

Commentary for The Lancet

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Reprogramming psychiatry: stem cells and bipolar disorder

Paul J Harrison,¹ M Zameel Cader,² John R Geddes¹

¹Department of Psychiatry, University of Oxford, and Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford OX3 7JX

²Weatherall Institute of Molecular Medicine, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford OX3 9DS

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Psychiatry continues to lag behind the rest of medicine in its ability to understand its disorders and develop novel effective treatments. Hot on the tail of the increasingly robust and informative genetic leads provided by genome-wide association studies, hopes have been raised by two further developments. The first is a concerted research move away from current syndromal diagnoses towards identification of the underlying neural and cognitive processes, as exemplified by the US NIMH Research Domain Criteria (RDoC) initiative. The second is the use of induced pluripotent stem cell (iPSC) technologies to investigate disease mechanisms and treatment targets. Both approaches have substantial challenges to overcome, but there is a widespread acceptance that disruptive innovations are essential given the major limitations of existing methods to study and model psychiatric disorders and the resulting failure to deliver new therapies.¹ Hence, despite the difficulties posed by the complexity and heterogeneity of psychiatric disorders, reprogramming of cells has rapidly been adopted in the field, and some high-profile iPSC papers already published on schizophrenia and autism.

Bipolar disorder is one of the common, severe adult psychiatric disorders. It has now joined the iPSC party, with researchers comparing cellular phenotypes between cases and controls²⁻⁴ and between patients responding or not responding to lithium (a leading treatment for bipolar disorder).⁴ In the most recent example, Mertens et al⁵ address both issues, using cells generated to have a hippocampal granule cell neuron-like phenotype. Cells derived from patients showed several differences from those derived from controls: greater expression of mitochondrial and calcium signalling genes, altered mitochondrial structure and function, increased sodium channel activation and action potential frequency. These changes, indicative of hyperexcitability, were normalised by lithium in cells from the patients who had responded clinically to lithium, but not in those who had not responded. The findings are noteworthy, not least because they are consistent with evidence that mitochondria⁶ and calcium signalling⁷ are important in the pathophysiology of bipolar disorder, and that lithium responsiveness identifies a distinct subtype.⁸

The work of Mertens et al⁵ highlights the potential for iPSC approaches in complex neuropsychiatric disorders. However, there are several caveats and limitations affecting this and all existing studies of this kind.⁹ Mertens and colleagues used cells from six patients and four controls, and their findings regarding lithium came from comparing three responders versus three non-responders. As such, the results are essentially pilot data; a crucial proof of principle, but requiring a substantial increase in sample size to be robust and generalizable. Scaling up the work to the necessary extent faces significant technical and financial obstacles, especially because the absence of a monogenic form of most psychiatric disorders limits the opportunity for genome-editing and use of isogenic controls. In

the short term, neurons induced directly from fibroblasts may be a pragmatic way forward, and this method has already been used in a study of 23 subjects to show the functional correlates of a bipolar disorder-associated risk polymorphism in a calcium channel gene.¹⁰ Ongoing collection and curation of repositories of reprogrammed cells, taken from well-phenotyped patients, is also essential; the StemBANCC program funded by the EU Innovative Medicines Initiative is one example.¹¹

The use of reprogrammed cells in psychiatric research must also address several other issues. There is the question as to the most appropriate cells to study (in bipolar disorder, one could make a case for several different cell types, both glial and neuronal). Similarly, what brain maturational stage they should attempt to recapitulate? This is a moot point presently, since stem cell-derived neurons have a fetal identity, and it is not yet possible to produce neurons with anything close to an adult-like transcriptional or functional profile.¹² And what should be the primary readouts from the cells – molecular, biochemical or morphological? This is another debatable issue, since bipolar disorder has no established pathological features or correlates, yet drug screening assays require the reduction of a disease process into a druggable target or a cellular phenotype suitable for phenotypic screens and target discovery. A final, fundamental question is the extent to which the pathophysiology of psychiatric disorders is detectable or definable in a single cell type in a dish (rather than, for example, arising from the interaction between cells, or emerging at the level of neural circuits). Advances in co-culturing of different reprogrammed cell types, and in the use of brain organoids, will therefore be valuable.

Despite all the complexities, reprogramming cell technologies are already driving new excitement and optimism. Psychiatry cannot afford to miss out on the enormous potential which these approaches have to offer patients with mental and cognitive disorders. The era of a biology-based deconvolution of mechanisms and discovery of new targets, with all the likely benefits in terms of improved diagnosis and treatment, is a step closer.

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