



Review Article

NMDAR hypofunction and somatostatin-expressing GABAergic interneurons and receptors: A newly identified correlation and its effects in schizophrenia



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ABSTRACT

This review investigates the association between *N*-methyl-D-Aspartate receptor (NMDAR) hypofunction and somatostatin-expressing GABAergic interneurons (SST+) and how it contributes to the cognitive deficits observed in schizophrenia (SZ). This is based on evidence that NMDAR antagonists caused symptoms resembling SZ in healthy individuals. NMDAR hypofunction in GABAergic interneurons results in the modulation of the cortical network oscillation, particularly in the gamma range (30–80 Hz). These gamma-band oscillation (GBO) abnormalities were found to lead to the cognitive deficits observed in the disorder. Postmortem mRNA studies have shown that SST decreased more significantly than any other biomarker in schizophrenic subjects. The functional role of Somatostatin (SST) in the aetiology of SZ can be studied through its receptors. Genetic knockout studies in animal models in Huntington's disease (HD) have shown that a specific SST receptor, SSTR2, is increased along with the increased NMDAR activity, with opposing patterns observed in SZ. A direct correlation between SSTR and NMDAR is hence inferred in this review with the hope of finding a potential new therapeutic target for the treatment of SZ and related neurological conditions.

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1. Introduction

Schizophrenia (SZ) is a neurodevelopmental disorder afflicting around 26 million people worldwide (Eaton et al., 2008). Its symptoms encompass hallucinations, delusions, social withdrawal and cognitive

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deficits, often emerging in late adolescence or early adulthood (Jadi et al., 2015). Cognitive function impairments are observed in aspects of attention, reasoning, memory and speed processing. Kahn and Keefe (2013) suggested that these cognitive deficits are the core clinical feature of SZ, but their response to current antipsychotic medications is minimal (Keefe and Harvey, 2012).

It is proposed that cortical information when performing cognitive tasks is transferred through synchronous oscillations in the cortical networks. The oscillatory activity varies across different behavioural states and cognitive tasks, showing several frequency bands such as theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–80 Hz) as reviewed by Wang (2010), as well as Uhlhaas and Singer (2010). Gamma band oscillations (GBO) are associated with neural ensemble synchronization during stimulus or task-driven cognitive states such as attention, complex processing of information, working memory and feature binding (Fries, 2009; Lesh et al., 2011; Salinas and Sejnowski, 2001). GBO power is consistently abnormal in SZ when compared to healthy individuals (Gonzalez-Burgos and Lewis, 2008; Jadi et al., 2015; Uhlhaas and Singer, 2010).

According to Lewis (2014), the cognitive deficits of SZ arise from GBO abnormalities, which directly depend on the synaptic inhibitory action of gamma-aminobutyric acid (GABA) interneurons in the brain's cortical circuitry (Buzsáki and Wang, 2012). Thus, cognitive dysfunctions in SZ are suggested to be a result of GABAergic inhibition abnormalities (Lewis et al., 2005).

Furthermore, it is proposed that *N*-methyl-D-aspartate receptor (NMDAR) hypofunction in these GABAergic interneurons is involved in the GBO alteration observed in schizophrenic patients. The NMDAR has attracted interest due to the effects of NMDAR antagonist phencyclidine (PCP) producing SZ-like symptoms in healthy individuals (Luby et al., 1959). Studies have since suggested links between NMDAR hypofunction and SZ (Carlsson and Carlsson, 1990; Olney and Farber, 1995). This was supported by the use of other NMDAR antagonists such as ketamine and MK801 causing a decrease in GABAergic interneurons in animals (Abekawa et al., 2011; Wang, 2010), and behavioural deficits similar to human SZ (Olney and Farber, 1995).

A certain type of cortical GABAergic interneurons is categorised by its expression of a unique molecular marker known as somatostatin (SST) as reviewed by Yavorska and Wehr (2016). SST is co-localized with GABA as an inhibitory neuropeptide with modulatory and inhibitory actions in the brain. It is also involved in the regulation of behavioural and physiological stress responses such as the inhibition of hypothalamic hormone release, cortical circuit integration of sensory input and the amygdala central nucleus output (Lin and Sibille, 2013).

