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Somatostatin-positive GABA Interneuron Deficits in Depression: Cortical Microcircuit and Therapeutic Perspectives

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Abstract

The functional integration of external and internal signals forms the basis of information processing and is essential for higher cognitive functions. This occurs in finely-tuned cortical microcircuits whose functions are balanced at the cellular level by excitatory glutamatergic pyramidal neurons and inhibitory γ-aminobutyric acid (**GABA**) interneurons. The balance of excitation and inhibition, from cellular processes to neural network activity, is characteristically disrupted in multiple neuropsychiatric disorders, including major depressive disorder (**MDD**), bipolar disorder (**BPD**), anxiety disorders, and schizophrenia (**SCZ**). Specifically, nearly three decades of research demonstrate a role for reduced inhibitory GABA level and function across disorders. In MDD, recent evidence from human postmortem and animal studies suggests a selective vulnerability of GABAergic interneurons that co-express the neuropeptide somatostatin ("**SST** cells/interneurons"). Advances in cell type-specific molecular genetics have now helped to elucidate several important roles for SST interneurons in cortical processing (regulation of pyramidal cell excitatory input) and behavioral control (mood and cognition). Here, we review evidence for altered inhibitory function arising from GABAergic deficits across disorders, and specifically in MDD. We then focus on properties of the cortical microcircuit, wherein SST-positive GABA interneuron deficits may disrupt functioning in several ways. Finally, we discuss the putative origins of SST cell deficits, as informed by recent research, and implications for therapeutic approaches. We conclude that deficits in SST interneurons represent a contributing cellular pathology, and therefore a promising target for normalizing altered inhibitory function in MDD and other disorders with reduced SST cell and GABA functions.

Keywords

Depression; Somatostatin; GABA; Microcircuit; Dimensional; Pathology

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Cognitive-Emotional Disruption and Excitation-Inhibition Balance in Depression

Major depressive disorder (**MDD**) is characterized by low mood, anhedonia, and cognitive deficits relating to negative biases in attention, sensory processing, and memory (1). Several mechanisms have been hypothesized, including low monoamine levels (2), reduced neuroplasticity through altered glutamate or growth factor signaling (3), impaired neuroendocrine stress response regulation (4), and more recently, altered activity of corticolimbic brain regions driven by altered excitatory and inhibitory neuron function (5, 6). Although interesting insight has emerged from these hypotheses, limited progress has been made in drug development, whereby current treatments remain ineffective in half of treated patients (7).

Maintaining the balance between excitation and inhibition is a fundamental attribute of brain function that is necessary for information processing and higher cognitive functions. At a reductionist level, neural “information” consists of excitatory signals originating from principal glutamatergic neurons that are matched by proportional GABAergic interneuron inhibition. Changes in cellular components underlying excitation-inhibition balance may affect the detection and propagation of information across cortical microcircuits, brain regions, and neural networks. Initially adaptive, chronic changes in the excitation-inhibition balance, as hypothesized to occur in psychiatric disorders, can become maladaptive and support the emergence of clinical symptoms. For instance, human and animal studies have demonstrated altered GABA-related inhibitory function in neurodevelopmental disorders, and associated these changes with cognitive deficits in information processing (8, 9). Reduced GABA levels and function may similarly account for disrupted cognitive-emotional processes in MDD (10, 11). For instance, functional neuroimaging identified MDD-related hyperactivity in the default mode network (**DMN**), a set of brain regions including the dorsolateral prefrontal cortex (**dlPFC**), posterior and anterior cingulate cortices (**ACC**), amygdala, and hippocampus (12, 13). In healthy individuals, the DMN is active during internal focus (e.g., attending to personal thoughts) and deactivated during externally-oriented events (e.g. goal-directed behavior) (14), hence a failure to suppress DMN activity during external tasks may contribute to negative self-referential processes (e.g., rumination) in MDD (15). Studies have now identified reduced molecular markers of GABA function in DMN regions (16–21) and correlated GABA content with functional connectivity (22–25), together suggesting a GABA-related inhibitory deficit contributing to altered activity in DMN regions and symptom emergence in MDD.

GABA Levels and Related Neurophysiological Measures in Depression

Studies in human live and postmortem subjects suggest a predominant role for altered GABA function underlying inhibitory deficits across multiple psychiatric disorders, including MDD (26–28), BPD, SCZ (29), and stress-related disorders (30). Reduced cerebrospinal fluid GABA levels were first reported in MDD and SCZ over 35 years ago (31), and have been consistently found in MDD and BPD (32–34), and extended to plasma levels correlating with illness severity, use of medication, and genetic risk (34–36).

