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Modeling psychiatric disorders at the cellular and network levels

KJ Brennand[1], **A Simone**[1], **N Tran**[1], and **FH Gage**[1]
[1]Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, CA, USA

Abstract

Although psychiatric disorders such as autism spectrum disorders, schizophrenia and bipolar disorder affect a number of brain regions and produce a complex array of clinical symptoms, basic phenotypes likely exist at the level of single neurons and simple networks. Being highly heritable, it is hypothesized that these disorders are amenable to cell-based studies *in vitro*. Using induced pluripotent stem cell-derived neurons and/or induced neurons from fibroblasts, limitless numbers of live human neurons can now be generated from patients with a genetic background permissive to the disease state. We predict that cell-based studies will ultimately contribute to our understanding of the initiation, progression and treatment of these psychiatric disorders.

Keywords

autism spectrum disorders; bipolar disorder; neurons; schizophrenia; stem cells

Introduction

Autism spectrum disorders (ASDs), schizophrenia (SCZD) and bipolar disorder (BD) combine to affect nearly 1 in 30 adults throughout the global population.[1] While these psychiatric disorders are characterized by markedly different clinical phenotypes, recent genetic studies have suggested that they may share common underlying molecular causes. ASD, SCZD and BD are believed to be developmental in origin, resulting from events that occur in fetal development or early childhood. The molecular mechanism of these disorders is difficult to study in patients or animal models because of the complex genetic etiologies and varying environmental effects contributing to disease.

Cell-based models produce live human neurons with genetic backgrounds permissive to the disease state. Temporal analysis of disease initiation and progression can be studied in the cell type relevant to disease. Human cell-based models can be ideal experimental paradigms with which to investigate disease mechanisms; for example, studies of amyotrophic lateral sclerosis have revealed a non-cell autonomous contribution of glial cells to this neuronal disease.[2, 3] In order to be studied using an *in vitro* model, a given disease must (1) be highly genetic, ensuring that cultured cells are afflicted by disease in the absence of any potentially unresolved environmental factors and (2) affect a cell type that can survive and, ideally, be robustly expanded when cultured *in vitro*. With respect to the first criterion, twin studies have calculated the heritability of ASD, SCZD and BD to be between 70 and 90%.[4, 5, 6] Our hypothesis is that this genetic predisposition to psychiatric illness is sufficient that cultured neurons will consistently undergo disease initiation and progression. Regarding the second

Correspondence: FH Gage, PhD, Laboratory of Genetics, Salk Institute for Biological, Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA. gage@salk.edu.

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criterion, while mature neurons are postmitotic and cannot be expanded in culture, conditions for the survival of human neurons are well described,[7] and robust quantities of neurons for study can be generated through the growth and subsequent differentiation of proliferative neural progenitor cells.

The ability to compare cellular and network properties of live human neurons *in vitro* represents an important new approach with which to study psychiatric disease because live human neurons from patients or controls are exceedingly rare. Recently, three new sources of live human neurons have been reported: primary olfactory neural precursors, neurons differentiated from human-derived induced pluripotent stem cells (hiPSC neurons) and induced neurons (iNeurons) generated from primary patient fibroblasts. Although olfactory neural precursors are capable of self-renewal and differentiation to mature neurons,[8, 9] olfactory neural precursors cannot yield cells from the neural lineages specifically implicated in psychiatric disorders, such as GABAergic or dopaminergic neurons. Because we believe it is critical that the relevant cell type affected in the disease state be studied, we will therefore focus on *in vitro* models of psychiatric disease utilizing hiPSC neurons and iNeurons (Figure 1).

While generally considered to be whole-brain disorders, we suggest that ASD, SCZD and BD can be broken down to component aberrations at the cellular and/or network levels. For example, at the cellular level, the subtle synaptic defects that are believed to contribute to illness can be studied with cell-based models. Furthermore, while the cyclical behavioral swings of BD cannot be reproduced, patterns of spontaneous and stimulated neuronal network activity can be measured *in vitro*. Using cell-based models, one can study ASD, SCZD and BD by observing the abnormal development of neurons and their circuitry *in vitro*.

In this review, we will discuss (1) post-mortem and animal studies demonstrating that cellular phenotypes exist at the neuronal level in these disorders (Tables 1 and 2), (2) functional magnetic resonance imaging (fMRI) and electrophysiological evidence from humans and rodents suggesting that network defects contribute to these disorders (Tables 1 and 2) and (3) the recent findings of novel *in vitro* models of psychiatric disorders (Table 3).

EVIDENCE FOR CELLULAR PHENOTYPES IN PSYCHIATRIC DISORDERS

Aberrant neuronal connectivity, as assessed by dendritic arborization and synaptic density, is a characteristic that appears to be shared between ASD, SCZD and BD. Perturbed neuronal migration has also been linked to psychiatric disorders, although whether this contributes to, or functions separately from, abnormal neuronal connectivity remains to be demonstrated.

Altered dendritic arborization

At onset, ASD is often characterized by excessive brain volume; MRI studies observed increased cerebral white matter volume in 2- to 4-year-old autistic children,[10, 11, 12] which has been correlated with an excess number of neurons in the prefrontal cortex.[13] Over the lifetime of the ASD patient, however, the brain overgrowth phenotype is typically reversed; studies of adults with ASD have observed cortical thinning[14, 15] and reduced frontal lobe[10, 16, 17] and corpus callosum[18] volumes. While we found few anatomical post-mortem studies of ASD, there are reports of reduced dendritic arborization in hippocampal neurons in two cases of ASD.[19] In Rett syndrome (RTT), a severe and rare ASD caused by the mutation of the *MECP2* gene,[20, 21] post-mortem studies report reduced neuronal cell size and dendritic arborization throughout the cortex.[22] Reports of fragile X syndrome (FX), another monogenetic form of ASD, have been less conclusive: while one study reported differences in dendritic arborization following *in vitro* differentiation of neurospheres

derived from post-mortem human FXS brain tissue,[23] a second group failed to observe significant differences in a similar study.[24]

