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Cell-based therapies for the treatment of schizophrenia

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Abstract

Schizophrenia is a devastating psychiatric disorder characterized by positive, negative and cognitive symptoms. While aberrant dopamine system function is typically associated with the positive symptoms of the disease, it is thought that this is secondary to pathology in afferent regions. Indeed, schizophrenia patients show dysregulated activity in the hippocampus and prefrontal cortex, two regions known to regulate dopamine neuron activity. These deficits in hippocampal and prefrontal cortical function are thought to result, in part, from reductions in inhibitory interneuron function in these brain regions. Therefore, it has been hypothesized that restoring interneuron function in the hippocampus and/or prefrontal cortex may be an effective treatment strategy for schizophrenia. In this article, we will discuss the evidence for interneuron pathology in schizophrenia and review recent advances in our understanding of interneuron development. Finally, we will explore how these advances have allowed us to test the therapeutic value of interneuron transplants in multiple preclinical models of schizophrenia.

Introduction

Schizophrenia is a devastating psychiatric disorder that affects approximately 1% of the population¹. Positive symptoms, such as paranoia, grandiosity, delusions, and hallucinations, are often the most striking features of the disorder; however, schizophrenia patients also display characteristic negative and cognitive symptoms, which can be severely debilitating. Negative symptoms, such as blunted affect, emotional withdrawal, and social avoidance and cognitive symptoms, including disruptions in working memory, attentional deficits, disorganized thought, and cognitive inflexibility, can negatively influence social and occupational functioning and diminish quality of life^{2–4}. Currently prescribed antipsychotic medications, which act as antagonists at the dopamine D2 receptor⁵, have been somewhat effective in treating the positive symptoms of schizophrenia⁶. However, these drugs have been associated with side effects such as weight gain, sedation, and extrapyramidal symptoms, resulting in a high rate of discontinuation⁶. Further, even among patients that respond to antipsychotic treatment, disability rates remain high and functional outcomes poor, highlighting the need to treat the residual negative and cognitive symptoms². Currently, there are no FDA-approved drugs specifically designed to target these symptom

domains⁴, suggesting an urgent need for more effective treatment strategies that target all three symptom classes observed in schizophrenia patients.

The neuroanatomy of schizophrenia

The dopamine hypothesis is one of the longest-standing and most widely accepted hypotheses explaining the potential neurobiological mechanisms underlying schizophrenia. The original dopamine hypothesis suggests that schizophrenia symptoms are caused by excessive subcortical dopamine. Support for this hypothesis stems from the fact that currently prescribed antipsychotic medications, which can alleviate positive symptoms, act as antagonists at the D2 receptor^{5,7}. Further, drugs that increase dopamine levels, such as amphetamine, can induce schizophrenia-like symptoms in otherwise healthy individuals⁸. When compared to controls, schizophrenia patients show potentiated amphetamine-induced dopamine release in the striatum⁹, which has been correlated with the severity of positive symptoms⁹. Despite this evidence, the dopamine hypothesis does not fully explain the complete array of symptoms present in schizophrenia. For example, antipsychotic medications have little effect on cognitive and negative symptoms², suggesting that excessive subcortical dopamine may not underlie these symptom domains. More recently, the dopamine hypothesis has been revised to suggest that dopamine system hyperactivity and increased D2 receptor activation in the mesolimbic regions underlie positive symptoms, while hypoactive dopamine transmission and reduced D1 receptor activation in the prefrontal cortex are responsible for negative and cognitive symptoms¹⁰. While animal models demonstrate that D1 antagonism in the prefrontal cortex can impair working memory¹¹, an effect that is reversed by co-administration of a D1 agonist¹², human studies do not demonstrate consistent abnormalities in dopamine tissue concentrations or D1 receptor binding in the prefrontal cortex of schizophrenia patients¹³. The inability to identify significant pathology in the dopamine system of schizophrenia patients, has led some to suggest that the pathology actually lies in upstream brain regions that regulate the dopamine system¹⁴.