Imaging studies using proton magnetic resonance spectroscopy provided evidence of central GABA deficits in MDD. A 50% reduction in occipital cortex GABA levels was first reported in medication-free depressed patients and later found to be more severe in patients with persistent melancholic depression (37). Low GABA levels were consistently identified in brain regions responsible for emotional-cognitive processes that are disrupted in mood disorders, including the PFC (16, 17), amygdala (18), and ACC (19–21). These reductions were more robust in treatment resistant depression (**TRD**) (19), but normalized in remitted patients (38). Imaging studies further identified a role for GABA in antidepressant response as brain levels were elevated following selective serotonin reuptake inhibitor (SSRI) treatment (39, 40), transcranial magnetic stimulation (**TMS**) (41, 42), electroconvulsive therapy (43), and cognitive-behavioral therapy (44).

Evidence of cortical inhibitory deficits arising from GABA alterations comes from TMS studies. Using TMS, single or repetitive magnetic fields are applied to the cortex to excite or inhibit cortical activity, as measured by electromyography or electroencephalogram. TMS showed efficacy as an antidepressant treatment in TRD patients (45), and is also used to experimentally probe cortical inhibition, including short-interval cortical inhibition (**SICI**), long-interval cortical inhibition (**LICI**), and cortical silent period (**CSP**). SICI is similar in duration to $GABA_A$ receptor (**$GABA_AR$**)-mediated inhibitory post-synaptic potentials (46, 47) and is lengthened by $GABA_A$-acting drugs (48, 49), and is therefore considered to measure $GABA_A$R-mediated neurotransmission. Conversely, the slower LICI and CSP time-courses resemble $GABA_B$ receptor (**$GABA_BR$**)-mediated post-synaptic potentials (50), and are increased by $GABA_B$R agonists (51, 52), suggesting a reflection of $GABA_B$R-mediated neurotransmission.

TMS studies in MDD patients demonstrated reduced SICI and CSP (27, 28). Although reduced cortical inhibition was not always reported (53), meta-analysis confirmed MDD-related deficits (54). Others found CSP deficits in MDD, but SICI reduction only in TRD, potentially implicating $GABA_B$R impairments in overall MDD pathophysiology, and $GABA_A$R impairments in more severe MDD (27). Reflecting findings in MDD (41, 42), repetitive TMS increased cortical inhibition (55) and lengthened CSP (56) in healthy individuals, suggesting enhanced GABA neurotransmission.

Evidence across treatment modalities implicates cortical inhibition in antidepressant effects. For instance, electroconvulsive therapy increased SICI and CSP in non-medicated MDD patients (57). Pharmacological treatment with the SSRI, citalopram, rapidly increased SICI and CSP (58), whereas the tricyclic antidepressant clomipramine increased only SICI in MDD patients (59). Finally, nucleus accumbens deep brain stimulation also showed antidepressant efficacy in TRD patients (60), and increased SICI in subjects with epilepsy (61).

Cortical Microcircuit Organization and Function

How can GABA-related neurophysiological measures be linked to cellular and molecular dysfunction in depression? Here, we briefly review microcircuit roles of SST-expressing GABAergic interneurons, and then discuss putative functional implications.

In the neocortex, external (e.g. sensory stimuli) and internal (e.g. past representations) information is coded by excitatory activation patterns that input onto pyramidal neurons (**PNs**). These signals are locally integrated, and, through interneuron inhibition, transformed into PN firing patterns. This neuronal output contributes to sensory processing and cognitive function (Figure 1). Studies suggest a compartmentalized integration of excitatory signals within PNs. Thalamic feed-forward excitation terminates onto the PN soma in L4-5, whereas cortico-cortical feedback excitation (alongside thalamocortical afferents) impinges separately onto PN distal dendrites (Figure 1A). These signals facilitate the integration of distinct information streams and combine to drive bursts of PN activity, forming the basis of neural coding (62, 63).

The input, output, and integration of excitatory signals is regulated by interconnected inhibitory GABAergic interneurons with heterogeneous morphology, distribution, electrophysiological properties, connectivity, and molecular identities. Nearly all interneurons belong to one of three non-overlapping classes based on co-expression of markers for the calcium-binding protein parvalbumin (**PV**; ~40%), the neuropeptide somatostatin (**SST**; ~30%), or the ionotropic serotonin receptor $5HT_{3a}R$ (~30%), including vasoactive intestinal peptide (**VIP**)-expressing interneurons (64) (Figure 1A).

SST Interneurons consist mainly of translaminar distal dendrite-targeting Martinotti cells, with low-threshold regular-spiking properties and high spontaneous activity levels, distributed throughout L2-6 (65). In the hippocampus and neocortex, SST interneurons mediate feedback and lateral inhibition, contributing to maintain sparse activity of PNs at rest (e.g. in L2/3), gate converging cortico-cortical and thalamic input from L1 signal streams (63, 66), and regulate microcircuit gain (67). Additionally, L4 non-Martinotti SST interneurons preferentially target local PV interneurons, and receive thalamic afferents, thus mostly exerting PN disinhibitory functions (68).

