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While attending a conference a few years ago I had the opportunity to make a pilgrimage to the Museo Galileo in Florence. Amongst the displays of early telescopes, and the bizarre spectacle of Galileo's preserved middle finger, I read a quote from the great scientist that stopped me in my tracks: 'Measure what is measurable, and make measurable what is not so'. At the souvenir shop I was able to buy a t-shirt with this particular quote. While my secular relic is not as intimate (nor defiant) as the grisly finger, this t-shirt gives me great comfort when jogging. Even nerdy psychiatry professors need heroes.

Australian researchers do not have to look far afield for inspiration. John Cade is a hero for Australian psychiatry (Cole and Parker, 2012; Mitchell and Hadzi-Pavlovic, 1999; Malhi and Gershon, 2009; Schioldann, 2009), and it is a great honour to receive a fellowship named after this pioneer. In this viewpoint, I will outline the scope of the work that will be supported by the John Cade Fellowship.

It was clear by the 1990s that the epidemiology of schizophrenia was much more interesting than previously thought (McGrath, 2007). Contrary to dogma, my research indicated that the incidence of the disorder varied widely (e.g. the high risk in dark-skinned migrants to the UK), and that schizophrenia affected men more than women (McGrath et al., 2004; McGrath, 2006). The oft-regurgitated mantra about schizophrenia affecting one in a 100, males and females equally, and with a constant

incidence across all sites, was not supported by the data (McGrath, 2005). Many researchers had measured the incidence of schizophrenia, and my early work in systematic reviews was able to make measurable the variation in the incidence of this poorly understood group of disorders. As the field became more aware of the informative gradients in the epidemiology of schizophrenia, it was clear that we should now be able to generate candidate risk factors underpinning some of these gradients. It was time to generate new hypotheses that could explain the epidemiology of schizophrenia.

Coming up with innovative hypotheses is the easiest and most entertaining part of the scientific process. On the other hand, collecting the data to test (i.e. reject) the hypothesis is much harder. This is where we need to develop new instruments to measure the previously *unmeasurable*.

The search for modifiable risk factors

Within the set of candidate risk factors for schizophrenia, we have fixed factors like sex and genetic variants, and potentially modifiable factors such as early life exposures (e.g. infection, nutrition, obstetric complications) and later exposures such as cannabis use, and trauma. Over the years my research efforts have increasingly focussed on a subset of modifiable risk factors (McGrath and Lawlor, 2011). For example, based on clues from season of birth (increased risk of schizophrenia in those born in winter/

spring) and the increased risk of schizophrenia in dark-skinned migrants, I proposed that low vitamin D during early development was an unexpectedly parsimonious risk factor (McGrath, 1999). The key issue was that at the time of publication, there was a marked absence of evidence one way or the other that vitamin D was involved in brain function. My colleagues Darryl Eyles, Tom Burne, Francois Feron and Alan Mackay-Sim decided to test the hypothesis in rodents. Some 10 years later, the results are unequivocal - low prenatal vitamin D alters brain development in rodents (Eyles et al., 2013). The animal model is now established in many laboratories around the world, and the paper describing the distribution of the vitamin D receptor in the human brain has been cited by researchers involved in an unexpectedly wide range of brain disorders (Eyles et al., 2005).

A critical test for the hypothesis was the measurement of neonatal vitamin D in individuals who later developed schizophrenia versus a matched well control group. The assay for 25 hydroxyvitamin D (the prohormone that is used to assess

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vitamin D status) requires a certain volume of blood or sera. At the time it was impossible to measure vitamin D based on neonatal dried blood spots. Not only did Darryl Eyles invent a way to achieve this goal, he improved the sensitivity of the assay to the point that we only required one 3.2 mm disc of dried blood spot (i.e. 'make measurable what is not so') (Eyles et al., 2010). Based on Danish neonatal dried blood spots, we confirmed that low vitamin D was associated with an increased risk of schizophrenia and uncovered new evidence that suggests an optimal range of neonatal vitamin D with respect to risk of schizophrenia (McGrath et al., 2010; McGrath et al., 2012).

Even if low vitamin D accounts for only a small proportion of all cases of schizophrenia, the notion that we could reduce the incidence of schizophrenia via the use of safe and cheap public health interventions like vitamin D supplements was irresistible. Just as folate supplementation has reduced the incidence of spina bifida, prenatal and neonatal vitamin D supplementation for those with low vitamin D may reduce the risk of later schizophrenia.

