Schizophrenia Bulletin vol. 47 no. 5 pp. 1385–1398, 2021
doi:10.1093/schbul/sbaa184
Advance Access publication December 28, 2020

A Role for Somatostatin-Positive Interneurons in Neuro-Oscillatory and Information Processing Deficits in Schizophrenia

Alice B. Van Derveer[1], Georgia Bastos[1,2], Antanovia D. Ferrell[1], Connor G. Gallimore[1], Michelle L. Greene[1], Jacob T. Holmes[1], Vivien Kubricka[1], Jordan M. Ross[1,3], and Jordan P. Hamm*[,1–3]

[1]Neuroscience Institute, Georgia State University, Petit Science Center, 100 Piedmont Ave, Atlanta, GA 30303; [2]Center for Neuroinflammation and Cardiometabolic Diseases, Georgia State University, Petit Science Center, 100 Piedmont Ave, Atlanta, GA 30303; [3]Center for Behavioral Neuroscience, Georgia State University, Petit Science Center, 100 Piedmont Ave, Atlanta, GA 30303

*To whom correspondence should be addressed; tel: 404-413-5398, fax: 404-413-5446; e-mail: jhamm1@gsu.edu

Alterations in neocortical GABAergic interneurons (INs) have been affiliated with neuropsychiatric diseases, including schizophrenia (SZ). Significant progress has been made linking the function of a specific subtype of GABAergic cells, parvalbumin (PV) positive INs, to altered gamma-band oscillations, which, in turn, underlie perceptual and feedforward information processing in cortical circuits. Here, we review a smaller but growing volume of literature focusing on a separate subtype of neocortical GABAergic INs, somatostatin (SST) positive INs. Despite sharing similar neurodevelopmental origins, SSTs exhibit distinct morphology and physiology from PVs. Like PVs, SSTs are altered in postmortem brain samples from multiple neocortical regions in SZ, although basic and translational research into consequences of SST dysfunction has been relatively sparse. We highlight a growing body of work in rodents, which now indicates that SSTs may also underlie specific aspects of cortical circuit function, namely low-frequency oscillations, disinhibition, and mediation of cortico-cortical feedback. SSTs may thereby support the coordination of local cortical information processing with more global spatial, temporal, and behavioral context, including predictive coding and working memory. These functions are notably deficient in some cases of SZ, as well as other neuropsychiatric disorders, emphasizing the importance of focusing on SSTs in future translational studies. Finally, we highlight the challenges that remain, including subtypes within the SST class.

Key words: GABA/cortex/theta/gamma/oscillations/parvalbumin

Introduction

Schizophrenia (SZ) is a polygenic disease with a complex and currently undetermined biological basis.[1,2] Novel genetic, molecular, and circuit-level tools developed over the past decade continue to provide transformative insight into neurobiological mechanisms, but these technologies are largely limited to animal studies. Since recapitulating a complex human disease like SZ in animal models is not possible, an emphasis on simpler disease features and "biomarkers," which may be more translatable to mouse research, represents a promising strategy.[3]

A dysregulation of gamma-band oscillations in electroencephalography (EEG) recordings is among the best replicated biomarkers of SZ.[4–7] Given current limitations of noninvasive neuroimaging, the neurobiological basis of such gamma-band dysregulation is not immediately clear from surface-level EEG alone. Postmortem brain samples from individuals diagnosed with SZ consistently identify abnormalities in neocortical GABAergic interneurons (INs).[8,9] Studies in animal models have provided myriad evidence linking parvalbumin (PV) positive INs, a subset of affected GABAergic INs in SZ, to the generation of synchronous gamma-band oscillations.[10,11] Because certain cognitive and perceptual aberrations in SZ correlate with altered gamma-band oscillations,[5] these findings together establish a translational roadmap for linking molecular to behavioral features of SZ.[12]

Given that other GABAergic INs are found to be abnormal in postmortem human brain tissue,[8,9] and animal models of neuropsychiatric risk,[13,14] it is important to understand how other subtypes contribute to pathophysiology. The current review focuses on a smaller but

growing body of work concerning the function of somatostatin (SST) positive INs in neocortex and their relationship with disease features common in neuropsychiatric diseases, including SZ. Interestingly studies investigating PV and SST messenger RNAs (mRNAs) and cell counts have identified mostly equivalent reductions in the neocortex of SZ,[8] yet PVs have received more attention in basic neurobiological investigations, perhaps due to their narrow/fast-spiking phenotype, making them easier to differentiate from excitatory pyramidal neurons (PYRs) in extracellular electrophysiology. The development of a suite of transgenic mice-expressing Cre-recombinase in genetically identified cell types,[15] together with enhanced optical techniques,[16] has opened the door for direct recording and manipulation of SSTs in awake, behaving animals. Here, we review such studies and hypothesize the potential consequences of SST dysfunction for SZ neurophysiology and information processing distinct from the PV domain: low-frequency oscillations and cortical feedback integration.

Properties of SST INs

SZ is a disease with significant cortical pathology.[8,17,18] While the principal neuron type of cortical circuits is the glutamatergic PYR, a smaller portion of neurons are inhibitory INs (15%–35%), which synapse locally and release GABA. INs densely target the local circuit and have high firing rates,[19] playing a disproportionately large role in controlling local computations and cortical circuit outputs.[20]

GABAergic INs in mammalian neocortex show remarkable diversity. Detailed classification is an area of active research and discussion.[21] Nevertheless, developmental origin and expression of calcium-binding proteins, neuropeptides, and receptors together support a widely accepted primary segregation into 3 major nonoverlapping IN subtypes: PVs, SSTs, and 5HT3a-positive Ins.[22,23] The morphology and electrophysiology of these cell types, their distribution across cortical laminae, connectivity profiles, and patterns of neurochemical innervation further confirm this categorization,[24,25] forming the basis for their differential roles in circuit motifs (feedforward inhibition, disynaptic inhibition, or disinhibition; figure 1), brain oscillations (gamma and theta), and computation (eg, orientation selectivity).[26] While this review focuses on SSTs, the reader is referred to available reviews on other subtypes.[22,23]

The distinctive features of SSTs are well defined in cortical circuits. SSTs release GABA synaptically and target apical dendrites of PYRs and other INs (but rarely other

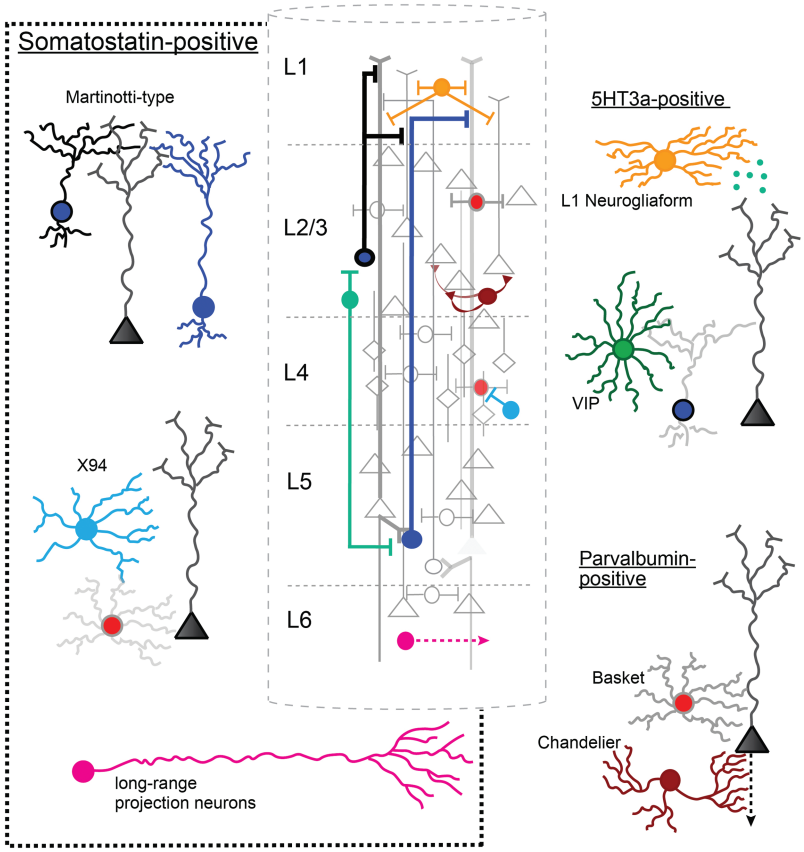

Fig. 1. Three major neocortical interneuron categories. Interneuron groups are depicted, with subtypes and their laminar (middle) and major postsynaptic cellular (eg, pyramidal neurons) and subcellular (eg, dendrites) targets are graphically depicted (left and right).