PV Interneurons have basket or chandelier cell morphologies, target PN perisomatic region with fast-spiking properties, and are distributed across L2-6 (65). PV interneurons regulate PN spiking output through thalamic feed-forward afferents simultaneously targeting PV interneurons and PNs. Recruitment of PV interneuron feed-forward inhibition is delayed compared to direct PN innervation, providing a short window for PN signal summation that facilitates coincidence detection and firing synchrony (69), the latter function supported further by PV-PV reciprocal connections (70). Regulation of thalamic sensory input positions PV interneurons to enhance stimulus selectivity (or “tuning”) of neuronal ensembles (71, 72). Rapid and massively divergent PV interneuron inhibition prevents saturation of PN sensory responses, thus also contributing to gain modulation (73, 74).

VIP Interneurons are $5HT_{3a}R$-expressing cells with double-bouquet, bipolar, and bi-tufted cell morphologies, and non-fast-spiking properties. These cells are highly distributed in L2/3, preferentially excited by cortico-cortical afferents, and mainly target other interneurons (75). Activated VIP interneurons inhibit SST interneurons, hence release inhibitory tone on PN dendrites, and facilitating excitatory input, which may contribute to top-down modulation of sensory information by behavioral state (76, 77).

GABA and SST interneuron-related Microcircuit Deficits in Depression

Although glutamate alterations are commonly reported in MDD (78), studies more consistently demonstrate GABA-related deficits. Postmortem studies found PFC and amygdala reductions in mRNA and protein levels of the GABA-synthesizing gene, GAD67, in MDD (18, 79). Reductions in neuron and glial cell size and density were identified across layers in the dlPFC of MDD subjects (80). An MDD-related reduction in size and density of neurons immunoreactive for calbindin, a calcium-binding protein co-expressed with SST, was also reported (65), in contrast to less pronounced PV changes (17). Reduced calbindin cell density was further reported in the occipital cortex (81).

Postmortem evidence suggests a selective vulnerability of SST cells in MDD (18, 82–84). MDD-related SST mRNA reductions were reported in dlPFC, amygdala, and ACC (83, 84). Follow-up investigation in the ACC demonstrated reduced SST expression per cell across all cortical layers (83), suggesting a common origin despite SST cell heterogeneity. A putative causal role for reduced SST cell function is supported by work showing that *Sst* knockout mice recapitulated several MDD hallmarks, including elevated depressive-/anxiety-like behaviors, increased corticosterone, and reduced expression of brain-derived neurotrophic factor (***Bdnf***) and *Gad67* genes, although, these changes were not seen in Sst^{Hz} mice, possibly due to compensatory cellular adaptations (85). Note that SST is co-released with GABA, has pre- and post-synaptic physiological and neuronal roles (See review (86)), and when infused into rodent corticolimbic brain regions, has anxiolytic- and antidepressant-like effects (87–90). However, in light of cortical inhibitory deficits in MDD (27, 28), we consider SST as a marker for susceptible cells, and focus on SST interneurons as a GABAergic entity that is altered in MDD.

In mice, acute pharmacogenetic inhibition of PFC SST interneurons increased behavioral emotionality, but chronic blockade had the opposite effect (91), supporting a role for SST cells in regulating emotionality, but also suggesting network adaptations recruiting other brain regions. Conversely, PV and VIP changes were either not, or inconsistently reported in MDD (17, 92); although see (93) for reduced ACC PV expression in MDD. In mice, SST cell function was also associated with fear learning and working memory, and with deficits in these cognitive dimensions (94, 95). Reduced SST cell function was further demonstrated to mediate cognitive impairments in Alzheimer's disease models (96).

Non-neuronal cells are also essential for cortical function. As microcircuit processing depends highly on temporal signal conductance, oligodendrocyte-mediated myelination can impact dendritic integration, synaptic plasticity, and synchronization of network activity. Indeed, postmortem MDD studies identified decreased size of PFC oligodendrocytes, associated with altered myelination (97), and putative reductions in amygdala oligodendrocyte numbers (98). Animal studies increasingly highlight a role for oligodendrocytes in mood regulation (99). Astrocytes also influence microcircuit function through modulation of synaptic transmission via calcium signaling, release of glutamate and purinergic neurotransmitters, and neurotransmitter recycling (100). Further, circuit connectivity depends on the formation of functional neuronal assemblies mediated by astrocytes and microglia that are similarly altered in MDD. Specifically, density of

astrocytes and expression of astrocyte-specific markers were decreased in MDD patients (101), whereas microglial activation was increased (102).

A Pathophysiological Model of Low SST Cell Function

Neural code is derived from excitatory signals that converge onto PNs and undergo modulation or “fine-tuning” by GABAergic interneurons (Figure 1A), with the resulting output signals being then propagated across cortical layers and brain regions. This code is partly derived from the relative change between baseline and stimulus-induced PN outputs, where the difference represents a signal-to-noise ratio contributing to encode neural information (103). In an SST interneuron deficient system, several outcomes are predicted (Figure 1B): i) Reduced SST interneuron dendritic inhibition increases baseline PN activity, namely in L2/3; ii) Given their role in disynaptic inhibition and superficial layer synaptic integration, impaired SST interneuron function reduces gating of associative feedback projections; iii) VIP-mediated inhibition of SST cells leads to normal or enhanced PN disinhibition; iv) An increased baseline activity, combined with possibly normal, increased, or altered PN excitatory output patterns, reduces the signal-to-noise ratio, resulting in reduced detection accuracy and altered encoding of neural content; v) The resulting altered information is propagated across brain areas. Although not discussed here, the impact of reduced SST cell function is likely to be exacerbated by glial deficits, which are predicted to increase processing errors by cortical microcircuits, i.e., oligodendrocyte myelination deficits may alter spike timing or network synchrony (104, 105), whereas astrocyte dysfunction may reduce regulation of neurotransmission or spiking (106, 107), and disrupt glutamate/GABA cycling (108).