The John Cade Fellowship will be used to accelerate the pace of discovery related to vitamin D and brain function. We will build on our long-standing collaboration with Danish researchers to explore neonatal vitamin D status and a wider range of neurodevelopmental disorders. Based on a Dutch birth cohort, we will explore the links between both prenatal and neonatal vitamin D versus autism. In Brisbane, we will examine the association of low vitamin D status during adolescents and mental health in young adulthood, based on a prospective cohort of young twins.

Here is the second take-home message for junior researchers – always have a back-up hypothesis. Apart from vitamin D, the Fellowship will be used to explore other potentially modifiable risk factors such as early cannabis use, trauma,

and infection. In collaboration with colleagues from Harvard University, we will explore the predictors of psychotic experiences in the World Mental Health Surveys. In particular, we are interested in how these experiences interact with common mental disorders such as depression and anxiety and how they may contribute to subsequent suicidal ideation and intent (Saha et al., 2011; Varghese et al., 2011).

There will be many more modifiable risk factors related to serious mental disorders that are yet to be discovered. Because these risk factors may be associated with small effect sizes, our ability to detect these signals from observational epidemiology will be a challenge. However, the search for modifiable risk factors has recently been provided with new investigative tools. We can now use the recent discoveries from genetics as a 'lens' to focus on clues from the environment (i.e. 'make measurable what is not so').

Combining clues from epidemiology and genetics

Remarkable progress has been made in recent years in unravelling the genetic architecture of schizophrenia (Mowry and Gratten, 2013). This success is due in no small part to the brute force of large collaborative samples organized by the Psychiatric Genetics Consortium, and to advances in genome-wide statistical genetics. Researchers focussed on either genetic or environmental risk factors have tended to explore their respective domains independently. As a consequence, these fields have drifted apart in their methodological thinking. The environmental risks for psychosis have generally been studied across an averaged genetic background. Conversely, while large samples have provided insights into the genetic architecture of schizophrenia, this has been studied against an averaged environmental background. In collaboration with respected researchers at the

Queensland Brain Institute (Peter Visscher and Naomi Wray) and using data from the samples described above, I will use the Fellowship to develop new methods to combine the influence of genetic and environmental risks factors for neuropsychiatric disorders. We will focus on modifiable exposures (e.g. vitamin D, cannabis, stress, infection) and leverage polygene scores and other statistical innovations in genomewide analyses (McGrath et al., 2013).

The ultimate goal for researchers is to find safe, population-based interventions that lead to the primary prevention of a disorder. However, uncovering the risk architecture of disorders can also reveal pathways related to pathogenesis and recovery. In other words, it is feasible that some clues related to the *cause* of a disorder may also have unexpected implications for understanding the *course* of that same disorder. Moving clues derived from aetiology into the realm of treatment requires a very different range of skills.

Building a clinical trial platform

Building research synergies requires an optimal mix of skills, funding, facilities and timing. In the next few years, we have an opportunity to strengthen skills in clinical trials in mental health. The Queensland Centre for Mental Health Research has formed a strategic alliance with a new academic health centre called the Diamantina Health Partners. This partnership will serve as an interface between a large, research-active health service, with a recently opened biomedical research institute (the Translational Research Institute (TRI)). The aim of TRI is to accelerate health and medical research and to translate that research into better patient care. In collaboration with Dr James Scott and the Queensland Early Psychosis Clinical Network, we aim to develop clinical trials related to the needs of those with first episode psychosis. By embedding more mental

health research within the general matrix of academic health centres, we hope to actively catalyze future discoveries. For example, it is entirely feasible that compounds initially generated for the treatment of one disorder (e.g. immune-related disorders) may have an unintended impact on neuropsychiatric outcomes. The history of great discoveries is rich in such serendipitous discoveries (e.g. the discovery of antipsychotic medications). We want to 'set traps' for discovery and build a platform for ongoing discovery.

To undertake this type of research we need to enlist the help of the next generation of clinical researchers.

Improving research literacy and building capacity

For the interested clinician, it is apparent that there are several barriers to accessing research training: (a) finding a mentor with the best skills, (b) finding suitable training programs, and (c) finding time to juggle clinical commitments and research training. To be realistic, not all mental health clinicians are interested in research. This requires a mix of curiosity, passion and tenacity. I wish to develop innovative ways to kindle this untapped interest, and to build pathways to set interested individuals on research careers. In collaboration with the Queensland Centre for Mental Health Learning, and with the University of Queensland, we will develop training packages for clinicians who wish to contribute to the clinical trials platform. This training will be based on a range of traditional and innovative methodologies. In addition to small group training, we will use web-based e-learning systems currently being developed at the University of Queensland as part of the EdX partnership. Mentorship is also a key ingredient in keeping research-interested clinicians on track to a successful research career. We will guide

interested clinicians into relevant PhD programs and 'match' these individuals with mentors from local senior researchers. In 2012, the Queensland Centre for Mental Health Research, the Queensland Brain Institute, and the QIMR Berghofer Medical Research Institute co-signed a Memorandum of Understanding to form the Queensland Mental Health Research Alliance. We are currently planning a series of research seminars, with a selection of disease and/or research methodology focus.

