Chapter 12

Personalized psychiatry with human iPSCs and neuronal reprogramming

Cedric Bardy[a,b], Zarina Greenberg[a], Seth W. Perry[c] and Julio Licinio[d]

[a]South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia, [b]The College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, [c]Psychiatry, and Neuroscience & Physiology; College of Medicine, SUNY Upstate Medical University, Syracuse, NY, United States, [d]Psychiatry, Neuroscience & Physiology, Pharmacology, and Medicine; College of Medicine, SUNY Upstate Medical University, Syracuse, NY, United States

1 Introduction

Human induced pluripotent stem cells (iPSCs) are, in a nutshell, a type of pluripotent stem cell that have been artificially derived (i.e., induced or "reprogrammed") from a mature (i.e., post-differentiated, non-pluripotent) human cell. Their major conceptual and practical advance over previously available stem cell technologies is their capacity to be derived from non-embryonic human tissue—that is, iPSCs can be derived from many types of cells that are easily obtained from adult human volunteer donors—thus unexpectedly demonstrating that fully mature adult cells can be "reversed" or "reprogrammed" to behave like embryonic stem cells capable of developing into all cell types of the body, and also significantly ameliorating ethical concerns of embryonic stem cell technologies in the process. This discovery has revolutionized medical research, and earned the 2012 Nobel Prize in Physiology or Medicine for its inventor Dr. Shinya Yamanaka, and his predecessor Dr. John B. Gurdon, who paved the way in 1962 by successfully cloning a frog using the nucleus from an adult frog cell inserted into a frog egg cell, thus showing that mature adult cells contained all the information necessary for creating any cells of the organism (Gurdon, 1962; Takahashi et al., 2007; Takahashi & Yamanaka, 2006). That all of the work to be described here has occurred since Takahashi and Yamanaka's (2006) pioneering and Nobel prize winning discovery of iPSC techniques is a testament to just how rapidly this field has grown, and how important it is to personalized psychiatry and medicine in general (Papapetrou, 2016).

This chapter will begin with a historical and contemporary overview of the importance of iPSC methods and technologies to personalized psychiatry, followed by a discussion of some of the challenges and opportunities for their application to personalized psychiatry and medicine. Next we will provide a focused exploration of how iPSC technologies have thus far been used to model and better understand psychiatric diseases, and finally, we will close by addressing what we consider to be the key needs and opportunities for maximizing the impact of iPSC research and technology on personalized psychiatry.

1.1 Psychiatry needs precision medicine

All disease therapies benefit from advances in precision medicine, but psychiatry is one of the medical fields that may need it the most. The etiology of psychiatric disorders lies in a dynamic combination of genetic predispositions, epigenetic factors, and brain plasticity. Despite decades of efforts to categorize psychiatric disorders to improve and standardize treatments (e.g., diagnostic and statistical manual of mental disorders, DSM-V), each psychiatric disorder is most accurately described as a spectrum. The severity and diversity of psychiatric symptoms are unique to individuals, and require personalized treatments.

Individual genetic predispositions result in vast phenotypical changes that require specific therapeutics. These findings have led to the pursuit of precision medicine and pharmacogenomics. The concept of personalized medicine is rooted in the idea that individuals possess unique genetic, epigenetic, physiological, and molecular predispositions, and therefore patient-tailored interventions are required for the optimal care of patients, and also to accurately evaluate novel treatment outcomes in clinical trials. With rapidly increasing accessibility to DNA sequencing and proteomics analysis, precision

Personalized Psychiatry. https://doi.org/10.1016/B978-0-12-813176-3.00012-2

medicine is already becoming routine clinical practice in several areas of medicine, including oncology (Gil, Laczmanska, Pesz, & Sasiadek, 2018; Schilsky, 2010). Currently, the majority of personalized medicine revolves heavily around symptomatic and DNA profiling. Patient-centric neural cell reprogramming approaches provide new opportunities to implement precision medicine, and may prove particularly useful in brain disorders. This method can take into consideration patients' genetic variations, helping us to elucidate the dynamic links between genotype, clinical phenotypes, and neuronal phenotypes in psychiatric disorders. Herein we examine the use and future of cell reprogramming technologies, specifically iPSCs, for personalized psychiatry.

Moreover, a difficult challenge in treating psychiatric disorders today is the high degree of variability in drug efficacy among patients. Despite the availability of a broad range of pharmacological interventions, the heterogeneous nature of these disorders, along with individual variabilities, result in inconsistent patient outcomes. Trial and error strategies for identifying effective drugs for patients are standard practice, and it can take months or years to figure out appropriate treatment regimes. Given the rates of non-compliance and the high-risk nature of some patients with psychiatric disorders, an extended unmedicated (or suboptimally medicated) time frame may have hazardous consequences (Bockting et al., 2008; Weich, Nazareth, Morgan, & King, 2007). Inappropriate treatment for an individual may trigger adverse side effects without significant improvement in symptoms (Kane, Kishimoto, & Correll, 2013; Lim et al., 2012; Liu-Seifert, Adams, & Kinon, 2005). Ineffective therapeutics also exacerbate economic and societal burdens. The advent of high-throughput genomic analysis has identified a large amount of inter-individual variation, and highlighted the importance of considering a patient's genetics to guide the choice in treatment.

1.2 Limitations of existing (non-iPSC) models

Our current understanding of psychiatric disorders relies heavily on research performed in post-mortem patient brains and animal models, which, despite clear demonstrated values, have significant shortcomings. Human post-mortem brain tissue only offers a glimpse into the late stages of a disease, and reveals little of the dynamics or pathogenesis. Animal models provide valuable insights into the disease pathogenesis, and have been useful in ascertaining the function of particular causal genes and cellular signaling pathways; however, there is a clear gap between the neurobiology of rodents and humans, particularly at the psychiatric level (Kaiser & Feng, 2015). Psychiatric symptoms arise from aberrant high order functioning, or dysfunction in limbic processing, and few symptoms can be outwardly observed and quantified, which makes accurate diagnosis challenging in humans, and arduous to transpose to rodents. Furthermore, psychiatric disorders rarely originate from a monogenic cause. Instead, they typically arise from several genetic mutations that synergistically drive or predispose the underlying pathophysiology (Gratten, Wray, Keller, & Visscher, 2014). Multigenic diseases are hard to recapitulate in animal models. Because of the shortcomings in past experimental models, slow progress has been made in translating basic neurobiological findings to improve patient outcomes in psychiatry. New assays of personalized neuronal tissue, generated from patient-derived iPSCs, provide unprecedented opportunities to overcome the limitations of animal and postmortem models.

2 iPSC-derived neurons for personalized psychiatry: Opportunities and challenges

2.1 Genetics, epigenetics, and iPSCs in psychiatric disease

Our fundamental understanding of the biological mechanisms underlying psychiatric disorders remains tenuous. To this date, the field of psychiatry still endures slow translational advances with minimal effective treatments available. Today's most widely used antipsychotic drugs, such as chlorpromazine and haloperidol, were the result of serendipitous findings more than 60 years ago, rather than a detailed understanding of the pathophysiology of psychosis (Baumeister, 2013; Preskorn, 2007; Watmuff et al., 2016). However, progress in human genomics provides new insights into the biological roots of psychiatric diseases, and has established links with multi-genic polymorphisms (Glatt & Lee, 2016; Licinio & Wong, 2011; Reynolds, McGowan, & Dalton, 2014; Wong, Dong, Andreev, Arcos-Burgos, & Licinio, 2012; Wong, Dong, Maestre-Mesa, & Licinio, 2008; Xia et al., 2018). The genetic burden associated with the risk factors for developing a psychiatric disorder may vary for individuals, but genetic predispositions, coupled with epigenetic influences, are generally well accepted to constitute the initial causes of most psychiatric disorders, including major depression, bipolar disorder, autism, and schizophrenia (Gratten et al., 2014; McGuffin et al., 2003; Plomin, Owen, & McGuffin, 1994; Sullivan, Kendler, & Neale, 2003). An in-depth understanding of genomic studies is very important, and strongly tied with the use of iPSCs, because the value of iPSC models relies on the presence of genomic predispositions captured in the cells that contain the full genetic background of the donor. Using monogenic mutant cell lines, or animal models with isogenic

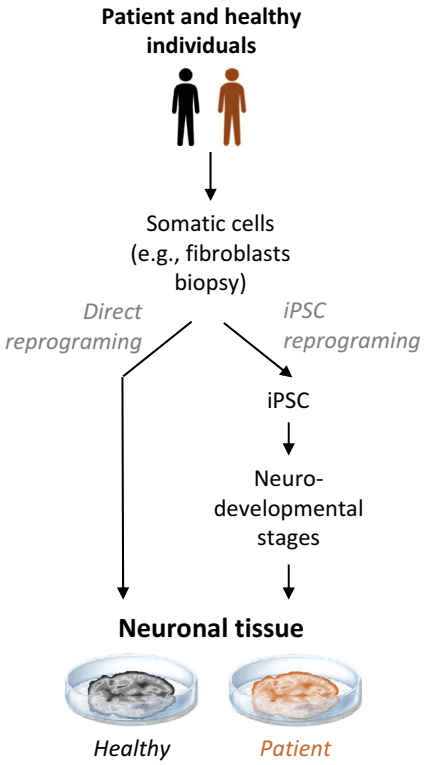

FIG. 1 Generating live human brain tissue with cell reprogramming technologies. Individual-specific neuronal cells can be generated through iPSC reprogramming or via direct conversion. Somatic cells taken from patients and healthy controls can be converted to iPSCs via exposure to specific transcription factors (such as Oct4, Sox2, Klf4, and c-Myc) (right-hand pathway). From this stage, iPSCs can be converted to a variety of neuronal and/or glial subtypes based on exposure to different culture conditions. Alternatively, somatic cells taken from patient biopsies can bypass pluripotency and be directly converted into neuronal tissue (left-hand pathway). Both pathways allow for direct comparison of neurons derived from both patients and healthy controls in vitro in a variety of applications.

controls, are valuable to study a variety of diseases. However, psychiatric disorders are rarely caused by a single highly penetrant mutation. For this reason, patient-derived iPSCs are particularly attractive for experimentally harnessing the complex genomic background of brain disorders.

However, because epigenetic factors are thought to play a significant role in psychiatric diseases, one potential disadvantage of iPSCs is that the epigenetic, i.e., "memory" of the cells may be "erased" during the reprogramming process (Lee, Hore, & Reik, 2014; Nashun, Hill, & Hajkova, 2015), to varying degrees dependent upon donor cell type (Kim et al., 2011) and methodology (Kim et al., 2010). iPSC sister technologies that allow "direct" reprogramming of somatic cells to a transdifferentiated state without need for a pluripotent cell intermediate (Fig. 1)—e.g., the generation of functional-induced neurons (iNs) directly from fibroblasts (Vierbuchen et al., 2010)—have been shown to maintain much of the cells' original epigenetic "memory" (Yang, Ng, Pang, Sudhof, & Wernig, 2011), and for these reasons may be a useful complementary method for some personalized psychiatry applications. However, iNs are not without their own limitations and trade-offs (discussed in Kalman, Hathy, & Rethelyi, 2016; Soliman, Aboharb, Zeltner, & Studer, 2017), as is any model system, and to our knowledge they have not yet been widely applied to psychiatric research. Nonetheless, this similar technology may have future applications in personalized psychiatry, and therefore we will touch upon it briefly herein.

2.1.1 iPSC technology, step 1: Reprogramming of patient-derived somatic cells to pluripotent states (iPSCs)

Embryonic stem cells (ESCs) have the potential to become any somatic cell type (Chen & Lai, 2015; Thomson et al., 1998). However, once ESCs differentiate, they lose their pluripotent capacity. Yamanaka, Takahashi, and colleagues demonstrated in a landmark study that adult fibroblasts could be reprogrammed into a pluripotent cellular state, which they called induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007; Takahashi & Yamanaka, 2006). Like ESCs, iPSCs possess the ability to self-renew and differentiate into any somatic cell type. Pluripotency can be induced in biopsied cells, such as human fibroblasts, by upregulating four key transcription factors known to have essential roles during early development:

Oct4, Sox2, Klf4, and c-Myc. The discovery of iPSC technology has generated tremendous hope in the field of medical research for at least two reasons: (1) iPSCs bypass some of the bioethical and practical limitations surrounding the use of embryonic tissues and (2) unlike ESCs, iPSCs can be generated from adult individuals, such as psychiatric patients and matched healthy subjects (Fig. 1).

