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Concise Review: The Promise of hiPSC-Based Studies of Schizophrenia

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Abstract

Schizophrenia (SCZD) is a heritable developmental disorder. While the molecular mechanism of disease remains unclear, insights into the disorder have been made through a vast array of experimental techniques. Together, MRI brain imaging, pharmacological and postmortem pathological studies have observed decreased brain volume, aberrant neurotransmitter signaling, reduced dendritic arborization and impaired myelination in SCZD. Genome wide association studies have identified common single nucleotide polymorphisms as well as rare copy number variants that contribute to SCZD, while mouse models of candidate SCZD genes show behavioral abnormalities and anatomical perturbations consistent with human disease. The advent of human induced pluripotent stem cells (hiPSCs) makes it possible to study SCZD using live human neurons with a genetic predisposition towards SCZD, even without knowledge of the genes interacting to produce the disease state. SCZD hiPSC neurons show cellular defects comparable to those identified in postmortem human and mouse studies, and gene expression changes consistent with predictions made by GWAS. SCZD hiPSC neurons represent a new tool to look beyond phenotype and begin to dissect the molecular mechanisms of SCZD.

Introduction

Schizophrenia (SCZD) is a neurological disorder characterized by three severe classes of symptoms: positive (hallucinations and delusions), negative (inability to speak, express emotion or find pleasure) and cognitive (deficits in attention, memory and planning) [1, 2]. The current treatment regime for SCZD involves chronic treatment with powerful antipsychotics, the strong unpleasant side effects of which often result in cessation of treatment [1]. The life expectancy of patients with SCZD is up to ten years less than the general population [3]; 40% of schizophrenics suffer from substance abuse [4], 20% are homeless [5] and 10% ultimately commit suicide [6, 7]. It is estimated that 1.1% of the population over 18 years of age has SCZD, including 3 million Americans [1].

Human studies of SCZD have relied primarily on brain imaging, pharmacology, postmortem pathology and genetic studies of patient lymphocytes. Animal studies are limited in two important ways: 1) they do not reflect the complex genetic interactions that result in the vast majority of cases of SCZD, and 2) it is difficult to evaluate classical symptoms of SCZD such as hallucinations, delusions and disorganized speech in mice. While many insights have been made through these methods, the molecular and cellular defects that contribute to disease initiation and progression in neurons remain unknown. Recently, a third approach

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has been described with which to study SCZD [10, 11]. Reprogramming of patient fibroblasts to human induced pluripotent stem cells (hiPSCs), followed by hiPSC differentiation to neurons, produces a near limitless source of live human neurons, genetically identical to those present in patients, with which to study this disorder.

This review will summarize the major findings of human and mouse studies of SCZD, and compare these to early reports of SCZD hiPSC neurons.

Insights from Human Studies

Human studies to date have utilized three major approaches: brain imaging, postmortem pathology and genome wide association studies (GWAS).

Observations from brain imaging

Magnetic resonance imaging (MRI) can be used to estimate the volume of various brain regions, though these studies must be interpreted in the context of the high variability of brain measures across individuals [12]. While group average differences exist between SCZD patients and controls, anatomic MRI differences are not adequate for diagnosis. For analogy, though men tend to be taller than women on average, height is not sufficient to determine sex; male/female height differences are twice as predictive of gender as most MRI neuroimaging experiments are predictive of a diagnosis of SCZD [13].

In first-episode patients with SCZD, MRI studies consistently observe decreased whole brain volume (and increased ventricular volume) [14–16]. Specifically, the greatest decreases are observed in the grey matter of the hippocampus, basal ganglia and thalamus (Figure 1)[16–18]. In chronically ill patients, the volume loss is most pronounced in the frontal and temporal grey matter areas of the cortex [19], but whether these changes result from disease or long-term treatment with antipsychotic medications is unclear. Longitudinal studies have observed progressive decrease in brain volume and increase in lateral ventricle volume for at least 20 years after the onset of symptoms.