SSTs), directly modulating excitatory inputs through $GABA_A$ and $GABA_B$ receptor-mediated inhibition.[25,27,28] SSTs exhibit more moderate intrinsic firing rates (6–8 Hz) than fast-spiking PVs,[29–31] correlating with local field potential (LFP) oscillatory power in theta/alpha (4–14 Hz; figure 2) and visually induced oscillations in the beta (15–30 Hz) range (figure 3).[30,32,33] Neurotransmission through slower $GABA_B$ receptors[34] produces slow inhibitory responses that are well suited to regulate lower-frequency oscillations, including the theta band.[32,33] Such oscillations may support temporally longer integration windows, a known feature of inputs in distal dendrites,[27] where SSTs synapse, altogether facilitating long-range coherence in distributed brain networks.[35] Compared to PVs, SSTs receive less feedforward excitatory drive from thalamus or layer 4 (L4), and more local and feedback/top-down inputs.[36]

Another key property of SSTs that may relate to this role in broader spatiotemporal coherence and integration is facilitating synapses. Whereas PYRs and PVs show rapidly depressing postsynaptic responses to repeated inputs,[36] SSTs show enhanced responses,[19,37] potentially gating in top-down feedback.[19] SSTs are largely considered "regular spiking," sharing electrophysiological features with PYRs (though some exhibit low-threshold-spiking, fast-spiking, or stuttering subtypes). SSTs play a significant role in gating plasticity of local circuits in both motor and sensory areas,[38] which may be mediated by cholinergic mechanisms.[39] SST inhibition is strongly modulated by cholinergic,[40,41] and feedback inputs, suggesting a role of SSTs for contextual, attentional, and cognitive modulation of fine-scale circuit computations.

Together, SSTs help regulate neural activity within and across different cortical laminae, through both inhibition and disinhibition, in accord with feedback and lateral inputs. The spatial and temporal properties of their innervation may optimally enable SSTs to serve as modulators of long-range cortical integration, tolerating longer conduction delays from distributed neural ensembles.[42,43]

As a class of neurons, SSTs also show discontinuous heterogeneity in numerous properties, indicating SST subclasses serving differential inhibitory roles within cortical circuits (figure 1). SSTs are divisible into at least 2 subcategories based on morphology and targeting: Martinotti cells (figure 2) and non-Martinotti cells (figure 3).[44] Martinotti cells constitute the majority of SSTs, and their somata reside mainly in layer 2/3 and layer 5a/b (L2/3; L5) and can arborize both locally and in L1.[45] Martinotti cells generally connect to other INs, such as PVs and vasoactive intestinal peptide (VIP) cells (a 5HT3a subtype that mutually inhibits SSTs), as well as densely targeting PYR apical dendrites in L1[46,47] but never other Martinotti

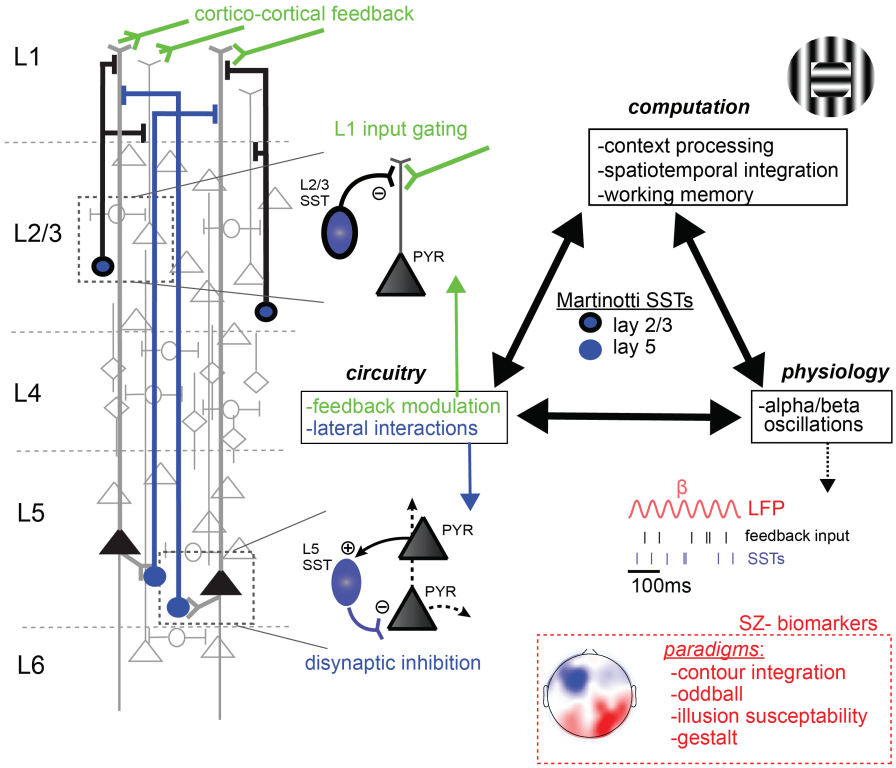

Fig. 2. Martinotti-type somatostatin-positive (SST) interneurons in cortical circuits. *Left:* Cortical-column schematic depicting known roles of SSTs in dendritic inhibition and integration of top-down feedback (top) and disynaptic inhibition between pyramidal neurons (PYRs; triangles). *Top-right:* Hypothetical computational, circuit, and physiological signatures of layers 2/3 and 5 Martinotti SSTs. A theoretical set neuron-type raster plots and local field potential (LFP) recording is drawn from the hypotheses of this paper. *Bottom-right:* Noninvasive biomarkers hypothetically related to Martinotti SST motifs.

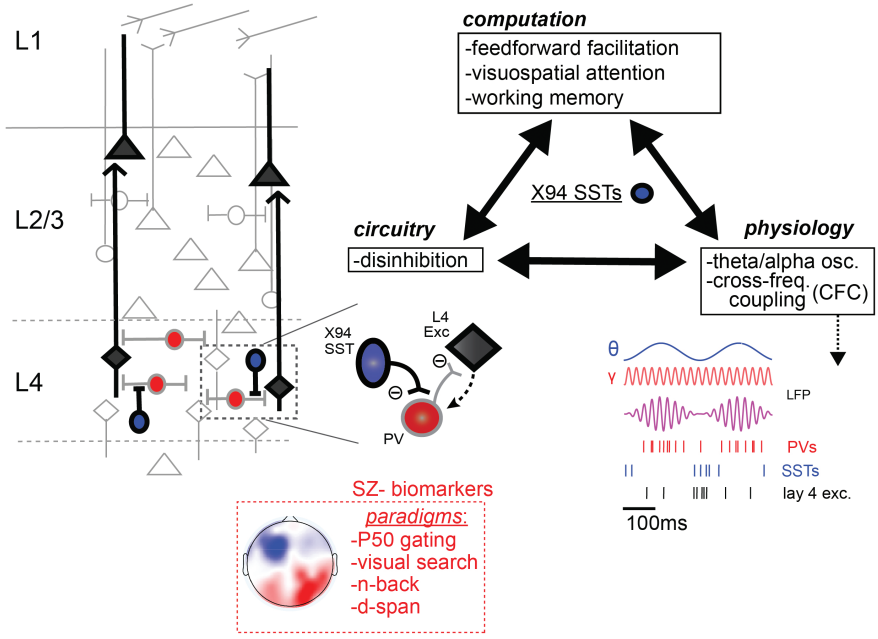

Fig. 3. Layer 4 X94 somatostatin-positive (SST) interneurons in cortical circuits. *Left:* Cortical-column schematic depicting known roles of SSTs (ovals) in inhibiting parvalbumin-positive (PV) interneurons (circles) to effectively disinhibit feedforward inputs of layer 4 excitatory cells (diamonds) to layer 2/3 pyramidal neurons (triangles). *Top-right:* Hypothetical computational, circuit, and physiological signatures of layer 4 X94-SSTs. A theoretical set neuron-type raster plots and local field potential recording is drawn from the hypotheses of this paper. *Bottom-right:* Noninvasive biomarkers hypothetically related to X94 SST-motifs.

cells. Martinotti neurons in L5 also subserve disynapatic inhibition, wherein neighboring L5 PYRs effectively inhibit each other by recruiting nearby SSTs.[48]

In contrast, non-Martinotti cells in L4 target L4 PVs preferentially (figure 1), effectively disinhibiting excitatory neurons and local responses to thalamic inputs and tend to be fast-spiking (like PVs).[46,49] L4 non-Martinotti SSTs may play a functionally distinct, disinhibitory role compared to L2/3 SSTs. It has been shown that L5 non-Martinotti cells target L4 excitatory neurons to provide translaminar inhibitory feedback.[50] An additional non-Martinotti cell primarily present in L6 (~7% of SSTs overall) also disinhibits local PYRs by suppressing PVs,[39] sends long-distance cortically and subcortically, and expresses a nicotinic receptor modulator LYPD6,[51] which may selectively gate cortical plasticity.[39]