Since their inception, iPSC reprogramming technologies have undergone continuous revisions and improvements, including increases in efficacy and quality (Beers et al., 2015; Malik & Rao, 2013). Initially, retrovirus transduction was used to upregulate the necessary factors for the cells to revert to a pluripotent state. Because retrovirus results in viral integration into the host genome, several papers have since expanded on different methods of transduction to reduce the genomic footprint of the reprogramming process, while maintaining or improving efficiency and reliability (Beers et al., 2015; Carey et al., 2009; Sommer et al., 2009). For example, integration-free methods, such as the Sendai virus, plasmids, or small molecules, are now more frequently used (Chen et al., 2013; Fusaki, Ban, Nishiyama, Saeki, & Hasegawa, 2009; Nishimura et al., 2017). Rigorous cell quality control with the additional safeguards and optimizations may increase costs and the length of the reprogramming process, but are essential for translational applications. Skin cell punch biopsy is most commonly used to obtain the initial patient-derived somatic cell sample, however, other (non-skin) somatic cell types may also be used. The choice of primary cell types might be guided by the importance of minimally invasive techniques, especially when dealing with donors suffering from paranoia and psychosis. Also, because certain cell types used for generating iPSCs can introduce epigenetic changes that may not be reflective of patient neurons, a tradeoff needs to be evaluated prior to each study (González, Boué, & Belmonte, 2011; Mertens, Marchetto, Bardy, & Gage, 2016).

2.1.2 *iPSC technology, step 2: Generating neurons relevant for psychiatric disorders from iPSCs*

Neuronal tissue can be generated from iPSCs with several protocols. (Herein, for simplicity, we will refer to neurons so derived as "iPSC-neurons.") A popular strategy consists of mimicking, in vitro, the sequence of human neural development that occurs in the embryo and fetus, from the blastocyst (iPSC embryonic bodies), neural tube (neural rosette-like progenitors), and radial glia (neural glia progenitors), to the brain (neurons and astrocytes). Another widely used strategy is the direct reprogramming of fibroblasts into neurons, which bypasses pluripotency and most neuronal developmental stages. This latter approach (Fig. 1) significantly reduces the amount of time required to generate neurons, with a tradeoff on other aspects that we have discussed elsewhere (Mertens et al., 2016) (see iNs in Section 2.1). Both iPSC differentiation and direct conversion have been used to generate a variety of neuronal subtypes, including GABAergic, glutamatergic, dopaminergic, and serotonergic neurons, and glial cells, usually by manipulation of a few key transcription factors and signaling pathways (Table 1). For example, we developed a protocol to differentiate serotoninergic neurons from human fibroblasts (Vadodaria et al., 2016), because serotonergic circuits are implicated in major depression, and many other brain disorders, but had previously been very difficult to recapitulate in vitro. Moreover, advances in stem cell protocols have allowed for more sophisticated modeling by recapitulating the molecular signatures of various brain regions affected in disease (Arber et al., 2015; Miskinyte et al., 2017; Sarkar et al., 2018; Shi et al., 2012; Victor et al., 2014; Yu et al., 2014). Cortical neurons were one of the first regional models generated (Shi et al., 2012), with the cortex, particularly the prefrontal and orbitofrontal cortices, being heavily implicated in psychiatric disorders.

Since then, several other specialized brain regions important to psychiatric disease pathology have been modeled with iPSCs. Yu and colleagues used iPSCs to model the hippocampal dentate gyrus, which is responsible for learning and

TABLE 1 Signalling factors used for differentiation into specific neuronal cell types.

Neural cell type	iPSC methods	iN methods
Dopaminergic	FGF2, FGF8, SHH (Ma, Liu, & Zhang, 2011)	MASH1, NURR1, LMX1A (Caiazzo et al., 2011)
GABAergic	ASCL1, DLX2, NKX2.1, LHX6 (Sun et al., 2016)	ASCL1, DLX2 (Yang et al., 2017)
Glutamatergic	RA, SMAD inhibition (Shi, Kirwan, Smith, Robinson, & Livesey, 2012)	BRN2, MYT1L, FEZF2 (Miskinyte et al., 2017)
Serotonergic	SHH, FGF4, WNT (Lu et al., 2016)	NKX2.2, FEV, GATA2, LMX1B, ASCL1, NGN2 (Vadodaria et al., 2016; Xu et al., 2016)
Astrocytes	FGFs, RA, CNTF (Krencik & Zhang, 2011)	NFIA, NFIB, SOX9 (Caiazzo et al., 2015)
Oligodendrocytes	RA, PDGF, NT3 (Gorris et al., 2015)	SOX10, OLIG2, ZFP536 (Yang et al., 2013)

memory through adult neurogenesis, and is implicated in nearly all neuropsychiatric disorders. They accomplished this by blocking Wnt, BMP, and TGF-β pathways (Yu et al., 2014). Like most brain structures, the hippocampus contains an assembly of neuronal cell types. Progress in refining the neuronal reprogramming toolbox is rapidly making more neuronal types available to study from various brain regions and subregions. For example, we recently established a protocol to generate CA3 hippocampal neurons. We then derived and cocultured CA3 and DG hippocampal neurons to compare the synaptic connectivity of schizophrenic subjects with matched controls (Sarkar et al., 2018). Similarly, the striatum was modeled using Activin A to drive iPSCs to become striatal projection neurons. Using direct conversion protocols, the microRNA, miR-9/9*-124, was sufficient to drive fibroblasts to become striatal neurons (Victor et al., 2014). Despite significant advances, differentiation protocols for many specialized regions that play functional roles in the pathophysiology of neuropsychiatric disorders remain to be identified, including many regions within the limbic system.

2.2 Applying iPSCs to personalized psychiatry

2.2.1 *Correlating neuronal phenotypes with clinical phenotypes*

The current criteria for diagnosis of psychiatric disorders are based on the DSM-V, which relies mainly on psychiatric evaluation of the patient. Using iPSCs to generate patient neurons allows for physiological, cellular, or molecular characterization of the neurons to identify known pathological characteristics or biomarkers. Over the years, there has been considerable interest in the use of biomarkers for psychiatric disorders (Chan et al., 2014; Kalia & Costa, 2015; Razafsha et al., 2015; Roffman, 2011; Scarr et al., 2015; Singh, Kalsan, Kumar, Saini, & Chandra, 2015; Sokolowska et al., 2015; Wium-Andersen, Vinberg, Kessing, & McIntyre, 2017), though this has often been stifled by limited access to relevant neuronal tissue. The use of skin biopsies to generate iPSC-neurons allows simple and minimally invasive collection of tissue from affected subjects and matched healthy donors. Comparing the biological and molecular phenotypes of patient-derived neuronal tissue with healthy tissue may help generate new diagnostic tools and advance precision medicine for psychiatric disease (Fig. 2A).

2.2.2 *Personalized investigations of the molecular neurobiology of psychiatric therapies*

Neuronal tissue may also be compared among patients representing a heterogeneous spectrum of clinical phenotypes. For example, cells from patients who have been refractory to some treatments may be used to better understand the underlying biological reasons (Fig. 2B). The potential of such a strategy has already been demonstrated with bipolar disorder. In this study, Mertens et al. showed that lithium was effective in reversing neuronal phenotypes in vitro, only on cells derived from patients who were clinically responsive to lithium (Mertens et al., 2015; Stern et al., 2018). Only half of bipolar patients see their symptoms improved by lithium therapy (Nierenberg, 2010), presumably because of diverse neurobiological profiles.

2.2.3 *Personalized drug screening with patient-derived neurons*

The use of neuronal reprogramming technologies for personalized drug screening may revolutionize the treatment of psychiatric disorders in the future. Psychiatric treatments are often associated with significant side effects. However, the main problem is that they are only effective in treating a small percentage of subjects, and in many cases the symptomatic benefits of the drugs take several months to emerge. For example, the most effective available antidepressants only benefit about 30% of people experiencing a major depressive event, after approximately 3 months of treatment (Fava, 2000; Machado-Vieira et al., 2010; Trivedi et al., 2006). The next most effective treatments have similar results. This means that it can take psychiatrists over a year of individual trial and error on their patients to find appropriate therapeutics. Therefore, a better system for predicting the personalized success of psychiatric treatments is of the utmost importance. Patient-derived neuronal tissues provide the opportunity to perform in vitro preclinical screening of hundreds of drugs in the laboratory setting to make evidenced-based predictions (Fig. 2C). In the future, psychiatrists may be able to use patient-tissue derived data to guide the choice of therapy. This may prove life-saving for individuals with psychiatric disorders (Bener, Dafeeah, & Salem, 2013; Kane et al., 2013).

2.2.4 *iPSCs as cell replacement therapies in psychiatry*

Another appeal of stem cell technology is the potential for cellular replacement therapies. Since their discovery, iPSC derived cells have been heavily investigated for use in transplantation and regenerative medicine (Brederlau et al.,

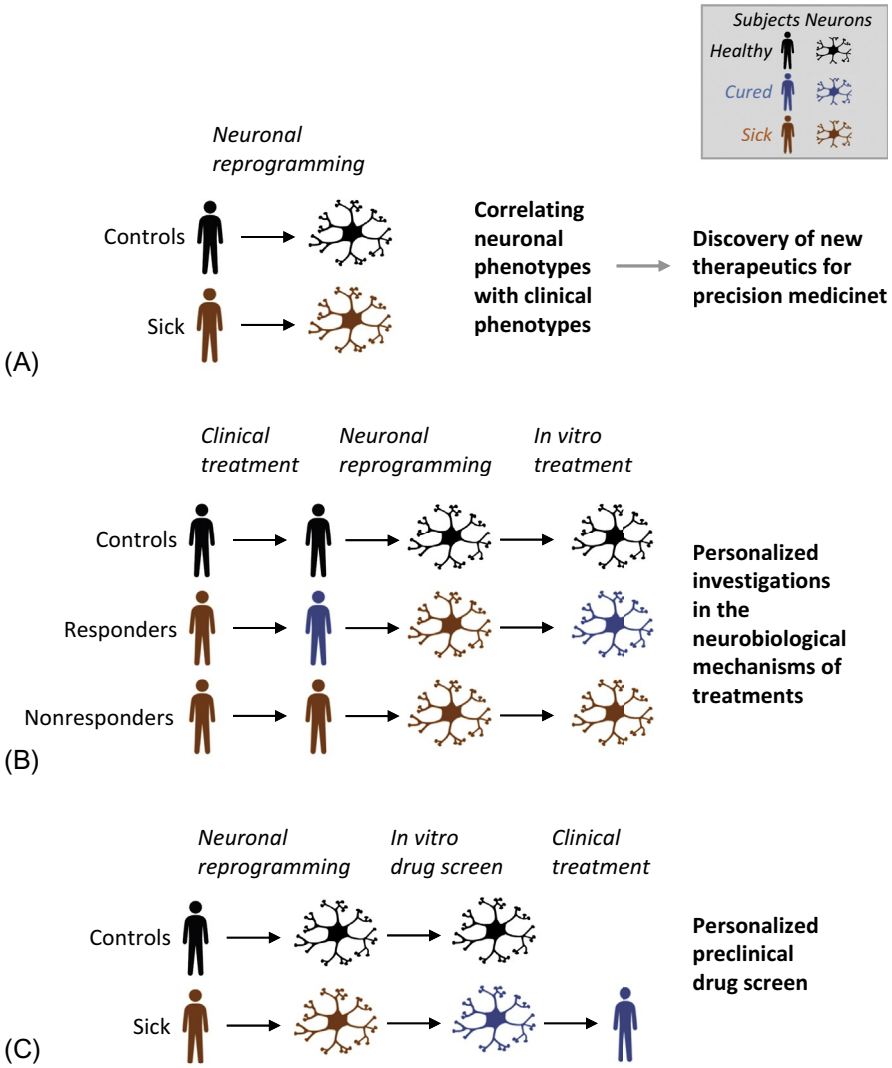

FIG. 2 Using patient-derived brain cells in-vitro for personalized medicine. (A) Correlating the clinical phenotypes of patients with their neuronal phenotypes to produce new therapeutics and diagnostics tools. (B) Reprogrammed neurons can be used to distinguish which patients will benefit from a specific drug (responders) to patients that show little or no benefit from treatment (nonresponders), ultimately improving efficacy of treatments. (C) High throughput drug screening can be performed on patient- vs healthy control-derived neurons, to provide evidence-based predictions of drug benefits, side-effects, and/or toxicity to patients.