In animal models, the ventral hippocampus (vHipp) is one such brain region that has been shown to regulate dopamine signaling via a polysynaptic pathway from the nucleus accumbens (nAcc) to the ventral pallidum (VP), and ultimately to dopamine cells in the ventral tegmental area (VTA, Figure 1). Activation of the vHipp by the glutamate agonist NMDA, has been shown to activate dopamine neurons in the VTA, resulting in an increase in the number of spontaneously active cells¹⁵ and extracellular dopamine¹⁶. Administration of a glutamate antagonists into the nAcc blocks the increase in dopamine population activity caused by vHipp activation, suggesting that the vHipp sends glutamatergic projections to the nAcc¹⁵. The nAcc then sends inhibitory GABAergic projections to VP, and bicuculline (GABA_A antagonist) injections into this brain region also block the increase in dopamine population activity induced by vHipp activation¹⁷. Further, inactivation of the ventral pallidum by muscimol/baclofen increased dopamine population activity, suggesting that under normal conditions, the VP maintains an inhibitory influence over the VTA¹⁷. Therefore, the vHipp can act through a multisynaptic pathway to regulate dopamine neuron population activity.

A change in dopamine population activity can influence both tonic dopamine levels in the nAcc and phasic dopamine release in response to motivationally relevant stimuli.^{16,18,19} An increase in burst firing by dopamine neurons is thought to provide the post-synaptic signal that predicts and detects reward. Dopamine neurons that are not spontaneously active are held in a hyperpolarized state by GABAergic inputs from the VP, therefore only spontaneously active dopamine neurons can increase burst firing in response to motivationally relevant stimuli¹⁹. By regulating the number of spontaneously active dopamine neurons in the VTA, the vHipp can set the ‘gain’ of the dopamine system.

Work in multiple animal models of schizophrenia has demonstrated that hyperactivity in the vHipp can drive an increase in dopamine population activity. For example, the mitotoxin methylazoxymethanol acetate (MAM) has been administered to pregnant female rats at gestational day 17 to induce schizophrenia-like changes in anatomy, physiology, and behavior²⁰. MAM-treated rats show hyperactivity in the vHipp and an increase in the number of spontaneously active dopamine neurons in the VTA²¹. Inactivation of the vHipp was able to normalize dopamine cell population activity²¹, suggesting that the dysregulation of the vHipp can result in aberrant dopamine system function. The sub-chronic PCP model (5mg/kg, 2 times/day, 7d) has also been shown to induce behavioral symptoms that model the positive, negative and cognitive symptoms of schizophrenia^{22,23}. We have demonstrated that sub-chronic PCP administration also produces an increase in the number of spontaneously active dopamine neurons in the VTA, an effect that can be reversed by inactivation of the vHipp²⁴. Further, the cyclin D2 knock-out mouse model displays a relatively selective deficit in vHipp inhibition, accompanied by schizophrenia-like behavioral deficits²⁵. Knock-out animals were shown to have an increase in dopamine population activity in the VTA²⁵, suggesting that dysregulated activity in the vHipp can underlie aberrant dopamine signaling associated with schizophrenia-like behaviors. Thus, data from a diverse number of rodent models suggests a pathological enhancement in dopamine neuron population activity is directly attributable to an increased drive from the vHipp. The consequence of the increase in the number of spontaneously active dopamine neurons may be that normally benign stimuli are ascribed an abnormally high salience which may contribute to the paranoia and delusions associated with schizophrenia.

Consistent with our preclinical data, anatomical and physiological changes are consistently observed in the hippocampus of schizophrenia patients. The rodent hippocampus is organized along a dorsal to ventral axis, which corresponds to a posterior to anterior axis in humans²⁶. Structurally, decreases in hippocampal volume are a consistent observation in both postmortem and imaging studies^{27,28}. The decrease in hippocampal volume is seen in first episode patients but also appears to progress throughout the course of the illness^{29,30}. Furthermore, decreases in hippocampal volume seem to be primarily limited to the anterior hippocampus^{31,32} and has been shown to predict deficits in executive function³³.