Although studying these subtypes separately is important, most recent basic and clinical research into SSTs have not differentiated. GIN and X94 mouse lines fluorescently label Martinotti and L4 non-Martinotti SST subtypes, respectively,[52] and have supported the notion of different morphologies and functional roles. The development of mice-expressing Cre-recombinase restricted to SST-expressing neurons made testing the causal roles of SSTs in cortical circuits in vivo more tractable (eg, with optogenetic manipulation and Cre-dependent viral expression). However useful, this Sst-IRES-Cre line[53] effectively labels all SSTs irrespective of subtype, leaving important questions regarding the functional roles of SSTs. Unless otherwise stated, the majority of the findings reviewed herein combine SST subtypes (though may likely reflect L2/3 or L5 Martinotti cells, given that they are the most numerous).[36] Future work is needed to study SST subtypes in isolation.[50,54]

By definition, SSTs express the neuropeptide SST, but the functional role of SST released by SSTs is less studied in cortical circuits than the faster, synaptic release of GABA from SSTs.[24,29] Most research on SSTs in rodent or human cortex refers to SST as a marker for a GABAergic IN subtype rather than a functionally relevant neuropeptide.[36] The peptide SST has a net inhibitory effect on local circuits, like GABA, activating 5 distinct G-coupled protein receptors[55] and is released under overlapping yet slightly different conditions (eg, long-duration high-frequency stimulation)[56] from different compartments of the cell (dendrites). SST peptides may serve a role in inhibiting pathological overactivity, eg, as observed in an epileptic seizure.[36] More research is needed to understand the functional conditions and effects of SST release, as well as how it may compliment or diverge from SST-neuron synaptic GABA release with regards to circuit roles and disease relevance. The current review focuses on SST as a distinguishing marker[24] rather than a functionally informative molecule (for more, see reference [57]).

SST INs and Postmortem Brain Studies of SZ

Although it is not currently possible to directly and noninvasively assess SST function in humans, multiple lines of evidence from postmortem brain samples

suggest that SSTs are affected in people with SZ (table 1; see Supplementary Material). A reliable reduction in the number of SSTs and PVs, as well as the levels of SST and PV mRNAs have been reported in the prefrontal cortex (PFC)[24] and hippocampus[58] in brains from people with SZ. SST abnormalities in SZ span across all layers except the superficial L1 and deep L6,[59] where few SSTs reside. It is unlikely that SST IN aberrations are due to antipsychotic medications,[60] suggesting a relationship to disease pathophysiology. Still, whether SSTs are affected differently in throughout the course of SZ and whether SSTs are affected in relatives of patients with SZ and, thus, the relationship of SST IN aberrations to underlying etiology in SZ remain unclear.

Although SZ is traditionally associated with PFC pathology, observations of SST markers in other neocortical regions reveal similar aberrations. Reductions of SST and PV mRNA are present in sensory and motor cortices,[8] as well as caudal entorhinal cortex.[65] While SST and PV IN abnormalities are often identified in the same studies,[8] PV and SST mRNA expression are inversely correlated across brain regions.[69] There is even evidence that SST mRNA reductions are more dramatic than PV-related abnormalities in the PFC.[8,22] Although the third major

Table 1. SST-related biomarkers in human cortical tissue

Authors	SST-related marker	Disorder(s) examined	Direction of SST effect	Brain region(s) examined	Markers of other INs (effect in SZ)
Roberts et al (1983)[66]	SST peptide	SZ	Decreased	Hippocampus, amygdala, and temporal cortex	CCK (decreased), VIP (unaffected)
Nemeroff et al (1983)[67]	SST peptide	SZ and Huntington's chorea	Decreased in SZ and increased in Huntington's chorea	Caudate, nucleus accumbens, amygdala, hypothalamus, and Brodmann areas 12, 24, and 32	None
Gabriel et al[61]	SST peptide levels	SZ and Alzheimer's disease	Decreased in SZ and AD	Frontal, temporal, and occipital cortices	CCK and NPY (reduced). VIP (no effect)
Nakatani et al (2006)[68]	mRNA	SZ and bipolar I disorder	No effect (n = 7)	DLPFC	None
Hashimoto et al (2008)[60]	mRNA	SZ	Decreased	DLPFC	Neuropeptide Y (decreased)
Hashimoto et al (2008)[8]	mRNA	SZ	Decreased	DLPFC, anterior cingulate cortex, primary motor cortex, and primary visual cortex	PV (decreased). calretinin (no effect)
Morris et al[59]	mRNA	SZ and SZA	Decreased in SZ and SZA	DLPFC	None
Mellios et al[62]	mRNA	SZ	Decreased (trend, P = .086)	PFC (frontal pole)	NPY and PV (decreased)
Fung et al[21]	mRNA	SZ	Decreased	DLPFC	PV, calretinin, CCK, VIP, and NPY (decreased). Calbindin (increased)
Konradi et al[58]	mRNA; SST-positive cells	SZ	Decreased	Hippocampus	PV (decreased)
Wang et al[63]	SST-positive cells	SZ, bipolar I disorder	Decreased in entorhinal cortex; no effect in subiculum	Entorhinal cortex, subiculum	PV (no effect in subiculum and decreased in entorhinal cortex). Calbindin (no effect)
Volk et al[9]	mRNA	SZ	Decreased	PFC	PV (decreased) and calretinin (increased)
Fung et al[22]	mRNA	SZ, BP1	Decreased in SZ and BP1	DLPFC, orbitofrontal cortex	PV and calretinin (no effect), VIP (decreased), and calbindin (increased in SZ only)
Volk et al[24]	mRNA	SZ, BP1, SZA	Decreased in SZ, BP1, and SZA	DLPFC	PV (decreased)
Tsubomoto et al[64]	mRNA	SZ	Decreased in all areas	DLPFC, PPC, V1, and V2	PV (decreased) and VIP (decreased only in V1)

Note: BP1: Bipolar I disorder; CCK: cholescystokinin; DLPFC: dorsolateral-prefrontal cortex; PPC, posterior parietal cortex; V1/V2, primary/secondary visual cortex; IN, interneuron; mRNA, messenger RNA; PFC, prefrontal cortex; PV, parvalbumin; SST, somatostatin; SZ, schizophrenia; SZA, schizoaffective disorder; VIP, vasoactive intestinal peptide.

IN subtype, 5HT3a-containing, has not been studied in SZ *en masse*, VIP INs appear less affected than SST or PVs.[22,61,64] Other markers of INs such as calbindin (CB), caretinin (CR), and neuropeptide Y (NPY) mRNA have been shown to be altered in SZ as well.[8,9,22,60,63,65] These effects are less consistent and not well correlated with SST effects (table 1). As there is significant overlap and heterogeneity in CR, CB, and NPY expression among the 3 cortical IN subtypes,[42] their reductions could be imperfect proxies for SST-neuron deficits.

Postmortem studies indirectly suggest SST dysfunction in the cortices of patients. Cell-wise expression of SST mRNA is activity dependent,[25,70] so links between SST function and SZ-related biomarkers (identified in animal studies) may be valuable for clarifying the core disease pathophysiology/ies. The nature of SST pathology in SZ remains unclear given difficulties in distinguishing between missing SSTs and SSTs with undetectable levels of SST mRNA. mRNA reductions are the most consistent, but a failure of SSTs to migrate to cortex has been evinced as well.[71] While the cause of SST dysfunction in SZ is currently unclear, SSTs and PVs share a developmental origin distinct from other cortical INs. Abnormal expression of Lhx6 (a key transcription factor expressed during this period in PVs and SSTs) suggest altered prenatal migration in SZ.[9] This could implicate a role of the established risk posed by maternal infection occurring contemporaneously.[71,72] Furthermore, microRNA-195 dysregulation, leading to reduced Brain Derived Neurtrophic Factor (BDNF), has been proposed.[62]

Although reductions in SST markers are consistent across studies, cluster analysis suggests dorsolateral PFC aberrations in SST mRNA are only present in a subset of patients.[9] Interestingly, a separate study found that low-frequency oscillations and cognitive deficits are also mostly present only in a subset of psychosis patients: ie, a psychosis "biotype."[73] Future work in larger patient samples, correlating behavior, and neurophysiology is critical to test whether these patient clusters overlap, suggesting that SST IN function could be a biotype-specific abnormality.

Brain Oscillations and the Time-Frequency Subspace of Cortical Circuits

EEG recordings demonstrate that the brain exhibits ongoing "waves" or oscillations spanning slow (delta/theta [1–7 Hz]), moderate (alpha/beta [8–24 Hz]), and fast (gamma [25–100 Hz]) frequency bands. At the local level, oscillations temporally group spikes from populations of individual neurons to modulate network synchrony in fast (<25 ms) and slow (1 s) time packets, temporally filtering inputs, segregating neuronal ensembles, and modulating synaptic plasticity.[74] Broadly, oscillations can be viewed as an organizational principle of the brain that routes distinct streams of information processing, supporting and/or reflecting dynamic synchrony among proximal and distal circuitries. The frequency of an oscillation within a given ensemble or circuit often scales with the distance between the cells involved due in part to aggregate conduction delays[75]; slower oscillations (delta and alpha) involve distributed networks, whereas higher-frequency oscillations (gamma) reflect local synchrony. Furthermore, feedback in hierarchically organized cortico-cortical circuits, typically originating in infragranular layers and synapsing in L1, is reflected in alpha- or beta-band oscillations, whereas feedforward information propagation, typically originating in supragranular layers and terminating in granular L4, is reflected in gamma-band oscillations.[76,77] Thus, separate, simultaneously present oscillatory activity reflects, and perhaps supports, the integration of information from distinct channels in the brain dedicated to certain processes.