Decreased whole-brain volume is consistently observed in SCZD,[25, 26, 27]particularly in the gray matter of the frontal cortex, temporal lobe (particularly the hippocampus and amygdala) and the basal ganglia,[27, 28, 29] and longitudinal studies report that progressive brain volume declines for at least 20 years after the onset of symptoms. Post-mortem studies of brains from patients with SCZD have not found evidence of neuronal loss; instead, they observe smaller neuronal somas[30, 31] reduced dendritic arborizations[31, 32] and increased neuronal density without changes in absolute cell number in the cortex and hippocampus.[30, 33]

Decreased brain volumes in the limbic system, particularly the amygdala and hippocampus, and in the frontal cortex are associated with BD.[34, 35] It remains unclear, however, whether brain volume changes are a preexisting factor contributing to the development of BD or a consequence of prolonged illness; one recent study suggests that brain volume changes are more tightly correlated to active psychosis than BD.[36] Despite observations of diminished brain volumes and reduced neuronal density in BD patients,[37, 38] we found no report of altered dendritic arborization or synaptic density in post-mortem studies of BD patient brains.

Mouse models of a number of psychiatric disorders have been developed. For the most part, these mice have reduced expression of rare, highly penetrant genes implicated in ASD, SCZD or BD. RTT (*Mecp2* null) mouse brains show a reduction in neuronal size;[39] and abnormalities in dendritic arborization.[39, 40, 41]Conversely, dendritic arborization defects have not been reported in FX (*Fmr1*null) mice. Many SCZD mouse models, including *Disc1* and heterozygous-null*Nrg1* and *Erbb4* mice, have reduced neurite outgrowth and reduced dendritic complexity.[42, 43, 44, 45] Although few genetic mouse models of BD have been reported, neurons from mice with a point mutation in the circadian *Clock* gene display complex changes in dendritic morphology,[46] which can be ameliorated with lithium, a drug routinely used in the treatment of BD.[46]

Altered synaptic density

A number of genes implicated in ASD, SCZD and BD have been associated with synaptic maturation and function.[47] Post-mortem synaptic spine density has not been adequately explored in human patients with ASD. One report found that relative to controls, spine densities on cortical pyramidal cells were greater in ASD subjects, and highest spine densities were most commonly found in ASD subjects with lower levels of cognitive functioning.[48] Conversely, the number of spines in dendrites of neurons from post-mortem RTT brains is reduced.[49] In FX patients, post-mortem studies have identified abnormalities in dendritic spine shape in cortical pyramidal cells, which tend to be both longer and more slender than controls.[50] Post-mortem studies of SCZD patient brains found reduced dendritic spine density in the cortex[51, 52] and hippocampus.[31, 53] What post-mortem analysis of ASD and SCZD has failed to resolve is whether disease progression reflects developmental aberrations during neuronal differentiation or activity-dependent atrophy of neuronal dendrites or synapses in mature neurons.[33]

Animal studies recapitulate these synaptic defects. Using mouse models of RTT, decreased *Mecp2* levels have been implicated in defects of synaptic contact formation and synaptic transmission.[41, 54, 55, 56] Comparably, inherited mutations of *Shank3*, which also model ASD, result in reduced dendritic synaptic spine induction and maturation.[57] Similar to post-mortem observations of FX patient brains, *Fmr1* mice have abnormally thin and elongated dendritic spine morphology and greater spine density.[58] *Fmr1*, the gene affected in FX,

regulates the translation of messages important for activity-dependent synaptic modulation.[59] Although a number of animal models of ASD recapitulate defects in synaptic maturation, the direction of the change varies depending upon the gene under investigation, which is consistent with the hypothesis that ASD is a spectrum of complex genetic disorders involving impaired developmental synaptic maturation, stabilization, elimination or pruning. Studies of mouse models of SCZD have also observed synaptic defects; there is reduced hippocampal synaptic transmission in *Disc1* mice,[42, 43] impaired synaptic maturation and function in *Nrg1* mice[60, 61, 62] and fewer cortical neurons with slightly smaller spines in mouse models of the human SCZD copy number variant at 22q11.2.[63, 64, 65] In mice with reduced Reelin (*Reln*) expression (putative models of SCZD and BD), there is decreased dendritic spine maturation and plasticity, leading to decreased spine density,[66] whereas *Clock* mice, a model of mania in BD, appear to have normal synaptic density.[46]

Particularly with respect to SCZD, aberrations in synaptic activity have also been observed in adult neurogenesis in the hippocampus. Similar to cortical embryonic development, where downregulation of *Disc1* results in premature cell cycle exit of neural progenitor cells,[67, 68] adult-born neurons with reduced *Disc1* have hastened neural development. *Disc1* knockdown results in accelerated dendritic development, soma hypertrophy, aberrant positioning and increased neural excitability.[69, 70, 71] It remains unknown if aberrant adult neurogenesis contributes to psychiatric disease in humans.

Aberrant neuronal migration

In ASD patients, defects of migration can lead to a variety of morphological outcomes, particularly heterotopias and dysplastic changes. One recent pathological study identified a number of abnormalities and lesions in most of the ASD brains studied, including a loss of vertical and horizontal organization of cortical layers in some patients.[72] It has been hypothesized that altered expression of cytoskeletal proteins and loss of neuronal polarity contribute to these cortical migration defects.[73]

Animal models also show phenotypes consistent with abnormal neuronal migration: mice with reduced *Disc1* activity have reduced cortical migration,[74] *Nrg1* mutant mice have reduced tangential neural migration from the ventral telencephalon[44, 45] and *Cntnap2*-null mice have impaired migration of cortical projection neurons.[75] *Disc1* mutant mice have altered distribution of hippocampal mossy fiber terminals on CA3,[42] and axons with *Disc1* knockdown miss CA3 altogether and project onto CA1.[70] dnDISC1 neurites have deficits in neurite repulsion *in vitro*.[42] Although *DISC1* is a rare SCZD allele, an understanding of the downstream targets or binding partners through which it mediates its cellular effects may identify drug targets relevant to the broader SCZD population. One putative downstream target of DISC1 is Glycogen Synthase 3-beta (*Gsk3*β),[67] *Gsk3*β functions within several central pathways (including cAMP and *Wnt*) is a direct target of lithium (a drug commonly used to treat BD)[76, 77] and mounting evidence indicates that *Gsk3*β may be a central mediator of axon outgrowth dynamics.[78] Cell-based assays will allow the study of the effects of *Gsk3*β, cAMP and WNT levels on neurite outgrowths and axon migration of live human neurons.