White matter is produced when oligodendrocytes wrap axons in sheaths of myelin, which increases the speed of neurotransmission as well as the timing and synchrony of neuronal firing patterns [20]. Beyond the well characterized changes in grey matter, some studies also identify changes in the white matter of the brain in SCZD, particularly in the prefrontal and temporal lobes and corpus collusum [21]. Longitudinal brain imaging studies of childhood onset (COS) cases of SCZD have observed both progressive loss of cortical grey matter during adolescence and delayed white matter development [13].

Changes in blood flow and blood oxygenation in the brain are closely linked to neural activity. Functional magnetic resonance imaging (fMRI) measures the change in blood flow as an indicator of brain activity and fMRI comparisons of control and SCZD patients have revealed brain activity changes in the dorsolateral prefrontal cortex. At rest, SCZD patients show cortical hyper-activity and hyper-connectivity between the cortex and hippocampus [22] while during working memory tasks, SCZD patients show reduced activation of the cortex [23]. The molecular mechanism of these changes has not been explained.

While brain imaging has associated clinical symptoms to the general brain areas affected, the relationship between brain imaging, cellular pathology and the molecular mechanism of SCZD remains unknown.

Observations from pharmacological studies

The accidental discovery that Chlorpromazine (Thorazine) reduces psychotic symptoms, likely by functioning as an antagonist of dopamine (DA) receptors, provided the basis for the "DA hypothesis" of SCZD. This hypothesis proposed that excessive activation of D2 receptors was the cause of (the positive symptoms of) SCZD. By Positron emission tomography (PET) imaging, researchers determine where given biological molecules, such as DA, bind in the brain. Such work has correlated DA receptor levels with the positive symptoms of SCZD (psychosis and delusions) [25] and strong evidence now links SCZD with increased DA synthesis, DA release, and resting-state synaptic DA concentrations [24]. Further support of this hypothesis is the psychosis-inducing effects of DA receptor agonists such as amphetamine.

The DA hypothesis is now believed to be overly simplistic. Among the DA antagonists, Clozapine is uniquely effective for treatment-resistant SCZD [26]. This ability may occur through a DA-independent mechanism, a hypothesis supported by anecdotal evidence that Clozapine effectively treats the psychotic symptoms associated with Parkinson's disease (PD) without exacerbating the tremors, rigidity and bradykinesis caused by the loss of DA neurons in PD [27]. Clozapine is an antagonist of D1, D2, D3, and D4 dopamine receptors, α1- and α2-adrenergic receptors, 5-hydroxytryptamine (5-HT) serotonin receptor, H1 histamine receptor, and M1, M2, M3, and M5 receptors; an agonist of the M4 muscarinic receptor[28]; a modulator of glutamatergic neurotransmission [29] and an inhibitor of GABAA receptor neurotransmission [30]; its complex pharmacological properties hint at the roles of others neuronal cell types in SCZD.

Glutamate (GLU)-blocking drugs such as ketamine induce many of the symptoms, including hallucinations and cognitive deficits, associated with SCZD [31], whereas the glutamate receptor (GLUR2/3) agonist LY2140023 has been shown to ameliorate the symptoms of SCZD in recent clinical trials by Eli Lilly [32] (Figure 2). The authors suggest that LY2140023 may work by reducing the presynaptic release of glutamate at limbic synapses where these receptors are expressed.

In summary, pharmacology of SCZD is intricate but evidence supports a role for altered DA and GLU neurotransmitter activity.

Observations from postmortem studies

While brain imaging identified decreased brain volume in SCZD, postmortem studies of brains from patients with SCZD have revealed no widespread neuronal loss or even a glial response to a potential neuronal injury. Instead, pathological studies have observed three major changes in SCZD brain tissue: increased density of pyramidal neurons, aberrations in interneurons, and decreased oligodendrocytes.