2006; Donegan et al., 2017; Singh et al., 2015; Southwell et al., 2014). Though neuropsychiatric disorders were not readily considered initially, research into the roles of particular neuronal subtypes in several psychiatric disorders has shown that neuronal loss or aberrant neuronal function are hallmark features of psychiatric disease (Heckers et al., 2002; Kida & Kato, 2015; Perry, Kish, Buchanan, & Hansen, 1979; Qiu et al., 2018). Furthermore, the unique properties of some neuronal cells make them ideal candidates for this therapy. One example of this is using iPSCs to generate GABAergic interneurons to then transplant into the brain of patients with schizophrenia. GABAergic interneurons have been shown to have the capacity to reintegrate into the neural circuitry, and this approach has shown success in treating psychosis in animal models (Donegan et al., 2017; Southwell et al., 2014; Spatazza, Mancia Leon, & Alvarez-Buylla, 2017; Tang, Stryker, Alvarez-Buylla, & Espinosa, 2014). Though cell replacement therapy is an exciting prospect, it is rife with challenges. In order to generate clinical grade cells for transplantation, there are several safety concerns with current techniques that must first be addressed, including avoiding the use of oncogenes (e.g., c-Myc), and maintaining genomic integrity (Riggs et al., 2013; Tapia & Scholer, 2016). Though it is possible to generate iPSCs without the use of c-Myc, these methods are far less efficient, and there is still a link between pluripotency and tumorigenicity (Ben-David & Benvenisty, 2011; Brickman & Burdon, 2002; Okita, Ichisaka, & Yamanaka, 2007; Riggs et al., 2013).

2.3 Challenges for optimal use of neuronal reprogramming in personalized psychiatry

In only 10 years, patient-derived neurological iPSC models have come a long way since the initial uncertainty of their potential to recapitulate complex brain disorders in vitro (Soldner & Jaenisch, 2018). iPSC models of psychiatric diseases have already begun to generate new biological insights (Bavamian et al., 2015; Cavalleri et al., 2018; Collo et al., 2018). However, to reap the full benefit of neuronal reprogramming for personalized psychiatry, researchers will need to continue refining the models and improve aspects such as (1) the timing and duration of cellular reprogramming and analysis, (2) the quality and safety of the reprogrammed cells, (3) the reproducibility of cellular phenotypes for high-throughput drug screening, and (4) the scalability for standard clinical practice.

2.3.1 Time to generate neurons

One of the important challenges surrounding the use of human iPSCs in personalized medicine is the amount of time needed to generate the neurons. This long culturing period may be problematic for their application to guiding treatment decisions in individualized clinical practice. It takes approximately 4–8 months to generate electrophysiologically mature neurons with iPSC reprogramming (Fig. 3A). Some specialized cell types may require even longer culture periods to reach maturity. An alternative is to analyze immature neurons instead, which can be done in 2–5 months from fibroblasts. Another option is to use direct reprogramming methods, which skips the pluripotency and neurodevelopmental stages and takes about 2–5 months (Fig. 3B). Direct reprogramming may be preferred for faster analysis. However, if a large set of analysis is required, or if experiments need to be repeated in independent laboratories, the frozen stocks of neuronal progenitors (NPCs) generated by iPSC reprogramming might become advantageous and save time in the long run. Some psychiatric disorders may require urgent intervention to prevent life-threatening behaviors, and using cellular evaluation that will take several months may not be appropriate. However, most psychiatric diseases are chronic. In these latter cases, even lengthy in vitro neuronal evaluation of a large number of therapeutics would be valuable, for example, as a means to optimize individual therapies while an initial treatment approach (trial) is underway.

2.3.2 The neurophysiological microenvironment in vitro

The exact culture conditions significantly impact the quality and physiology of the neurons (Bardy et al., 2015; Perry, Norman, Litzburg, & Gelbard, 2004). Fluctuations in the cellular microenvironment in vitro can lead to changes in cellular function that are not reflective of neurons in vivo, and may confound translational predictions. Advances in media formulation more representative of neurophysiological conditions will at least partially address this issue (Bardy et al., 2015; Perry et al., 2004). Significant advances have also been made in generating brain organoid cultures that provide a more realistic 3D environment (Clevers, 2016; Di Lullo & Kriegstein, 2017; Dyer, 2016; Lancaster & Knoblich, 2014). However, to this date, brain organoids take even longer to generate, and may introduce a large degree of variability. Although brain organoids might not be suitable for personalized psychiatry in their current states, further optimization is likely to fulfill their potential in the future.

2.3.3 Optimizing reproducibility and reducing variability

The reproducibility of disease phenotypes observed with in vitro models remains a challenge. Slight changes introduced by tissue culture manipulation may be quickly amplified over several months in vitro and affect the final quality of any cell line, including healthy controls. Therefore, it is absolutely critical that control and experimental cell lines to be compared are handled identically in every way throughout the culture process, and cell quality checkpoints are required at every step of the reprogramming. Researchers have access to an array of tools to evaluate the quality of stem cells and neurons. The most accurate assays include genomic and electrophysiological analyses of the cells. Although such analyses are becoming more accessible, they remain costly and time-consuming. New faster quality controls will be required to accommodate the constraints of urgent clinical time-frames. Ultimately, personalized psychiatry with neuronal reprogramming will only be possible on the premise that robust and reproducible cellular phenotypes exist. As such, some psychiatric diseases with well-defined cellular phenotypes will be better suited for personalized psychiatry with iPSCs.

2.3.4 The number of patient cell lines

Drug discovery pipelines with patient-derived iPSC models need to integrate a large number of cell lines. However, the exact number of patients and clones to use is often a matter of debate among researchers. High-throughput platforms might be able to process a large number of cell lines at once, but the resources needed to maintain cell quality standards and perform in-depth analyses grow exponentially with the number of lines. Currently, only a minority (~20%) of studies that

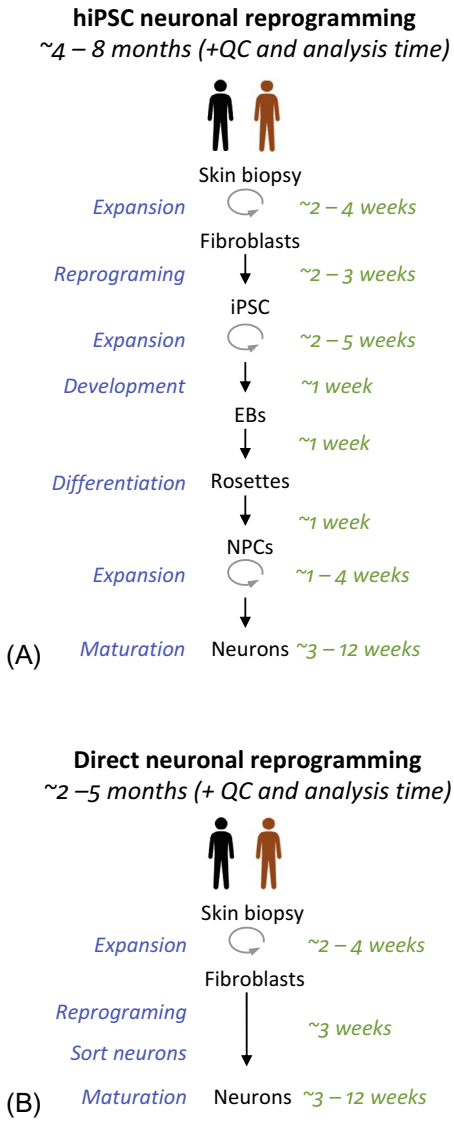

FIG. 3 Time constraints for neuronal reprogramming. (A) iPSC cell reprogramming is a lengthy process, taking between 4 and 6 months to generate viable neurons. The reprogramming process involves converting the cells to several states that recapitulate embryonic structures, including rosettes representing the neural tube. The majority of this time is spent converting somatic cells to iPSCs, with maturation time of neurons dependent on the neuronal subtype cultured. Once iPSCs have been generated, there is a relatively short differentiation period to produce NPCs. (B) Direct reprogramming is a comparatively shorter process, bypassing several lengthy steps and only taking between 2 and 5 months to generate mature neurons. *EBs*, embryonic bodies; *NPCs*, neural progenitor cells.

have reported the identification of therapies for neurological disorders using human iPSCs have integrated more than five patients in their analysis (Avior, Sagi, & Benvenisty, 2016). However, most (~80%) of these same studies focused on monogenic or chromosomal disorders. Given the diverse etiologies of psychiatric diseases, a larger cohort of psychiatric patients might be required. Alternatively, smaller subgroups of individuals experiencing very similar clinical phenotypes might also help increase statistical power.

2.3.5 Scalability

The feasibility of using iPSC models in personalized psychiatry largely depends on a balance among reliability, time, and cost efficiency. It is unlikely that a method that is too expensive will be used in the clinic. Several papers have proposed strategies to economically improve scalability (Wang et al., 2017). The less laborious and more time efficient protocols that can easily be reproduced by independent laboratories will ultimately lead to scalability (Wang et al., 2017).

3 Using iPSCs for psychiatric disease modeling

Psychiatric disease modeling using iPSCs generally falls into one of two broad categories: (1) Using iPSCs derived from healthy donors to study the impact of established drugs or therapies on molecular mechanisms known or believed to be pertinent to the disease under investigation, or (2) Comparing iPSCs between healthy-diseased or diseased-diseased donors to uncover differences in molecular mechanisms, physiology, phenotypes, and/or response to therapies that can inform the quest for more targeted or effective treatments for psychiatric disease. It is this latter application, depicted in Fig. 2, that may yield the most direct or immediate benefits to personalized psychiatry, by uncovering disease-relevant phenotypic or mechanistic differences between healthy donors and those suffering from psychiatric illnesses (Fig. 2A); identifying drug responders vs nonresponders, and the pathways that predict drug response, in those with a particular disease (Fig. 2B); and/or by identifying subtypes or individually unique phenotypes or biology among patients with the disease (Fig. 2C). This, in turn, will help guide which existing drugs or other therapies may be most effective on an individual or population basis, as well as identify novel molecular targets and therapies with improved efficacy and tolerability.

Thus far, a significant portion of the work on iPSCs for modeling psychiatric disease has focused on schizophrenia, bipolar disorder, and autism spectrum disorder (ASD), and yielded a wealth of information that has significantly advanced our understanding of these disorders (Table 2). Fewer studies have utilized iPSC technologies to directly explore depression and anxiety disorders, and these areas are ripe with opportunity and need. We will very briefly cover major advances in each of these areas, and refer the reader to excellent detailed reviews for further discussions.

3.1 iPSCs in bipolar disorder

Bipolar disorder (BD) is a psychiatric illness characterized by emotional highs (mania) and lows (depression) and is the sixth leading cause of disability worldwide, afflicting about 60 million people (Hoffmann, Sportelli, Ziller, & Spengler, 2018, and references therein), with an estimated prevalence and lifetime prevalence of about 1.5% and 2.4%, respectively (Yatham et al., 2018). It carries high rates of morbidity and mortality, accounting for 3.4%–14% of suicide deaths, and roughly 25% of BD patients attempt suicide (Hoffmann et al., 2018; Schaffer et al., 2015). There are few new or specific therapies for BD, and often around half of BD patients may not be effectively treated by the available medications (Nierenberg, 2010), making development of more effective BD therapies a critical need.

However, before there were, to our knowledge, any studies comparing iPSCs from healthy vs bipolar disorder (BD) subjects, as in the kinds of paradigms depicted in Fig. 2, the Haggarty group used iPSCs reprogrammed from a normal human fibroblast cell line to derive neural progenitor cells (NPCs) in high volume, with the potential to then be subsequently differentiated into large numbers of neuronal or glial cells (Zhao et al., 2012). Using this model, they reported demonstrating for the first time that human iPSC-derived NPCs had a functionally active Wnt/β-catenin pathway with expected responsivity to the well-established BD therapeutic lithium, and could be used in large numbers in a high throughput screening (HTS) assay to identify multiple novel and known small molecule compounds that modulated the Wnt/β-catenin pathway in this model system (Zhao et al., 2012). Lithium inhibits glycogen synthase kinase-three beta (GSK-3β) to activate Wnt/β-catenin signaling (Hedgepeth et al., 1997; Jope, 2003), and as such, these intertwined pathways are increasingly thought to be integral to BD pathophysiology (Valvezan & Klein, 2012). Hence, this work was an elegant early example of how some of the challenges of population heterogeneity and low cell numbers were overcome to provide a robust and scalable method for producing self-renewing and genomically stable NPC precursors, with the potential to be subsequently differentiated into large numbers of functional post-mitotic neurons (Zhao et al., 2012), and used for exploring questions relevant to psychiatric disease, particularly BD.