EVIDENCE FOR NETWORK PHENOTYPES IN PSYCHIATRIC DISORDER

While comparable neuronal phenotypes, particularly aberrant dendritic arborization, synaptic density and neuronal migration, are shared between ASD, SCZD and BD, these cellular phenotypes likely result in vastly different network effects in each disorder. Functional imaging facilitates the study of the abnormal neural circuitry behind cognitive dysfunction.

One hypothesis concerning ASD is that short-distance over-connectivity in the cortex leads to a failure of long-distance coupling.[79] This hypothesis predicts that impaired long-distance connectivity in the cortex impedes information integration across diverse functional systems (emotional, sensory, autonomic, memory). Consistent with this prediction, fMRI studies of resting state brain activity have observed increased connectivity between proximal regions, such as the posterior cingulate and the parahippocampal gyrus,[80] and decreased connectivity between the distal regions, such as the frontal cortex and the parietal lobe,[81] the insular cortices and the somatosensory cortices or amygdala,[82] the frontal cortex and the posterior cingulate,[80] as well as decreased interhemispheric synchronization.[83] Comparable defects in long-distance connectivity were found when ASD patients performed social and introspective tasks.[84] Among ASD patients, a negative correlation exists between functional connectivity in these regions and severity of social and communication impairment.[80, 82]

Just as pathological studies of SCZD reported decreased frontal and temporal lobe volumes, early fMRI studies of SCZD patients revealed brain activity abnormalities in the frontal and temporal lobes.[85, 86] More recent studies have further shown that SCZD patients exhibit cortical hyper-activity and hyper-connectivity of the prefrontal cortex at rest, but reduced activation of the medial prefrontal cortex during working memory tasks.[87] While functional connectivity of the parietal cortex to the ventral prefrontal cortex is greater in SCZD, it is reduced to the dorsal prefrontal cortex.[88] This is consistent with anatomical neuronal network maps, which reveal a loss of network ‘hubs’ in the frontal cortex, and increased connection distance. These network aberrations are thought to result from neurodevelopmental abnormalities impacting cortical organization.[89]

Although fMRI studies can reveal regions of the brain with aberrant activity in the disease state, they cannot elucidate the specific neuronal cell types affected. Therefore, pharmacological and post-mortem studies have generated hypotheses concerning the cell types affected by SCZD. Similar studies of ASD and BD have been less successful in identifying the specific cell types relevant to disease.

Good evidence now links aberrant neurotransmitter signaling to SCZD. Dopamine receptor antagonists reduce the symptoms of SCZD and evidence now links SCZD with increased dopamine receptor levels and sensitivity.[90, 91] Comparably, glutamate-blocking drugs such as ketamine produce symptoms generally associated with SCZD,[92] whereas the glutamate receptor2/3 agonist LY2140023 may ameliorate the symptoms of SCZD.[93] Post-mortem studies of SCZD brains have found decreased glutamate receptor expression,[94] whereas among GABAergic interneurons, a decrease in GAD67 and calcium-binding proteins was found. Changes in GABAergic neurons are particularly relevant as they are thought to produce gamma oscillations, which synchronize pyramidal neuron firing, an activity that is impaired in SCZD. Evidence in mice suggests that SCZD results, at least in part, from reduced excitatory glutamatergic input onto GABAergic inhibitory neurons.[60, 95, 96] It remains unclear whether aberrant dopamine, glutamate or GABA signaling is the primary cause of SCZD, as aberrant activity of any neuronal cell type could affect neurotransmitter activity of the remaining cell types in the disease state.

In model organisms from *Drosophila* to mice, genes associated with ASD, SCZD and BD have been shown to regulate synaptic activity and plasticity. For example, a screen in *Drosophila* for genes critical in maintaining homeostatic modulation of synaptic transmission identified the SCZD gene *Dysbindin*(*DTNBP1*). *Dtnbp1* acts presynaptically, in a dose-dependent manner, to regulate adaptive neural plasticity.[97] In *Mecp2* mice, although synapse formation, elimination and strengthening are normal, the experience-dependent phase of synapse remodeling is impaired[98] and *Mecp2* mice show altered activity-dependent neural gene expression.[99] *Cntnap2*-null mice, lacking a gene associated

with ASD, have reduced GABAergic neurons and decreased neuronal synchrony.[100] *Disc1* mice have reduced hippocampal synaptic transmission.[42, 43] *Nrg1* mice have impaired synaptic maturation and function[58, 60, 61, 62, 101] and 22q11.2 mice show altered short- and long-term synaptic plasticity as well as calcium kinetics in CA3 presynaptic terminals. Defects in synaptic plasticity at the cellular level likely contribute to the network aberrations observed in psychiatric disorders.

One characteristic network defect observed in SCZD is prepulse inhibition (PPI). PPI is a measure of sensory gating, in which a weaker prestimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse). Deficits in PPI are observed in *Nrg1* mice[60, 95] and are reversed by dopamine receptor antagonists.[102, 103] *Dtnbp1* mice display not only decreased PPI but also reduced evoked γ-activity, a second pattern seen in patients with SCZD.[104] In humans, polymorphisms in circadian genes such as *CLOCK* convey risk for BD; mutant *Clock* mice also have dysfunctional γ-activity across limbic circuits, which can be improved by chronic lithium treatment.[46]

While PPI is attributed to glutamatergic activity, reduced γ-activity indicates abnormal GABAergic neurotransmission. Therefore, although pharmacological evidence implicates dopaminergic and glutamatergic neurons in SCZD, network analysis reveals defects in both glutamatergic and GABAergic activity in SCZD and BD. Aberrations originating in any one neuronal subtype would ultimately be expected to affect activity in other types of neurons and in a variety of brain regions. The ability to test synaptic activity in defined populations of human glutamatergic, GABAergic and dopaminergic neurons affected by ASD, SCZD or BD might help to elucidate the neuronal subtypes at the core of each disorder.