In support of these predictions, *in vitro* and *in vivo* calcium imaging studies demonstrated that L5 Martinotti (SST+) cells control PN population firing via disynaptic inhibition, and computational modeling of the data suggested that dendritic inhibition regulates microcircuit gain and cortical sensory response dynamics (63). Combined whole-cell recordings and calcium imaging in the mouse barrel cortex, an area of sensorimotor integration, demonstrated reduced SST interneuron firing and greater (L1) dendritic excitability of L2/3 PNs during active behavior (109). Optogenetic silencing of SST interneurons increased PN activity and burst firing, supporting a SST cell-mediated top-down integration of behaviorally relevant information (109), which in a system with reduced dendritic inhibition is predicted to impact perception (62). In contrast to these findings, L4 SST interneuron silencing decreased local PN activity due to SST-PV connections (68), suggesting that regulation of neuronal output may be layer-dependent. Increased PN burst firing from SST interneuron silencing was also demonstrated in hippocampal CA1 (110) and cortical V1 (111).

Ultimately, we predict a two-fold impact of reduced SST cell function: altered integrity of internal information through impaired cortico-cortical signaling, and simultaneously decreased coding (and transfer) of external information through reduced L4 thalamocortical input integration. At the psychological and symptom levels, this may manifest in shifting attention away from external focus towards internal focus, potentially underlying rumination symptoms in MDD (see review (10)). However, much remains to be elucidated regarding

both the role of SST interneurons in normal microcircuit functions and whether chronically low SST cell function in psychiatric disorders leads to cellular or network-level adaptations. Several sophisticated genetic, optogenetic, and chemogenetic techniques now exist (e.g., see: 97, 117, 118), allowing fine control of distinct SST cell populations (113), and facilitating high-resolution imaging and electrophysiological recording. However, current experiments have mainly focused on short-term interneuron manipulations, whereas longer-term deficits may be more informative of human pathology (91). Another issue lies in SST cell heterogeneity, as the extent to which the expression of overlapping neurochemical markers (e.g., calbindin, calretinin, neuropeptide Y) or morphologies (e.g., Martinotti vs. non-Martinotti) bias towards functionally distinct properties is unclear (114). It also remains to be seen how upstream neuromodulators may affect microcircuit function. For example, acetylcholine and serotonin can activate or inhibit SST interneurons through direct and indirect (VIP-mediated) pathways (115, 116), which may drive brain state-dependent changes in microcircuit function (71, 117).

Origins of SST Deficits

Reduced SST expression or cell number/density is reported across several neuropsychiatric (e.g. MDD, SCZ, BPD) and neurodegenerative disorders (e.g. Alzheimer's, Parkinson's, and Huntington's diseases) (118). The fact that these findings span multiple brain regions and, at least in MDD, all cells across cortical layers, suggests a cell type-specific vulnerability affecting most, if not all, SST interneurons.

Several etiological factors contributing to SST cell deficits have been identified from preclinical and postmortem MDD studies. Mouse models of depression using unpredictable chronic mild stress (**UCMS**) or elevated glucocorticoid exposure recapitulated SST and GABA-related deficits (85). Sex differences have also been implicated, as MDD-related SST reductions are more severe in females (82, 83), who are twice as likely to develop mood disorders (119). Reduced neurotrophic support was also implicated, as human and animal studies demonstrated that decreased gene expression of SST or GABA-synthesizing enzymes occurred downstream from BDNF signaling deficits (18, 93).

Age strongly predicts SST expression levels, which decline over time (82, 120). Cross-sectional postmortem studies demonstrated progressive early reductions of SST in SCZ and MDD (120, 121), and BDNF-dependent genes in MDD (93), suggesting that accelerated brain molecular aging may contribute to SST cell vulnerability (120). Similarly, rodent chronic stress models showed altered SST cell function from disrupted cellular homeostatic mechanisms, including endoplasmic reticulum (**ER**) and mitochondrial-related oxidative stress (85, 118). ER stress is a form of cellular stress implicated in normal aging and neurodegenerative disorders, resulting from allostatic overload or extracellular stimuli impairing ER protein translation, leading to an accumulation of unfolded proteins. ER stress is countered by the unfolded-protein response signaling pathway that is mediated by protein kinase RNA-like endoplasmic reticulum (**Perk**)-mediated phosphorylation of eukaryotic initiation factor 2α (**Eif2a**). SST cell-specific suppression of Eif2a signaling was observed in UCMS and in chronically-elevated corticosterone mouse models, including highly correlated *Sst* and *Eif2a* expression. Notably, inhibition of Eif2a phosphorylation via PERK

reduced behavioral emotionality in UCMS-exposed mice (85), together suggesting that altered proteostasis may contribute to SST cell-selective vulnerability.