Two years later, the first reports using iPSCs derived from individuals with BD began to emerge. Several studies have identified changes in gene expression of numerous proteins related to neurodevelopment and synaptic function in iPSC-derived neurons from BD compared with healthy subjects (Bavamian et al., 2015; Chen et al., 2014; Kim et al., 2015; Madison et al., 2015; Wang et al., 2014), and a subset of these studies investigated and found that these differences seen in the BD subjects were partially or largely prevented by lithium treatment (Chen et al., 2014; Madison et al., 2015; Wang et al., 2014). These findings validate both the utility of iPSCs for modeling BD, and the importance of lithium-responsive pathways (e.g., Wnt, GSK-3β) in its molecular pathophysiology, and help identify additional novel therapeutic targets. Other elegant studies have found distinct differences in synaptic function between lithium responsive (LR) and lithium non-responsive (NR) BD subjects. Mertens et al. found hyperactive synaptic activity in BD, but not healthy iPSC-derived hippocampal neurons, that could be selectively normalized by lithium (with greater accompanying gene expression changes) in only LR subjects, but not in NR subjects (Mertens et al., 2015). Moreover, in a follow-up study, this group

TABLE 2 Psychiatric diseases modeled with iPSC technologies, organized by neuronal subtypes and brain regions studied.

Disease	Brain region affected	Neuronal types affected	Brain region modeled with iPSCs	Neuronal types modeled with iPSCs
Schizophrenia	Hippocampus (Lodge & Grace, 2005; Weiss et al., 2003) Cortex (Abi-Dargham, 2004; Pierri, Volk, Auh, Sampson, & Lewis, 2003) Prefrontal cortex (Farzan et al., 2010; Volk, Austin, Pierri, Sampson, & Lewis, 2000) Ventricles, striatum (Kegeles, Abi-Dargham, Frankle, et al., 2010; Kessler et al., 2009)	GABAergic (Beasley & Reynolds, 1997; Farzan et al., 2010; Perry et al., 1979; Volk et al., 2000; Yoon et al., 2010) Dopaminergic (Abi-Dargham, 2004; Abi-Dargham et al., 2000; Bogerts, Hantsch, & Herzer, 1983; Kegeles et al., 2010; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999; Lodge & Grace, 2005) Glutamatergic (Javitt, 1987; Olney & Farber, 1995) Serotonergic (Stahl, 2018; Xia et al., 2018)	Hippocampus-CA3 (Sarkar et al., 2018) Hippocampus dentate gyrus PROX1 (Yu et al., 2014) Forebrain (Liu et al., 2013)	GABAergic (Brennand et al., 2011a; Liu et al., 2013; Sun et al., 2016) Dopaminergic (Brennand et al., 2011a; Robicsek et al., 2013) Glutamatergic (Robicsek et al., 2013)
Bipolar disorder	Amygdala (DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004) Prefrontal cortex (Lyoo et al., 2006; Rajkowska, 2000) Hippocampus (Bertolino et al., 2003; Rajkowska, 2000) Basal ganglia (Caligiuri et al., 2003) Thalamus (Caligiuri et al., 2003; DelBello et al., 2004)	Pyramidal (Rajkowska, 2000; Rajkowska, Halaris, & Selemon, 2001) Glia (Rajkowska, 2000; Rajkowska et al., 2001) Serotonergic (Young, Warsh, Kish, Shannak, & Hornykeiwicz, 1994)	Hippocampus dentate gyrus PROX1 (Mertens et al., 2015; Stern, Santos, et al., 2018)	Hippocampal dentate gyrus PROX1 (Mertens et al., 2015; Stern, Santos, et al., 2018)
William syndrome	Hippocampal (Meyer-Lindenberg et al., 2005) Visual cortex (Mobbs et al., 2007) Orbitofrontal cortex (Meyer-Lindenberg et al., 2005) Amygdala (Capitão et al., 2011) Intraparietal sulcus (Meyer-Lindenberg et al., 2005)	Pyramidal (Lew, Brown, Bellugi, & Semendeferi, 2016)	Forebrain (Chailangkarn et al., 2016; Khattak et al., 2015)	Cortical layer V/VI (Chailangkarn et al., 2016; Khattak et al., 2015)
Autism	Prefrontal cortex (Goldberg et al., 2011) Amygdala (Schumann et al., 2004), Primary motor cortex (Nebel et al., 2014), Cerebellum (Ritvo et al., 1986; Yip, Soghomonian, & Blatt, 2007)	Purkinje cells (Ritvo et al., 1986; Yip et al., 2007) GABAergic (Yip et al., 2007)	Forebrain (Karina Griesi-Oliveira et al., 2015)	Forebrain (Karina Griesi-Oliveira et al., 2015)
Major depression	Anterior cingulate (Cotter, Mackay, Landau, Kerwin, & Everall, 2001) Hippocampus (Klumpers et al., 2010)	Glia (Cotter et al., 2001) Serotonergic (Åsberg et al., 1984; Coccaro, Siever, Klar, et al., 1989; Träskman, Åsberg, Bertilsson, & Sjüstrand, 1981) GABAergic (Klumpers et al., 2010) Pyramidal (Cotter et al., 2001)	Midbrain (Vadodaria et al., 2016)	Serotonergic (Lu et al., 2016; Vadodaria et al., 2016; Xu et al., 2016)
Anxiety	Anterior cingulate (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Thomaes et al., 2013) Hippocampus (Hettema et al., 2012) Thalamus (Giménez et al., 2012) Amygdala (Etkin et al., 2010; Schienle, Ebner, & Schäfer, 2011)	Serotonergic (Murphy, 1990) GABAergic (Klumpers et al., 2010)	Midbrain (Vadodaria et al., 2016)	Serotonergic (Lu et al., 2016; Vadodaria et al., 2016; Xu et al., 2016)

from Fred Gage's laboratory found that these hyper-excitable BD neurons had distinctly different electrophysiological properties in the LR vs NR groups, which enabled highly accurate prediction of a patient's responsiveness to lithium based on the electrophysiological "signature" of the neurons derived from their iPSCs (Stern, Santos, et al., 2018). This exciting and seminal finding is an excellent example of how iPSCs can be used to predict drug responsiveness for personalized psychiatry. Another seminal study using iPSC-neurons from LR, NR, control, and unrelated psychiatric disease donors identified collapsin response mediator protein-2 (CRMP2) as perhaps the most critical major molecular player underlying LR BD pathogenesis (Tobe et al., 2017). We refer the reader to several excellent reviews for very detailed discussions of these and other studies that have used iPSCs to model BD (Hoffmann et al., 2018; Liu, Lu, & Yao, 2017; Watmuff et al., 2016).

Studies such as these and others (Oedegaard et al., 2016) utilizing iPSCs to uncover the genetics and functional neurobiology of lithium responsivity in BD have provided exceptional insights that should lead to improved therapies in the coming years, and have reinforced the notion that differing responses to lithium or other mood stabilizers reflect multiple different disease mechanisms that contribute to BD pathology (Leckband, McCarthy, & Kelsoe, 2012). On the basis of their findings (Tobe et al., 2017), some even speculate "that cases of bipolar disorder that do not respond to the drug [lithium] are actually a different disease altogether" (Leckband et al., 2012). Whether this viewpoint will gain traction as more research unfolds remains to be seen.

3.2 iPSCs in depression and anxiety disorders

Depression and anxiety disorders, respectively, afflicted about 268 and 275 million people globally in 2016, compared with 40 and 21 million people for BD and schizophrenia, respectively (Ritchie & Roser, 2018). That's about nine times the number of people affected by depression and anxiety disorders combined, vs BD and schizophrenia combined. Depressive disorders are also the leading cause of disability worldwide, and a key trigger for suicide, which causes one million deaths per year, and rising. BD and schizophrenia are indeed devastating and serious disorders, also linked to high suicide rates, and by no means is it our intent to diminish their significance and toll on public health. At the same time, given these discrepancies in prevalence, it is perhaps surprising that, to our knowledge, no studies have yet sought to use iPSCs derived from depressed subjects to model depressive disorders, as has been done for BD and schizophrenia. For example, given the vast variability in patients' therapeutic responses to antidepressants, it would be worthwhile to investigate whether depression-derived iPSC-neurons can be used to model or predict antidepressant response, similar to what has been done for lithium using BD-derived iPSC-neurons.

This is not to say, however, that no progress has been made using iPSCs to model depression and anxiety disorders. Several studies have utilized iPSCs derived from healthy subjects to model mechanisms or drug responses relevant to depression. Using iPSCs from healthy donors differentiated into midbrain dopamine neurons, Collo et al. found that ropinirole and pramipexole—two dopamine D3 receptor agonists used to treat Parkinson's disease and as adjunctive therapeutics for treatment resistant depression—dose-dependently increased dendritic arborization and soma size, likely through brain-derived neurotrophic factor (BDNF) dependent pathways (Collo et al., 2018). BDNF has been consistently implicated in depression, particularly treatment resistant depression (TRD), and increased BDNF signaling is believed to be central to ketamine's therapeutic effect on TRD (Allen et al., 2015; Haile et al., 2014; Lepack, Fuchikami, Dwyer, Banasr, & Duman, 2014). This work suggests ropinirole and pramipexole may act through similar mechanisms to benefit treatment resistant depression, and in fact, this same group, using the same human iPSC-dopaminergic neuron system, demonstrated similar neuroplasticity effects and mechanisms with ketamine (Cavalleri et al., 2018). Another group used human iPSC models (again, not from depressed subjects) to explore the potential mechanistic role of fibroblast growth factor 2 (FGF2) and its upstream and downstream mediators, and effects in major depressive disorder (MDD) (Gupta et al., 2018), and at least two other groups have used iPSC model systems to explore the toxicology of select antidepressants (Huang et al., 2017; Pei et al., 2016).

However, perhaps the most significant accomplishments to date involving the use human iPSCs in depression research have been methodological developments (Licinio & Wong, 2016). The serotonin system is integrally involved in depression and antidepressant actions, yet much like dopamine neurons, primary central nervous system serotonergic neurons have historically been difficult to reliably culture in large numbers, even from animals, let alone human sources. Surmounting these obstacles, dopamine neurons have now been cultivated from human iPSCs, and also recently, two groups independently reported methods for generating functionally active serotonergic (5HT) neurons from primary human fibroblasts (Vadodaria et al., 2016; Xu et al., 2016). Both teams used direct conversion methods (i.e., iN; Fig. 1, Fig. 3B), with Vadodaria et al. demonstrating that primary human dermal fibroblasts obtained from skin biopsies could be transdifferentiated to 5HT neurons by overexpression of four transcription factors (NKX2.2, FEV, GATA2, and LMX1B), along

with ASCL1 and NGN2 (Vadodaria et al., 2016). Xu et al. showed that human lung fibroblasts (obtained from three different human lung fibroblast cell lines) could be induced to serotonergic neurons with just four transcription factors—ASCL1, FOXA2, LMX1B, and FEV (AFLV) (Xu et al., 2016)—three of which were shared with the Vadodaria method, and one (FOXA2) different. These recently developed methods will, for example, facilitate personalized prediction of drug response for serotonergic antidepressants, as has been done for lithium in bipolar (Stern, Santos, et al., 2018), and open a realm of exciting opportunities for understanding and treating depression (Vadodaria, Stern, Marchetto, & Gage, 2018).

3.3 iPSCs in schizophrenia

Both BD and schizophrenia (SCZ) are understood to have complex genetic, epigenetic, and neurodevelopmental origins, and accordingly, use of iPSCs to model SCZ has largely mirrored the work done with iPSCs in BD. As such, we will not discuss these studies in great detail here, as they have been touched upon in the preceding sections and tables herein, and have been thoroughly reviewed elsewhere. However, we will highlight a few general concepts. Several groups have identified abnormalities in gene expression, neurodevelopment, mitochondrial function, oxidative stress, neuronal connectivity (typically reduced), neuronal activity, and other elements of synaptic function in iPSC-neurons derived from individuals with SCZ compared with healthy controls (reviewed in Ahmad, Sportelli, Ziller, Spengler, & Hoffmann, 2018; Liu, Lu, & Yao, 2017; Watmuff et al., 2016). In these models, a few studies have had success blocking some of their observed effects with drugs sometimes prescribed for SCZ such as loxapine (Brennand et al., 2011b) or valproate (Paulsen Bda et al., 2012), but perhaps less reliably so than has been demonstrated for lithium in the BD iPSCs experiments described in the previous section. For example, of five antipsychotics tested—clozapine, loxapine, olanzapine, risperidone, and thioridazine—only loxapine ameliorated the reduced neuronal connectivity and altered gene expression seen in the SCZ-derived vs healthy-derived iPSC-neurons (Brennand et al., 2011b). Intriguingly, this suggests that loxapine's therapeutic effect in this model system may be mediated by yet-unknown off-target effects, which in turn may suggest an even greater etiogenic and mechanistic complexity for SCZ than previously imagined. Both of these possibilities require further exploration in future experiments such as these using human iPSCs to uncover the neurobiology of SCZ.