INTRODUCTION TO hiPSCS and iNEURONS

The transient expression of four factors (*OCT3/4, KLF4, SOX2* and *c-MYC*) is sufficient to directly reprogram adult somatic cells into an iPSC state.[105, 106, 107] Because hiPSCs can be derived from adult patients after the development of disease, hiPSCs represent a potentially limitless source of human cells with which to study disease, even without knowing which genes are interacting to produce the disease state in an individual patient. Methods to efficiently differentiate pluripotent stem cells to neurons were developed initially in studies using human embryonic stem cells.[108] Through the addition of various morphogens to recapitulate the cues of embryonic development, ESCs and iPSCs can be directed to differentiate to regional identities including forebrain,[109] midbrain/hindbrain[110, 111] and spinal cord.[112, 113] It is generally thought that every cell type present *in vivo* can be differentiated *in vitro* using hiPSCs, although methods for many remain unexplored or inefficient.

An alternative approach for generating patient-specific neurons to study complex psychiatric disorders is now possible. Expression of four factors (*ASCL1, BRN2, MYT1L* and *NEUROD*) can convert fibroblasts into functional iNeurons *in vitro*.[114,115] The process is rapid, generating electrophysiologically mature neurons with functional synapses within 14 days, and it is efficient, yielding up to 8% neurons. To date, methods exist to transform fibroblasts directly to glutamatergic[115] and dopaminergic neurons,[116] but methods to generate GABAergic iNeurons have not yet been reported. The regional identity of each neurotransmitter subtype remains unclear.

Both hiPSC neurons and iNeurons have the capacity to generate vast numbers of live human neurons for the study of psychiatric disorders. Because iNeuron generation bypasses neuronal differentiation and maturation, hiPSC neurons are likely the best method by which to model developmental facets of disease. For example, if SCZD ultimately results from abnormal synaptic maturation, it is possible that direct reprogramming would bypass the

developmental window in which the SCZD cellular phenotype can be observed *in vitro*. Additionally, as aberrant *ASCL1, BRN2* and *MYT1L* have all been linked to neurological disease,[117, 118, 119, 120] it is not unreasonable to predict that overexpression of one or more of these key neuronal genes might affect the initiation or progression of a psychiatric disorder *in vitro*. Conversely, the rapid experimental timeframe of iNeuron generation makes it an ideal system with which to study phenotypic effects in mature neurons. If ASD is indeed a disease of activity-dependent synaptic modulation rather than synaptic maturation, iNeurons represent a more direct cell type with which to assay network properties. As the efficiency of iNeuron generation increases, and spontaneous neuronal networks result, this method may facilitate robust and swift network analysis of ASD, SCZD and BD neurons. It is important to note that both strategies facilitate novel experiments of innate neuron-specific deficits in psychiatric disease that are not confounded by environmental factors, such as treatment history, drug and alcohol abuse or poverty, that typically plague clinical studies.

PSYCHIATRIC DISORDERS RESULT IN hiPSC NEURONAL PHENOTYPES IN VITRO

While no reported studies have yet characterized iNeurons from patients with psychiatric disorders, a number of groups, including ours, have now published studies of hiPSC neurons derived from patients with ASD and SCZD. During neuronal differentiation of hiPSCs, a number of neuronal genes already implicated in ASD, SCZD and BD, such as transcription factors and chromatin modifiers like *POU3F2* and *ZNF804A* and cell adhesion genes like *NRXN1* and*NLGN1*,[121] are upregulated, permitting comparisons of expression levels in diseased and healthy live human neurons.

Three groups have now generated hiPSCs from a total of seven RTT patients, representing a number of unique point mutations and deletions in the *MeCP2*gene (Q244X, 1155del 32, T158M, R306C,Δ3–4, R294X, V247X).[122, 123, 124] None of the groups observed altered replication or differentiation of RTT hiPSCs or neural progenitor cells. Rather, consistent with animal and post-mortem patient studies, all three groups reported that neuronal soma size of RTT hiPSC neurons is reduced by approximately 10–20% compared with controls.[122, 123, 124]Furthermore, we observed that RTT hiPSC neurons have reduced spine density, decreased neuronal spontaneous calcium signaling and decreased spontaneous excitatory and inhibitory postsynaptic currents. The reproducibility of these findings across three independent reports validates the use of hiPSC-based models. Furthermore, by demonstrating the ability to test drugs to rescue synaptic deficiency in RTT neurons, these studies hint at future uses of hiPSC neurons for high-throughout drug screening to identify new therapeutic drugs for psychiatric disorders.

FX is caused by the absence of expression of the *fragile X mental retardation 1*(*FMR1*) gene,[125] which is believed to result from transcriptional silencing during embryonic development, owing to a CGG triplet-repeat expansion in the 5′ untranslated region of the gene.[126] Although the somatic cells of three FX patients were successfully reprogrammed to pluripotency, the *FMR1* gene remained inactive in all FX hiPSC lines, unlike FX embryonic stem cell lines. Consequently, the authors of this first report of FX hiPSCs concluded that ‘FX-iPSCs do not model the differentiation-dependent silencing of the *FMR1* gene,’ and therefore chose not to assess their FX-hiPSC neurons for phenotypic abormalities.[127] More recently, a second group generated hiPSCs from three patients (including one patient common to the first group) via nearly identical methods. They noted that a number of hiPSC lines had *FMR1* CGG-repeat lengths that were clearly different from the original fibroblasts, and they also failed to detect *FMR1* gene expression in the original FX fibroblasts or their FX hiPSCs.[128]Despite also not observing reactivated *FMR1* expression in FX hiPSCs, this

group compared neural differentiation of FX and control hiPSCs. They observed that neural cultures generated from FX hiPSCs consisted of neurons with fewer and shorter processes, as well as a larger number of glial cells with more compact morphology, suggesting that decreased *FMR1* expression levels, rather than the slow silencing of *FMR1* during neuronal differentiation, are sufficient to produce the disease state in FX.