Brain oscillations are an emergent phenomenon of neural networks, arising from the confluence of mechanisms across multiple scales, including intrinsic properties of individual receptors and membranes, ephaptic coupling, cell morphology, and circuit interactions.[75,78] They may arise due to a single pacemaker cell or ensemble or due to distributed intrinsic properties in multiple interconnected ensembles.[78] In cortical circuits, inhibitory INs play a significant role in generating oscillations due to their dense local innervation and fast tonic firing.[71]

Oscillations are just one aspect of the complex spatiotemporal activity in a neural circuit. A thorough study of pathological neural systems may require the consideration of space, time, and frequency domains together, relating circuit firing to ongoing rhythms that gate and organize information flow.[5] Regardless of whether the status of network rhythms or responses in the time-frequency subspace is directly informative regarding underlying circuit properties, studying cortical oscillations may serve as a translational bridge, as oscillatory signals could be used to relate noninvasive human EEG recordings to intracortical investigations in animal models.[79]

High- vs Low-Frequency EEG Oscillations and SZ

Within the taxon of SZ, irregularities across multiple frequency bands have been reported with scalp-level neurophysiology (EEG and magnetoencephalography [MEG]).[5,33,80,81] SZ effects in a particular frequency band depend on the signal of interest (resting, stimulus induced, and phase locked), paradigm (attended or passive), and brain region of interest (sensory vs motor). Variability in particular time-frequency measures is common across studies, which may be attributable to paradigmatic variables (eg, stimulus characteristics and attention),[82] data analysis,[83] and medication status,[84] for example.

Even when these variables are held constant, deviations in particular frequency bands do not present uniformly across patients. For instance, augmented background

gamma activity during passive sensory stimulation has been reported in some[83,85] but not all studies in SZ.[82] A study of a large, multidiagnostic sample demonstrated that increased baseline or nonspecific gamma-band power in the EEG may be characteristic of one-third of people with psychotic disorders, suggestive of a cortically hyperactive "biotype."[73] Increased resting activity (eg, 5 min of recording with eyes open or closed with no explicit stimulation or task) in delta–theta ranges and decreased power in alpha ranges in SZ is consistently reported, while aberrations in the gamma range are a less consistent finding for resting-state studies.[81,86,87] Furthermore, decreased passive stimulus-evoked responses in the delta–theta bandwidth show larger effect sizes and greater reliability than stimulus-induced gamma-band responses.[4,88] Abnormalities in stimulus-evoked and resting low-frequency activity may also be characteristic of a subset of psychosis patients, indicating a different biotype than augmented gamma biotype (above). These low-frequency responses show significant heritability in psychosis families[89] and associations with psychosis-relevant risk genes.[86]

Alternatively, evidence suggests a primacy of deficits in low-frequency oscillating circuits in SZ cortical pathology. Even with the same paradigms, inconsistent findings differ between augmented,[85,90–95] and attenuated,[5,96,97] gamma-band activity in SZ. Again, this may be due to gamma abnormalities that are present in only a subset of psychosis patients,[73] though, within this subset, a general dysregulation of gamma-band dynamics may best explain such findings.[81] In cortical systems, separate frequency bands interact, as the phase of low-frequency oscillation is known to group gamma-range activity (eg, amplitude modulation),[98] termed "cross-frequency coupling" (CFC; figure 2). For instance, in direct human neocortical recordings, gamma power (80 Hz) is modulated in time with theta phase such that higher gamma amplitude occurs during theta peaks vs troughs.[99] This CFC relationship correlates directly with working memory processes, suggesting theta–gamma coupling reflects how local neuronal ensembles are bound with global information processing. Furthermore, alpha frequency oscillations bind together appropriately timed high-frequency oscillations, like gamma, for accurate perception of stimuli.[78]

Altogether, differences in heritability, genetic associations, patterns, and reliabilities of effects in passive or resting contexts suggest that EEG signals in low vs high oscillatory bands, if both equally present, are at least differentially related to underlying neuropathology. These trends are reviewed at length elsewhere.[81] An important caveat is that patterns of oscillatory aberrations may change across the course of an illness and medication status, especially with regards to high-frequency abnormalities.[100] Still, identifying these bands as potentially separate neural biomarkers represents an important inroad for neuropsychiatric studies as a better mechanistic understanding of these distinct signals could help refine diagnoses and treatment approaches.[101]

A Role of SST INs in Low-Frequency Oscillations

A growing body of literature has implicated INs in the generation of oscillations in neural circuits brain-wide.[33,102] Aberrations in EEG signals in a given frequency band measured at the scalp could represent a number of distinct underlying circuit mechanisms and cortical activities.[33] That is, eg, 40-Hz gamma-band stimulus-induced power (from a given electrode or scalp distribution) likely does not arise from the same or even overlapping neural circuits as baseline 40-Hz power, even though both can be referred to as "gamma." In this sense, identifying the mechanisms of a given oscillatory band in EEG may be overdetermined. On the other hand, logically proceeding in the forward direction, a given circuit motif may exhibit a relatively stable oscillatory signature.[33] For instance, PVs in sensory cortex provide feedforward inhibition, which synchronizes local ensembles and enhances responses to sensory inputs in a 40-Hz rhythm,[103] while alteration of excitatory inputs to these cells dysregulates the background gamma-band power.[104] In general, the fast-spiking PV IN subtype is responsible for generating and influencing gamma-band activity,[8,10,26,32,105,106] which facilitates fast local processing and feedforward information flow.[77] Multiple reviews have been written on the idea that PV IN deficits in SZ lead to the myriad of gamma-range EEG biomarkers.[106,107] Although no direct evidence exists evincing disrupted PV IN activity in SZ patients, the pattern of gamma-band abnormalities across a number of SZ studies, in the context of known brain-wide PV mRNA aberrations, supports this hypothesis.

Although less studied than the link between PVs and gamma, evidence suggests that SSTs may play a significant role in low-frequency oscillations and, by extension, related deficits in SZ. SSTs are affected in SZ postmortem brain samples and show lower intrinsic firing rates (in the 7-Hz range).[31] Some direct links have been identified between SSTs and lower-frequency bandwidths in cortical circuits.[102] In visual cortex, rhythmic optogenetic stimulation of SSTs during LFP recordings suggests an intrinsic resonance in the 5–30-Hz range (theta to beta), while the suppression of SSTs directly disrupts visually induced beta (20 Hz; figure 2).[32] As expected, the same manipulations of PVs affected gamma-range oscillations (30–80 Hz).

The distinct physiology and anatomy of SST circuitry suggests a role in slower neuronal processing and/or oscillations. SSTs and PVs may serve different roles in regulating information integration across the somatodendritic axis. For instance, Martinotti SSTs synapse on distal, apical dendrites of PYRs (figures 1 and 2), where time windows of synaptic integration are longer than in proximal dendritic compartments.[27]

In contrast, PV inhibition targets dendritic and somatic regions proximal to the axon hillock and thus may be better positioned for modulation in shorter integration windows (gamma oscillations).[10] At the synaptic level, SSTs also show facilitating presynaptic inputs and less adaptation of postsynaptic outputs to PYRs.[19,102] In contrast, PVs exhibit rapid adaptation in their inhibition of PYRs, a dynamic that matches the transient gamma response better. The dynamics of low-frequency oscillations to sensory innervation in cortical circuits, both beta and alpha, match the slower activity of SSTs.[89,108]

Finally, non-Martinotti SSTs in L4 directly inhibit and modulate PV activity. It remains an intriguing but untested hypothesis whether this SST subcircuit could support theta–gamma CFC (figure 3). EEG and MEG studies in SZ suggest that, although theta and gamma oscillations are both affected, albeit differently, theta–gamma CFC remains intact.[109]

SST-Positive INs and Broad-Scale Spatiotemporal Integration

Here, we posit low-frequency oscillatory activity in cortical circuits indexes the integration of local information processing with broader spatial or temporal context as mediated and modulated by local SSTs. Cortico-cortical feedback inputs, which integrate local processing with higher-level sensory processing and behavioral goals, tend to synapse in supragranular layers of cortex,[110] wherein L2/3 SSTs are well positioned to influence local integration of such inputs.[111] In contrast, PVs are most prevalent in L4, suggesting a greater role in feedforward cortical processing. Beta- and alpha-range oscillations, which may be more of the domain of SSTs, correlate strongly with cortico-cortical feedback, while gamma-band oscillations, which are linked to PVs, correlate with feedforward processing,[76] further emphasizing that the difference in oscillatory bandwidths of SST and PV circuits may relate to their difference in information processing.