Excess ER load can also lead to reactive oxygen species accumulation, which is linked to inflammatory processes and cell death, and implicated in MDD pathophysiology (102). Notably, neuronal nitric oxide synthase and NADPH diaphorase, two reactive oxygen species-producing enzymes, are heavily expressed in SST interneurons, supporting the involvement of stress-inflammation processes in SST cell-specific vulnerability (122).

Reports of low SST expression or cell function across disorders suggests a dimensional contribution to psychopathology, converging at the cellular level on disrupted microcircuit information processing in cortical and cortical-like brain regions. How disrupted information processing manifests at the symptom level may depend on the biological context and brain region affected. For instance, preclinical studies have consistently demonstrated altered emotionality, cognitive deficits, and neuroendocrine changes associated with low SST and SST cell function (85, 91, 94–96). Importantly, reduced SST cell function may occur in different biological contexts across disorders, wherein interactions with distinct (e.g. cholinergic deficits in Alzheimer's disease) and/or overlapping pathophysiological deficits (e.g. low GABA or reduced BDNF-TRKB signaling in MDD, BPD, and SCZ) may lead to distinct clinical symptoms (123, 124). This is further impacted by interacting biological (e.g. age, sex) and environmental (e.g. stress) factors, together contributing to the heterogeneous association of a single pathology (i.e. low SST/SST cell) with multiple symptomatic presentations.

Target Engagement and Therapeutic Approach

Following evidence of GABA and SST disruptions, studies have investigated the potential of monitoring and remediating these deficits for antidepressant activity (Figure 2). First, recent insights into the mechanisms underlying TMS-induced cortical inhibition suggest utility for this tool to diagnose and treat MDD-related SST cellular deficits. In rodents, single-pulse TMS inhibition of sensory-evoked L5 PN dendritic activity was demonstrated to occur via recruitment of L1-L2/3 dendrite-targeting interneurons acting through $GABA_AR$- and $GABA_BR$-mediated inhibition (125), hence implicating both SST and neurogliaform interneurons (126, 127). Notably, SST interneuron inhibition is thought to occur mainly through α5-subunit-containing $GABA_ARs$, due to their preferential localization to extrasynaptic distal dendritic regions where they regulate tonic inhibition (128, 129), but also through $GABA_BRs$ (130). Therefore, considering well-characterized SST cell deficits, and lacking evidence of neurogliaform cell pathology, MDD-related deficits in SICI and LICI/CSP may reflect reduced dendrite-level inhibition via low SST interneuron function through $GABA_ARs$ and $GABA_BRs$, respectively (27, 28, 54). Similarly, increased GABA and cortical inhibitory function across antidepressant treatment modalities may reflect SST interneuron remediation, implicating these cells in the pathophysiology, diagnosis, and treatment of MDD.

Advances in understanding the mechanisms of rapid-acting antidepressants further implicate SST interneurons in putative therapeutic activity. Ketamine, an NR2B-subtype NMDAR

antagonist, and scopolamine, a mAChR antagonist, have converging mechanisms associated with a rapid “glutamate surge”, downstream activation of neurotrophic support pathways, and subsequent synaptogenesis, together with lasting antidepressant action (131, 132) (reviewed in: (133)). How these effects impinge on GABAergic cells are still being elucidated. However, it was recently demonstrated in mice that the antidepressant-like effects of scopolamine depend partially on mAChR antagonism specifically in mPFC SST cells (134), suggesting a mechanism involving PN disinhibition via suppression of SST-mediated inhibition. At first this seems inconsistent with evidence of MDD-related SST reductions and that low SST cell function is pro-depressive-like in animals (85, 91). However, rapid-acting antidepressant response is observed following drug clearance (134). Therefore, one possible explanation is that an immediate glutamatergic surge feeds-back to enhance GABAergic interneuron function on a longer scale (e.g., synaptogenesis), potentially through excitatory feedback afferents that preferentially recruit SST interneurons. Indeed, rapid-acting antidepressants increased recycling of both glutamate and GABA in rats (131). This idea is further supported by γ2-subunit knockout mice (exhibiting mild $GABA_AR$ deficits) that demonstrate elevated behavioral emotionality and a homeostatic-like reduction of glutamate synaptic function and receptor cell surface expression (135). Specifically, ketamine-treated γ2-heterozygous mice demonstrated reversal of glutamatergic synaptic deficits together with enhanced pre- and post-synaptic GABA function and antidepressant-like behavioral changes, suggesting that ketamine promotes GABAergic innervation in a GABA-deficient system (135). More specifically, work in cultured cortical and hippocampal murine neurons showed that ketamine selectively potentiated extrasynaptic $GABA_AR$–mediated tonic inhibition (136), a function fulfilled largely by α5-$GABA_ARs$, hence providing a putative mechanism reconciling acute SST cell blockade by rapid-acting antidepressants, with prolonged cellular effects ultimately leading to increased SST cell function. Notably, rapid-acting antidepressant mechanisms may also depend on subcortical structures, as ventral hippocampus inactivation prevented sustained antidepressant-like effects of ketamine in rats (137).