Timothy syndrome is caused by a mutation in the *L-type calcium channel Ca(v)1.2* and is associated with heart arrhythmias and ASD. From two patients with Timothy syndrome, hiPSC-derived cortical neural progenitor cells (NPCs) and neurons were generated. Neurons from these individuals were shown to have aberrant calcium signaling,[129] while an earlier publication by this same group demonstrated that hiPSC-derived cardiomyocytes from these same patients had irregular contraction, abnormal calcium transients and irregular electrical activity.[130] Timothy syndrome hiPSC neurons underwent abnormal cortical differentiation, showing decreased expression of cortical genes and increased production of norepinephrine and DA. Notably, treatment with roscovitine, a cyclin-dependent kinase inhibitor and atypical L-type-channel blocker, was sufficient to ameliorate many characteristics of Timothy syndrome neurons *in vitro*.[129]

DISC1 mutations cause a rare monogenic form of SCZD. The generation of hiPSCs from SCZD patients with a *DISC1* mutation have now been reported,[131]although neurons differentiated from these hiPSCs have not yet been characterized. We predict that *DISC1*–hiPSC-derived neurons will ultimately be shown to recapitulate the cellular phenotypes observed in dnDISC mice, just as RTT and FX-hiPSC neurons have replicated findings from mouse studies.

We recently reported neuronal phenotypes of hiPSC neurons from four patients with complex genetic forms of SCZD. When assayed by retrograde transmission of rabies virus neuronal labeling, SCZD-hiPSC neurons showed reduced neuronal connectivity and altered gene expression profiles.[132] While nearly 25% of genes with altered expression had been previously implicated in SCZD, we also identified a number of new pathways that may contribute to SCZD. A second group has now reported an oxygen metabolism phenotype associated with SCZD;[133] they observed a twofold increase in extra-mitochondrial oxygen consumption as well as elevated levels of reactive oxygen species in neural progenitor cells derived from hiPSCs from one SCZD patient relative to controls. Although a small study, this observation is consistent with animal studies[134, 135]and deserves attention. Oxygen metabolism defects have not been well demonstrated in human neurons, owing to a lack of live human cells for study. This is an excellent example of the type of hiPSC study that can investigate hypotheses not testable in human patients.

LIMITATION OF hiPSC-BASED MODELLING

A number of major limitations currently restrict hiPSC-based studies, particularly concerning the scalability of hiPSC generation, neural differentiation and phenotypic characterization of derived neurons and neural networks. These technical limitations have made it hard to accurately address the inherent variability of cell-based studies, which exist in three major forms: (1) neuron-to-neuron (intra-patient), (2) hiPSC-to-hiPSC (intra-patient) and (3) patient-to-patient (inter-patient). To produce meaningful data, each cell-based experiment should ideally compare multiple neuronal differentiations from multiple independent hiPSC lines from multiple patients. Owing to cost and time constraints, such large experiments have not yet been completed. Consequently, the hiPSC studies reported to date may ultimately prove to be proof-of-concept demonstrations until methods to compare derived neurons from hundred or thousands of patients and controls are refined.

Intra-patient variability results from differences between neurons and iPSCs generated from a single patient; it is the major constraint on signal to noise in cell-based experiments. Differences between individual hiPSC neurons derived from a single patient produce neuron-to-neuron variability. To some extent, this variability may be unavoidable, although it is currently exacerbated by the heterogeneity of cellular subtypes in hiPSC neural populations; none of the reports described in this review compare pure neuronal populations of a specific subtype. At the experimental level, neural subtype heterogeneity results because current neuronal differentiation protocols are not 100% efficient and, in contrast to the hematopoietic system, cell surface markers by which specific subtypes of neurons might be purified have not been developed. It is well established that individual hiPSC lines vary genetically, epigenetically and in terms of neural differentiation propensities to produce hiPSC-to-hiPSC variability. Genetic differences include the location and number of viral integrations produced during the reprogramming process and spontaneous mutations that have been observed during hiPSC generation and expansion.[136] Epigenetic differences reflect the somatic cell type used for reprogramming and the completeness of its chromatin remodeling.[137] Differences in developmental potential exist among human embryonic stem cell lines[138] and between individual hiPSC lines.[139]

Inter-patient variability reflects the heterogeneity in clinical outcomes between patients with ASD, SCZD or BD. Consequently, given the small sample size (typically 1–4 patients) of the current hiPSC-based studies discussed in this review, a major concern is whether their findings are representative of the larger patient population. In the short term, this has been addressed by recruiting patients with well-defined clinical or genetic characteristics as well as matched healthy controls. Ultimately, methods will have to be developed to permit comparisons of thousands of patients.

FUTURE DIRECTIONS OF CELL-BASED STUDIES

Whole-brain disorders should be studied at the level of component aberrations of cells and neural networks. Neuroimaging, post-mortem anatomical and pharmacological studies of patients may be measuring consequences of the disease state, rather than its origin. Cell-based studies will lead to the discernment and characterization of the molecular causes of ASD, SCZD and BD and facilitate studies of the cellular and network phenotypes that serve as neuronal predispositions to disease. Furthermore, these studies confer the ability to test various neuron non-cell-autonomous effects, such as inflammation, oxidative stress, activity-dependent modulations and the influence of stress hormones in psychiatric disorders. High-throughput screening of new classes of compounds capable of pharmacological amelioration of neuronal and/or network phenotypes for treatment of these disorders is possible.

Small defects at the cellular level could ultimately manifest as complex psychiatric disorders with an array of symptoms in patients. For example, if neurons derived from psychiatric patients show a decrease in the absolute number of connections between cells, and if this phenotype is restricted to a specific subtype of neurons, this finding might hint at the central cell type relevant to the disease state. Because synaptic strength is highly modulated by synaptic activity, a decrease in the strength of individual connections between neurons in psychiatric patients could indicate aberrant synaptic activity or plasticity in patient brains. Finally, perturbed neuronal migration or axon targeting *in vitro* might suggest that mis-targeted neuronal connections, rather than decreased neuronal connectivity, is central to disease. Cellular phenotypes hint at the neuronal predispositions contributing to psychiatric disorders and may help to unlock the complexities of psychiatric illness.

While overlapping genetic susceptibilities might produce a common cellular phenotype, or predisposition, to psychiatric illness, clinical outcome may be determined by activity at the network level. Synaptic pruning (either whole brain or in specific regions) is an activity-dependent process that could generate the clinical differences distinguishing ASD, SCZD and BD. Cell-based studies of neuronal and network aberrations in psychiatric disorders may lead to predictions of activity-dependent environmental influences that contribute to disease progression.

