

# Mouse models and induced pluripotent stem cells in researching psychiatric disorders

**Bowei Deng**

Masters of Science in Biomedical Sciences Program, Tufts University School of Medicine, Boston, Massachusetts, USA

*Correspondence to:* Bowei Deng. Masters of Science in Biomedical Sciences Program, Tufts University School of Medicine, Boston, Massachusetts, USA. Email: bowei.deng@tufts.edu.

**Abstract:** Psychiatric disorders are a problem for society both on a micro level involving patients and their families as well as on a macro level involving global economic costs. For years, scientists have relied on mouse models for research, but these have shortcomings that greatly hinder efforts to understand the pathophysiology and genetic factors of psychiatric disorders. Induced pluripotent stem cells (iPSCs) have shown potential to overcome obstacles that mouse models face and can provide patient-specific cells that allow for better understanding of genetic effects on psychiatric disorders. This review explores the current progress using iPSCs to model psychiatric disorders, specifically bipolar disorder and schizophrenia, while discussing remaining issues with iPSC use and how these issues can be resolved in the future.

**Keywords:** Mouse models; induced pluripotent stem cell; psychiatric disorders

Received: 14 May 2017; Accepted: 25 May 2017; Published: 17 July 2017.

doi: 10.21037/sci.2017.06.10

**View this article at:** <http://dx.doi.org/10.21037/sci.2017.06.10>

## Introduction

Psychiatric disorders place a large burden on society, and the burden has risen by 22% in the past 20 years (1). These disorders have a tremendous impact on both the well-being of patients and their families as well as the welfare of the economy. In terms of number of years lost due to disabilities, psychiatric disorders make up close to 10% of the total disease burden globally (2). Psychiatric disorders are estimated to cause close to a \$200 billion loss in personal wealth in the United States alone (1). Worldwide, the economic impact of psychiatric disorders parallels that of cancer care (3). To make matters worse, research indicates that the effect of psychiatric disorders on the world has been undervalued by close to 33%, signifying that the issue is even greater than previously believed (2).

## Obstacles to psychiatric disorders research

Presently, psychiatric disorders are thought to be caused by an intricate combination of hereditary and environmental factors. Though much progress has been made in the past

few decades, psychiatric disorders are still far from being deciphered. Our incomplete understanding of the human brain and the complex genetic basis of psychiatric disorders are some of the obstacles that hinder the progression of research. Psychiatric disorders are often polygenic, with several different genetic variants each contributing to the total risk and phenotype, which only complicates matters more (4). However, the greatest deterrent to the advancement of research in the field is the lack of model systems for psychiatric disorders. Disease-relevant tissues are limited to cell lines, patient biopsies, and post-mortem tissues, and each has its own shortcomings. Popular cell lines are unable to fully paint the picture of the causes and genetics associated with psychiatric disorders. Biopsies are expensive, invasive, and yield low amounts of tissue to work with. Post-mortem sampling provides researchers with great access to patient-specific tissues; however, those tissues are from the late stages of disease and reveal little about the pathogenesis of disorders that may have an early onset. Post-mortem tissue data is also affected by comorbidities that the patient may have had and the particular fixation and storage techniques used. Thus, researchers have turned

to mouse models, which are currently the most widely used system for researching psychiatric disorders, but these models are not without flaws.

### Mouse models in psychiatric disorders research

Mouse models are attractive for studying mammalian development and disease for many reasons. Due to their high reproductive rate and large litter size, mouse models are relatively inexpensive to use. Mice have an accelerated life span, with one mouse year equal to roughly 30 human years, which allows for disease progression to be studied (5). Furthermore, the mouse genome is fully sequenced and genetic manipulations are well developed, which allows us to create specific mouse models, proving most useful when testing molecular pathways as well as evaluating the neuronal circuits in the brain (6). However, psychiatric disorders are often classified as syndromes, which are conditions that are characterized by a group of associated symptoms that consistently occur together. Each psychiatric disorder likely constitutes several pathway-specific mechanisms that each represent a specific symptom. Thus, it is difficult and sometimes impossible to represent a psychiatric disorder in individual animal models.

### Progress with induced pluripotent stem cells (iPSCs) in psychiatric disorders research

Recently, iPSCs have been used as a model to study psychiatric diseases. iPSCs provide researchers with better access to human neuronal cells types that are affected by psychiatric disorders and are also representative of the patient's genetic make-up, allowing researchers to study the relationship between the pathophysiology and genetic basis of psychiatric disorders in one model.