What direct evidence exists supporting this tripartite relationship, involving SSTs, low-frequency activity, and broad spatiotemporal integration and top-down feedback in cortical circuits? Studies relating cortical INs to both local computations and oscillations are somewhat sparse. In sensory cortices, SSTs respond to different physical stimulus features than other INs. In contrast to PVs, SSTs in primary visual cortex (V1) exhibit size tuning (figure 2, top), in that they are most responsive to visual stimuli, which occupy more retinotopic space. In this manner, SSTs support "surround suppression" of PYRs by integrating excitatory input from intralaminar horizontal axons.[112] A similar finding was reported in auditory cortex with regard to "spectral" space.[113] Although LFP oscillatory activity was not recorded in these studies, V1 SSTs have been shown to display intrinsic entrainment to stimulation in the 5–30-Hz range (theta to beta).[32]

SSTs may also support the integration of sensory processing with broader (>2 s) temporal context as well.[114] The variability and nature of cortical responses to sensory stimuli have been described in a "predictive coding" framework, wherein cortical regions higher in an information processing hierarchy build a generative model of the environment based on experience. Model predictions are projected downward (eg, to sensory cortex) to both reduce responses to predictable external stimuli and generate "prediction error" responses to stimuli not predicted.[76,115] Sensory "oddball" paradigms have been employed to study these phenomena in humans and animals.[114] Here, a series of the same stimulus (ie, "redundant") is rapidly presented (0.5–2 Hz) to attenuate cortical responses to the stimulus (so-called "stimulus specific adaptation," SSA). A different stimulus is then rarely interspersed (ie, "deviant") to generate a cortical response that is above normative response levels to that stimulus (ie, deviance detection, DD), suggestive of a cortical prediction error. DD is strongly correlated with theta-band oscillatory responses in both humans and mice.[79,116] One study found that chemicogenetic silencing of SSTs in the visual cortex reduced DD, but not SSA, in PYRs. Similar findings in auditory cortex suggest a different or absent role of PVs when compared to SSTs.[117,118] Suppressing SSTs selectively altered deviance-related theta–beta activity while leaving gamma-band activity intact.[30] Future work is needed to determine what role SST subtypes play in predictive coding, with a particular focus on the frequency-domain signature of these subcircuits.

Beyond sensory cortex, higher cortical SSTs are involved in the complex integrative process of working memory, which requires a distributed network to integrate information processing while maintaining behavioral goals (figures 2 and 3). Temporal coordination between the ventral hippocampus and PFC is critical,[119] and the functional coupling between the 2 regions is strongest in the theta band (3–8 Hz in humans and 4–10 Hz in rodents).[28,120,121] The strength of this theta-band coupling directly correlates to spatial and contextual memory performance.[120,122–124] Abbas et al[28] determined that SSTs and low-frequency oscillatory dynamics play a crucial role in modulating hippocampal-prefrontal synchrony. Optogenetic inhibition of medial prefrontal cortex (mPFC) SSTs, but not PVs, during the encoding phase of a task impaired working memory performance due to decreased hippocampal-mPFC synchrony in the theta band. Additionally, SSTs can shape temporal dynamics of mPFC ensembles and contribute to the maintenance of working memory when an animal is in the "delay" portion of a working memory task.[125] Together, these studies suggest that SSTs play an integral part in working memory through the low-frequency synchronization of neural communication across distal brain regions.

Low-Frequency Oscillations Mark Information Integration and Context-Processing Deficits in SZ

Although SZ involves global deficits in many forms of information processing, some of the most consistent findings in SZ have come from EEG studies, which highlight intrinsic dysregulation of low-frequency oscillations in contexts where sensory and behavior information must be integrated across space and time.

Long-range neural synchrony is globally impaired in SZ.[126] Specifically, dysfunction between the medial temporal lobe (mTL) and PFC is implicated in SZ[127,128] and demonstrated behaviorally through impairments during spatial memory tasks in individuals with SZ.[129–132] This is consistent with previous findings that SZ involves reductions in evoked theta/alpha and beta oscillatory activity during the encoding phase of working memory tasks (figures 2 and 3).[133] Additionally, mPFC–mTL (primarily left anterior mTL) dysconnectivity is attributed to theta band (1–8 Hz) decreases, and loss of phase coupling has been observed during memory retrieval in individuals with SZ.[120]

Individuals with SZ show consistent deficits in spatial context processing (figure 2).[134] Integration of visual motion,[135] and contour information,[136] across space are uniquely aberrant in the disease, while simpler components of neural processing are spared. Regarding temporal context, studies using sensory oddball sequences have identified reduced mismatch negativity (MMN) and P300 EEG potentials in SZ (indices of DD), which together constitute two of the most consistent physiological markers of SZ to date.[137,138] In healthy human subjects and mice, the MMN co-occurs with oscillatory activity in the theta range, and both MMN and theta depend on cortical SSTs.[33] In SZ, MMN deficits correlate to theta reductions.[116,139–141]

These context processing deficits in sensory processing have been interpreted in a predictive coding framework,[115,142] wherein individuals with SZ show aberrant integration of top-down (feedback) predictive information with bottom-up (feedforward) sensory information in basic sensory cortices. This leads to perceptual sequalae and delusions.[115,142] Altogether, a disruption of SSTs may disrupt cortical feedback integration of broad contextual information, manifesting in altered low-frequency oscillations and the high-level perceptual and cognitive deficits fundamental to SZ.[143]

Conclusion

Here, we review what is known regarding the GABAergic cortical IN class containing SST, as well as various potential subtypes therein. Postmortem studies demonstrate that SSTs are altered in the cerebral cortex in SZ. We draw links between known aberrations in SSTs in SZ and the distinct patterns of low-frequency oscillatory aberrations and complex information integration seen in the disease. We hypothesize that deficiencies in SSTs in the cortex, potentially specific to L2/3 or L5 Martinotti-type SSTs, disrupt the alpha/beta oscillations that facilitate long-range communication, as well as information integration processes, such as the integration of local processing with temporal context and behavioral goals (ie, working memory; figure 2). Furthermore, we hypothesize that SSTs in L4 (X94 subtypes) may play a key role in modulating PV gamma-band activity in the theta range, supporting the generation of CFC known to underlie working memory and to be disrupted in SZ EEG studies, as well as disinhibiting feedforward information flow, eg, in accord with attentional demands (figure 3). Though tools to directly test this association in humans are lacking, evidence of decreased SSTs,[8,9,22,24,25,58,63,65,70,144–146] disrupted theta/alpha oscillations,[4,5,33,78,80,81,88,116,120,139–141,147–150] and slow-time course information processing, as well as working memory deficits,[81,89,120,126,129–133,151] have all been observed in individuals with SZ, and the connection between these phenomena has also been observed in animal models. Thus, we propose tripartite models,[33] which link specific cell-, systems-, and cognitive-level pathology in SZ (figures 2 and 3). Future work should investigate whether in vivo measurements of SST (eg, via cortical spectroscopy) correlates with oscillatory biomarkers (eg, theta band sensory responses; MMN) and distinct cognitive deficits (eg, working memory or visuospatial integration).

The aforementioned hypotheses leave some questions unanswered. Firstly, IN subtypes are not evenly distributed across the cortical laminae[152] and include SST subclasses, which may play distinct roles in controlling circuit dynamics.[54] However, layer-specific aberrations in SZ have not been currently explored in postmortem studies. Additionally, the distinct roles of each IN subtype and their interconnections across cortical layers in coordinating theta vs beta oscillations remain untested, as well as how these electrophysiological signals relate to working memory and context-dependent information processing in both mice and SZ patients.

Overall, the hypothetical framework presented serves to highlight a promising link between basic and clinical findings, suggesting important follow-up work required to better understand this link. Characterizing the distinct neurochemical channels for which circuits selectively engage or inhibit SSTs may lead to the development of precision treatments for related cognitive deficits in SZ.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

Funding

This work was supported by the National Institutes of Mental Health (F32MH125445 to J.M.R.; R00MH115082 to J.P.H.) and the Whitehall Foundation (2019-05-44 to J.P.H.).