Human iPSC- and iNeuron-based methods have the potential to simplify whole-brain disorders like ASD, SCZD and BD to their cellular and network components, contributing to our understanding of these conditions. Although many technical issues, particularly, concerning the scalability of hiPSC generation, neuronal differentiation and neural assays remain, we believe that studies of neuronal networks constructed from defined neuronal populations are feasible. By recapitulating and monitoring healthy and disease networks in a dish, it is likely that new methods of *in vitro* modeling of psychiatric disorders will result in new insights into the mechanism of disease initiation, progression and, ultimately, treatment.

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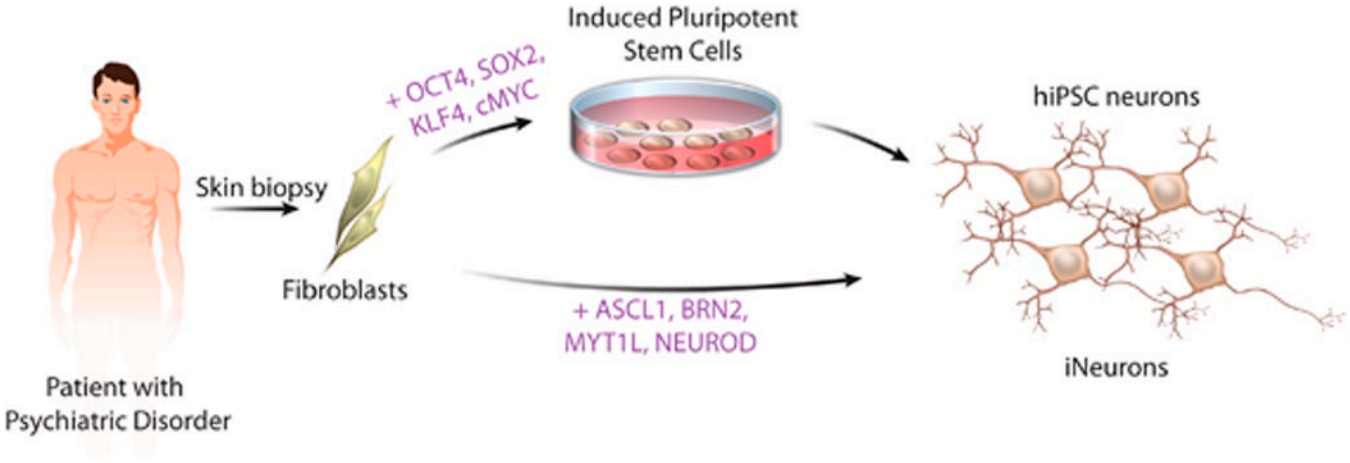

Figure 1.

Table 1

Summary of published cellular and network phenotypes in human SCZD patients

Disease	Study	Brain region/cell type	Observation	Reference
ASD	MRI, post-mortem	Cerebrum	Increased cerebral white matter volume in children, excess number of neurons in prefrontal cortex in children	Carper *et al.*,[10]Courchesne,[11]Hazlet *et al.*,[12]Courchesne *et al.*[13]
ASD	MRI	Cerebrum, corpus callosum	Reduced frontal and parietal lobe gray matter volume in older children and adults, increased ventricular volume, reduced corpus callosum volume	Courchesne *et al.*,[14] Schmitz *et al.*,[16] Brun *et al.*,[17]Wright *et al.*,[27]Frazier and Harden[18]
ASD	Post-mortem	Hippocampus, cortex	Reduced dendritic arborization in hippocampus, greater cortical pyramidal spine density correlated with decreased cognitive function, loss of vertical and horizontal organization of cortical layers	Raymond *et al.*,[19]Hutsler and Zhang,[48] Wegiel *et al.*[72]
ASD	fMRI	Cortex	Increased connectivity between proximal:posterior cingulate/ parahippocampal gyrus, decreased connectivity between distal:frontal lobe-parietal lobe, insular cortices-somatosensory cortices of amygdala, frontal cortex-posterior cingulated, decreased interhemispheric synchronization	Monk *et al.*,[80]Kennedy and Courchesne,[81]Ebisch *et al.*,[82]Dinstein *et al.*,[83]Kennedy and Courchesne [84]
ASD (RTT)	Post-mortem	Cortex, hippocampus	Reduced cell size and dendritic arborization in cortex, reduced number of dendritic spines in hippocampus	Bauman *et al.*,[22]Chapleau *et al.*[49]
ASD (FX)	*In vitro*	Post-mortem neurosphere culture, fetal cortical NPC culture	Neurons with fewer and shorter neurites, smaller cell body volume and decreased glial	Castren *et al.*,[23]Bhattacharyya *et al.*[24]

Disease	Study	Brain region/cell type	Observation	Reference
			differentiation; normal neurogenesis by fetal NPCs	
ASD (FX)	Post-mortem	Cortical pyramidal cells	Longer, more slender dendritic spine shape	Irwin *et al.*[50]
SCZD	MRI	Gray matter frontal cortex, temporal lobe, hippocampus, amygdala, basal ganglia	Decreased volume (whole brain) in early phase SCZD	Vita *et al.*,[25] Steen*et al.*,[26] Thompson*et al.*,[28] Ellison-Wright *et al.*[29]
SCZD	Post-mortem	Cortex, hippocampus	Reduced dendritic arborization, reduced soma size, increased neuronal density, decreased synaptic density	Rajkowska *et al.*,[30]Kolomeets *et al.*,[31]Black *et al.*,[32]Selemon *et al.*,[33]Garey *et al.*,[51]Glantz and Lewis[52], Kolomeets *et al.*[53]
SCZD	fMRI	Frontal/temporal lobe	Brain activity abnormality in frontal and temporal lobes	Yurgelun-Todd *et al.*,[85] Yurgelun-Todd *et al.*[86]
SCZD	fMRI	Cortex	Cortical hyper-activity and hyper-connectivity in prefrontal cortex at rest, reduced activation of medial prefrontal during working memory tasks in early phase SCZD, increased functional connectivity between the ventral prefrontal cortex and posterior parietal cortex greater, decreased functional connectivity between the dorsal prefrontal cortex and posterior parietal cortex greater	Whitfield-Gabrieli*et al.*,[87] Tan *et al.*[88]
SCZD	Anatomical networks analysis	Cortex	Cortical organization altered, loss of network hubs in frontal cortex, emergence of hubs outside cortex	Bassett *et al.*[89]
SCZD	Post-mortem, PET	Substania nigra, striatum, cortex	Increased DA receptor sensitivity, increased DA receptor levels in substania nigra, correlation of DA receptor expression level in temporal cortex and striatum to positive	Owen *et al.*,[91]Kessler *et al.*,[90]