Recent preclinical work supports the potentiation of SST interneuron function as an antidepressant strategy. Increasing SST interneuron inhibitory input onto target neurons (through genetic deletion of the γ2-subunit gene restricted to SST cells) demonstrated antidepressant- and anxiolytic-like activity in mice (112). Directly enhancing post-synaptic targets of SST interneurons may represent an alternative strategy. Based on restricted corticolimbic distribution of α5-$GABA_ARs$ (138), and that these receptors partially mediate SST interneuron inhibition, SH-053-2′F-R-CH3, a compound with α5-selective positive allosteric modulation activity demonstrated antidepressant-like properties in female mice exposed to chronic stress (139). However, others found anxiolytic-, but not antidepressant-like effects of benzodiazepines, which act as $GABA_AR$ positive allosteric modulators, mediated specifically by α5-$GABA_ARs$ in rodents (140). Although depressive- and anxiety-like behaviors are closely related in animal models (141), a thorough behavioral characterization of SST interneuron potentiation will provide further insight on how deficits in this system contribute to symptom emergence. Interestingly, GABA-elevating pharmacological treatment (e.g. the anticonvulsant lamotrigine) showed evidence of antidepressant/anxiolytic action in BPD and MDD patients (142). Benzodiazepines also

showed efficacy comparable to tricyclic antidepressants in some studies (143), and may improve treatment response in TRD patients when combined with traditional pharmacotherapy (144). However, utility of benzodiazepines in treating MDD is not established and may be outweighed by a significant side-effect profile and abuse liability (145).

Note that others have also shown antidepressant-like action of an α5-selective negative allosteric modulator in chronic stress-exposed rats (146), potentially reflecting a feedback mechanism similar to that hypothesized for rapid-acting antidepressants. Alternatively, this may reflect a putative inverted-U effect for α5-$GABA_AR$ function, wherein both high and low function may have therapeutic potential. However, reducing α5-$GABA_AR$ function is predicted to worsen the pathology associated with low SST cell function; hence it is potentially associated with higher risk for long-term detrimental effects.

Preserving SST cell integrity may represent an additional antidepressant strategy. BDNF is selectively decreased in rodents following chronic stress and reversed by antidepressant treatment (147). BDNF signaling significantly contributes to SST cell markers (18, 93) and is necessary for rapid-acting antidepressant response (148). Chronic administration of 7,8-DHF, a BDNF receptor (TrkB) agonist, reversed elevated behavioral emotionality in UCMS-exposed mice and increased downstream expression of synaptic proteins that are reduced in MDD (149). Cell survival, dendritic growth, and increased neurotrophic pathway gene expression may therefore be critical to maintaining healthy SST interneuron function (see review: (150)).

Conclusion

Reduced SST expression and cell function is a replicated pathology in MDD which extends to other psychiatric and neurodegenerative disorders, suggesting a dimensional and potentially combinatorial contribution to symptoms across disorders (124). Evidence supports a role for SST interneurons in the antidepressant efficacy of current treatments and in experimental manipulations with fast-acting antidepressant-like activity (Figure 2). Together, this offers a unique opportunity for gaining insight into mechanisms underlying psychopathology, and for novel drug development in MDD and other brain disorders characterized by low SST cell function.