In the cortex, pathological changes are consistent with decreased neuronal connectivity in SCZD. Postmortem studies have observed an increased density of cortical pyramidal neurons without changes in cell number [33, 34]. Neuronal soma are smaller [34], dendrites are shorter with reduced arborizations [35] and there is reduced dendritic spine density [3637]. The disturbances in prefrontal cognitive functioning in SCZD may be mediated by a process which involves atrophy of neuronal processes or synapses but stops short of actual neuronal loss [33].

Changes in RNA and protein levels of a number of key genes involved in neurotransmission have been observed in postmortem SCZD brain tissue. Glutamate receptor expression is altered in SCZD; expression is decreased in the hippocampus and increased in the cortex [38]. Specifically in GABAergic interneurons, one finds decreased GAD67 and calcium-binding

proteins in parvalbumin- and calbindin-positive GABAergic neurons. Changes in parvalbumin-positive 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. It is unclear whether decreased GABAergic inhibitory activity is a cell autonomous cause of SCZD or if it results from decreased glutamatergic input on GABAergic inhibitory neurons in the disease state.

Finally, a number of studies have observed both fewer oligodendrocytes and decreased expression of myelin genes in postmortem SCZD brains. This finding may be consistent with decreases in white matter observed in SCZD.

Genome wide association studies of SCZD

A complex genetic psychiatric disorder, SCZD has a large inherited component with an estimated heritability of 80–85% [39, 40]. With tens of thousands of SCZD patients genotyped to date, it is now widely accepted that the complicated heritability of SCZD results from polygenic inheritance of a combination of inherited common polymorphisms and both inherited and de novo rare copy number variations (CNVs). Because a large number of markers collectively account for risk of SCZD, the risk of each one is so small it can be difficult to detect by GWAS. To date, most of the heritable variance of SCZD remains unaccounted for.

Early genetic studies of SCZD focused on traditional pedigree analyses. In a family identified in northern Scotland, more than half of the members suffer from mental illness, generally SCZD, and it was found that a balanced chromosomal translocation (1:11) segregated with disease. The disrupted gene on chromosome 1 was subsequently termed Disrupted-in-Schizophrenia-1 (DISC1)[41]. The genetic association between Neuregulin-1 (NRG1) and SCZD was first identified in association studies of Icelandic families [42] and subsequently confirmed in follow-up studies in multiple populations in Scotland, Ireland, Netherlands, Taiwan, Korea and China [43–49]. Mutations in DISC1 are much more penetrant that those in NRG1, but are also exceedingly rare. While studies of postmortem brain tissue have consistently failed to detect alterations in DISC1 levels in typical SCZD patients, they do observe increased NRG1 in the hippocampus [50] and prefrontal cortex [51, 52] and decreased expression of its receptor ERBB4 [53–55], suggesting that NRG1 and ERBB4 may be affected even in the absence of detectable genetic lesions.

Common polygenic variation has been shown to contribute to SCZD. Studies of single nucleotide polymorphisms (SNPs) have estimated that thousands of alleles of very small effect account for nearly 30% of the genetic variance of SCZD [56–58]. Much of this common polygenic variation encompasses the major histocompatibility complex region (MHC) region at 6p22–p21 that contains over 200 genes. Though MHC genes have been implicated in immune diseases such as type I diabetes, multiple sclerosis, Crohn's disease, and rheumatoid arthritis, they also contribute to synaptic maturation [59–61]; therefore, this genetic evidence should not be presumed to be proof of immune abnormalities in SCZD.

Other common variants now well-implicated in SCZD include TCF4 (transcription factor 4) on chromosome 18q21, zinc finger protein 804A (ZNF804A) on 2q32.1, and neurogranin (NRGN) on 11q24.2 [57, 62]. TCF4 is a neuronal transcription factor essential for neurogenesis [63], NRGN encodes a postsynaptic protein kinase substrate that binds calmodulin and is enriched in CA1 pyramidal neurons in the hippocampus [64], and ZNF804A is associated with altered neuronal connectivity in the dorsolateral prefrontal cortex [65].