In addition to the anatomical changes, schizophrenia patients also show differences in hippocampal activity. The hippocampus plays an important role in declarative memory and schizophrenia patients demonstrate impaired recruitment of the hippocampus during memory tasks^{34,35}. Despite these seeming reductions in hippocampal function, unmedicated schizophrenia patients show increased hippocampal activity at rest^{34,36–38}, an effect that can

be attenuated by antipsychotic treatment³⁸. This increase in hippocampal activity has been correlated with the severity of positive symptoms³⁹, suggesting that hippocampal hyperactivity may drive increased activity in the dopamine system and underlie some symptoms of schizophrenia. Indeed, this is consistent with the preclinical data described above where inactivation of the vHipp can reduce dopamine population activity and normalize behavioral correlates of positive symptoms in a rodent model of schizophrenia²¹. Further, hippocampal connectivity is disrupted in schizophrenia patients⁴⁰. Specifically, the anterior hippocampus shows decreased connectivity with regions such as the anterior cingulate and the medial prefrontal cortex⁴⁰.

Finally, cellular and molecular changes have also been observed in the hippocampus of schizophrenia patients. For example, schizophrenia patients have a reduction in neural stem cell proliferation in the dentate gyrus, as determined by Ki-67, a marker of adult neurogenesis⁴¹. Further, schizophrenia patients show a reduced number of synapses between dentate gyrus mossy fibers and CA3 pyramidal neurons^{42,43}, which is accompanied by changes in markers of synaptic plasticity⁴⁴. Specifically, an increase in GluN2B-containing NMDA receptors, PSD95 protein, and spine density were observed in the CA3, but not CA1, region of the hippocampus of schizophrenia patients⁴⁴. Together, these findings support the role of hippocampal pathology in schizophrenia.

The prefrontal cortex (PFC) has also been implicated in the pathology of schizophrenia⁴⁵ (Figure 1). The dorsolateral prefrontal cortex (DLPFC) is one region of the PFC that is critically involved in working memory⁴⁶, which is disrupted in schizophrenia⁴⁷. Schizophrenia patients show reduced DLPFC activation during working memory tasks, with activation levels correlated to performance⁴⁸. Even schizophrenia patients that perform normally on working memory tasks show higher levels of DLPFC activation compared to controls, suggesting a deficit in efficiency⁴⁹. Further, anatomical changes, such as reduced dendritic spine density have been observed the DLPFC of schizophrenia patients^{50–52}. Thus, it is likely that aberrant PFC activity contributes to the cognitive dysfunction observed in patients. The DLPFC has also been associated with negative symptoms of schizophrenia. For example, one study demonstrated a correlation between activity in the DLPFC and the severity of negative symptoms in schizophrenia patients⁵³. Further, negative symptoms have also been associated with volumetric reductions in the prefrontal cortex⁵⁴. Therefore, changes in PFC activity may also underlie the negative symptoms of schizophrenia.

Interestingly, the PFC and hippocampus are interconnected neuronal systems with the anterior hippocampus directly regulating activity in the PFC⁵⁵. Moreover, deficits in connectivity between these regions have been observed in schizophrenia patients^{40,56,57}. Indeed, we have previously demonstrated that hippocampal manipulations not only alter behavioral deficits consistent with positive symptoms, but can also regulate cognitive functions dependent on the PFC⁵⁸. Together, these findings suggest that dysregulated prefrontal and hippocampal activity are present in schizophrenia patients and may underlie some of the symptoms of the disorder.