Alterations in somatostatin-expressing (SST+) GABA interneurons are found to be associated with SZ (Morris et al., 2008). SST+ interneurons exert differential inhibitory effects on excitatory neurons in specific layers of the neocortex (Xu et al., 2013). Moreover, SST mRNA levels in the GABAergic interneurons are significantly decreased in the cortices of SZ patients. In fact, SST deficits were also observed in many other human psychiatric and neurological disorders such as major depressive disorder, bipolar disorder, Alzheimer's disease and Parkinson's disease as reviewed and summarized by Lin and Sibille (2013).

Rajput et al. (2011) showed that SST functions as a neuroprotective agent in the central nervous system through acting on five different receptor subtypes (SSTR1–5). When the SSTR1 and SSTR5 genes are knocked out in mice, symptoms resembling Huntington's disease (HD) are generated. This also lead to an increase in SSTR2 to perhaps compensate for the loss of SSTR1 and SSTR5 in order to protect neurons from excitotoxicity caused by the well-established increase in NMDAR activation seen in HD models (Chen et al., 1999; Fan and Raymond, 2007; Rajput et al., 2011). Conversely, a decrease in SSTR2 was also observed in SZ postmortem brain samples by Beneyto et al. (2012).

Based on the increase in SSTR2 expression and NMDAR activity in HD as well as their simultaneous decrease in SZ, a direct correlation can be inferred. This may imply that SST+ interneurons are indeed

associated with the hypofunction of NMDARs and hence the alterations of GBO in SZ. However, this relationship needs to be further investigated in this review and in future studies.

2. Methodology

2.1. Research design

This article reviews the evidence relating to SST + GABAergic interneurons effects on cortical network oscillations and the cognitive deficits in SZ using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) system (Moher et al., 2015).

2.2. Literature search strategy

The search keywords (*schizophrenia*), (*NMDA**), (*Somatostatin or interneuron**), (*receptor**), and (*Oscillation* or wave* or rhythm*) were implemented in the Web of Science, Medline (PubMed), and Google Scholar to find the relevant resources through October 2016 to April 2016. Citations from review articles and significant papers were scrutinized to find additional related articles.

2.3. Inclusion criteria

The most relevant studies were included as their relevance was calculated based on whether they covered the following topics: NMDAR hypofunction, GABAergic interneurons, specifically those expressing SST, SSTRs, and changes in brain oscillations. Only original papers published in English were considered.

2.4. Quality assessment

The methodological quality of the studies included was evaluated based on the gold standard publication checklist (GSPC) for animal studies by Hooijmans et al. (2010) and the Cochrane Collaboration's tool for evaluating the risk of bias for the remaining studies (Higgins and Green, 2011). Critical appraisal of each study was conducted by means of systematic assessment of risks of bias, the relevance of populations, interventions and outcomes (Appendix A). Table 1 summarizes the studies reviewed in this research.

3. Results and discussions

3.1. Somatostatin changes in schizophrenia models

SST was analyzed by Hashimoto et al. (2008a) based on 14 pairs of SZ and control subjects with an extended cohort of 23 pairs for further investigations. DNA microarray analysis showed a 1.59 fold reduction in SST mRNA levels in SZ subjects when compared to control subjects. The results were verified by quantitative polymerase chain reaction (PCR) results showing a mean reduction of 44% in SST mRNAs in the DLPFC of schizophrenic subjects compared to control subjects ($p < 0.01$). The differences in mRNA expression detected by the quantitative PCR and the microarray analyses for SST were in fact highly correlated yielding a Pearson's correlation coefficient (r) of 0.79 ($p = 0.001$).

Assessment of SZ subjects through in situ hybridization, further verified the decrease in SST mRNA expression by 36% ($p = 0.001$) in the gray matter of SZ subjects. This correlated with the quantitative PCR results with $r = 0.90$ ($p < 0.001$). Indeed, SST expression exhibited the largest and most robust decrease of mRNA expressions found throughout the study.

Other areas of the neocortex such as the anterior cingulate cortex, the primary motor cortex and the primary visual cortex along with the DLPFC were investigated in a different study by Hashimoto et al. (2008b) 12 pairs of SZ and normal comparison subjects were included. The results indicated a mean decrease of 57% in SST transcript

Table 1
Summary of the main reviewed studies, the models tested and methods used.