Copy number variants (CNVs) are large deletions or duplications in the genome. So far, only rare (<1% of cases) and large CNVs (>100kb) have been shown to confer high risk of

SCZD. SCZD CNVs are highly penetrant and account for up to 20% of SCZD cases. CNVs identified to date disrupt genes, such as ERBB4 [66] or NRXN1 [67], or regions, including 1q21.1, 15q11.2, 15q13.3, 16p11.2, 22q11.2 [66, 68–70]. By comparing the DNA of both parents to the SCZD patient (proband), it was shown that CNV mutations frequently occur de novo and are not inherited from either parent. Given that the CNV mutation rate far exceeds the rate for nucleotide substitutions [71] and that current CNV assays detect only the largest CNVs, constituting just 5% of total CNVs, researchers may be underestimating the contribution of CNVs to SCZD [72].

The genetic basis of SCZD does not necessarily conform to classical disease boundaries. Many CNVs that confer high risk of SCZD have been implicated in autism, mental retardation and epilepsy, while many SNPs associated with SCZD are shared with bipolar disorder [66, 68–70]. It is likely that numerous disruptions in any number of key neurodevelopmental pathways may be sufficient to produce a diseased state that could ultimately manifest as SCZD.

Insights from Mouse Models

While causal mutations for SCZD have not been identified, several genetic mouse models of SCZD have been developed. Of these, mice with decreased activity of DISC1, NRG1, ERBB4 or the 22q11 genes show behavioral abnormalities and anatomical perturbations that may be relevant to SCZD.

DISC1 mice recapitulate aspects of the SCZD phenotype

DISC1-mutant animals demonstrate behavioral abnormalities such as decreased learning and memory[73–75], decreased sociability[73, 74], depression[73, 74], hyperactivity[74, 75] and aggression [74], which are consistent SCZD. Mice with reduced DISC1 activity during development have reduced neurite outgrowth[76], reduced cortical migration [76], reduced dendritic complexity[73, 75], reduced hippocampal synaptic transmission[73, 75] and slightly enlarged ventricles[74], but no significant structural defects or signs of neurodegeneration (Figure 3). Conversely, down-regulation of DISC1 in adulthood causes accelerated neural differentiation and increased neural excitability in newborn neurons[77]. DISC1 seems to function as a molecular scaffold; it interacts with multiple proteins, including the centrosomal protein NUDEL[76, 77] required for neurite outgrowth and neuronal migration[78, 79], as well as phosphodiesterase 4B (PDE4B)[80], a key regulator of cyclic adenosine monophosphate (cAMP), linked to learning, memory and mood[81–83]. It remains unknown which of these functions is responsible for SCZD pathogenesis.

NRG1 and ERBB4 mice demonstrate role of excitatory glutamatergic input onto GABAergic inhibitory neurons in SCZD

Though mice lacking both copies of either the NRG1 or ERBB4 genes are embryonic lethal due to cardiac defects, heterozygous null NRG1 and ERBB4 animals have behavioral abnormalities such as hyperactivity, increased aggression, and deficiencies in prepulse inhibition, a measure of sensory gating that is abnormal in SCZD [42, 84, 85]. While cell layers in the cerebral cortex, hippocampus, and cerebellum develop normally in the mutant mice, there are defects in neurite outgrowth and arborization neuronal migration [86, 87] and impaired synaptic maturation and function [85, 88, 89]. Treatment with the antipsychotic drug Clozapine reverses the behavioral and spine defects in these mice [85]. ERBB4 is enriched in GABAergic interneurons, while NRG1 is primarily localized at synapses in excitatory glutamatergic neurons. NRG1 increases the number, size and activity of excitatory synapses on GABAergic interneurons [90, 91], renewing support for the hypothesis that SCZD results, at

least in part, due to reduced excitatory glutamatergic input onto GABAergic inhibitory neurons.