The first human embryonic stem cells were harvested from blastocysts, and these stem cells had the ability to differentiate into neurons and glial cells under the guidance of specific proteins and growth factors (7). However, the protocol was ethically contentious as the technique required the stem cells to be obtained from human embryos. Luckily, a method was discovered that could reprogram adult somatic cells into embryonic stem cell-like cells using a few specific transcription factors (7). Modern advancement of stem cell research has led to the development of iPSCs from patient hair follicles, keratinocytes, fibroblasts, and peripheral blood (8), allowing the complete genetic background of the donor to be encompassed in the

iPSCs. This makes iPSCs advantageous in patient-specific treatment, particularly pertaining to psychiatric disorders, which are believed to have a genetic component in their etiology. For example, a group of researchers created iPSCs from the fibroblasts of bipolar disorder (BPD) patients, and these iPSC model neurons appeared hyperexcitable, firing action potentials at a higher frequency. They also showed altered expression of their neuronal excitability, calcium-signaling, and mitochondrial genes (9). In a controlled experiment, after a week of lithium treatment, only the iPSC model neurons from BPD patients showed differences in the hyperexcitability phenotype as well as mitochondrial gene expression. This led researchers to believe that mitochondrial signaling is important in bipolar disorder and pushed them to explore potential mechanisms in lithium treatment (9). iPSCs are also successful in summarizing and modeling psychiatric disorders *in vitro*, which mimics patient biopsies but circumvents the invasive procedures that the patient would have to undergo (10). This gives researchers an opportunity to work with ample amounts of disease-like tissues, potentially discovering new disease mechanisms which can lead to better treatment or better preventative care in the future (9). When using iPSC model neurons from schizophrenic patients, researchers noticed a discrepancy in effectiveness between the dopaminergic antagonist loxapine and its structural analog clozapine. iPSC model neurons treated with loxapine showed increased connectivity while neurons treated with clozapine did not. This caused scientists to question exactly how loxapine functioned in this system (11). Having such a robust model *in vitro* advances drug development as well. High-throughput screening can be developed for drugs, and toxicity of new and existing drugs can be tested much more easily (12). This technology can seemingly bypass the numerous impediments that have greatly hindered progress towards the understanding and treatment of psychiatric disorders, potentially lifting a heavy burden off society.

### Limitations of iPSCs in psychiatric disorders research

Though iPSCs can theoretically solve many of the issues currently faced in psychiatric disorder research, a few limitations still exist. When reprogramming the donor cells to allow them to differentiate into any cell type of the body, not only are the cells' original differentiation pathways reset, but the epigenetic changes that the cell had undergone until that point are erased as well. For

disorders like depression or anxiety, in which environmental factors play a large role in epigenetic modification, this is a major concern (12). Secondly, iPSCs can slowly develop mutations in culture, which under current protocol can lead to heterogeneous populations of neuronal subtypes. These subtypes could play differing roles in the pathophysiology of psychiatric diseases (12). Also, neurons developed from iPSCs represent cells of a fetal brain, so this can be problematic when studying disorders that may have a later onset (13). Lastly, generating iPSCs is relatively expensive and time consuming, and developing them into neurons often only produces small samples to work with.

## Conclusions

In conclusion, both mouse models and iPSCs have advantages and disadvantages when used in psychiatric disorders research. However, with further advancement in stem cell technology, many of the limitations that iPSCs currently face can be resolved, and iPSCs will become the leading model system for psychiatric disorders. In the future, developing transdifferentiation methods that do not pass over crucial neuronal development points can be a promising solution for the current production of heterogeneous populations (14). New advancements in imitating cell growth and maturation can allow us to study later onset psychiatric disorders. Additionally, developing a method to mass produce patient-specific neurons will save time and money and give researchers access to greater quantities of tissue to study. Although our current knowledge of psychiatric disorders is limited, the vast potential of iPSC technology will allow us to explore new frontiers and unravel the mysteries of psychiatric disorders.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

## References

- Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry* 2016;3:171-8.
- GBD 2013 DALYs and HALE Collaborators, Murray CJ, Barber RM, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet* 2015;386:2145-91.
- Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013;382:1575-86.
- Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. *Nat Neurosci* 2010;13:1161-9.
- Sengupta P. The Laboratory Rat: Relating its Age with Human's. *Int J Prev Med* 2013;4:624-30.
- Salgado JV, Sandner G. A critical overview of animal models of psychiatric disorders: challenges and perspectives. *Rev Bras Psiquiatr* 2013;35 Suppl 2:S77-81.
- Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007;131:861-72.
- Wen Z, Nguyen HN, Guo Z, et al. Synaptic dysregulation in a human iPSC cell model of mental disorders. *Nature* 2014;515:414-8.
- Mertens J, Wang QW, Kim Y, et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* 2015;527:95-9.
- Tabar V, Studer L. Pluripotent stem cells in regenerative medicine: challenges and recent progress. *Nat Rev Genet* 2014;15:82-92.
- Mertens J, Wang QW, Kim Y, et al. Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* 2015;527:95-9.
- Soliman MA, Aboharb F, Zeltner N, et al. Pluripotent stem cells in neuropsychiatric disorders. *Mol Psychiatry* 2017. [Epub ahead of print].
- Cocks G, Curran S, Gami P, et al. The utility of patient specific induced pluripotent stem cells for the modelling of Autistic Spectrum Disorders. *Psychopharmacology (Berl)* 2014;231:1079-88.
- Vierbuchen T, Wernig M. Molecular roadblocks for cellular reprogramming. *Mol Cell* 2012;47:827-38.

doi: 10.21037/sci.2017.06.10

**Cite this article as:** Deng B. Mouse models and induced pluripotent stem cells in researching psychiatric disorders. *Stem Cell Investig* 2017;4:62.