Study	Models	Methods
<i>Somatostatin changes in schizophrenia models</i>		
Hashimoto et al. (2008a)	Human and monkey postmortem DLPFC samples	Customized DNA microarray, quantitative PCR, and in situ hybridization
Hashimoto et al. (2008b)	Human postmortem anterior cingulate, primary motor and primary visual cortices	Quantitative PCR, regional survey of GABAergic transcripts expressions, and statistical analyses
Morris et al. (2008)	Human postmortem prefrontal cortex samples	In situ hybridization
Fung et al. (2010)	Human postmortem DLPFC samples	Quantitative reverse transcription PCR, western blot analysis, and statistical analysis
Konradi et al. (2011)	Human postmortem hippocampus samples	Immunocytochemistry, morphometric analysis, real-time PCR and statistical analysis
Fung et al. (2014)	Human postmortem DLPFC and OFC samples	Quantitative PCR and statistical analysis
Joshi et al. (2015)	Human postmortem OFC samples	In situ hybridization, quantitative reverse transcription PCR, image analysis and statistical analysis
<i>Somatostatin receptors changes in relation to NMDAR activity</i>		
Weickert et al. (2013)	Human postmortem DLPFC samples	Quantitative reverse transcription PCR and Western blot analysis
Rajput et al. (2011)	Transgenic mice postmortem striatum samples	Immunohistochemical and Western blot analysis
Beneyto et al. (2012)	Human and monkey postmortem DLPFC samples	In situ hybridization and statistical analysis
<i>Cortical oscillations changes and NMDAR hypofunction in schizophrenia</i>		
Kwon et al. (1999)	Schizophrenic and healthy humans	EEG synchronization analysis and statistical analysis
Cho et al. (2006)	Schizophrenic and healthy humans	EEG synchronization analysis
Ford et al. (2008)	Schizophrenic and healthy humans	Phase locking factor in EEG analysis
Spencer et al. (2008)	Schizophrenic and healthy humans	Synchronization and phase locking factor analysis with EEG
Leishman et al. (2015)	Adult male rats	Phase locking factor and power in EEG analysis
Kittelberger et al. (2012)	Adult male rats	EEG and histological analysis
McNally et al. (2011)	Prefrontal cortices of adult mice	EEG and immunocytochemistry analysis
McNally et al. (2013)	Prefrontal cortices of adult mice	EEG and statistical analysis

expression across the four cortical areas in subjects with SZ when compared to matched normal subjects based on the quantitative PCR data and MANOVA tests. Significant effects of both diagnosis ($F = 36$, $df = 1, 9.1$, $p < 0.001$) and area ($F = 130$, $df = 3, 6.5$, $p < 0.001$) were revealed for the SST transcript. The decrease was found to be consistent across the different cortical areas tested, suggesting that SST + interneurons are selectively involved in the aetiology of SZ in a similar manner, despite the various cellular compositions, connectivities and functions.

Morris et al. (2008) found that SST mRNA expression was significantly decreased in most of the cortical layers in SZ, with the highest decrease of 36.6% ($p < 0.01$) in the 2/3s layer. The compartmental expression analysis results showed that SST mRNA decreased significantly in the gray matter of schizophrenic subjects compared to the control subjects by 36% ($p < 0.01$). Cellular level analysis was carried out in layers 2/3s and 5 showing a 31% decrease in SST expression per neuron ($p = 0.003$) and 25% ($p = 0.012$) respectively in SZ subjects compared to the control subjects. Furthermore, the mean SST + interneuron density was 26% lower in layer 2/3s ($p = 0.002$) of SZ subjects. These alterations in SST expression are not likely to be a consequence of other factors, but are thought to be a reflection of the disease process itself.

A postmortem study by Fung et al. (2010) involved a developmental cohort of subjects aged between 6 weeks to 49 years ($N = 68$), and a comparison cohort of SZ and normal subjects (37 pairs). It measured mRNA expression in the DLPFC and found that a decrease in SST occurs gradually over postnatal development, with around 70% being down-regulated from the neonatal stage to adulthood in normal individuals. There was also a marked decrease in SST mRNA expression by 31% ($p < 0.001$) in SZ patients compared to the comparison cohort.