22q11 models impaired long-range synchrony of neural activity

Mouse models of 22q11.2 represent the first studies of a CNV associated with SCZD; SCZD develops in about 20–25% of individuals with a chromosome 22q11.2 microdeletion. Mice with disruptions of 22q11.2 genes have fewer cortical neurons with slightly smaller spines, altered short- and long-term synaptic plasticity, enhanced neurotransmitter release, altered calcium kinetics in CA3 presynaptic terminals and impaired long-range synchrony between the hippocampus and prefrontal cortex [92–94].

Insights from Olfactory Neural Precursors

Olfactory neural precursors (ONPs) can be expanded following exfoliation of the nasal cavity via a non-invasive method [95]. ONPs are capable of self-renewal as well as differentiation to mature electrophysiologically active neurons. ONPs from SCZD patients and controls have been generated and banked [95] to ask whether genetic, structural and/or functional abnormalities are present in SCZD neurons. By similar methods, a second group generated ONPs from control and SCZD patients and performed gene expression comparisons, which identified differences in neurodevelopmental pathways associated with cell migration and axon guidance [96].

ONPs are one source of live human neurons for the study of SCZD. Though differences between SCZD and control ONPs have been identified, it is unclear whether SCZD ONPs will recapitulate all of the neuronal defects present in brain regions such as the cortex or hippocampus. Additionally, ONPs cannot yet be used as a source of cells from the neural lineages specifically implicated in SCZD: glutamatergic neurons, GABAergic neurons, dopaminergic neurons, and oligodendrocytes.

Insights from hiPSC Neurons

Chiang et al first published the generation of hiPSCs from SCZD patients with a DISC1 mutation [11] but did not characterize neurons differentiated from these hiPSCs. We then demonstrated that SCZD hiPSC neurons had defects in neuronal connectivity and gene expression which could be ameliorated following treatment with the antipsychotic Loxapine [10]. Specifically, we observed reduced neuronal connectivity, reduced outgrowths from soma, and reduced PSD95 dendritic protein levels, all of which are cellular phenotypes previously described in postmortem SCZD brain tissue as well as animal models of SCZD (Figure 4). Additionally, we observed gene expression differences in SCZD neurons relative to controls, 25% of which had been previously implicated in SCZD, with significant perturbations in genes associated with the WNT pathway, cAMP signaling and glutamate receptor expression. We hypothesize that studies of SCZD hiPSC neurons from an increased number of patients might identify core pathways of genes contributing to SCZD. Pedrosa et al have also generated SCZD hiPSCs from three patients and report that SCZD hiPSC neurons express a number of transcription factors, chromatin remodeling proteins and synaptic proteins relevant to SZCD pathogenesis, independently validating the potential utility of hiPSC neurons in modeling SCZD [97].

While hiPSC-based studies show exciting promise for the study of SCZD, they remain limited by three types of variability: neuron-to-neuron, hiPSC-to-hiPSC, and patient-to-patient. Interneuron variability is countered by studying more homogeneous populations of hiPSC neurons, generated by directed differentiation protocols to specific neuronal subtypes and subsequent purification by Fluorescence-activated cell sorting (FACS). Inter-hiPSC

variation is addressed by comparing multiple hiPSC lines per patient, particularly as it is well established that genetic and epigenetic differences exist between hiPSC lines. Finally, inter-patient variability can be tackled by studying an increased number of patients and controls, and particularly by selecting homogenous patient cohorts characterized by common clinical endophenotypes, pharmacological responses or genetic mutations. Using hiPSC neurons, researchers can now begin to dissect the molecular mechanism of pharmacological response and screen for new drugs to improve cellular phenotypes in SCZD neurons from patients with clear clinical pharmacological non-responsiveness.