Interneuron dysfunction in schizophrenia

The cortex is composed of two primary cell types: excitatory pyramidal cells that use glutamate as their neurotransmitter and inhibitory interneurons that use GABA. A significant literature examining post mortem tissue from schizophrenia patients has demonstrated that the pathology of schizophrenia may involve a deficit in inhibitory signaling (Figure 1). As early as 1979, Bird and colleagues demonstrated that activity of glutamic acid decarboxylase (GAD), the enzyme required for the synthesis of GABA, was reduced across multiple brain regions in schizophrenia patients, including the prefrontal cortex and hippocampus. This study was confounded by the fact that most of the patients died of a protracted illness, which has also been shown to increase GAD activity⁵⁹. However, there is now considerable evidence to suggest that the GABAergic system is disrupted in schizophrenia patients. For example, patients possess fewer GABA uptake sites⁶⁰ and a reduction in non-pyramidal cells in the hippocampus⁶¹. In addition, multiple studies have demonstrated a decrease in GAD mRNA expression in the hippocampus⁶². However, it should be noted that other studies have not observed a decrease in GAD mRNA expression in the hippocampus^{62,63}. Further, GAD67 protein levels have not been observed in the hippocampus⁶⁴, leading some to suggest that the GABAergic deficits present in the hippocampus may be restricted to certain sub-classes of interneurons. Indeed, these changes seem to be restricted specifically to interneurons that express the Ca²⁺-binding protein, parvalbumin (PV), and those that express the neuropeptide, somatostatin (SST). For example, Zhang and Reynolds demonstrated a reduction in the number of PV-immunoreactive interneurons in the hippocampus of schizophrenia patients⁶⁵ while the number of interneurons that express calretinin were not changed in any of the hippocampal subfields examined⁶⁵. However, this result has not been replicated⁶⁶. In addition, reductions in SST-positive interneurons have also been observed in the hippocampus of schizophrenia patients⁶⁶. Reductions in particular classes of interneurons may be significant, as different interneuron sub-types have unique anatomical and physiological features, allowing these cells to differentially regulate pyramidal cell function⁶⁷.

In animal models, deficits in PV-positive interneuron function have been shown to induce schizophrenia-like behaviors in otherwise normal animals. For example, GAD knock-out restricted to PV-positive cells causes deficits in pre-pulse inhibition, changes in social interaction and impaired fear conditioning⁶⁸. Further, we have demonstrated that shRNA knock-down of PV specifically in the vHipp causes an increase in the number of spontaneously active dopamine neurons in the VTA and an increase in amphetamine-induced locomotor activity⁶⁹. Using a pharmacogenetic approach, Nguyen and colleagues demonstrated that inhibition of PV-positive interneurons in the vHipp impairs prepulse inhibition and spontaneous alternation while inhibition of GAD65-positive cells increases amphetamine-induced locomotor activity and reduces spontaneous alternation⁷⁰. These results suggest that the loss of interneurons observed in the vHipp of schizophrenic patients may underlie some symptoms of the disorder.

It is important to note that although hippocampal hyperactivity is consistently observed in schizophrenia patients, the mechanism by which this occurs is not universally accepted. As described above, interneuron deficits have not always been in the hippocampus of

schizophrenia patients^{62–64,66}. Instead, many believe that the increase in hippocampal hyperactivity is due to increases in glutamate signaling⁷¹. Regardless of the mechanism by which it occurs, the end result is an increase in hippocampal activity, which has been consistently observed in schizophrenia patients and across animal models of schizophrenia. Therefore, despite the mechanism of pathology, it is likely that enhancing interneuron function would reduce hippocampal hyperactivity and have a beneficial effect in schizophrenia.

Deficits in interneuron function have also been observed in the prefrontal cortex of schizophrenia patients. For example, schizophrenia patients have reductions in GAD67 mRNA in the DLPFC^{72–75}. Interestingly, there does not appear to be a loss of cells, rather a subset of interneurons express less GAD^{72,75}. This effect seems to be specific to psychosis, as patients with bipolar depression also show GAD reductions but those with unipolar depression do not⁷³. In addition, the GAD reduction is independent of antipsychotic treatment⁷⁵. More recent work has begun to explore changes in specific interneuron subtypes in the DLPFC. Hashimoto and colleagues found that schizophrenia patients show reduced mRNA expression of the neuropeptides SST and cholecystokinin⁷⁶. Together, these results demonstrate a change in hippocampal and PFC interneuron function in schizophrenia and suggest that targeting the GABAergic system may be an effective treatment strategy for schizophrenia. Toward this end, multiple groups have begun to explore the use of cell-based therapies to replace dysfunctional interneurons.