3.4 iPSCs in autism spectrum disorder

As defined in the DSM-5, autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent abnormalities or deficits in social communication and interaction, and restricted and/or repetitive patterns of behavior, interests, or activities. Intellectual or language disabilities may or may not be present (American Psychiatric Association, 2013). It is, in effect, a disorder characterized or defined by a pattern of related behaviors or phenotypes, but that may have multiple causes or etiologies of known (traditionally referred to as syndromic ASD) or unknown (traditionally referred to as non-syndromic or idiopathic ASD) origin. As with BD and SCZ, most cases of ASD are believed to arise from an interaction of multiple genetic, environmental, and epigenetic factors; that is, they are nonsyndromic or idiopathic ASD. Some cases of ASD arise from known genetic mutations that also cause other identified syndromes, such as Rett syndrome, Fragile X syndrome, and Timothy syndrome; that is, they are syndromic ASD. However, this "syndromic" and "nonsyndromic" nomenclature system for ASD can quickly become both complex and blurred, leading some to propose alternative classification systems (Fernandez & Scherer, 2017). For the purposes of our discussions on iPSCs and personalized psychiatry herein, a more useful division is simply whether the ASD's origin is monogenic (i.e., resulting from a single known gene mutation) or polygenic (resulting from multiple known or unknown genetic influences) in nature.

Both monogenic and polygenic ASD have been modeled by human iPSCs, yielding useful insights for understanding ASD disease mechanisms and personalized psychiatry. Using iPSC-neurons derived from patients with monogenic ASDs such as Rett, Fragile X, Timothy, and Phelan-McDermid syndromes, a number of studies have demonstrated deficits in iPSC-neuron synaptic architecture and function that often mimic clinical disease phenotypes, and have identified numerous potential genetic and molecular therapeutic targets that, in some cases, could rescue these aberrant ASD phenotypes (reviewed in Adegbola, Bury, Fu, Zhang, & Wynshaw-Boris, 2017; Brennand, Simone, Tran, & Gage, 2012; Falk et al., 2016; Kim, Kim, Oh, Lee, & Kim, 2016; Lim et al., 2015; Marchetto, Brennand, Boyer, & Gage, 2011; Shen, Yeung, & Lai, 2018; Vitrac & Cloez-Tayarani, 2018). In some respects, studies modeling monogenic ASD may have the potential to offer the most immediate benefits to personalized psychiatry and medicine, because the iPSCs derived from these monogenic ASD subjects will, by definition, carry a single identifiable genetic mutation (Yoo, 2015), which may therefore offer the most direct insights into disease mechanisms and targets that are explicitly responsible for the ASD phenotype. On the other hand, iPSC studies of polygenic ASD have also identified potential molecular targets for novel therapeutic intervention (Bury & Wynshaw-Boris, 2018; Liu et al., 2017). One such study has identified TRPC6 (transient

receptor potential cation channel, subfamily C, member 6) as an attractive potential therapeutic target for non-syndromic (polygenic) ASD (Griesi-Oliveira et al., 2015). This and other research modeling ASD with human iPSCs has been covered in depth elsewhere (Ben-Reuven & Reiner, 2016; Brito, Russo, Muotri, & Beltrao-Braga, 2018). The ongoing challenge for ASD personalized psychiatry will be to uncover iPSC-neuron phenotypes or characteristics that predict drug response and/or identify druggable targets that will provide novel treatments for ASD on either a population or individualized basis, as has thus far perhaps been done most successfully for BD.

4 Conclusions and future directions

Continuing to advance iPSC technology and methods for improved understanding of psychiatric diseases will benefit personalized medicine in at least three ways: (1) Identifying novel and clarifying known or suspected molecular disease mechanisms for developing more targeted and effective therapies, (2) better *individualized* prediction of response to drug therapies for psychiatric disease (Stern, Linker, Vadodaria, Marchetto, & Gage, 2018), and (3) conceivably, iPSCs could ultimately serve as stem cell therapies for severe or refractory psychiatric disease (Chen, Song, & Ming, 2018; Samoilova et al., 2018). With the exception of Section 2.3.4, most of our discussions herein have focused on the first two areas, while the latter area has thus far received relatively little attention in the literature, as applicable to psychiatric disease, and would benefit from further research. The comparative lack of attention to this third area thus far may reflect a perception that neurorestorative stem cell therapies for psychiatric illnesses are highly invasive and risky treatments of last resort. Yet, when we consider that large numbers of individuals worldwide suffer from severe and/or refractory forms of psychiatric diseases such as schizophrenia, bipolar disorder, obsessive-compulsive disorder (OCD), or treatment resistant depression, for which they may have found no effective treatment or may be considering ablative surgical options, then neurorestorative stem cell therapies certainly appear more attractive. And with continued progress in iPSC technologies, they will also become more feasible as viable treatment options with reasonable risk-reward. Here, experimentation in chimera models (i.e., transfer of human iPSCs to animal models) will likely prove both necessary and informative for advancing iPSC-based stem cell therapies for psychiatric diseases. In these endeavors, further progress in three dimensional organoid- and tissue-based iPSC approaches that better recapitulate native neural architectures (Quadrato, Brown, & Arlotta, 2016), and including understanding and harnessing the integral role of glia in modulating neuronal development and behavior in iPSC models (Gonzalez, Gregory, & Brennand, 2017), will be of utmost importance. We expect that these kinds of ongoing research into the use of iPSCs for modeling and treating psychiatric disease will yield exciting new personalized treatment opportunities, improved outcomes, and reduction in disease burdens, thus improving individual and global health.

References

Abi-Dargham, A. (2004). Do we still believe in the dopamine hypothesis? New data bring new evidence. *International Journal of Neuropsychopharmacology*, *7*(Supplement_1), S1–S5.

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L. S., … Laruelle, M. (2000). Increased baseline occupancy of D(2) receptors by dopamine in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(14), 8104–8109.

Adegbola, A., Bury, L. A., Fu, C., Zhang, M., & Wynshaw-Boris, A. (2017). Concise review: Induced pluripotent stem cell models for neuropsychiatric diseases. *Stem Cells Translational Medicine*, *6*(12), 2062–2070.

Ahmad, R., Sportelli, V., Ziller, M., Spengler, D., & Hoffmann, A. (2018). Tracing early neurodevelopment in schizophrenia with induced pluripotent stem cells. *Cell*, *7*(9).

Allen, A. P., Naughton, M., Dowling, J., Walsh, A., Ismail, F., Shorten, G., … Clarke, G. (2015). Serum BDNF as a peripheral biomarker of treatment-resistant depression and the rapid antidepressant response: A comparison of ketamine and ECT. *Journal of Affective Disorders*, *186*, 306–311.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Arber, C., Precious, S. V., Cambray, S., Risner-Janiczek, J. R., Kelly, C., Noakes, Z., … Li, M. (2015). Activin A directs striatal projection neuron differentiation of human pluripotent stem cells. *Development (Cambridge, England)*, *142*(7), 1375–1386.

Åsberg, M., Bertilsson, L., Mårtensson, B., Scalia-Tomba, G. P., Thorén, P., & Träskman-Bendz, L. (1984). CSF monoamine metabolites in melancholia. *Acta Psychiatrica Scandinavica*, *69*(3), 201–219.

Avior, Y., Sagi, I., & Benvenisty, N. (2016). Pluripotent stem cells in disease modelling and drug discovery. *Nature Reviews Molecular Cell Biology*, *17*(3), 170–182.

Bardy, C., Van den Hurk, M., Eames, T., Marchand, C., Hernandez, R. V., Kellogg, M., … Gage, F. H. (2015). Neuronal medium that supports basic synaptic functions and activity of human neurons in vitro. *Proceedings of the National Academy of Sciences*, *112*(20), E2725–E2734.

Baumeister, A. A. (2013). The chlorpromazine enigma. *Journal of the History of the Neurosciences*, *22*(1), 14–29.

Bavamian, S., Mellios, N., Lalonde, J., Fass, D. M., Wang, J., Sheridan, S. D., … Haggarty, S. J. (2015). Dysregulation of miR-34a links neuronal development to genetic risk factors for bipolar disorder. *Molecular Psychiatry*, *20*(5), 573–584.

Beasley, C. L., & Reynolds, G. P. (1997). Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. *Schizophrenia Research*, *24*(3), 349–355.

Beers, J., Linask, K. L., Chen, J. A., Siniscalchi, L. I., Lin, Y., Zheng, W., … Chen, G. (2015). A cost-effective and efficient reprogramming platform for large-scale production of integration-free human induced pluripotent stem cells in chemically defined culture. *Scientific Reports*, *5*, 11319.

Ben-David, U., & Benvenisty, N. (2011). The tumorigenicity of human embryonic and induced pluripotent stem cells. *Nature Reviews Cancer*, *11*, 268.

Bener, A., Dafeeah, E. E., & Salem, M. O. (2013). A study of reasons of non-compliance of psychiatric treatment and patients' attitudes towards illness and treatment in Qatar. *Issues in Mental Health Nursing*, *34*(4), 273–280.

Ben-Reuven, L., & Reiner, O. (2016). Modeling the autistic cell: iPSCs recapitulate developmental principles of syndromic and nonsyndromic ASD. *Development, Growth & Differentiation*, *58*(5), 481–491.

Bertolino, A., Frye, M., Callicott, J. H., Mattay, V. S., Rakow, R., Shelton-Repella, J., … Weinberger, D. R. (2003). Neuronal pathology in the hippocampal area of patients with bipolar disorder: A study with proton magnetic resonance spectroscopic imaging. *Biological Psychiatry*, *53*(10), 906–913.

Bockting, C. L. H., ten Doesschate, M. C., Spijker, J., Spinhoven, P., Koeter, M. W. J., & Schene, A. H. (2008). Continuation and maintenance use of antidepressants in recurrent depression. *Psychotherapy and Psychosomatics*, *77*(1), 17–26.

Bogerts, B., Hantsch, J., & Herzer, M. (1983). A morphometric study of the dopamine-containing cell groups in the mesencephalon of normals, Parkinson patients, and schizophrenics. *Biology Psychiartry*, *18*(9), 951–969.

Brederlau, A., Correia, A. S., Anisimov, S. V., Elmi, M., Paul, G., Roybon, L., … Li, J. Y. (2006). Transplantation of human embryonic stem cell-derived cells to a rat model of Parkinson's disease: Effect of in vitro differentiation on graft survival and teratoma formation. *Stem Cells*, *24*(6), 1433–1440.

Brennand, K., Simone, A., Jou, J., Gelboin-Burkhart, C., Tran, N., Sangar, S., … Gage, F. H. (2011a). Modeling schizophrenia using hiPSC neurons. *Nature*, *473*(7346), 221–225.

Brennand, K. J., Simone, A., Jou, J., Gelboin-Burkhart, C., Tran, N., Sangar, S., … Gage, F. H. (2011b). Modelling schizophrenia using human induced pluripotent stem cells. *Nature*, *473*(7346), 221–225.

Brennand, K. J., Simone, A., Tran, N., & Gage, F. H. (2012). Modeling psychiatric disorders at the cellular and network levels. *Molecular Psychiatry*, *17*(12), 1239–1253.

Brickman, J. M., & Burdon, T. G. (2002). Pluripotency and tumorigenicity. *Nature Genetics*, *32*, 557.

Brito, A., Russo, F. B., Muotri, A. R., & Beltrao-Braga, P. C. B. (2018). Autism spectrum disorders and disease modeling using stem cells. *Cell and Tissue Research*, *371*(1), 153–160.

Bury, L. A., & Wynshaw-Boris, A. (2018). Modeling non-syndromic autism with human-induced pluripotent stem cells. *Neuropsychopharmacology*, *43*(1), 219–220.

Caiazzo, M., Dell'Anno, M. T., Dvoretskova, E., Lazarevic, D., Taverna, S., Leo, D., … Broccoli, V. (2011). Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. *Nature*, *476*, 224.

Caiazzo, M., Giannelli, S., Valente, P., Lignani, G., Carissimo, A., Sessa, A., … Broccoli, V. (2015). Direct conversion of fibroblasts into functional astrocytes by defined transcription factors. *Stem Cell Reports*, *4*(1), 25–36.

Caligiuri, M. P., Brown, G. G., Meloy, M. J., Eberson, S. C., Kindermann, S. S., Frank, L. R., … Lohr, J. B. (2003). An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. *Psychiatry Research: Neuroimaging*, *123*(3), 171–182.

Capitão, L., Sampaio, A., Sampaio, C., Vasconcelos, C., Férnandez, M., Garayzábal, E., … Gonçalves, Ó. F. (2011). MRI amygdala volume in Williams syndrome. *Research in Developmental Disabilities*, *32*(6), 2767–2772.

Carey, B. W., Markoulaki, S., Hanna, J., Saha, K., Gao, Q., Mitalipova, M., & Jaenisch, R. (2009). Reprogramming of murine and human somatic cells using a single polycistronic vector. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(1), 157–162.