References

1. Boyle EA, Li YI, Pritchard JK. An expanded view of complex traits: from polygenic to omnigenic. *Cell.* 2017;169(7):1177–1186.
2. Gogos JA, Crabtree G, Diamantopoulou A. The abiding relevance of mouse models of rare mutations to psychiatric neuroscience and therapeutics. *Schizophr Res.* 2020;217:37–51.
3. Kozak MJ, Cuthbert BN. The NIMH research domain criteria initiative: background, issues, and pragmatics. *Psychophysiology.* 2016;53(3):286–297.
4. Hamm JP, Gilmore CS, Picchetti NA, Sponheim SR, Clementz BA. Abnormalities of neuronal oscillations and temporal integration to low- and high-frequency auditory stimulation in schizophrenia. *Biol Psychiatry.* 2011;69(10):989–996.
5. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci.* 2010;11(2):100–113.
6. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci USA.* 2006;103(52):19878–19883.
7. Tan H-RM, Lana L, Uhlhaas PJ. High-frequency neural oscillations and visual processing deficits in schizophrenia. *Front Psychol.* 2013;4:621.
8. Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry.* 2008;165(4):479–489.
9. Volk DW, Matsubara T, Li S, et al. Deficits in transcriptional regulators of cortical parvalbumin neurons in schizophrenia. *Am J Psychiatry.* 2012;169(10):1082–1091.
10. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature.* 2009;459(7247):698–702.
11. Kim T, Thankachan S, McKenna JT, et al. Cortically projecting basal forebrain parvalbumin neurons regulate cortical gamma band oscillations. *Proc Natl Acad Sci USA.* 2015;112(11):3535–3540.
12. Lewis DA. Inhibitory neurons in human cortical circuits: substrate for cognitive dysfunction in schizophrenia. *Curr Opin Neurobiol.* 2014;26:22–26.
13. Nakamura JP, Schroeder A, Hudson M, et al. The maternal immune activation model uncovers a role for the Arx gene in GABAergic dysfunction in schizophrenia. *Brain Behav Immun.* 2019;81:161–171.
14. Duchatel RJ, Harms LR, Meehan CL, et al. Reduced cortical somatostatin gene expression in a rat model of maternal immune activation. *Psychiatry Res.* 2019;282:112621.
15. Daigle TL, Madisen L, Hage TA, et al. A suite of transgenic driver and reporter mouse lines with enhanced brain-cell-type targeting and functionality. *Cell.* 2018;174(2):465–480 e422.
16. DeFelipe J, López-Cruz PL, Benavides-Piccione R, et al. New insights into the classification and nomenclature of cortical GABAergic interneurons. *Nat Rev Neurosci.* 2013;14(3):202–216.
17. Curley AA, Eggan SM, Lazarus MS, Huang ZJ, Volk DW, Lewis DA. Role of glutamic acid decarboxylase 67 in regulating cortical parvalbumin and GABA membrane transporter 1 expression: implications for schizophrenia. *Neurobiol Dis.* 2013;50:179–186.
18. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry.* 2000;57(1):65–73.
19. Karnani MM, Agetsuma M, Yuste R. A blanket of inhibition: functional inferences from dense inhibitory connectivity. *Curr Opin Neurobiol.* 2014;26:96–102.
20. Zhou S, Yu Y. Synaptic E-I balance underlies efficient neural coding. *Front Neurosci.* 2018;12:46.
21. Fung SJ, Webster MJ, Sivagnanasundaram S, Duncan C, Elashoff M, Weickert CS. Expression of interneuron markers in the dorsolateral prefrontal cortex of the developing human and in schizophrenia. *Am J Psychiatry.* 2010;167(12):1479–1488.
22. Fung SJ, Fillman SG, Webster MJ, Shannon Weickert C. Schizophrenia and bipolar disorder show both common and distinct changes in cortical interneuron markers. *Schizophr Res.* 2014;155(1-3):26–30.
23. Rudy B, Fishell G, Lee S, Hjerling-Leffler J. Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. *Dev Neurobiol.* 2011;71(1):45–61.
24. Volk DW, Edelson JR, Lewis DA. Altered expression of developmental regulators of parvalbumin and somatostatin neurons in the prefrontal cortex in schizophrenia. *Schizophr Res.* 2016;177(1–3):3–9.
25. Kimoto S, Zaki MM, Bazmi HH, Lewis DA. Altered markers of cortical γ-aminobutyric acid neuronal activity in schizophrenia: role of the NARP gene. *JAMA Psychiatry.* 2015;72(8):747–756.
26. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci.* 2012;35(1):57–67.
27. Branco T, Häusser M. Synaptic integration gradients in single cortical pyramidal cell dendrites. *Neuron.* 2011;69(5):885–892.
28. Abbas AI, Sundiang MJM, Henoch B, et al. Somatostatin interneurons facilitate hippocampal-prefrontal synchrony and prefrontal spatial encoding. *Neuron.* 2018;100(4):926–939 e923.
29. Gonzalez-Burgos G, Lewis DA. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. *Schizophr Bull.* 2012;38(5):950–957.
30. Hamm JP, Yuste R. Somatostatin interneurons control a key component of mismatch negativity in mouse visual cortex. *Cell Rep.* 2016;16(3):597–604.
31. Urban-Ciecko J, Barth AL. Somatostatin-expressing neurons in cortical networks. *Nat Rev Neurosci.* 2016;17(7):401–409.
32. Chen G, Zhang Y, Li X, et al. Distinct inhibitory circuits orchestrate cortical beta and gamma band oscillations. *Neuron.* 2017;96(6):1403–1418 e1406.
33. Womelsdorf T, Valiante TA, Sahin NT, Miller KJ, Tiesinga P. Dynamic circuit motifs underlying rhythmic gain control, gating and integration. *Nat Neurosci.* 2014;17(8):1031–1039.
34. Urban-Ciecko J, Fanselow EE, Barth AL. Neocortical somatostatin neurons reversibly silence excitatory transmission via GABAb receptors. *Curr Biol.* 2015;25(6):722–731.
35. Veit J, Hakim R, Jadi MP, Sejnowski TJ, Adesnik H. Cortical gamma band synchronization through somatostatin interneurons. *Nat Neurosci.* 2017;20(7):951–959.

36. Yavorska I, Wehr M. Somatostatin-expressing inhibitory interneurons in cortical circuits. *Front Neural Circuits.* 2016;10:76.
37. Beierlein M, Gibson JR, Connors BW. Two dynamically distinct inhibitory networks in layer 4 of the neocortex. *J Neurophysiol.* 2003;90(5):2987–3000.
38. Adler A, Zhao R, Shin ME, Yasuda R, Gan WB. Somatostatin-expressing interneurons enable and maintain learning-dependent sequential activation of pyramidal neurons. *Neuron.* 2019;102(1):202–216 e207.
39. Sadahiro M, Demars MP, Burman P, Yevoo P, Zimmer A, Morishita H. Activation of somatostatin interneurons by nicotinic modulator lypd6 enhances plasticity and functional recovery in the adult mouse visual cortex. *J Neurosci.* 2020;40(27):5214–5227.
40. Chen N, Sugihara H, Sur M. An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity. *Nat Neurosci.* 2015;18(6):892–902.
41. Urban-Ciecko J, Jouhanneau JS, Myal SE, Poulet JFA, Barth AL. Precisely timed nicotinic activation drives SST inhibition in neocortical circuits. *Neuron.* 2018;97(3):611–625 e615.
42. Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. *Neuron.* 2016;91(2):260–292.
43. Ma WP, Liu BH, Li YT, Huang ZJ, Zhang LI, Tao HW. Visual representations by cortical somatostatin inhibitory neurons—selective but with weak and delayed responses. *J Neurosci.* 2010;30(43):14371–14379.
44. Wang Y, Toledo-Rodriguez M, Gupta A, et al. Anatomical, physiological and molecular properties of Martinotti cells in the somatosensory cortex of the juvenile rat. *J Physiol.* 2004;561(Pt 1):65–90.
45. Jiang X, Shen S, Cadwell CR, et al. Principles of connectivity among morphologically defined cell types in adult neocortex. *Science.* 2015;350(6264):aac9462.
46. Ma Y, Hu H, Berrebi AS, Mathers PH, Agmon A. Distinct subtypes of somatostatin-containing neocortical interneurons revealed in transgenic mice. *J Neurosci.* 2006;26(19):5069–5082.
47. Pfeffer CK, Xue M, He M, Huang ZJ, Scanziani M. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. *Nat Neurosci.* 2013;16(8):1068–1076.
48. Silberberg G, Markram H. Disynaptic inhibition between neocortical pyramidal cells mediated by Martinotti cells. *Neuron.* 2007;53(5):735–746.
49. Xu H, Jeong HY, Tremblay R, Rudy B. Neocortical somatostatin-expressing GABAergic interneurons disinhibit the thalamorecipient layer 4. *Neuron.* 2013;77(1):155–167.
50. Naka A, Veit J, Shababo B, et al. Complementary networks of cortical somatostatin interneurons enforce layer specific control. *Elife* 2019;8:e43696.
51. Demars MP, Morishita H. Cortical parvalbumin and somatostatin GABA neurons express distinct endogenous modulators of nicotinic acetylcholine receptors. *Mol Brain.* 2014;7:75.
52. Oliva AA Jr, Jiang M, Lam T, Smith KL, Swann JW. Novel hippocampal interneuronal subtypes identified using transgenic mice that express green fluorescent protein in GABAergic interneurons. *J Neurosci.* 2000;20(9):3354–3368.
53. Taniguchi H, He M, Wu P, et al. A resource of Cre driver lines for genetic targeting of GABAergic neurons in cerebral cortex. *Neuron.* 2011;71(6):995–1013.
54. Muñoz W, Tremblay R, Levenstein D, Rudy B. Layer-specific modulation of neocortical dendritic inhibition during active wakefulness. *Science.* 2017;355(6328):954–959.
55. Hoyer D, Bell GI, Berelowitz M, et al. Classification and nomenclature of somatostatin receptors. *Trends Pharmacol Sci.* 1995;16(3):86–88.
56. Kits KS, Mansvelder HD. Regulation of exocytosis in neuroendocrine cells: spatial organization of channels and vesicles, stimulus-secretion coupling, calcium buffers and modulation. *Brain Res Brain Res Rev.* 2000;33(1):78–94.
57. Alherz F, Alherz M, Almusawi H. NMDAR hypofunction and somatostatin-expressing GABAergic interneurons and receptors: a newly identified correlation and its effects in schizophrenia. *Schizophr Res Cogn.* 2017;8:1–6.
58. Konradi C, Yang CK, Zimmerman EI, et al. Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res.* 2011;131(1–3):165–173.
59. Morris HM, Hashimoto T, Lewis DA. Alterations in somatostatin mRNA expression in the dorsolateral prefrontal cortex of subjects with schizophrenia or schizoaffective disorder. *Cereb Cortex.* 2008;18(7):1575–1587.
60. Hashimoto T, Arion D, Unger T, et al. Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry.* 2008;13(2):147–161.
61. Gabriel SM, Davidson M, Haroutunian V, et al. Neuropeptide deficits in schizophrenia vs. Alzheimer's disease cerebral cortex. *Biol Psychiatry.* 1996;39(2):82–91.
62. Mellios N, Huang HS, Baker SP, Galdzicka M, Ginns E, Akbarian S. Molecular determinants of dysregulated GABAergic gene expression in the prefrontal cortex of subjects with schizophrenia. *Biol Psychiatry.* 2009;65(12):1006–1014.
63. Wang AY, Lohmann KM, Yang CK, et al. Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathol.* 2011;122(5):615–626.
64. Tsubomoto M, Kawabata R, Zhu X, et al. Expression of transcripts selective for GABA neuron subpopulations across the cortical visuospatial working memory network in the healthy state and schizophrenia. *Cereb Cortex.* 2019;29(8):3540–3550.
65. Pantazopoulos H, Wiseman JT, Markota M, Ehrenfeld L, Berretta S. Decreased numbers of somatostatin-expressing neurons in the amygdala of subjects with bipolar disorder or schizophrenia: relationship to circadian rhythms. *Biol Psychiatry.* 2017;81(6):536–547.
66. Roberts LJ, 2nd, Bloomgarden ZT, Marney SR, Jr., Rabin D, Oates JA. Histamine release from a gastric carcinoid: provocation by pentagastrin and inhibition by somatostatin. *Gastroenterology* 1983;84(2):272–275.
67. Nemeroff CB, Youngblood WW, Manberg PJ, Prange AJ, Jr., Kizer JS. Regional brain concentrations of neuropeptides in Huntington's chorea and schizophrenia. *Science* 1983;221(4614):972–975.
68. Nakatani N, Hattori E, Ohnishi T, et al. Genome-wide expression analysis detects eight genes with robust alterations specific to bipolar I disorder: relevance to neuronal network perturbation. *Hum Mol Genet*. 2006;15(12):1949–1962.
69. Anderson KM, Collins MA, Chin R, Ge T, Rosenberg MD, Holmes AJ. Transcriptional and imaging-genetic association of cortical interneurons, brain function, and schizophrenia risk. *Nat Commun.* 2020;11(1):2889.