Understanding interneuron development

Interneuron transplant therapy would not be possible without an understanding of the developmental origins of cortical interneurons and in recent years, fate-mapping experiments have provided insight into interneuron development. GABAergic interneurons are born in the telencephalic structures known as the ganglionic eminences (medial, lateral, and caudal). Interneuron precursors born in the ganglionic eminences have the remarkable ability to migrate tangentially across cortical regions⁷⁷. The particular subclass of interneuron that develops is determined by a combination of spatial and temporal factors. For example, the medial ganglionic eminence (MGE) is the primary source of SST- and PV-positive interneurons^{77,78} while the caudal ganglionic eminence (CGE) gives rise to calretinin-positive interneurons⁷⁹. Interneuron precursors in the MGE cease proliferation before migrating into the cortex⁸⁰ and the fate of these interneuron precursors is determined by the signals that are present at the time the cells are born, rather than those that are encountered during migration^{79,81}. Using BrdU to label MGE cells, it has been demonstrated that SST-positive cells are generally born before PV-positive interneurons⁸². Interneurons fill in the cortex in an inside-out pattern with deep layer interneurons born earlier than those in more superficial layers⁸³, suggesting that PV- and SST-positive interneurons may demonstrate laminar targeting.

Spatial factors can also influence the particular interneuron sub-type that develops. The dorsal region of the MGE, for example, shows a bias toward SST-positive interneurons, while the more ventral region of the MGE shows a bias toward PV-positive cells, although both areas produce both cell types⁸⁴. This biased interneuron development may result from a

concentration gradient of the morphogen sonic hedgehog (SHH). SHH is expressed at higher levels in the more dorsal regions of the MGE, resulting in an increased percentage of SST-positive cells⁸⁵. SHH is important for the activation and maintenance of NK2 transcription factor-related 2.1 (Nkx2.1)⁸⁰, which is required for both the development of both PV- and SST-positive interneurons in the MGE^{86,87}. Downstream, Nkx2.1 activates lim-homeodomain transcription factor (Lhx6). As PV- and SST-positive MGE cells exit the cell cycle and begin their migration, Nkx2.1 is down-regulated and Lhx6 expression increases and is maintained throughout the life of the cell⁸⁸.

This enhanced understanding of interneuron development has allowed us to start evaluating the use of interneuron transplants in preclinical models of disease. In the first proof of concept experiment, Wichterle demonstrated that dissociated MGE cells from fetal brain tissue survived after being transplanted into the brain. Moreover, these cells migrated extensively into the striatum, thalamus, and neocortex⁷⁷. Subsequent experiments have demonstrated that by 21 days after transplantation, MGE cells have migrated to their final destination and a majority (~70%) express GABA or GAD67. Excitingly, these cells display firing patterns similar to endogenous interneurons. Further, the cells integrate into the cortical circuitry, both increasing inhibitory input to and receiving excitatory input from surrounding pyramidal cells⁸⁹. These experiments demonstrate that MGE tissue can be used to transplant GABAergic cells into preclinical models of disease.

The use of fetal tissue, however, is not a viable treatment strategy for humans. Therefore, many groups are working to develop interneurons from embryonic stem cells (ESCs). In 2005, Watanabe and colleagues developed a protocol for generating telencephalic precursors from ESCs, including those that express Nkx2.1⁹⁰. However, not all cells develop into GABAergic cells, and tumor formation is a significant limitation; therefore the development of transgenic ESC lines has allowed the exclusion of other cell types. For example, a mouse ESC line was modified to express GFP under the control of the Lhx6 promoter. The Lhx6::GFP cells were sorted by flow cytometry, then transplanted into the brain. These GFP + cells survived in the brain and migrated throughout the cortex where they express markers of GABAergic cells, including PV and SST. Furthermore, these transplanted cells display firing properties reminiscent of endogenous PV- or SST- cells. Importantly, no tumor formation was observed in transplanted animals, even up to 240 days after the cells were transplanted⁹¹. The Lhx6::GFP ESC cell line was further modified to also express mCherry under the control of the Nkx2.1 promoter, allowing the differentiation of specific sub-classes of interneurons. Using these Lhx6::GFP::Nkx2.1::mCherry cells, a protocol employing differential expression of SHH and timing was developed to form enriched populations of PV- or SST-positive interneurons. SST-positive cells were exposed to high levels of SHH and cultured for a shorter period of time (12 days) while PV-positive cells were exposed to low levels of SHH and were cultured for 17 days, as this interneuron subtype is generally born earlier. Once transplanted into the brain, the PV- or SST-positive cells expressed interneuron markers and displayed firing properties similar to endogenous SST- and PV-positive interneurons⁹².