Cavalleri, L., Merlo Pich, E., Millan, M. J., Chiamulera, C., Kunath, T., Spano, P. F., & Collo, G. (2018). Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Molecular Psychiatry*, *23*(4), 812–823.

Chailangkarn, T., Trujillo, C. A., Freitas, B. C., Hrvoj-Mihic, B., Herai, R. H., Yu, D. X., … Muotri, A. R. (2016). A human neurodevelopmental model for Williams syndrome. *Nature*, *536*(7616), 338–343.

Chan, M. K., Gottschalk, M. G., Haenisch, F., Tomasik, J., Ruland, T., Rahmoune, H., … Bahn, S. (2014). Applications of blood-based protein biomarker strategies in the study of psychiatric disorders. *Progress in Neurobiology*, *122*, 45–72.

Chen, H. M., DeLong, C. J., Bame, M., Rajapakse, I., Herron, T. J., McInnis, M. G., & O'Shea, K. S. (2014). Transcripts involved in calcium signaling and telencephalic neuronal fate are altered in induced pluripotent stem cells from bipolar disorder patients. *Translational Psychiatry*, *4*.

Chen, I. P., Fukuda, K., Fusaki, N., Iida, A., Hasegawa, M., Lichtler, A., & Reichenberger, E. J. (2013). Induced pluripotent stem cell reprogramming by integration-free Sendai virus vectors from peripheral blood of patients with craniometaphyseal dysplasia. *Cellular Reprogramming*, *15*(6), 503–513.

Chen, Y., & Lai, D. (2015). Pluripotent states of human embryonic stem cells. *Cellular Reprogramming*, *17*(1), 1–6.

Chen, H. I., Song, H., & Ming, G. L. (2018). Applications of human brain organoids to clinical problems. *Developmental Dynamics*, *248*(1), 53–64.

Clevers, H. (2016). Modeling development and disease with organoids. *Cell*, *165*(7), 1586–1597.

Coccaro, E. F., Siever, L. J., Klar, H. M., et al. (1989). Serotonergic studies in patients with affective and personality disorders: Correlates with suicidal and impulsive aggressive behavior. *Archives of General Psychiatry*, *46*(7), 587–599.

Collo, G., Cavalleri, L., Bono, F., Mora, C., Fedele, S., Invernizzi, R. W., … Spano, P. (2018). Ropinirole and Pramipexole promote structural plasticity in human iPSC-derived dopaminergic neurons via BDNF and mTOR signaling. *Neural Plasticity*, *2018*, 4196961.

Cotter, D., Mackay, D., Landau, S., Kerwin, R., & Everall, I. (2001). Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Archives of General Psychiatry*, *58*(6), 545–553.

DelBello, M. P., Zimmerman, M. E., Mills, N. P., Getz, G. E., & Strakowski, S. M. (2004). Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. *Bipolar Disorders*, *6*(1), 43–52.

Di Lullo, E., & Kriegstein, A. R. (2017). The use of brain organoids to investigate neural development and disease. *Nature Reviews. Neuroscience*, *18*(10), 573–584.

Donegan, J. J., Tyson, J. A., Branch, S. Y., Beckstead, M. J., Anderson, S. A., & Lodge, D. J. (2017). Stem cell-derived interneuron transplants as a treatment for schizophrenia: Preclinical validation in a rodent model. *Molecular Psychiatry*, *22*(10), 1492–1501.

Dyer, M. A. (2016). Stem cells expand insights into human brain evolution. *Cell Stem Cell*, *18*(4), 425–426.

Etkin, A., Prater, K. E., Hoeft, F., Menon, V., & Schatzberg, A. F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *The American Journal of Psychiatry*, *167*(5), 545–554.

Falk, A., Heine, V. M., Harwood, A. J., Sullivan, P. F., Peitz, M., Brustle, O., … Djurovic, S. (2016). Modeling psychiatric disorders: From genomic findings to cellular phenotypes. *Molecular Psychiatry*, *21*(9), 1167–1179.

Farzan, F., Barr, M. S., Levinson, A. J., Chen, R., Wong, W., Fitzgerald, P. B., & Daskalakis, Z. J. (2010). Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain*, *133*(5), 1505–1514.

Fava, M. (2000). New approaches to the treatment of refractory depression. *The Journal of Clinical Psychiatry*, *61*, 26–32.

Fernandez, B. A., & Scherer, S. W. (2017). Syndromic autism spectrum disorders: Moving from a clinically defined to a molecularly defined approach. *Dialogues in Clinical Neuroscience*, *19*(4), 353–371.

Fusaki, N., Ban, H., Nishiyama, A., Saeki, K., & Hasegawa, M. (2009). Efficient induction of transgene-free human pluripotent stem cells using a vector based on Sendai virus, an RNA virus that does not integrate into the host genome. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*, *85*(8), 348–362.

Gil, J., Laczmanska, I., Pesz, K. A., & Sasiadek, M. M. (2018). Personalized medicine in oncology. New perspectives in management of gliomas. *Contemporary Oncology*, *22*(1A), 1–2.

Giménez, M., Pujol, J., Ortiz, H., Soriano-Mas, C., López-Solà, M., Farré, M., … Martín-Santos, R. (2012). Altered brain functional connectivity in relation to perception of scrutiny in social anxiety disorder. *Psychiatry Research: Neuroimaging*, *202*(3), 214–223.

Glatt, C. E., & Lee, F. S. (2016). Common polymorphisms in the age of research domain criteria (RDoC): Integration and translation. *Biological Psychiatry*, *79*(1), 25–31.

Goldberg, M. C., Spinelli, S., Joel, S., Pekar, J. J., Denckla, M. B., & Mostofsky, S. H. (2011). Children with high functioning autism show increased prefrontal and temporal cortex activity during error monitoring. *Developmental Cognitive Neuroscience*, *1*(1), 47–56.

González, F., Boué, S., & Belmonte, J. C. I. (2011). Methods for making induced pluripotent stem cells: Reprogramming à la carte. *Nature Reviews Genetics*, *12*(4), 231–242.

Gonzalez, D. M., Gregory, J., & Brennand, K. J. (2017). The importance of non-neuronal cell types in hiPSC-based disease modeling and drug screening. *Frontiers in Cell and Development Biology*, *5*, 117.

Gorris, R., Fischer, J., Erwes, K. L., Kesavan, J., Peterson, D. A., Alexander, M., … Brüstle, O. (2015). Pluripotent stem cell-derived radial glia-like cells as stable intermediate for efficient generation of human oligodendrocytes. *Glia*, *63*(12), 2152–2167.

Gratten, J., Wray, N. R., Keller, M. C., & Visscher, P. M. (2014). Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Neuroscience*, *17*, 782.

Griesi-Oliveira, K., Acab, A., Gupta, A. R., Sunaga, D. Y., Chailangkarn, T., Nicol, X., … Muotri, A. R. (2015). Modeling non-syndromic autism and the impact of TRPC6 disruption in human neurons. *Molecular Psychiatry*, *20*(11), 1350–1365.

Gupta, S., M-Redmond, T., Meng, F., Tidball, A., Akil, H., Watson, S., … Uhler, M. (2018). Fibroblast growth factor 2 regulates activity and gene expression of human post-mitotic excitatory neurons. *Journal of Neurochemistry*, *145*(3), 188–203.

Gurdon, J. B. (1962). The developmental capacity of nuclei taken from intestinal epithelium cells of feeding tadpoles. *Journal of Embryology and Experimental Morphology*, *10*(4), 622.

Haile, C. N., Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Foulkes, A., … Mathew, S. J. (2014). Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. *The International Journal of Neuropsychopharmacology*, *17*(2), 331–336.

Heckers, S., Stone, D., Walsh, J., Shick, J., Koul, P., & Benes, F. M. (2002). Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger rna in bipolar disorder and schizophrenia. *Archives of General Psychiatry*, *59*(6), 521–529.

Hedgepeth, C. M., Conrad, L. J., Zhang, J., Huang, H. C., Lee, V. M., & Klein, P. S. (1997). Activation of the Wnt signaling pathway: A molecular mechanism for lithium action. *Developmental Biology*, *185*(1), 82–91.

Hettema, J. M., Kettenmann, B., Ahluwalia, V., McCarthy, C., Kates, W. R., Schmitt, J. E., … Fatouros, P. (2012). A pilot multimodal twin imaging study of generalized anxiety disorder. *Depression and Anxiety*, *29*(3), 202–209.

Hoffmann, A., Sportelli, V., Ziller, M., & Spengler, D. (2018). From the Psychiatrist's couch to induced pluripotent stem cells: Bipolar disease in a dish. *International Journal of Molecular Sciences*, *19*(3), E770.

Huang, J., Liu, F., Tang, H., Wu, H., Li, L., Wu, R., … Chen, J. (2017). Tranylcypromine causes neurotoxicity and represses BHC110/LSD1 in human-induced pluripotent stem cell-derived cerebral organoids model. *Frontiers in Neurology*, *8*, 626.

Javitt, D. (1987). Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. *The Hillside Journal of Clinical Psychiatry*, *9*(1), 12–35.

Jope, R. S. (2003). Lithium and GSK-3: One inhibitor, two inhibitory actions, multiple outcomes. *Trends in Pharmacological Sciences*, *24*(9), 441–443.

Kaiser, T., & Feng, G. (2015). Modeling psychiatric disorders for developing effective treatments. *Nature Medicine*, *21*(9), 979–988.

Kalia, M., & Costa, E. S. J. (2015). Biomarkers of psychiatric diseases: Current status and future prospects. *Metabolism*, *64*(3 Suppl 1), S11–S15.

Kalman, S., Hathy, E., & Rethelyi, J. M. (2016). A dishful of a troubled mind: Induced pluripotent stem cells in psychiatric research. *Stem Cells International*, *2016*, 7909176.

Kane, J. M., Kishimoto, T., & Correll, C. U. (2013). Non-adherence to medication in patients with psychotic disorders: Epidemiology, contributing factors and management strategies. *World Psychiatry*, *12*(3), 216–226.

Kegeles, L. S., Abi-Dargham, A., Frankle, W., et al. (2010). Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Archives of General Psychiatry*, *67*(3), 231–239.

Kessler, R. M., Woodward, N. D., Riccardi, P., Li, R., Ansari, M. S., Anderson, S., … Meltzer, H. Y. (2009). Dopamine D2 receptor levels in striatum, thalamus, Substantia Nigra, limbic regions, and cortex in schizophrenic subjects. *Biological Psychiatry*, *65*(12), 1024–1031.

Khattak, S., Brimble, E., Zhang, W., Zaslavsky, K., Strong, E., Ross, P. J., … Ellis, J. (2015). Human induced pluripotent stem cell derived neurons as a model for Williams-Beuren syndrome. *Molecular Brain*, *8*(1), 77.

Kida, S., & Kato, T. (2015). Microendophenotypes of psychiatric disorders: Phenotypes of psychiatric disorders at the level of molecular dynamics, synapses, neurons, and neural circuits. *Current Molecular Medicine*, *15*(2), 111–118.

Kim, K., Doi, A., Wen, B., Ng, K., Zhao, R., Cahan, P., … Daley, G. Q. (2010). Epigenetic memory in induced pluripotent stem cells. *Nature*, *467*(7313), 285–290.

Kim, S., Kim, M. K., Oh, D., Lee, S. H., & Kim, B. (2016). Induced pluripotent stem cells as a novel tool in psychiatric research. *Psychiatry Investigation*, *13*(1), 8–17.

Kim, K. H., Liu, J., Sells Galvin, R. J., Dage, J. L., Egeland, J. A., Smith, R. C., … Paul, S. M. (2015). Transcriptomic analysis of induced pluripotent stem cells derived from patients with bipolar disorder from an old order Amish pedigree. *PLoS One*, *10*(11).

Kim, K., Zhao, R., Doi, A., Ng, K., Unternaehrer, J., Cahan, P., … Daley, G. Q. (2011). Donor cell type can influence the epigenome and differentiation potential of human induced pluripotent stem cells. *Nature Biotechnology*, *29*(12), 1117–1119.

Klumpers, U. M. H., Veltman, D. J., Drent, M. L., Boellaard, R., Comans, E. F. I., Meynen, G., … Hoogendijk, W. J. G. (2010). Reduced parahippocampal and lateral temporal GABAA-[11C]flumazenil binding in major depression: Preliminary results. *European Journal of Nuclear Medicine and Molecular Imaging*, *37*(3), 565–574.

Krencik, R., & Zhang, S.-C. (2011). Directed differentiation of functional Astroglial subtypes from human pluripotent stem cells. *Nature Protocols*, *6*(11), 1710–1717.

Lancaster, M. A., & Knoblich, J. A. (2014). Organogenesis in a dish: Modeling development and disease using organoid technologies. *Science*, *345*(6194).