Moving Forward: Future hiPSC studies of SCZD

Brain-imaging studies have identified structural changes in SCZD brains, but cannot resolve which neuronal cell types are affected in SCZD. Pharmacological studies have identified a role for DA and GLU; however, chronic antipsychotic treatment alters brain structure and neural activity, confounding studies of human patients affected with SCZD. GWAS studies have yet to account for most of the heritable variance of SCZD. Though animal models have recapitulated aspects of the behavioral and cellular phenotypes of SCZD, they lack the ability to define the complex interacting genetic factors that contribute to disease. hiPSC-based studies will complement brain-imaging, pathological, pharmacological, genetic and animal studies of SCZD.

It will be critical that researchers carefully consider which specific subtypes of neurons should be compared using hiPSC neurons studies. We propose that the field begin to characterize cell-autonomous defects in midbrain DA (mDA) and cortical glutamatergic (cGLU) and GABAergic (cGABA) SCZD hiPSC neurons.

An efficient protocol can now differentiate pluripotent stem cells to populations consisting of approximately 20% DA neurons [98] by recapitulating developmental cues found in the ventral midline when SHH, FGF8 and WNT1 initiate DA differentiation; immature mDA neurons express NURR1, EN1/2 and LMX1A/B, whereas mature mDA neurons also express tyrosine hydoxylase (TH) and aromatic L-amino acid decarboxylase (AADC) [99]. Studies using mouse ESCs have shown that NODAL antagonists (LEFTYA) induce expression of the forebrain marker Brain-factor 1 (BF1, FOXG1) and subsequent treatment with WNT antagonists causes regional specification towards cortical fate [100]. Genes such as EMX1, FEZF2, and FEZ, are expressed in immature cGLU neurons [101–103], while mature cGLU neurons express CTIP2 and OTX1. [101, 104, 105]. Subsequent culture with FGF2 has been shown to increase GABAergic differentiation [106]; GABA neurons can be identified by expression of key GABAergic markers, such as Glutamate decarboxylase (GAD65/67), DARPP32, ARPP21, CALBINDIN, or CALRETININ [107], although few if any regional markers of basal ganglia identity have been identified.

Future molecular studies of hiPSC neurons should incorporate SNP, CNV and gene expression data. Studies of quantitative trait loci (eQTLs) will determine how genetic lesions affect gene expression in SCZD neurons. Current eQTL studies can only compare a limited supply of heterogeneous post-mortem brain tissue confounded by variables such as patient treatment history, drug/alcohol abuse and poverty. Ideally, hiPSC-based eQTL studies would produce a renewable supply of more homogeneous cell populations. As hiPSC generation, neuronal differentiation and subtype purification are streamlined and made more efficient, it will become possible to generate any defined neuronal subtypes from hiPSCs generated from hundreds of patients with known genetic backgrounds.

Currently, laborious single cell electrophysiological analysis is the best method to establish the maturity and assess synaptic function of the SCZD hiPSC neurons. Electrophysiological characterization can verify that hiPSC neurons have membrane potentials, undergo induced

action potentials and show evidence of spontaneous synaptic activity. However, in order to study functional synaptic activity defects contributing to SCZD, and detect significant effects in heterogeneous patient populations, it will be necessary to increase both the number of patients and neurons that can be studied, We believe that developing more efficient and higher throughput synaptic analyses needs to become a priority of the field.

Beyond neurons, hiPSCs can of course also be differentiated to any other cell type implicated in SCZD, particularly oligodendrocytes [108, 109]. Given that consider data suggests that myelin dysfunction contributes to SCZD, comparisons of co-cultures of control and SCZD neurons and oligodendrocytes should reveal whether reduced myelination in SCZD neurons is a cell autonomous effect. Should studies of hiPSC-derived cells reveal aberrant oligodendrocyte activity in SCZD, this may indicate a new point of therapeutic intervention in SCZD.

Moving forward, hiPSC studies must make several critical advances. Future studies should focus on defined neuronal subtypes. More efficient hiPSC generation and neuronal differentiation will ultimately permit eQTL studies of SCZD. More scalable assays of synaptic function will allow characterization of increased numbers of control and patient neurons. New studies will need to recruit better-characterized patient populations with well-defined clinical endophenotypes, pharmacological responses and/or genetic lesions.