70. Sánchez-Muñoz I, Sánchez-Franco F, Vallejo M, et al. Activity-dependent somatostatin gene expression is regulated by cAMP-dependent protein kinase and Ca2+-calmodulin kinase pathways. *J Neurosci Res.* 2010;88(4):825–836.
71. Yang Y, Fung SJ, Rothwell A, Tianmei S, Weickert CS. Increased interstitial white matter neuron density in the dorsolateral prefrontal cortex of people with schizophrenia. *Biol Psychiatry.* 2011;69(1):63–70.
72. Karlsson H, Dalman C. Epidemiological studies of prenatal and childhood infection and schizophrenia. *Curr Top Behav Neurosci.* 2020;44:35–47.
73. Clementz BA, Sweeney JA, Hamm JP, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. *Am J Psychiatry.* 2016;173(4):373–384.
74. Buzsáki G. Neural syntax: cell assemblies, synapsembles, and readers. *Neuron.* 2010;68(3):362–385.
75. Whittington MA, Traub RD, Kopell N, Ermentrout B, Buhl EH. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Int J Psychophysiol.* 2000;38(3):315–336.
76. Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ. Canonical microcircuits for predictive coding. *Neuron.* 2012;76(4):695–711.
77. Bastos AM, Vezoli J, Bosman CA, et al. Visual areas exert feedforward and feedback influences through distinct frequency channels. *Neuron.* 2015;85(2):390–401.
78. Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. *Science.* 2004;304(5679):1926–1929.
79. Lee M, Balla A, Sershen H, Sehatpour P, Lakatos P, Javitt DC. Rodent mismatch negativity/theta neuro-oscillatory response as a translational neurophysiological biomarker for N-Methyl-D-Aspartate receptor-based new treatment development in schizophrenia. *Neuropsychopharmacology.* 2018;43(3):571–582.
80. Buzsaki G. *Rhythms of the Brain*. New York, NY: Oxford Press; 2006.
81. Moran LV, Hong LE. High vs low frequency neural oscillations in schizophrenia. *Schizophr Bull.* 2011;37(4):659–663.
82. Hamm JP, Bobilev AM, Hayrynen LK, et al. Stimulus train duration but not attention moderates γ-band entrainment abnormalities in schizophrenia. *Schizophr Res.* 2015;165(1):97–102.
83. Hirano Y, Oribe N, Kanba S, Onitsuka T, Nestor PG, Spencer KM. Spontaneous gamma activity in schizophrenia. *JAMA Psychiatry.* 2015;72(8):813–821.
84. Hong LE, Summerfelt A, McMahon R, et al. Evoked gamma band synchronization and the liability for schizophrenia. *Schizophr Res.* 2004;70(2–3):293–302.
85. Hamm JP, Ethridge LE, Shapiro JR, et al. Spatiotemporal and frequency domain analysis of auditory paired stimuli processing in schizophrenia and bipolar disorder with psychosis. *Psychophysiology.* 2012;49(4):522–530.
86. Narayanan B, Soh P, Calhoun VD, et al. Multivariate genetic determinants of EEG oscillations in schizophrenia and psychotic bipolar disorder from the BSNIP study. *Transl Psychiatry.* 2015;5:e588.
87. Mitra S, Nizamie SH, Goyal N, Tikka SK. Evaluation of resting state gamma power as a response marker in schizophrenia. *Psychiatry Clin Neurosci.* 2015;69(10):630–639.
88. Hamm JP, Gilmore CS, Clementz BA. Augmented gamma band auditory steady-state responses: support for NMDA hypofunction in schizophrenia. *Schizophr Res.* 2012;138(1):1–7.
89. Hamm JP, Ethridge LE, Boutros NN, et al. Diagnostic specificity and familiality of early versus late evoked potentials to auditory paired stimuli across the schizophrenia-bipolar psychosis spectrum. *Psychophysiology.* 2014;51(4):348–357.
90. Basar-Eroglu C, Brand A, Hildebrandt H, Karolina Kedzior K, Mathes B, Schmiedt C. Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol.* 2007;64(1):39–45.
91. Clementz BA, Wang J, Keil A. Normal electrocortical facilitation but abnormal target identification during visual sustained attention in schizophrenia. *J Neurosci.* 2008;28(50):13411–13418.
92. Farzan F, Barr MS, Levinson AJ, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain.* 2010;133(Pt 5):1505–1514.
93. Flynn G, Alexander D, Harris A, et al. Increased absolute magnitude of gamma synchrony in first-episode psychosis. *Schizophr Res.* 2008;105(1–3):262–271.
94. Lee K, Williams LM, Breakspear M, Gordon E. Synchronous gamma activity- a review and contribution to an integrative neuroscience model of schizophrenia. *Brain Res Rev.* 2003;41:57–78.
95. Spencer KM, Nestor PG, Perlmutter R, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci USA.* 2004;101(49):17288–17293.
96. Brenner CA, Krishnan GP, Vohs JL, et al. Steady state responses: electrophysiological assessment of sensory function in schizophrenia. *Schizophr Bull.* 2009;35(6):1065–1077.
97. Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron.* 2006;52(1):155–168.
98. Jensen O, Colgin LL. Cross-frequency coupling between neuronal oscillations. *Trends Cogn Sci.* 2007;11(7):267–269.
99. Canolty RT, Edwards E, Dalal SS, et al. High gamma power is phase-locked to theta oscillations in human neocortex. *Science.* 2006;313(5793):1626–1628.
100. Tada M, Nagai T, Kirihara K, et al. Differential alterations of auditory gamma oscillatory responses between pre-onset high-risk individuals and first-episode schizophrenia. *Cereb Cortex.* 2016;26(3):1027–1035.
101. Javitt DC, Siegel SJ, Spencer KM, et al. A roadmap for development of neuro-oscillations as translational biomarkers for treatment development in neuropsychopharmacology. *Neuropsychopharmacology.* 2020;45(9):1411–1422.
102. Cardin JA. Inhibitory interneurons regulate temporal precision and correlations in cortical circuits. *Trends Neurosci.* 2018;41(10):689–700.
103. Cardin JA, Carlén M, Meletis K, et al. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature.* 2009;459(7247):663–667.
104. Carlén M, Meletis K, Siegle JH, et al. A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Mol Psychiatry.* 2012;17(5):537–548.
105. Bartos M, Vida I, Jonas P. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci.* 2007;8(1):45–56.
106. Gonzalez-Burgos G, Cho RY, Lewis DA. Alterations in cortical network oscillations and parvalbumin neurons in schizophrenia. *Biol Psychiatry.* 2015;77(12):1031–1040.
107. Dienel SJ, Lewis DA. Alterations in cortical interneurons and cognitive function in schizophrenia. *Neurobiol Dis.* 2019;131:104208.