Using interneurons to treat schizophrenia

Multiple groups have begun to explore the use of interneuron transplants for the treatment of schizophrenia (Table 1). As detailed above, schizophrenia patients show reductions in GABAergic cells in the prefrontal cortex. Dysfunction in the prefrontal cortex is thought to be especially important for development of negative⁹³ and cognitive symptoms⁹⁴. Therefore, it is possible that replacing interneurons in the prefrontal cortex may have beneficial effects on negative and cognitive symptoms of schizophrenia. The first group to test this hypothesis used the phencyclidine (PCP) model of schizophrenia. PCP, an NMDA antagonist induces acute psychosis in humans⁹⁵ and can produce schizophrenia-like deficits in rodents^{22,23}. Using the sub-acute PCP model, Tanaka and colleagues demonstrated that deficits in novel object recognition and prepulse inhibition were prevented by transplanting MGE tissue into the medial prefrontal cortex (mPFC) of newborn animals⁹⁶. These experiments suggested that interneuron transplants may be a useful strategy to prevent the development of negative and cognitive symptoms that model schizophrenia. While exciting, enthusiasm for these results was limited by two important considerations. First, there is no definitive biomarker to indicate that a person will develop schizophrenia, therefore preventative treatment using cell transplants is unlikely to become a viable treatment option for human patients. Further, the acute PCP model of schizophrenia does not recapitulate the developmental aspects of the disorder⁹⁷.

Recently, a developmental model of schizophrenia was used to test the efficacy of MGE transplants. Injections of methylazoxymethanol (MAM) on gestational day 17 produces anatomical, behavioral, and physiological deficits that model schizophrenia²⁰. Specifically, the MAM model produces deficits that model the negative and cognitive symptoms of schizophrenia, including deficits in cognitive flexibility⁵⁸ and reductions in social interaction⁹⁸. We have shown that MGE transplants into the mPFC of MAM rodents can restore cognitive flexibility and increase social interaction time⁹⁹. Our results suggest that interneuron transplants may be an effective treatment strategy for negative and cognitive symptoms even after the pathology has developed.

The MAM model also produces deficits that model the positive symptoms of schizophrenia. MAM rodents show an increase in the firing rate of hippocampal pyramidal cells, an increase in dopamine population activity in the VTA, and enhanced amphetamine-induced locomotor activity, a model of the positive symptoms of schizophrenia. Interestingly, prenatal MAM treatment also produces a decrease in PV-positive interneurons in the ventral hippocampus¹⁰⁰. Transplantation of fetal MGE tissue into the vHipp of MAM rats was able to reduce pyramidal cell activity in the hippocampus, decrease dopamine population activity in the VTA, and normalize amphetamine-induced locomotor activity, suggesting that interneuron transplants into the vHipp may be effective in reducing positive symptoms of schizophrenia¹⁰¹. However, the hippocampus projects directly to the prefrontal cortex⁵⁵, therefore it is possible that transplants into the vHipp may influence negative and cognitive symptoms as well.

Recently, Giliani and colleagues demonstrated that hippocampal interneuron transplants may influence cognitive function in addition to alleviating positive symptoms. The cyclin D2

knock-out mouse has been used as a model of hippocampal hyperactivity. These animals display schizophrenia-like features, including an increase in cerebral blood volume in the ventral hippocampus, an increase in dopamine population activity in the VTA, and increased amphetamine-induced locomotor activity, all of which were reversed by MGE transplants into the vHipp. Interestingly, the MGE transplants also alleviated deficits in contextual fear conditioning, a hippocampal-dependent cognitive function²⁵, suggesting that interneuron transplants into the vHipp may be able to influence the cognitive symptoms of schizophrenia, an area that is currently poorly treated.