Disease	Study	Brain region/cell type	Observation	Reference
			symptoms of SCZD	
SCZD	Pharmacology	Not determined	NMDA antagonist ketamine induces SCZD-like symptoms, MGLUR2/3 agonists ameliorate them	Krystal *et al.,*[92]Patil *et al.*[93]
SCZD	Post-mortem	Hippocampus, cortex	Reduced GLU receptor expression	Meador-Woodruff and Healy[94]
BD	MRI	Limbic system (amygdala/hippocampus)	Reduced brain volume: limbic system (amygdala, hippocampus, frontal cortex) in adolescents	Karchemskiy *et al.,*[34] Frazier, [35]
BD	Post-mortem	Entorhinal cortex	Decreased cell number and density of GABA neurons	Rajkowska *et al.,*[37]Pantazopoulos *et al.*[38]

Abbreviations: ASD, autism spectrum disorder; BD, bipolar disorder; DA, dopamine; GLU, glutamate; FX, fragile X syndrome; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; NPC, neural progenitor cell; RTT, Rett syndrome; SCZD, schizophrenia disorder.

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Table 2

Summary of published cellular and network phenotypes in rodent models of SCZD

Disease	Gene	Brain region/cell type	Observation	Reference
ASD	*Cntnap2*	Cortex, GABA	Impaired migration of cortical projection neurons, reduced GABAergic neurons, decreased neural synchrony	Penagarikano *et al.*[100]
ASD	*Shank3*	Hippocampal neural cultures	Reduced dendritic spine induction/maturation *in vitro*	Durand *et al.*[57]
ASD (RTT)	*Mecp2*	Hippocampus, cortex, cerebellum, retinogeniculate synapse, NPCs	Reduction in neuronal size, dendritic arborization abnormalities, thinner cortical layers, reduced spine density, defects in synaptic maturation and synaptic transmission, impaired experience dependent remodeling, and altered gene expression	Chen *et al.*,[39] Kishi and Macklis,[40] Smrt *et al.*,[41]Asaka *et al.*,[54] Moretti *et al.*,[55] Nelson *et al.*,[56] Noutel*et al.*,[98] Dani *et al.*[99]
ASD (FX)	*Fmr1*	Cortex, neurosphere culture	Thin and elongated dendritic spines on pyramidal neurons, increased spine density along apical dendrites, *in vitro*differentiated neurons have fewer and shorter neurites and a smaller cell body volume	Comery *et al.*,[58] Castren *et al.*[23]
SCZD	*Disc1*	Cortex, hippocampus	Reduction in fetal cortical neural progenitor proliferation and premature neural differentiation, reduced cortical migration, diminished response to cAMP-sensitive repulsive cues, reduced neurite outgrowth, synaptic transmission and altered distribution of hippocampal neurons	Mao *et al.*,[67] Kamiya *et al.*,[74] Kvajo *et al.*,[42] Li *et al.*[43]
SCZD	*Disc1 knockdown*	Hippocampal adult-born neurons	Adult newborn neurons show accelerated dendritic development and synapse formation, defects in axonal targeting, enhanced excitability	Faulker *et al.*,[70] Duan *et al.*[69]
SCZD	*Nrg1*	Cortex, peripheral nerves	Aberrant tangential migration of neurons derived from the ventral telencephalon, impaired synaptic maturation and function, hypomyelination	Lopez-Bendito *et al.*,[44]Barros *et al.*,[60] Chen *et al.*[62]
SCZD	*ErbB4*	Hippocampus, cortex	Aberrant neurite outgrowth and synapse maturation, reduced long-term potentiation, suppressed Src-dependent enhancement of NMDAR responses during theta-burst stimulation, reduced excitatory input onto GABAergic neurons, PPI deficits	Krivosheya *et al.*,[45] Pitcher*et al.*,[61] Pitcher *et al.*,[101]Barros *et al.*,[60] Li *et al.*,[95]Chen *et al.*[62]
SCZD	22q11.2	Cortex, hippocampus	Fewer cortical neurons with smaller spines, altered short- and long- term synaptic plasticity and calcium kinetics, impaired hippocampal-prefrontal synchrony	Fenelon *et al.*[63] Earls *et al.*,[64] Sigurdsson *et al.*[65]
SCZD	*Reln*	Cortex, hippocampus	Decreased dendritic spine maturation, density and plasticity	Pappas *et al.*[66]
SCZD	*Dtnbp1*	GABA	Decreased PPI, reduced evoked gamma activity	Carlson *et al.*[104]
BD	*Clock*	Striatum (nucleus accumbens)	Increased length and complexity of dendrites, normal synaptic density, dysfunctional gamma activity across limbic circuits, improved by lithium treatment	Dzirasa *et al.*[46]

Abbreviations: ASD, autism spectrum disorder; BD, bipolar disorder; FX, fragile X syndrome; PPI, prepulse inhibition; RTT, Rett syndrome; SCZD, schizophrenia disorder.