Conclusion

It is now time to begin to synthesize the disparate fields of brain imaging, neurobiology and genetics. By generating hiPSC neurons from more and better-characterized patient cohorts, one can now test whether the severity of clinical outcome is predictive of the magnitude of cellular phenotype, if genetic lesions correlate to neuronal gene expression differences or if clinical pharmacological response is predictable by hiPSC neuronal drug response. Beyond correlating genetic lesions to the disease state, we can assay the expression or activity of genes identified through GWAS, both in the specific patient in whom the lesion was identified and across cohorts of SCZD patients. By carefully selecting from patients with well characterized diagnosis, MRI brain scans, genotyping data and clinical treatment history, hiPSCs can be generated specifically from SCZD patients with extreme endophenotypes, for example, patients showing drastically altered brain volumes by MRI or clear treatment resistance. Neurons derived from these patients will allow testing of the genetic causes of each endophenotype. With hiPSCs, we can finally move beyond phenotyping of SCZD patients and begin to develop well-controlled experiments to test the specific molecular and cellular effects of disease and pharmacological treatment and response. It is time to begin correlating clinical, genetic and pharmacological studies in vitro.

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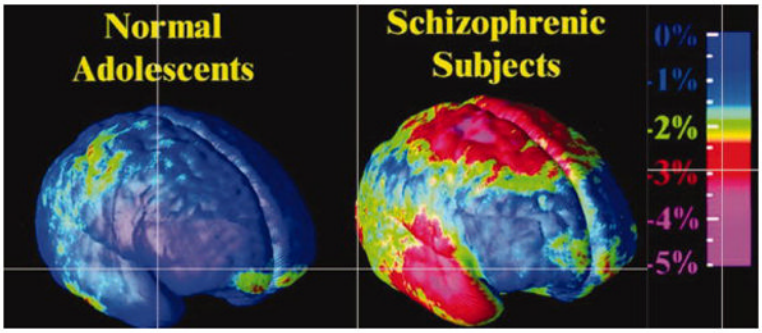

Figure 1.
Average high-resolution magnetic resonance images (MRI scans) showing gray matter loss in adolescents with schizophrenia. Severe loss is observed (red and pink; up to 5% annually) in parietal, motor, and temporal cortices, whereas inferior frontal cortices remain stable (blue; 0–1% loss). Adapted from Thompson et al (2001).

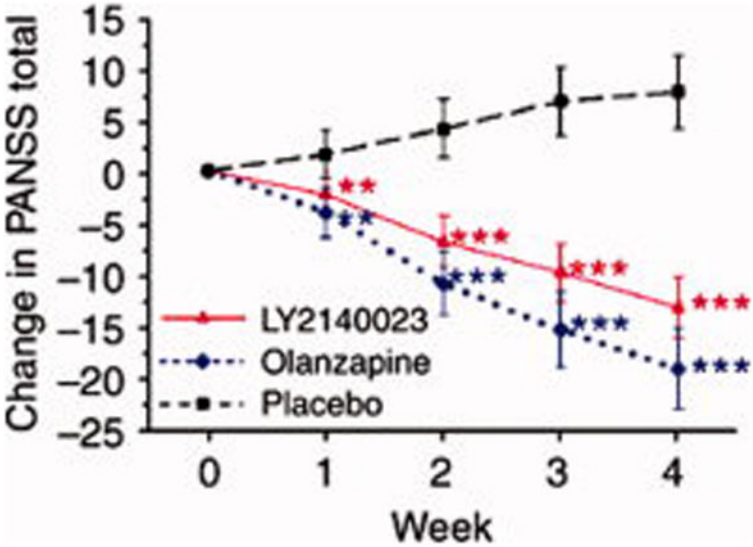

Figure 2.
Weekly change in clinical assessment of psychosis, measured using the clinical Positive and Negative Symptom Scale (PANSS). Abbreviation: PANSS: positive and negative symptom scale. **p<0.01; ***p<0.001 Adapted from Patil et al (2007).