A study by Konradi et al. (2011) used immunocytochemistry, morphometric analysis, and real-time PCR in human postmortem hippocampus samples for 13 SZ subjects and 20 healthy control subjects. Their results indicated a significant decrease in SST + interneurons numbers and densities ($p < 0.001$) as well as somatostatin mRNA expression levels ($p < 0.021$) in SZ.

Fung et al. (2014) tested for the changes in SST levels in the DLPFC and orbitofrontal cortex (OFC) of schizophrenia ($n = 34$) and bipolar disorder subjects ($n = 31$) compared to control subjects ($n = 35$). SST mRNA expression was consistently lower in SZ relative to the control subjects by 20.9% ($p < 0.05$) in the DLPFC region, and 23.9%

($p < 0.01$) in the OFC region. A greater reduction in SST mRNA expression was also demonstrated by the bipolar disorder group suggesting a substantial overlap in the neuropathologies of the two disorders. Joshi et al. (2015) found that SST decreased in layers 1 to 6 in the OFC region with the most notable decrease in SST mRNA of 67% ($p < 0.001$) found in layer 2 of the neocortex. A decrease of 29% ($p < 0.05$) in SST + interneuron density in layer 2 was also observed in SZ patients when compared to the control group.

These results collectively show a definite pattern of SST reduction of 21% to 67% in various areas of the neocortex in SZ patients through changes in mRNA expression levels, changes in SST + interneuron numbers and densities. This concludes that SST + interneurons are certainly implicated in the pathology of the neurodevelopmental disorder.

3.2. Somatostatin receptors changes in relation to NMDAR activity

Somatostatin disturbances have been noted in a variety of human degenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD) and schizophrenia among others. The decrease in SST in the cortices of AD patients was found to be directly linked to memory impairment and poor cognitive function (Grouselle et al., 1998). On the contrary, SST is increased in HD in which it is related to the motor co-ordination disability (Beal et al., 1986). Studies also found that SST + interneurons are selectively resistant to neurodegeneration induced through NMDAR agonists (Kumar, 2004).

SST + interneurons were found to have a distinct NMDAR phenotype that expresses lower levels of NMDAR1 and NMDAR2B subunits and hence are likely to exhibit NMDA channels with distinctive physiological and perhaps pharmacological properties (Landwehrmeyer et al., 1995). This could be one of the reasons behind the selective resistance of SST + interneurons against NMDAR-mediated neurodegeneration. More recently, a study by Weickert et al. (2013) provided evidence of NMDAR hypofunction in SZ based on postmortem human DLPFC samples from 37 pairs of schizophrenic control subjects. The results indicated a marked reduction in the mRNA levels by 22% ($p = 0.004$), and protein levels by 36% ($p = 0.01$) of the NMDAR1 subunit in SZ subjects.

Nevertheless, NMDAR activity alterations are not only involved in SZ but were also noted in Huntington's disease (HD) models. An increase in NMDAR activation causes excitotoxicity in HD (Chen et al., 1999; Fan

and Raymond, 2007). Moreover, SST is also found to be increased at the same time in HD, and it has been shown to exert neuroprotective effects against NMDA-mediated excitotoxicity (Forloni et al., 1997). Using genetic knock-out models, Rajput et al. (2011) argued that the neuroprotective characteristics of SST in the nervous system arises from its action on five receptor subtypes (SSTR1–5). Through knocking out SSTR1 and SSTR5 genes in mice, HD-like symptoms were generated due to an increased NMDAR activity. In parallel, SSTR2 was also increased by 25% compared to the control wild-type mice. Perhaps, the increased SSTR2 levels are a compensatory mechanism for the increased NMDAR activity which causes toxicity in HD. Rajput et al. (2011) argued the importance of SST and SSTRs roles in regulating NMDAR activity and neurodegeneration in the central nervous system.

In SZ models however, NMDAR activity is decreased rather than increased. The NMDAR hypofunction theory in SZ is based on the effect of the NMDAR antagonist phencyclidine (PCP) in producing symptoms resembling SZ in healthy individuals (Luby et al., 1959). Other NMDAR antagonists including ketamine and MK801 lead to a decrease in GABAergic interneurons and to SZ-like behaviours in animal studies (Abekawa et al., 2011; Olney and Farber, 1995; Wang et al., 2008). The effects of NMDAR antagonists were shown to specifically target inhibitory circuits that cause disinhibition of the neurotransmitter systems (Olney et al., 1999). These findings have since supported the NMDAR hypofunction theory and its relation to the pathology of SZ.