108. Hamm JP, Shymkiv Y, Mukai J, Gogos JA, Yuste R. Aberrant cortical ensembles and schizophrenia-like sensory phenotypes in Setd1a+/- Mice. *Biol Psychiatry.* 2020;88(3):215–223.
109. Murphy N, Ramakrishnan N, Walker CP, Polizzotto NR, Cho RY. Intact auditory cortical cross-frequency coupling in early and chronic schizophrenia. *Front Psychiatry.* 2020;11:507.
110. Glickfeld LL, Andermann ML, Bonin V, Reid RC. Cortico-cortical projections in mouse visual cortex are functionally target specific. *Nat Neurosci.* 2013;16(2):219–226.
111. Douglas RJ, Martin KA. Neuronal circuits of the neocortex. *Annu Rev Neurosci.* 2004;27:419–451.
112. Adesnik H, Bruns W, Taniguchi H, Huang ZJ, Scanziani M. A neural circuit for spatial summation in visual cortex. *Nature.* 2012;490(7419):226–231.
113. Lakunina AA, Nardoci MB, Ahmadian Y, Jaramillo S. Somatostatin-expressing interneurons in the auditory cortex mediate sustained suppression by spectral surround. *J Neurosci.* 2020;40(18):3564–3575.
114. Ross JM, Hamm JP. Cortical microcircuit mechanisms of mismatch negativity and its underlying subcomponents. *Front Neural Circuits.* 2020;14:13.
115. Sterzer P, Adams RA, Fletcher P, et al. The predictive coding account of psychosis. *Biol Psychiatry.* 2018;84(9):634–643.
116. Lee M, Sehatpour P, Hoptman MJ, et al. Neural mechanisms of mismatch negativity dysfunction in schizophrenia. *Mol Psychiatry.* 2017;22(11):1585–1593.
117. Natan RG, Rao W, Geffen MN. Cortical interneurons differentially shape frequency tuning following adaptation. *Cell Rep.* 2017;21(4):878–890.
118. Natan RG, Briguglio JJ, Mwilambwe-Tshilobo L, et al. Complementary control of sensory adaptation by two types of cortical interneurons. *Elife*. 2015;4:e09868.
119. Godsil BP, Kiss JP, Spedding M, Jay TM. The hippocampal-prefrontal pathway: the weak link in psychiatric disorders? *Eur Neuropsychopharmacol.* 2013;23(10):1165–1181.
120. Adams RA, Bush D, Zheng F, et al. Impaired theta phase coupling underlies frontotemporal dysconnectivity in schizophrenia. *Brain.* 2020;143(4):1261–1277.
121. Jacobs J. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. *Philos Trans R Soc Lond B Biol Sci.* 2014;369(1635):20130304.
122. Benchenane K, Peyrache A, Khamassi M, et al. Coherent theta oscillations and reorganization of spike timing in the hippocampal-prefrontal network upon learning. *Neuron.* 2010;66(6):921–936.
123. Hyman JM, Zilli EA, Paley AM, Hasselmo ME. Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front Integr Neurosci.* 2010;4:2.
124. Jones MW, Wilson MA. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 2005;3(12):e402.
125. Kim D, Jeong H, Lee J, et al. Distinct roles of parvalbumin- and somatostatin-expressing interneurons in working memory. *Neuron.* 2016;92(4):902–915.
126. Spellman TJ, Gordon JA. Synchrony in schizophrenia: a window into circuit-level pathophysiology. *Curr Opin Neurobiol.* 2015;30:17–23.
127. Ellison-Wright I, Bullmore E. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. *Schizophr Res.* 2010;117(1):1–12.
128. Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry.* 1992;149(7):890–897.
129. Fleming K, Goldberg TE, Binks S, Randolph C, Gold JM, Weinberger DR. Visuospatial working memory in patients with schizophrenia. *Biol Psychiatry.* 1997;41(1):43–49.
130. Myles-Worsley M, Park S. Spatial working memory deficits in schizophrenia patients and their first degree relatives from Palau, Micronesia. *Am J Med Genet.* 2002;114(6):609–615.
131. Glahn DC, Therman S, Manninen M, et al. Spatial working memory as an endophenotype for schizophrenia. *Biol Psychiatry.* 2003;53(7):624–626.
132. Park S, Holzman PS. Schizophrenics show spatial working memory deficits. *Arch Gen Psychiatry.* 1992;49(12):975–982.
133. Haenschel C, Bittner RA, Waltz J, et al. Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J Neurosci.* 2009;29(30):9481–9489.
134. Silverstein SM, Kovács I, Corry R, Valone C. Perceptual organization, the disorganization syndrome, and context processing in chronic schizophrenia. *Schizophr Res.* 2000;43(1):11–20.
135. Chen Y. Abnormal visual motion processing in schizophrenia: a review of research progress. *Schizophr Bull.* 2011;37(4):709–715.
136. Silverstein SM, Harms MP, Carter CS, et al. Cortical contributions to impaired contour integration in schizophrenia. *Neuropsychologia.* 2015;75:469–480.
137. Haigh SM, Coffman BA, Salisbury DF. Mismatch negativity in first-episode schizophrenia: a meta-analysis. *Clin EEG Neurosci.* 2017;48(1):3–10.
138. Kremláček J, Kreegipuu K, Tales A, et al. Visual mismatch negativity (vMMN): a review and meta-analysis of studies in psychiatric and neurological disorders. *Cortex.* 2016;80:76–112.
139. Hong LE, Moran LV, Du X, O'Donnell P, Summerfelt A. Mismatch negativity and low frequency oscillations in schizophrenia families. *Clin Neurophysiol.* 2012;123(10):1980–1988.
140. Javitt DC, Shelley A, Ritter W. Associated deficits in mismatch negativity generationand tone matching in schizophrenia. *Clin Neurophysiol.* 2000;111:1733–1737.
141. Kaser M, Soltesz F, Lawrence P, et al. Oscillatory underpinnings of mismatch negativity and their relationship with cognitive function in patients with schizophrenia. *PLoS One.* 2013;8(12):e83255.
142. Kirihara K, Tada M, Koshiyama D, et al. A predictive coding perspective on mismatch negativity impairment in schizophrenia. *Front Psychiatry.* 2020;11:660.
143. Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry.* 2013;70(10):1107–1112.
144. Lacaille H, Vacher CM, Bakalar D, O'Reilly JJ, Salzbank J, Penn AA. Impaired interneuron development in a novel model of neonatal brain injury. *eNeuro*. 2019;6(1):ENE URO.0300-18.2019.
145. Zhu Q, Ke W, He Q, et al. Laminar distribution of neurochemically-identified interneurons and cellular co-expression of molecular markers in epileptic human cortex. *Neurosci Bull.* 2018;34(6):992–1006.

146. Joshi D, Fullerton JM, Weickert CS. Elevated ErbB4 mRNA is related to interneuron deficit in prefrontal cortex in schizophrenia. *J Psychiatr Res.* 2014;53:125–132.
147. Hamm JP, Sabatinelli D, Clementz BA. Alpha oscillations and the control of voluntary saccadic behavior. *Exp Brain Res.* 2012;221(2):123–128.
148. Spellman T, Rigotti M, Ahmari SE, Fusi S, Gogos JA, Gordon JA. Hippocampal-prefrontal input supports spatial encoding in working memory. *Nature.* 2015;522(7556):309–314.
149. Javitt DC, Lee M, Kantrowitz JT, Martinez A. Mismatch negativity as a biomarker of theta band oscillatory dysfunction in schizophrenia. *Schizophr Res.* 2018;191:51–60.
150. Chen IW, Helmchen F, Lütcke H. Specific early and late oddball-evoked responses in excitatory and inhibitory neurons of mouse auditory cortex. *J Neurosci.* 2015;35(36):12560–12573.
151. Haigh SM, Coffman BA, Murphy TK, Butera CD, Leiter-McBeth JR, Salisbury DF. Reduced late mismatch negativity and auditory sustained potential to rule-based patterns in schizophrenia. *Eur J Neurosci.* 2019;49(2):275–289.
152. Sultan KT, Brown KN, Shi SH. Production and organization of neocortical interneurons. *Front Cell Neurosci.* 2013;7:221.