stimulation is targeted to cortical sites that optimally suit a person's unique brain connectivity architecture. We hope that this improves treatment efficacy, and we are currently running a large-scale trial in Australia to test efficacy. Together with our clinical collaborators, we recently opened the first clinic in Australia to offer our personalization technique via robot-assisted transcranial magnetic stimulation (TMS). A new and unrelated research direction in our group is mapping brain–body axes and understanding the effect of physical health comorbidities on brain function in mental health disorders. This is an exciting area for our group because physical health is so often overlooked in psychiatric care and services.

Exactly, psychiatric disorders often co-occur with physical illnesses, and your own work[1] from the past year has shown that poor body health was a more pronounced illness manifestation compared with brain changes in several neuropsychiatric disorders. Unfortunately, mental health research seems to have drifted away from somatic health. Do you think that not only physical health care should be integrated into treatment but also that somatic health domains need to be considered to capture the biotypes of depression and other psychiatric disorders in a more reliable way?
I'm glad that you asked! Recognizing and managing chronic physical health conditions in people with mental health disorders is such an important topic in my view. Diabetes, obesity and hypertension, for example, are way more prevalent in people with schizophrenia and depression, yet these physical comorbidities are often overlooked and undertreated. Managing these comorbidities is crucial because they are tightly linked with brain health. We think that treating chronic physical health conditions can improve brain and mental health. The body and brain are connected not only via the nervous system, but also by hormonal, immune, gastrointestinal and many other body systems. Disturbances in these systems can ultimately impact brain function and potentially exacerbate mental health symptoms. So, we need to adopt a more holistic approach to treating mental disorders, integrating both physical and mental health.

When we talk about big data, it is not just the volume and modalities' features that make them 'big'. One of the key factors is capturing heterogeneity, as individual data are extremely heterogenous even within the spectrum of one disorder. To harness heterogeneity using representative samples, rather than just

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using big samples that are often not at all representative, is crucial. What in your opinion are the best strategies to ensure the high representative value of the sample, from the demographic, clinical and other perspectives?

Big data are important but big data per se are probably not going to solve many of the challenges facing our field. We know that most large neuroimaging cohort studies such as the UK Biobank are not representative in certain demographic and clinical dimensions. Although large-scale cohort studies are of course valuable, I still think that we need to support smaller-scale neuroimaging studies undertaken in targeted clinical cohorts. Researchers are less willing to acquire new neuroimaging data nowadays owing to the abundance of established biobanks. While this is clearly a win for open science and resource sharing, I worry that it may stifle research into rare disorders and conditions that are underrepresented in large-scale biobanks.

Neuroimaging is an expensive method, especially for implementation into clinical practice when we talk about personalizing treatment and predicting treatment response. What are your thoughts on this, and as there is also work being done on much less expensive electroencephalography in this direction, do you think it could be a more scalable alternative?

Yes — MRI is expensive and accessibility remains an issue in many developing countries. That said, if acquiring an MRI scan can improve treatment efficacy by only a small percentage (for example, by personalizing treatment), the economic benefits can be enormous and far outweigh the cost. We need a health economist to crunch the numbers. Portable brain MRI systems may further reduce costs and improve accessibility in the future. Electroencephalography is an important modality, but it currently is not as good at capturing brain activity in deep subcortical structures compared with MRI. These are the structures that we are usually most interested in studying in many psychiatric disorders. Work is still needed to establish low-cost and readily available proxies for the MRI-derived markers that we currently use in the clinic to personalize TMS therapy.

Mental status can change very rapidly. The current behavioral scales are often retrospective and static. However, to understand patterns of variation across time we would need more dynamic measurements. What are your thoughts on this?

This is an important issue and one of the likely reasons why brain–behavior associations are often weak and not reproducible. Wearables and smart devices can yield huge amounts of data about a person's daily rhythms and can potentially provide insight into psychiatric episodes. These data can also be analyzed in real-time, allowing for adjustments to an intervention based on a patient's dynamic behavior. I am currently involved in a project that aims to use anonymized data from a patient's phone to predict acute bipolar episodes. An ethical challenge in this area is individual privacy and data security concerns.

For precision psychiatry to become fruitful we need to bring patient input at each step of precision, so that precision is achieved not only from the scientific but from the patient perspective. There is a good quote for this "No decision about me without me". Can you tell us a bit what work is done in this respect in the Australian clinics and research and how do you bring the lived experience into your own work?

The concept of lived experience is relatively new in Australia, but it is now expected when designing and planning most clinical studies. My experience in this area is limited but I can say that most individuals with lived experience are usually very keen to provide feedback and participate in community outreach. With the support of the Tally Poppy Foundation, a few years ago, I teamed up with a person with a lived experience and we participated in a school outreach program aimed at raising mental health awareness. Having both perspectives really captivated the students.

What do you think are big questions that the psychiatry field faces?

This is a difficult question and I bet that if you asked ten different people, you'd probably get ten different responses. Taking the perspective of a computational neuroscientist working in psychiatry, I often ask myself whether the new models and algorithms that we develop will ultimately improve the lives of people living with mental health conditions. As a field, we are often (too) focused on developing evermore fancier models and methods that might be more accurate, overcome technical limitations, and bring to light novel analytical paradigms. And although these advances are undeniably important from the perspective of scholarly rigor, it is often unclear whether they will ever truly benefit an individual with a mental health condition. That is why fostering clinical translation pathways and building stronger bridges between clinical and basic research is crucial.

Interviewed by Natalia Gass

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References

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