Nonetheless, along with the reduction in NMDAR activity in SZ, a significant reduction of 19.1% ($p < 0.05$) in SSTR2 expression was observed by Beneyto et al. (2012). The results were based on postmortem samples of the human DLPFC area in 23 pairs of schizophrenic and normal comparison subjects.

Hence, a relationship between SST, SSTRs and NMDAR hypofunction can be inferred in relation to SZ. The increase in SSTR2 and NMDAR activity in HD as well as their opposed decrease in SZ indicates a direct positive correlation between the two receptors. It also seems to play an important role in a number of neurological conditions and is not specific to SZ.

3.3. Cortical oscillation changes and NMDAR hypofunction in schizophrenia

The consequences of NMDAR hypofunction on the cortical activity must be studied in terms of cortical oscillation modulation, and how that is related to the cognitive deficits in SZ. Functional techniques such as electroencephalography (EEG) and Magneto-encephalography (MEG) are used to detect the oscillations as a measure of activity in neural synchronous populations. According to Salinas and Sejnowski (2001), Fries (2009), and Lesh et al. (2011), stimulus or task-driven cognitive states are related to neural ensembles synchronization that represent GBOs. The magnitude of GBO power in EEG and MEG analyses is consistently found to be abnormal in SZ patients in comparison to healthy individuals (Gonzalez-Burgos and Lewis, 2008; Jadi et al., 2015; Uhlhaas and Singer, 2010).

Kwon et al. (1999) studied GBO changes in SZ and healthy control subjects (15 pairs). The results showed a decrease in EEG synchronization power during 40 Hz of auditory stimulation in the SZ group, based on a significant group effect ($F_{1,28}, 5.29; p = 0.03$) for power as calculated by ANOVA, indicating a reduced power of GBO. Cho et al. (2006) measured induced GBO activity in the prefrontal cortices of SZ subjects and healthy control subjects using a cognitive control task. The EEG results showed that higher GBO activity was achieved for higher cognitive control levels in the healthy control subjects, however, such modulation of the GBO activity was absent in SZ subjects.

Ford et al. (2008) tested the phase synchronization of GBO prior to a motor act, using in EEG analysis. The study found that GBO neural synchrony significantly correlated with the event-related potential amplitude evoked by the motor act, but was also decreased in the SZ group when compared to healthy participants.

Moreover, a study by Spencer et al. (2008) measured a significant decrease in the EEG analysis of visual sensory-evoked GBOs in SZ patients compared to control subjects. A later study by Spencer et al. in 2009 tested the gamma synchronization using EEG recordings in 16 healthy control subjects and 18 schizophrenic subjects based on the auditory steady-state response (ASSR). The results have also shown reduced gamma synchronization activity in SZ.

Abnormalities in GBO are found to be directly dependent on the synaptic inhibition of GABAergic interneurons (Buzsáki and Wang, 2012). Hashimoto et al. (2008b) claimed that cortical oscillation abnormalities in SZ are attributed to impaired GABAergic neurotransmission that is partially specific to SST + interneurons. NMDAR hypofunction in these GABAergic interneurons is associated with the cortical network oscillations changes as demonstrated by NMDAR antagonists effects in recapitulating SZ symptoms, and in modulating brain oscillations (Kantrowitz and Javitt, 2010).

Leishman et al. (2015) found similar results to Spencer et al. (2009) through testing the ASSR in rats with the use of the NMDAR antagonist, phencyclidine (PCP) at different frequencies of stimulation. The ASSR was indeed found to be reduced at frequencies of stimulation over 40 Hz.

Furthermore, Kittelberger et al. (2012) examined the effects of the NMDAR antagonist ketamine on the oscillatory activity in the hippocampus of rats, and found that chronic administration of ketamine gradually decreased the power GBOs.