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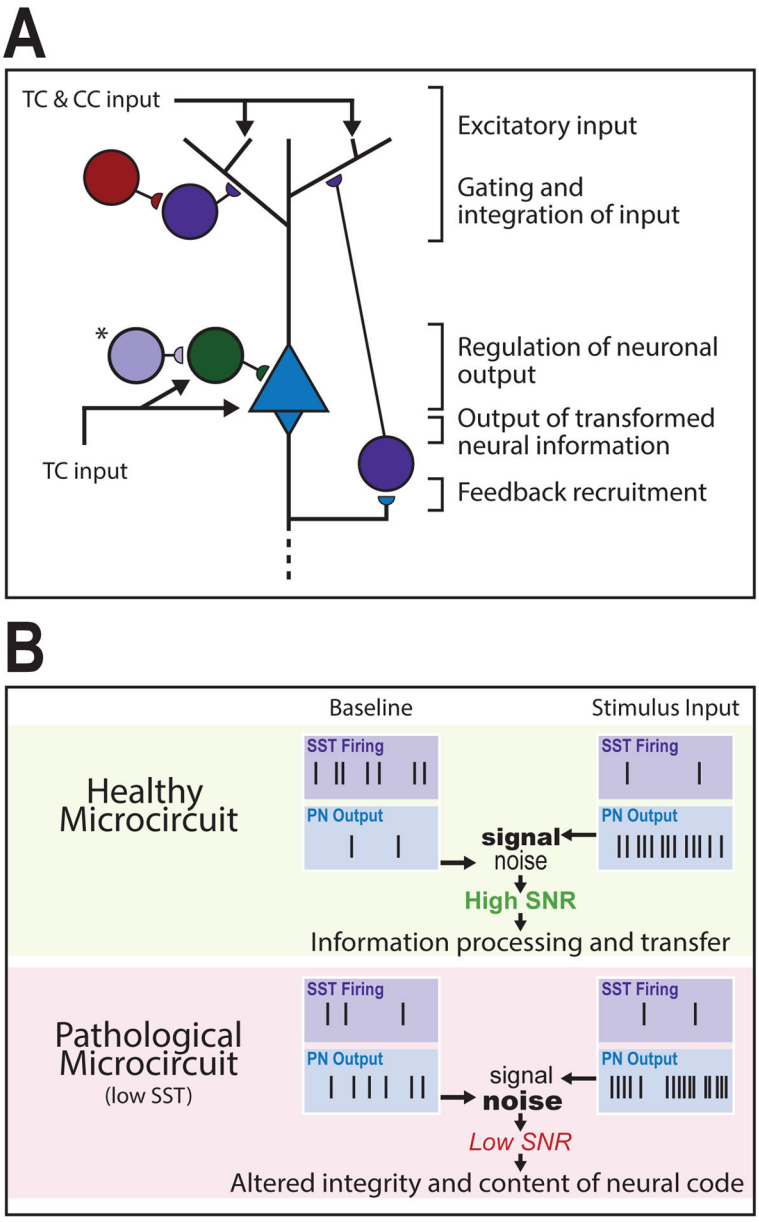

Figure 1. Cortical microcircuit roles and pathological consequences of low SST cell function

(A) Excitatory signals originate through thalamocortical (TC) and cortico-cortical (CC) projections that converge upon pyramidal neurons (PNs). Somatostatin-expressing interneurons (SST interneurons) primarily regulate gating and integration of dendritic input through PN feedback recruitment. Vasoactive intestinal peptide-expressing (VIP) interneurons inhibit supragranular SST interneurons to facilitate excitatory input. TC input targets the PN soma and parvalbumin-expressing (PV) interneurons simultaneously, generating low-frequency PN output that is regulated by PV feed-forward inhibition. (*), In layer 4 a distinct SST interneuron population targets PV interneurons for somatic disinhibition of PN output. Dendrite- and soma-level activity combines to drive PN output, which is propagated across cortical layers and brain regions. **(B)** In a healthy microcircuit

(top) at baseline, SST interneurons exhibit high spontaneous activity that maintains sparse PN activation. Upon stimulus input, SST interneurons reduce firing (e.g. through VIP-SST inhibition) resulting in sustained and ordered bursts of PN output. The difference between activated and baseline PN output patterns represents a signal-to-noise ratio (SNR) that facilitates coherent information processing and transfer. In a pathological microcircuit (bottom), low SST function is predicted to result in increased PN baseline activity (i.e., increased noise) and decreased regulation of stimulus-induced PN firing (i.e., altered signal) through altered input gating, disynaptic inhibition, and other disinhibitory roles, hence leading to low SNR and translating into altered integrity and content of neural code.