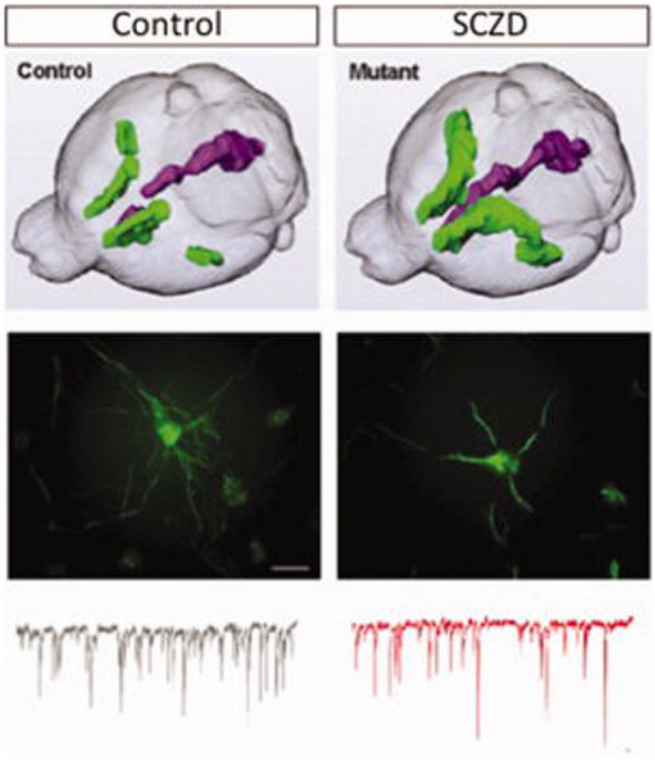

Figure 3.
Representative phenotypes present in dominant negative DISC1 mouse models of SCZD. Top, increased ventricular volume in dnDISC1 mice. Middle, reduced dendritic arborization in dnDISC1 mice. Bottom, reduced frequency of spontaneous inhibitory postsynaptic currents (IPSPs) in dnDISC1 mice. Adapted from Li et al (2007) and Pletnikov et al (2008).

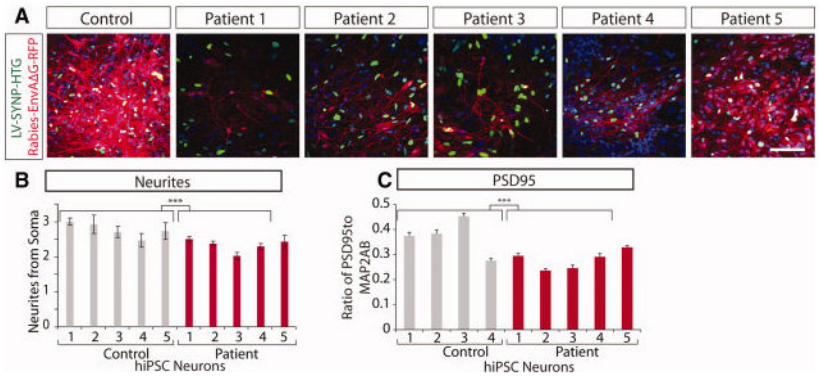

Figure 4.

Decreased neuronal connectivity in SCZD hiPSC neurons. A. Representative images of reduced trans-neuronal labeling (red) in SCZD hiPSC neurons relative to controls. B. Graph showing decreased neurites in SCZD hiPSC neurons. C. Graph showing decreased PSD95 protein levels relative to the dendritic marker MAP2AB for control and SCZD hiPSC neurons. Adapted from Brennand et al (2011). Abbreviations: hiPSCs, human induced pluripotent stem cells; Microtubule-associated protein 2AB (MAP2AB); Postsynaptic density protein 95 (PSD95). *** $p<0.001$