McNally et al. (2011) tested the GBO changes in the prefrontal cortex of mice through EEG and immunocytochemistry analysis. The results showed that the oscillatory frequency of GBO was decreased with acute ketamine administration. The effects of chronic administration of ketamine were also studied by McNally et al. (2013), showing that ketamine altered neocortical oscillations in the prefrontal cortices of mice. The frequency of oscillations decreased from 47 Hz to 40 Hz ($p < 0.01$) after chronic ketamine administration when compared to normal saline solution. The power of GBO at 40–50 Hz was also reduced by ketamine. The presented results mean that gamma frequency alterations could indeed be attributed to the NMDAR hypofunction.

4. Conclusions

SST + interneurons and NMDARs are undoubtedly associated with the pathology of SZ. This has been investigated by reviewing SST level changes in postmortem studies in which it was shown to be decreased significantly in schizophrenic subjects throughout a number of areas tested in the brain including the DLPFC, OFC and the hippocampus.

NMDARs activity is reduced in SZ as shown by the effects of the NMDAR antagonists in producing SZ-like symptoms in healthy animal models. These symptoms arise from changes in the cortical oscillations found in both schizophrenic patients and healthy models treated with NMDAR antagonists, mostly in the frequency of GBO. Abnormalities in GBO are partially responsible for the cognitive deficits in SZ. The generation of GBO is also dependent on the inhibitory action of GABAergic interneurons as well as the activity of NMDARs.

The decrease in SST levels must have an effect on its receptors activity. Genetic knock-out studies showed that SSTR2 is increased in Huntington's disease (HD) to perhaps protect cells from the neurotoxicity caused by the increased NMDAR activation. Conversely, both SSTR2 and NMDAR activity are decreased in the SZ model at the same time they are both increased in HD. Thus, a direct positive correlation has been inferred in this review. Yet, this link is still to be investigated and validated and the mechanism behind is still to be discovered.

Certain studies have noted that SST expression depends on the signalling of a molecule known as the brain-derived neurotrophic factor (BDNF) (Glorioso et al., 2006; Guilloux et al., 2012; Martinowich et al., 2011). It was also shown that blocking NMDAR activity caused a decrease in neurotrophins gene expression, especially BDNF (Hansen et al., 2004), which could contribute to the link between SST and

NMDAR activity; however, the underlying molecular mechanism is still unknown (Lin and Sibille, 2013).

To realise whether the proposed link is central to the pathophysiology of SZ or a consequence of other unknown mechanisms, the effects of decreased SST levels on the cognitive symptoms of SZ must also be considered. Recent studies have focused on the cortical synaptic plasticity changes associated with SST. After associative learning, SST + interneurons were found to express more SST and GABA, which shows that the SST inhibitory network is involved in shaping cortical responses and neural activity and may thus play a role in circuit plasticity (Liguz-Leczna et al., 2016; Yavorska and Wehr, 2016). Sensory training was also found to specifically increase the density of SST + interneurons in comparison to other types of interneurons based on a study by Cybulska-Klosowicz et al. (2013). On the other hand, SST + interneurons dysfunction was found to be associated with memory deficits and cognitive function in Alzheimer's disease models in a recent study by Schmid et al. (2016). This suggests that the SST system is indeed involved in the cognitive functions and symptoms associated with SZ, perhaps through different mechanisms other than the GBO changes that require further research and analysis.

Although the scope of this review is limited, it could potentially provide future directions for further research and experiments with the hopes of finding novel therapeutic targets and effective interventions in SZ as well as other implicated neurological disorders. Many pharmacological and therapeutic challenges are involved in targeting the intricate SST system, such as the lack of high affinity SST modulators. Therefore if investigated this newly identified correlation may provide a new indirect target that can specifically and effectively be used for the treatment of SZ. A feasible investigation of this correlation can employ genetic knock-out studies of the SSTR2 gene in mice to assess the consequences this has on the NMDAR and other relevant markers of SZ.

Disinhibition of SST + interneurons through the inactivation of the $\gamma 2$ subunit gene of GABA_A receptors has shown to increase the excitability of SST + interneurons, which was recently found to have anxiolytic and antidepressant effects in major depressive disorder in mice models (Fuchs et al., 2016). This can also be possibly replicated in an antipsychotic model given the shared pathophysiology with regards to SST expression found in the two diseases. It would also be interesting to look at the NMDAR activity in this particular model to confirm the correlation identified in this review. This shows an example of how modifying gene expression can have a therapeutic impact on SZ and other disorders.

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Appendix A

Available on request from the authors.

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