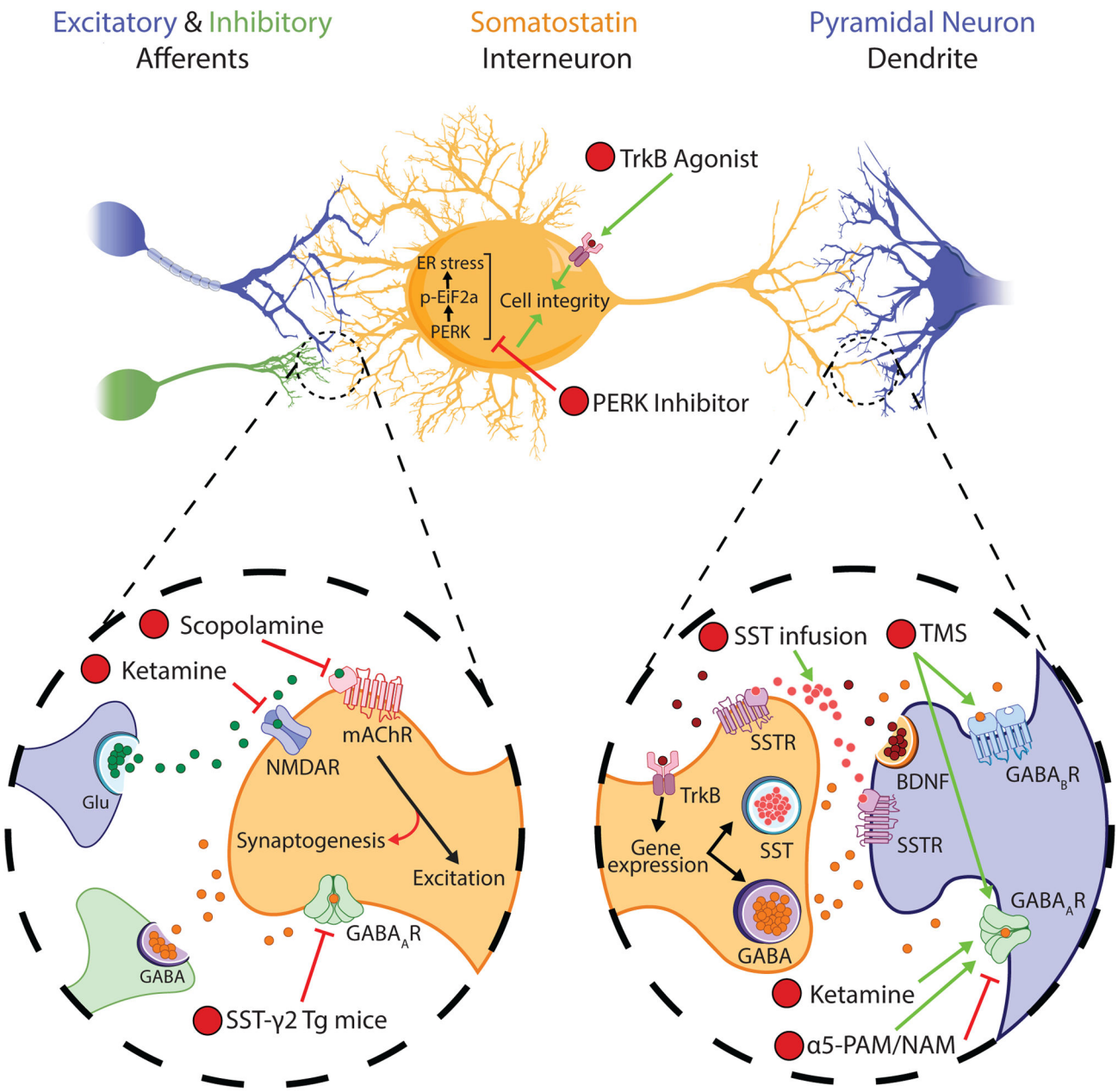

Figure 2. Targeting SST-expressing GABA interneuron signaling as an antidepressant strategy

(1) Preclinical studies demonstrate that antidepressant-like effects of the rapid-acting antidepressant scopolamine depends upon expression of mAChRs specifically in mPFC SST interneurons (134). **(2)** Further evidence suggests that the antidepressant-like effects of the NMDAR antagonist, ketamine **(2)**, may similarly occur through potentiation of GABA interneuron function. These drugs may converge on antagonism of receptors that drive excitatory activity of SST interneurons, resulting in a rapid cortical glutamatergic surge (through acute inhibition of SST interneurons) that feeds-back on a longer time-scale to promote SST interneuron function (e.g. through synaptogenesis or potentiation of α5-$GABA_A$ receptor (α5-$GABA_A$R) function (135, 136)). **(3)** Similarly, transgenic (Tg) mice

heterozygous for SST interneuron γ2-$GABA_A$R-subunit knockout demonstrate an antidepressant- and anxiolytic-like behavioral profile, putatively resulting from disinhibition of SST interneuron function (112). Experimental compounds that promote SST cell integrity, e.g., by increasing brain-derived neurotrophic factor (BDNF)-TrKB signaling **(4)** or inhibiting protein kinase RNA-like endoplasmic reticulum (PERK) and therefore endoplasmic reticulum (ER) stress **(5)**, have shown antidepressant-like action in rodent stress models (85, 149). **(6)** Interventions that potentiate the post-synaptic modulators of SST interneuron inhibition also show potential for monitoring and remediating SST interneuron deficits. Notably, pharmacologic α5-$GABA_A$R positive and negative allosteric modulation (α5-PAM/NAM) show antidepressant-like activity in mice (139, 146). **(7)** In human, transcranial magnetic stimulation (TMS) has efficacy in patients with treatment-resistant depression (45), and was recently demonstrated in rodent to induce cortical inhibition through recruitment of dendrite-targeting supragranular interneurons acting through $GABA_A$R- and $GABA_B$R-mediated neurotransmission, putatively implicating SST interneurons in the antidepressant effects of TMS (125). **(8)** Finally, direct infusion of SST or SST agonists into corticolimbic brain regions produces antidepressant-like effects in rodents (87–90). Glu, glutamate; GABA, γ-aminobutyric acid; NMDAR, N-methyl-D-aspartate receptor (NR2B subunit-containing); mAChR, muscarinic acetylcholine receptor (m1 subtype); p-Eif2a, phosphorylated eukaryotic initiation factor 2α; TrKB, tropomyosin receptor kinase B; SSTR, somatostatin receptor (pre- and post-synaptic).