Conclusions

The goals for this Fellowship application are ambitious, but based on a solid understanding of what is feasible. I will use the Fellowship to make strategic investments in innovative research and capacity building. Evidence shows that research creativity is optimized when we talk to colleagues from other disciplines – this can spark the creative exchange of fresh metaphors, and provide missing pieces of the intellectual jigsaw puzzle (Cech and Rubin, 2004). Based on my experience, the engine of discovery comes from transdisciplinary research that facilitates 'productive collisions' between different disciplines. This Fellowship application builds a shared research platform that is engineered to encourage 'intellectual collisions' between diverse scientists.

John Cade faced considerable resistance when he proposed that simple lithium salts could treat mental illness. The evidence now demonstrates that modifiable risk factors are associated with many major mental disorders and thus we urgently need to accelerate this field of research. It is time that we start to 'think the unthinkable' – we may be able to prevent serious mental disorders. The John Cade Fellowship will allow my colleagues and I to follow Galileo's dictum – we will do a great deal of *measuring* and we will earnestly try to *make measurable what is not so*.

Keywords

Epidemiology, schizophrenia, prevention

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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References

- Cech TR and Rubin GM (2004) Nurturing interdisciplinary research. *Nature Structural & Molecular Biology* 11: 1166–1169.
- Cole N and Parker G (2012) Cade's identification of lithium for manic-depressive illness - the prospector who found a gold nugget. *The Journal of Nervous and Mental Disease* 200: 1101–1104.
- Eyles DW, Burne TH and McGrath JJ (2013) Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Frontiers in Neuroendocrinology* 34: 47–64.
- Eyles DW, Morley R, Anderson C, et al. (2010) The utility of neonatal dried blood spots for the assessment of neonatal vitamin D status. *Paediatric and Perinatal Epidemiology* 24: 303–308.
- Eyles DW, Smith S, Kinobe R, et al. (2005) Distribution of the Vitamin D receptor and 1 α -hydroxylase in human brain. *Journal of Chemical Neuroanatomy* 29: 21–30.
- Malhi GS and Gershon S (2009) Ion men and their mettle. *Australian and New Zealand Journal of Psychiatry* 43: 1091–1095.
- McGrath J (1999) Hypothesis: is low prenatal vitamin D a risk-modifying factor for schizophrenia? *Schizophrenia Research* 40: 173–177.
- McGrath J, Saha S, Welham J, et al. (2004) A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* 2: 13.
- McGrath JJ (2006) Variations in the incidence of schizophrenia: data versus dogma. *Schizophrenia Bulletin* 32: 195–197.
- McGrath JJ (2007) The surprisingly rich contours of schizophrenia epidemiology. *Archives of General Psychiatry* 64: 14–16.
- McGrath JJ and Lawlor DA (2011) The search for modifiable risk factors for schizophrenia. *American Journal of Psychiatry* 168: 1235–1238.
- McGrath JJ, Burne TH, Feron F, et al. (2010) Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. *Schizophrenia Bulletin* 36: 1073–1078.
- McGrath JJ, Eyles DW, Pedersen CB, et al. (2010) Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. *Archives of General Psychiatry* 67: 889–894.

- McGrath JJ, Mortensen PB, Visscher PM, et al. (2013) Where GWAS and epidemiology meet: opportunities for the simultaneous study of genetic and environmental risk factors in schizophrenia. *Schizophrenia Bulletin* 39: 955–959.
- Mitchell PB and Hadzi-Pavlovic D (1999) John Cade and the discovery of lithium treatment for manic depressive illness. *Medical Journal of Australia* 171: 262–264.
- Mowry BJ and Gratten J (2013) The emerging spectrum of allelic variation in schizophrenia: current evidence and strategies for the identification and functional characterization of common and rare variants. *Molecular Psychiatry* 18: 38–52.
- Saha S, Scott JG, Johnston AK, et al. (2011) The association between delusional-like experiences and suicidal thoughts and behaviour. *Schizophrenia Research* 132: 197–202.
- Schioldann J (2009) *History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949*. Adelaide: Adelaide University Press.
- Varghese D, Scott J, Welham J, et al. (2011) Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophrenia Bulletin* 37: 389–393.