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Table 3

Summary of published reports of hiPSC-based models of ASD, SCZD and BD

Disease	Reference	Genetic mutation	Neuronal phenotype	hiPSC method	Source of cells	Patient sex; age at biopsy (years); available phenotypic information
RTT	Cheung *et al.*[122]	*MeCP2*(Δ3–4, T158M, R306C)	Decreased soma size	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: patient biopsy (1) and Coriell GM11270 (2), GM17880 (3)	**1** Female; 6 growth and developmental delay, inability to walk without assistance, ataxia, nonverbal, has no hand use and constant repetitive hand motions, some tremor, has had epileptic seizures and significant abnormal electroencephalogram, teeth grinding, some sleep difficulties, and breath holding and hyperventilation **2** Female; 8; normal lysosomal enzymes, clinically affected, classical symptoms **3** Female; 5; assistance required for walking, delay in growth and development, sleep problems, abnormal EEG with no symptoms of seizures, grinding of teeth, breath holding, hyperventilation, nonverbal, lack of hand usage, repetitive hand motions, difficulty eating and slight refluxes, slight tremor, small feet
RTT	Marchetto*et al.*[123]	*MeCP2*(1155del3, Q244X, T158M, R306C)	Reduced soma size and spine density, fewer synapses, altered calcium signaling, electrophysiological abnormalities	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: Coriell GM11272 (1), GM16548 (2), GM17880 (3), GM11270 (4)	**1** Female; 3; normal lysosomal enzymes, clinically affected, classical symptoms **2** Female; 5; clinically affected, slightly curved spine, ambulatory, slight rigidity and spasticity, decreasing head circumference, aberrant sleep patterns, decreased hand usage, repetitive hand motions, breath holding, nonverbal, constipation, decreased hand and feet circulation, rare self-injurious behavior, slight eating problems and refluzes, teeth grinding, slight EEG abnormalities, tremors

Disease	Reference	Genetic mutation	Neuronal phenotype	hiPSC method	Source of cells	Patient sex; age at biopsy (years); available phenotypic information
						3 Female; 5; assistance required for walking, delay in growth and development, sleep problems, abnormal EEG with no symptoms of seizures, grinding of teeth, breath holding, hyperventilation, nonverbal, lack of hand usage, repetitive hand motions, difficulty eating and slight refluxes, slight tremor, small feet **4** Female; 8; normal lysosomal enzymes, clinically affected, classical symptoms
RTT	Ananiev *et al.*[124]	*MeCP2*(T158M, V247X, R306C)	Decrease in nuclear and neuron size	Lentivirus: four factors (*OCT4, NANOG, SOX2, LIN28*), Retrovirus: 4 factors (*OCT4, SOX2, KLF4, c-MYC*)	Fibroblast: Coriell GM17880 (1), GM07982 (2), GM11270 (3)	**1** Female; 5; assistance required for walking, delay in growth and development, sleep problems, abnormal EEG with no symptoms of seizures, grinding of teeth, breath holding, hyperventilation, nonverbal, lack of hand usage, repetitive hand motions, difficulty eating and slight refluxes, slight tremor, small feet **2** Female; 25; clinically affected, microcephaly, severely retarded, hand wringing starting at age 2, scoliosis at age 12, kyphoscoliosis at age 25, started to lose skills at 2 years old, CT scan at 25 showed atrophy, slow, abnormal EEG, no sleep problems **3** Female; 8; normal lysosomal enzymes, clinically affected, classical symptoms
Timothy syndrome	Paşca *et al.*[129]	*CACNA1C*	Defects in calcium signaling, decreased expression of cortical genes, increased production of norepinephrine and dopamine	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: patient biopsy	**1** Female; not stated; not stated **2** Not stated; not stated; not stated

Disease	Reference	Genetic mutation	Neuronal phenotype	hiPSC method	Source of cells	Patient sex; age at biopsy (years); available phenotypic information
FXS	Urbach *et al.*[127]	*FMR1*	No neurons generated	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: Coriell GM05848 (1), GM07072 (2), GM09497 (3)	**1** Male; 4; increased ear size, elongated face, appears prognathic, mental retardation, undefined connective tissue dysplasia **2** Male; 22; 9/50 cord blood lymphocytes showed fra(X), mother is an obligate carrier for fra(x) **3** Male; 28; affected brother, large ears, mental retardation, macro-orchidism, hyperactive, 20% of PBL positive for fra(x)
FXS	Sheridan*et al.*[128]	*FMR1*	Fewer and shorter neural processes, increased glial cells with more compact morphology	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: Coriell GM05848 (1), GM05131 (2), GM05185 (3)	**1** Male; 4; increased ear size, elongated face, appears prognathic, mental retardation, undefined connective tissue dysplasia **2** Male; 3; affected brother and uncle, **3** Male; 26; 46,fra(X),Y present in 30–50% of PBL
SCZD	Chiang *et al.*[131]	*DISC1*	No neurons generated	Episome: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: patient biopsy	**1** Male; NA; diagnosed with chronic undifferentiated schizophrenia, auditory and visual hallucinations, multiple delusions and had formal thought disorder **2** Female; NA; diagnosed chronic paranoid schizophrenia, auditory and visual hallucinations, multiple delusions and had formal thought disorder
SCZD	Brennand*et al.*[132]	Sporadic	Reduced neuronal connectivity, fewer neurites, decreased PSD95 and glutamate receptor expression levels	Tetracycline-inducible lentivirus: five factors (*OCT4, SOX2, KLF4,c-MYC, LIN28*)	Fibroblast: Coriell GM02038 (1), GM01792 (2), GM01835 (3), GM02497 (4)	**1** Male; 22; onset at age 6, committed suicide **2** Male; 26; recurrences of agitation, delusions of persecution, fear of assassination, father and sister affected **3** Female; 27; schizoaffective disorder, problems of drug

Disease	Reference	Genetic mutation	Neuronal phenotype	hiPSC method	Source of cells	Patient sex; age at biopsy (years); available phenotypic information
						abuse, hospitalized, father affected **4** Male; 23; paralogical thinking, splitting of effect from content, suspiciousness, affective shielding, onset at age 15, hospitalized, positive family history
SCZD	Paulsen *et al.*[133]	Sporadic	Elevated extra-mitochondrial oxygen consumption, increased levels of reactive oxygen species	Retrovirus: four factors (*OCT4, SOX2, KLF4,c-MYC*)	Fibroblast: patient biopsy	Female; 48; clozapine-resistant

Abbreviations: ASD, autism spectrum disorder; BD, bipolar disorder; EEG, electroencephalogram test; FX, fragile X syndrome; hiPSC, human-derived induced pluripotent stem cell; NA, not applicable; PBL, peripheral blood lymphocyte; RTT, Rett syndrome; SCZD, schizophrenia disorder.