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., & Innis, R. (1999). Increased dopamine transmission in schizophrenia: Relationship to illness phases. *Biological Psychiatry*, *46*(1), 56–72.

Leckband, S. G., McCarthy, M., & Kelsoe, J. R. (2012). The pharmacogenomics of mood stabilizer response in bipolar disorder. *Mental Health Clinician*, *1*(9), 217–221.

Lee, H. J., Hore, T. A., & Reik, W. (2014). Reprogramming the methylome: Erasing memory and creating diversity. *Cell Stem Cell*, *14*(6), 710–719.

Lepack, A. E., Fuchikami, M., Dwyer, J. M., Banasr, M., & Duman, R. S. (2014). BDNF release is required for the behavioral actions of ketamine. *The International Journal of Neuropsychopharmacology*, *18*(1).

Lew, C. H., Brown, C., Bellugi, U., & Semendeferi, K. (2016). Neuron density is decreased in the prefrontal cortex in Williams syndrome. *Autism Research*, *10*(1), 99–112.

Licinio, J., & Wong, M. L. (2011). Pharmacogenomics of antidepressant treatment effects. *Dialogues in Clinical Neuroscience*, *13*(1), 63–71.

Licinio, J., & Wong, M. L. (2016). Serotonergic neurons derived from induced pluripotent stem cells (iPSCs): A new pathway for research on the biology and pharmacology of major depression. *Molecular Psychiatry*, *21*(1), 1–2.

Lim, S.-W., Kwon, Y.-S., Ha, J., Yoon, H.-G., Bae, S.-M., Shin, D.-W., … Oh, K.-S. (2012). Comparison of treatment adherence between selective serotonin reuptake inhibitors and moclobemide in patients with social anxiety disorder. *Psychiatry Investigation*, *9*(1), 73–79.

Lim, C. S., Yang, J. E., Lee, Y. K., Lee, K., Lee, J. A., & Kaang, B. K. (2015). Understanding the molecular basis of autism in a dish using hiPSCs-derived neurons from ASD patients. *Molecular Brain*, *8*(1), 57.

Liu, X., Campanac, E., Cheung, H. H., Ziats, M. N., Canterel-Thouennon, L., Raygada, M., … Rennert, O. M. (2017). Idiopathic autism: Cellular and molecular phenotypes in pluripotent stem cell-derived neurons. *Molecular Neurobiology*, *54*(6), 4507–4523.

Liu, Y., Liu, H., Sauvey, C., Yao, L., Zarnowska, E. D., & Zhang, S.-C. (2013). Directed differentiation of forebrain GABA interneurons from human pluripotent stem cells. *Nature Protocols*, *8*(9), 1670–1679.

Liu, Y. N., Lu, S. Y., & Yao, J. (2017). Application of induced pluripotent stem cells to understand neurobiological basis of bipolar disorder and schizophrenia. *Psychiatry and Clinical Neurosciences*, *71*(9), 579–599.

Liu-Seifert, H., Adams, D. H., & Kinon, B. J. (2005). Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: A pooled post-hoc analysis of four atypical antipsychotic drugs. *BMC Medicine*, *3*(1), 21.

Lodge, D. J., & Grace, A. A. (2005). The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology*, *31*, 1356.

Lu, J., Zhong, X., Liu, H., Hao, L., Huang, C. T.-L., Sherafat, M. A., … Zhang, S.-C. (2016). Generation of serotonin neurons from human pluripotent stem cells. *Nature Biotechnology*, *34*(1), 89–94.

Lyoo, I. K., Sung, Y. H., Dager, S. R., Friedman, S. D., Lee, J. Y., Kim, S. J., … Renshaw, P. F. (2006). Regional cerebral cortical thinning in bipolar disorder. *Bipolar Disorders*, *8*(1), 65–74.

Ma, L., Liu, Y., & Zhang, S.-C. (2011). Directed differentiation of dopamine neurons from human pluripotent stem cells. In P. H. Schwartz, & R. L. Wesselschmidt (Eds.), *Human pluripotent stem cells: Methods and protocols* (pp. 411–418). Totowa, NJ: Humana Press.

Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I. D., Salvadore, G., & Zarate, C. A. (2010). The timing of antidepressant effects: A comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals (Basel, Switzerland)*, *3*(1), 19–41.

Madison, J. M., Zhou, F., Nigam, A., Hussain, A., Barker, D. D., Nehme, R., … Haggarty, S. J. (2015). Characterization of bipolar disorder patient-specific induced pluripotent stem cells from a family reveals neurodevelopmental and mRNA expression abnormalities. *Molecular Psychiatry*, *20*(6), 703–717.

Malik, N., & Rao, M. S. (2013). A review of the methods for human iPSC derivation. *Methods in molecular biology (Clifton, NJ)*, *997*, 23–33.

Marchetto, M. C., Brennand, K. J., Boyer, L. F., & Gage, F. H. (2011). Induced pluripotent stem cells (iPSCs) and neurological disease modeling: Progress and promises. *Human Molecular Genetics*, *20*(R2), R109–R115.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry*, *60*(5), 497–502.

Mertens, J., Marchetto, M. C., Bardy, C., & Gage, F. H. (2016). Evaluating cell reprogramming, differentiation and conversion technologies in neuroscience. *Nature Reviews Neuroscience*, *17*, 424.

Mertens, J., Wang, Q. W., Kim, Y., Yu, D. X., Pham, S., Yang, B., … Yao, J. (2015). Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature*, *527*(7576), 95–99.

Meyer-Lindenberg, A., Mervis, C. B., Sarpal, D., Koch, P., Steele, S., Kohn, P., … Berman, K. F. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *Journal of Clinical Investigation*, *115*(7), 1888–1895.

Miskinyte, G., Devaraju, K., Grønning Hansen, M., Monni, E., Tornero, D., Woods, N. B., … Kokaia, Z. (2017). Direct conversion of human fibroblasts to functional excitatory cortical neurons integrating into human neural networks. *Stem Cell Research & Therapy*, *8*, 207.

Mobbs, D., Eckert, M. A., Menon, V., Mills, D., Korenberg, J., Galaburda, A. M., … Reiss, A. L. (2007). Reduced parietal and visual cortical activation during global processing in Williams syndrome. *Developmental Medicine and Child Neurology*, *49*(6), 433–438.

Murphy, D. L. (1990). Neuropsychiatric disorders and the multiple human brain serotonin receptor subtypes and subsystems. *Neuropsychopharmacology*, *3*(5–6), 457–471.

Nashun, B., Hill, P. W., & Hajkova, P. (2015). Reprogramming of cell fate: Epigenetic memory and the erasure of memories past. *The EMBO Journal*, *34*(10), 1296–1308.

Nebel, M. B., Joel, S. E., Muschelli, J., Barber, A. D., Caffo, B. S., Pekar, J. J., & Mostofsky, S. H. (2014). Disruption of functional organization within the primary motor cortex in children with autism. *Human Brain Mapping*, *35*(2), 567–580.

Nierenberg, A. A. (2010). A critical appraisal of treatments for bipolar disorder. *Prim Care Companion Journal of Clinical Psychiatry*, *12*(Suppl 1), 23–29.

Nishimura, K., Ohtaka, M., Takada, H., Kurisaki, A., Tran, N. V. K., Tran, Y. T. H., … Nakanishi, M. (2017). Simple and effective generation of transgene-free induced pluripotent stem cells using an auto-erasable Sendai virus vector responding to microRNA-302. *Stem Cell Research*, *23*, 13–19.

Oedegaard, K. J., Alda, M., Anand, A., Andreassen, O. A., Balaraman, Y., Berrettini, W. H., … Kelsoe, J. R. (2016). The Pharmacogenomics of Bipolar Disorder study (PGBD): Identification of genes for lithium response in a prospective sample. *BMC Psychiatry*, *16*, 129.

Okita, K., Ichisaka, T., & Yamanaka, S. (2007). Generation of germline-competent induced pluripotent stem cells. *Nature*, *448*, 313.

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Archives of General Psychiatry*, *52*(12), 998–1007.

Papapetrou, E. P. (2016). Induced pluripotent stem cells, past and future. *Science*, *353*(6303), 991–992.

Paulsen Bda, S., de Moraes Maciel, R., Galina, A., Souza da Silveira, M., dos Santos Souza, C., Drummond, H., … Rehen, S. K. (2012). Altered oxygen metabolism associated to neurogenesis of induced pluripotent stem cells derived from a schizophrenic patient. *Cell Transplantation*, *21*(7), 1547–1559.

Pei, S., Liu, L., Zhong, Z., Wang, H., Lin, S., & Shang, J. (2016). Risk of prenatal depression and stress treatment: Alteration on serotonin system of offspring through exposure to Fluoxetine. *Scientific Reports*, *6*, 33822.

Perry, T., Kish, S., Buchanan, J., & Hansen, S. (1979). Gamma-aminobutyric-acid deficiency in brain of schizophrenic patients. *Lancet*, *1*(8110), 237–239.

Perry, S. W., Norman, J. P., Litzburg, A., & Gelbard, H. A. (2004). Antioxidants are required during the early critical period, but not later, for neuronal survival. *Journal of Neuroscience Research*, *78*(4), 485–492.

Pierri, J. N., Volk, C. L. E., Auh, S., Sampson, A., & Lewis, D. A. (2003). Somal size of prefrontal cortical pyramidal neurons in schizophrenia. *Biological Psychiatry*, *54*(2), 111–120.

Plomin, R., Owen, M. J., & McGuffin, P. (1994). The genetic basis of complex human behaviors. *Science*, *264*(5166), 1733.

Preskorn, S. H. (2007). The evolution of antipsychotic drug therapy: Reserpine, chlorpromazine, and haloperidol. *Journal of Psychiatric Practice*, *13*(4), 253–257.

Qiu, M., Zhang, H., Mellor, D., Shi, J., Wu, C., Huang, Y., … Peng, D. (2018). Aberrant neural activity in patients with bipolar depressive disorder distinguishing to the unipolar depressive disorder: A resting-state functional magnetic resonance imaging study. *Frontiers in Psychiatry*, *9*, 238.

Quadrato, G., Brown, J., & Arlotta, P. (2016). The promises and challenges of human brain organoids as models of neuropsychiatric disease. *Nature Medicine*, *22*(11), 1220–1228.

Rajkowska, G. (2000). Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biological Psychiatry*, *48*(8), 766–777.

Rajkowska, G., Halaris, A., & Selemon, L. D. (2001). Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biological Psychiatry*, *49*(9), 741–752.

Razafsha, M., Khaku, A., Azari, H., Alawieh, A., Behforuzi, H., Fadlallah, B., … Gold, M. S. (2015). Biomarker identification in psychiatric disorders: From neuroscience to clinical practice. *Journal of Psychiatric Practice*, *21*(1), 37–48.

Reynolds, G. P., McGowan, O. O., & Dalton, C. F. (2014). Pharmacogenomics in psychiatry: The relevance of receptor and transporter polymorphisms. *British Journal of Clinical Pharmacology*, *77*(4), 654–672.

Riggs, J. W., Barrilleaux, B. L., Varlakhanova, N., Bush, K. M., Chan, V., & Knoepfler, P. S. (2013). Induced pluripotency and oncogenic transformation are related processes. *Stem Cells and Development*, *22*(1), 37–50.

Ritchie, H., & Roser, M. (2018). *Mental health*. Published online at OurWorldInData.org. Retrieved from: https://ourworldindata.org/mental-health. (Accessed 22 October 2018).

Ritvo, E. R., Freeman, B. J., Scheibel, A. B., Duong, T., Robinson, H., & Guthrie, D. (1986). Lower Purkinje cell counts in the cerebella of four autistic subjects: Initial findings of the UCLA-NSAC autopsy research report. *American Journal of Psychiatry*, *143*(7), 862–866.

Robicsek, O., Karry, R., Petit, I., Salman-Kesner, N., Müller, F. J., Klein, E., … Ben-Shachar, D. (2013). Abnormal neuronal differentiation and mitochondrial dysfunction in hair follicle-derived induced pluripotent stem cells of schizophrenia patients. *Molecular Psychiatry*, *18*, 1067.

Roffman, J. L. (2011). Biomarkers and personalized psychiatry. *Harvard Review of Psychiatry*, *19*(3), 99–101.

Samoilova, E. M., Kalsin, V. A., Kushnir, N. M., Chistyakov, D. A., Troitskiy, A. V., & Baklaushev, V. P. (2018). Adult neural stem cells: Basic research and production strategies for neurorestorative therapy. *Stem Cells International*, *2018*, 4835491.

Sarkar, A., Mei, A., Paquola, A. C. M., Stern, S., Bardy, C., Klug, J. R., … Gage, F. H. (2018). Efficient generation of CA3 neurons from human pluripotent stem cells enables modeling of hippocampal connectivity in vitro. *Cell Stem Cell*, *22*(5). 684–697.e689.