The experiments described above are exciting and demonstrate that in multiple preclinical models, interneuron transplants effectively reduce schizophrenia-like symptoms. In order to move away from the use of fetal tissue to a more translational option, we have recently begun to explore the use of embryonic stem cells to grow interneurons. Specifically, we used the Lhx6::GFP::Nkx2.1::mCherry transgenic ESC line to grow enriched populations of SST- or PV-positive interneurons⁹². Interestingly, we demonstrated that the interneuron transplants into the vHipp integrated into the circuitry, effectively reducing spontaneous IPSCs in hippocampal pyramidal cells¹⁰². Further, both interneuron sub-types normalized the firing rate of putative hippocampal cells in MAM animals¹⁰². These hippocampal effects were accompanied by a reduction in dopamine population activity in the VTA¹⁰². Excitingly, the ESC-derived interneuron transplants also affected behavior, reducing not only positive but also cognitive and negative symptoms in the MAM model. However, the two interneuron subtypes had dramatically different effects on behavior. Latent inhibition is disrupted in schizophrenia patients and has been used as a model for the dopamine-dependent positive symptoms¹⁰³. We found that both SST- and PV-enriched transplants into the vHipp restored latent inhibition that was disrupted in the MAM animals¹⁰². Further, both interneuron subtypes alleviated MAM-induced deficits in reversal learning¹⁰², a form of cognitive flexibility mediated by the orbital frontal cortex¹⁰⁴ and dependent on subcortical dopamine signaling¹⁰⁵. PV-positive cells, however, were also able to increase social interaction time and restore extradimensional set-shifting performance in MAM rats¹⁰², two behaviors that critically depend on the mPFC⁹³. These results suggest that interneuron, specifically PV-positive cell, transplants into the vHipp may be an effective treatment strategy to target positive, negative, and cognitive symptoms of schizophrenia (Figure 1).

Outstanding questions and future directions

These experiments provide evidence that interneuron transplants may be an effective treatment strategy for schizophrenia. However, before this strategy can move to the clinic, many questions must be answered. For example, the source of the cells will be a major issue. The use of MGE tissue from human fetuses has obvious moral implications; therefore, many labs have begun to develop protocols for generating interneuron precursors from human pluripotent stem cells^{106–108}. Using patient-specific ESCs would have the additional advantage of eliminating the potential of rejection. It should be noted that human development is much longer than that of a rodent and therefore growing personalized interneurons from patient-derived stem cells would require a great deal of time and resources. Alternatively, some have proposed the development of stem cell banks, which would provide about 150 human ESC lines that would have sufficient homology for the use

in more than 90% of the population¹⁰⁹. Further, the ability to grow highly enriched populations of interneurons remains a challenge. In the experiments described above, flow cytometry was used to exclude cells that did not express interneuron-specific markers. Such an approach would likely be required for human cells as non-differentiated stem cell transplants can lead to the formation of tumors and other undesirable side effects¹¹⁰. In conclusion, the results presented here are promising and suggest that interneuron transplants may be an effective treatment strategy for schizophrenia. However, more work needs to be done at the preclinical level to understand the specific role of interneuron sub-types and the long-term effects of ESC transplants. Further, improved methods for generating large quantities of purified interneuron precursors rapidly will be required before this exciting new therapy can move to the clinic.

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Figure 1.

Table 1

Efficacy of interneuron transplants in preclinical models of schizophrenia

Cell Source	Target Region	Rodent Model	Behavioral and Physiological Effects	Reference
MGE	mPFC	Acute PCP	Improved novel object recognition and normalized prepulse inhibition	Tanaka 2011
MGE	mPFC	MAM	Improved reversal learning and increased social interaction time	Perez 2015
MGE	vHipp	MAM	Reduced amphetamine-induced locomotor activity, normalized dopamine population activity, reduced hippocampal hyperactivity	Perez 2013
MGE	vHipp	Cyclin D2 knock-out	Reduced amphetamine-induced locomotor activity, improved contextual fear conditioning normalized dopamine population activity, and reduced hippocampal hyperactivity	Giliani 2014
ESC	vHipp	MAM	Normalized latent inhibition (PV, SST), increased social interaction time (PV), improved reversal learning (PV, SST) and extradimensional set shifting (PV), normalized dopamine population activity (PV, SST), reduced hippocampal hyperactivity (PV, SST)	Donegan 2015