Scarr, E., Millan, M. J., Bahn, S., Bertolino, A., Turck, C. W., Kapur, S., … Dean, B. (2015). Biomarkers for psychiatry: The journey from fantasy to fact, a report of the 2013 CINP think tank. *The International Journal of Neuropsychopharmacology*, *18*(10).

Schaffer, A., Isometsa, E. T., Tondo, L., Moreno, H. D., Turecki, G., Reis, C., … Yatham, L. N. (2015). International society for bipolar disorders task force on suicide: Meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disorders*, *17*(1), 1–16.

Schienle, A., Ebner, F., & Schäfer, A. (2011). Localized gray matter volume abnormalities in generalized anxiety disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *261*(4), 303–307.

Schilsky, R. L. (2010). Personalized medicine in oncology: The future is now. *Nature Reviews Drug Discovery*, *9*, 363.

Schumann, C. M., Hamstra, J., Goodlin-Jones, B. L., Lotspeich, L. J., Kwon, H., Buonocore, M. H., … Amaral, D. G. (2004). The amygdala is enlarged in children but not adolescents with Autism: The hippocampus is enlarged at all ages. *The Journal of Neuroscience*, *24*(28), 6392.

Shen, X., Yeung, H. T., & Lai, K. O. (2018). Application of human-induced pluripotent stem cells (hiPSCs) to study synaptopathy of neurodevelopmental disorders. *Developmental Neurobiology*, *79*(1), 20–35.

Shi, Y., Kirwan, P., Smith, J., Robinson, H. P. C., & Livesey, F. J. (2012). Human cerebral cortex development from pluripotent stem cells to functional excitatory synapses. *Nature Neuroscience*. *15*(3). https://doi.org/10.1038/nn.3041.

Singh, V. K., Kalsan, M., Kumar, N., Saini, A., & Chandra, R. (2015). Induced pluripotent stem cells: Applications in regenerative medicine, disease modeling, and drug discovery. *Frontiers in Cell and Development Biology*, *3*, 2.

Sokolowska, I., Ngounou Wetie, A. G., Wormwood, K., Thome, J., Darie, C. C., & Woods, A. G. (2015). The potential of biomarkers in psychiatry: Focus on proteomics. *Journal of Neural Transmission (Vienna)*, *122*(Suppl 1), S9–18.

Soldner, F., & Jaenisch, R. (2018). Stem cells, genome editing, and the path to translational medicine. *Cell*, *175*(3), 615–632.

Soliman, M. A., Aboharb, F., Zeltner, N., & Studer, L. (2017). Pluripotent stem cells in neuropsychiatric disorders. *Molecular Psychiatry*, *22*(9), 1241–1249.

Sommer, C. A., Stadtfeld, M., Murphy, G. J., Hochedlinger, K., Kotton, D. N., & Mostoslavsky, G. (2009). iPS cell generation using a single lentiviral stem cell cassette. *Stem Cells (Dayton, Ohio)*, *27*(3), 543–549.

Southwell, D. G., Nicholas, C. R., Basbaum, A. I., Stryker, M. P., Kriegstein, A. R., Rubenstein, J. L., & Alvarez-Buylla, A. (2014). Interneurons from embryonic development to cell-based therapy. *Science (New York, NY)*, *344*(6180), 1240622.

Spatazza, J., Mancia Leon, W. R., & Alvarez-Buylla, A. (2017). Chapter 3—Transplantation of GABAergic interneurons for cell-based therapy. In S. B. Dunnett, & A. Björklund (Eds.), *Progress in brain research* (pp. 57–85): Elsevier.

Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: Dopamine, serotonin, and glutamate. *CNS Spectrums*, *23*(3), 187–191.

Stern, S., Linker, S., Vadodaria, K. C., Marchetto, M. C., & Gage, F. H. (2018). Prediction of response to drug therapy in psychiatric disorders. *Open Biology*, *8*(5), 180031.

Stern, S., Santos, R., Marchetto, M. C., Mendes, A. P. D., Rouleau, G. A., Biesmans, S., … Gage, F. H. (2018). Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium. *Molecular Psychiatry*, *23*(6), 1453–1465.

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*(12), 1187–1192.

Sun, A. X., Yuan, Q., Tan, S., Xiao, Y., Wang, D., Khoo, A. T., … Je, H. S. (2016). Direct induction and functional maturation of forebrain GABAergic neurons from human pluripotent stem cells. *Cell Reports*, *16*(7), 1942–1953.

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*, *131*(5), 861–872.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*(4), 663–676.

Tang, Y., Stryker, M. P., Alvarez-Buylla, A., & Espinosa, J. S. (2014). Cortical plasticity induced by transplantation of embryonic somatostatin or parvalbumin interneurons. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(51), 18339–18344.

Tapia, N., & Scholer, H. R. (2016). Molecular obstacles to clinical translation of iPSCs. *Cell Stem Cell*, *19*(3), 298–309.

Thomaes, K., Dorrepaal, E., Draijer, N., de Ruiter, M. B., Elzinga, B. M., Sjoerds, Z., … Veltman, D. J. (2013). Increased anterior cingulate cortex and hippocampus activation in complex PTSD during encoding of negative words. *Social Cognitive and Affective Neuroscience*, *8*(2), 190–200.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S., & Jones, J. M. (1998). Embryonic stem cell lines derived from human blastocysts. *Science*, *282*(5391), 1145.

Tobe, B. T. D., Crain, A. M., Winquist, A. M., Calabrese, B., Makihara, H., Zhao, W. N., … Snyder, E. Y. (2017). Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(22), E4462–E4471.

Träskman, L., Åsberg, M., Bertilsson, L., & Sjüstrand, L. (1981). Monoamine metabolites in csf and suicidal behavior. *Archives of General Psychiatry*, *38*(6), 631–636.

Trivedi, M. H., Fava, M., Wisniewski, S. R., Thase, M. E., Quitkin, F., Warden, D., … Rush, A. J. (2006). Medication augmentation after the failure of SSRIs for depression. *New England Journal of Medicine*, *354*(12), 1243–1252.

Vadodaria, K. C., Mertens, J., Paquola, A., Bardy, C., Li, X., Jappelli, R., … Gage, F. H. (2016). Generation of functional human serotonergic neurons from fibroblasts. *Molecular Psychiatry*, *21*(1), 49–61.

Vadodaria, K. C., Stern, S., Marchetto, M. C., & Gage, F. H. (2018). Serotonin in psychiatry: in vitro disease modeling using patient-derived neurons. *Cell and Tissue Research*, *371*(1), 161–170.

Valvezan, A. J., & Klein, P. S. (2012). GSK-3 and Wnt signaling in neurogenesis and bipolar disorder. *Frontiers in Molecular Neuroscience*, *5*, 1.

Victor, M. B., Richner, M., Hermanstyne, T. O., Ransdell, J. L., Sobieski, C., Deng, P.-Y., … Yoo, A. S. (2014). Generation of human striatal neurons by MicroRNA-dependent direct conversion of fibroblasts. *Neuron*, *84*(2), 311–323.

Vierbuchen, T., Ostermeier, A., Pang, Z. P., Kokubu, Y., Sudhof, T. C., & Wernig, M. (2010). Direct conversion of fibroblasts to functional neurons by defined factors. *Nature*, *463*(7284), 1035–1041.

Vitrac, A., & Cloez-Tayarani, I. (2018). Induced pluripotent stem cells as a tool to study brain circuits in autism-related disorders. *Stem Cell Research & Therapy*, *9*(1), 226.

Volk, D. W., Austin, M. C., Pierri, J. N., Sampson, A. R., & Lewis, D. A. (2000). Decreased glutamic acid decarboxylase67 messenger rna expression in a subset of prefrontal cortical γ-aminobutyric acid neurons in subjects with schizophrenia. *Archives of General Psychiatry*, *57*(3), 237–245.

Wang, J. L., Shamah, S. M., Sun, A. X., Waldman, I. D., Haggarty, S. J., & Perlis, R. H. (2014). Label-free, live optical imaging of reprogrammed bipolar disorder patient-derived cells reveals a functional correlate of lithium responsiveness. *Translational Psychiatry*, *4*.

Wang, C., Ward, M. E., Chen, R., Liu, K., Tracy, T. E., Chen, X., … Gan, L. (2017). Scalable production of iPSC-derived human neurons to identify tau-lowering compounds by high-content screening. *Stem Cell Reports*, *9*(4), 1221–1233.

Watmuff, B., Berkovitch, S. S., Huang, J. H., Iaconelli, J., Toffel, S., & Karmacharya, R. (2016). Disease signatures for schizophrenia and bipolar disorder using patient-derived induced pluripotent stem cells. *Molecular and Cellular Neurosciences*, *73*, 96–103.

Weich, S., Nazareth, I., Morgan, L., & King, M. (2007). Treatment of depression in primary care: Socio-economic status, clinical need and receipt of treatment. *British Journal of Psychiatry*, *191*(2), 164–169.

Weiss, A. P., Schacter, D. L., Goff, D. C., Rauch, S. L., Alpert, N. M., Fischman, A. J., & Heckers, S. (2003). Impaired hippocampal recruitment during normal modulation of memory performance in schizophrenia. *Biological Psychiatry*, *53*(1), 48–55.

Wium-Andersen, I. K., Vinberg, M., Kessing, L. V., & McIntyre, R. S. (2017). Personalized medicine in psychiatry. *Nordic Journal of Psychiatry*, *71*(1), 12–19.

Wong, M. L., Dong, C., Andreev, V., Arcos-Burgos, M., & Licinio, J. (2012). Prediction of susceptibility to major depression by a model of interactions of multiple functional genetic variants and environmental factors. *Molecular Psychiatry*, *17*(6), 624–633.

Wong, M. L., Dong, C., Maestre-Mesa, J., & Licinio, J. (2008). Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. *Molecular Psychiatry*, *13*(8), 800–812.

Xia, X., Ding, M., Xuan, J. F., Xing, J. X., Pang, H., Wang, B. J., & Yao, J. (2018). Polymorphisms in the human serotonin receptor 1B (HTR1B) gene are associated with schizophrenia: A case control study. *BMC Psychiatry*, *18*(1), 303.

Xu, Z., Jiang, H., Zhong, P., Yan, Z., Chen, S., & Feng, J. (2016). Direct conversion of human fibroblasts to induced serotonergic neurons. *Molecular Psychiatry*, *21*(1), 62–70.

Yang, N., Chanda, S., Marro, S., Ng, Y.-H., Janas, J. A., Haag, D., … Wernig, M. (2017). Generation of pure GABAergic neurons by transcription factor programming. *Nature Methods*, *14*(6), 621–628.

Yang, N., Ng, Y. H., Pang, Z. P., Sudhof, T. C., & Wernig, M. (2011). Induced neuronal cells: How to make and define a neuron. *Cell Stem Cell*, *9*(6), 517–525.

Yang, N., Zuchero, J. B., Ahlenius, H., Marro, S., Ng, Y. H., Vierbuchen, T., … Wernig, M. (2013). Generation of oligodendroglial cells by direct lineage conversion. *Nature Biotechnology*, *31*(5), 434–439.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian network for mood and anxiety treatments (CANMAT) and international society for bipolar disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*(2), 97–170.

Yip, J., Soghomonian, J.-J., & Blatt, G. J. (2007). Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: Pathophysiological implications. *Acta Neuropathologica*, *113*(5), 559–568.

Yoo, H. (2015). Genetics of autism spectrum disorder: Current status and possible clinical applications. *Experimental Neurobiology*, *24*(4), 257–272.

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., & Carter, C. S. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *The Journal of Neuroscience*, *30*(10), 3777–3781.

Young, L. T., Warsh, J. J., Kish, S. J., Shannak, K., & Hornykeiwicz, O. (1994). Reduced brain 5-HT and elevated NE turnover and metabolites in bipolar affective disorder. *Biological Psychiatry*, *35*(2), 121–127.

Yu, D. X., Giorgio, D., Francesco, P., Yao, J., Marchetto, M. C., Brennand, K., … Gage, F. H. (2014). Modeling hippocampal neurogenesis using human pluripotent stem cells. *Stem Cell Reports*, *2*(3), 295–310.

Zhao, W. N., Cheng, C., Theriault, K. M., Sheridan, S. D., Tsai, L. H., & Haggarty, S. J. (2012). A high-throughput screen for Wnt/beta-catenin signaling pathway modulators in human iPSC-derived neural progenitors. *Journal of Biomolecular Screening*, *17*(9), 1252–1263.

Further reading

Singh, I., & Rose, N. (2009). Biomarkers in psychiatry. *Nature*, *460*, 202.