Chapter 28

Altered GABAergic Function, Cortical Microcircuitry, and Information Processing in Depression

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ABBREVIATIONS

1H-MRS	proton magnetic resonance spectroscopy
ACC	anterior cingulate cortex
AD	antidepressant
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BOLD	blood-oxygen level-dependent
CC	corticocortical
CM	cortical microcircuit
CP	conditioning pulse
CSF	cerebrospinal fluid
CSP	cortical silent period
dlPFC	dorsolateral prefrontal cortex
DMN	default mode network
DSM	diagnostic and statistical manual of mental disorders
EEG	electroencephalography
EIB	excitation-inhibition balance
eIF2	eukaryotic initiation factor 2
EMG	electromyography
EN	executive network
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GAD	glutamate decarboxylase
LICI	long-interval cortical inhibition
mAChR	muscarinic acetylcholine receptor
MDD	major depressive disorder
MEP	motor-evoked potential
MRI	magnetic resonance imaging
NMDAR	*N*-methyl-D-aspartate receptor
OC	occipital cortex
PERK	protein kinase R-like endoplasmic reticulum kinase
PV	parvalbumin
PYC	pyramidal cell
RDoC	research domain criteria
rTMS	repetitive transcranial magnetic stimulation
SCZ	schizophrenia
sgACC	subgenual anterior cingulate cortex
SICI	short-interval cortical inhibition

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SSRI	selective serotonin reuptake inhibitor
SST	somatostatin
TC	thalamocortical
TMS	transcranial magnetic stimulation
TP	test pulse
TRD	treatment-resistant depression
UCMS	unpredictable chronic mild stress
VIP	vasoactive intestinal peptide
WT	wild type

INTRODUCTION

The profound mood and cognitive impairment associated with major depressive disorder (MDD) represents an immense individual and societal burden for the 300 million people affected worldwide [1]. Current antidepressant (AD) pharmacotherapy typically consists of a selective serotonin reuptake inhibitor (SSRI) or similar monoaminergic treatment (e.g., serotonin-norepinephrine reuptake inhibitors). Although these ADs are effective in ~50% of patients, an equal number of patients are left with minimal or no symptom remission, even after repeated AD trials [2]. The need for, and development of, the next generation of ADs is an overarching theme of this book. In this chapter, we will explore the viability of targeting deficits in inhibitory neurotransmission as a novel AD modality with potential to remediate not only mood, but cognitive symptoms in MDD.

Cortical Microcircuits (CMs): Functional Units of the Cortex

The majority of the cerebral cortex is comprised of 6 layers, though some layers are lacking in certain regions or are less distinct (e.g., the anterior cingulate cortex lacks L4) [3]. These layers contain excitatory, glutamatergic pyramidal cells (PYCs) and multiple types of inhibitory interneurons which signal via γ-aminobutyric acid (GABA). PYCs and interneurons form microcircuits that regulate cortical excitation at the single cell and population level, together contributing to neuronal information processing [4]. Three primary subtypes of interneurons are defined by non-overlapping expression of molecular markers: somatostatin (SST), parvalbumin (PV), or the ionotropic serotonin receptor ($5HT3_a$), of which vasoactive intestinal peptide (VIP) neurons are a subset. For the remainder of this chapter, we will refer to interneurons subtypes by these markers, e.g., SST-positive interneurons as SST neurons. Although commonly cited ratios of these interneurons are, approximately, 40% PV, 30% SST, and 30% $5HT3_a$, the division of interneuron subtypes varies considerably across cortical layers and brain regions. For instance, VIP neurons are overrepresented in superficial layers, compared to deeper layers which contain a greater proportion of SST and PV neurons [5]. However, PV neurons generally show less drastic variations across layers compared to SST neurons. Mouse studies have found that regions analogous to human frontal cortical structures (such as the prelimbic, infralimbic, and orbital frontal cortices) have an increased proportion of SST neurons across layers, compared to other regions [5]. Interneuron subtypes target distinct regions of the PYC, having important functional consequences (Fig. 1) and considerable diversity in connectivity, laminar distribution, and electrophysiological properties (see [4] for a comprehensive review). Here, we will give only a brief overview of their characteristics for the sake of brevity.

PV neurons are distributed across L2-6, and target the perisomatic region (basket cells) or axon initial segment (chandelier cells) of PYCs, thus regulating PYC output. Excitatory thalamocortical (TC) inputs in deeper layers target both PYCs and PV neurons, thus PV neurons regulate both the overall activity of PYCs and the synchrony of local PYC firing (via PV-PV connections). SST neurons are distributed in L2-6 and primarily target PYC dendrites (Martinotti cells—L2/3 and L5/6), regulating excitatory TC and corticocortical (CC) inputs onto PYCs. Preferential targeting of SST neurons by recurrent PYC activity positions these interneurons to mediate feedback inhibition, and high spontaneous activity of SST neurons at rest contributes to low resting PYC activity. A distinct subgroup of L4 SST neurons (non-Martinotti cells) target PV neurons and disinhibit PYCs. VIP neurons are similarly distributed across L2-6, but are enriched in L2/3, and primarily target SST neurons, thus disinhibiting PYCs. VIP neurons are driven primarily by CC excitatory and subcortical neuromodulatory inputs, thus PYC disinhibition is typically activity-dependent (i.e., top-down).

Excitation Inhibition Balance (EIB): Importance to Healthy Brain Functioning

In addition to the primary axon projections of PYCs targeting other cortical or subcortical regions, these cells also synapse onto interneurons, thus regulating their own activity through a process called feedback inhibition, contributing to an

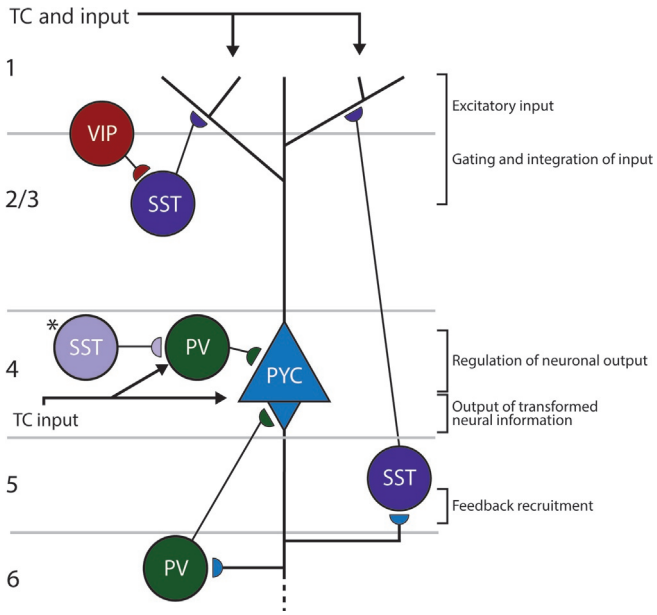

FIG. 1 Canonical organization of the cortical cell microcircuit. Excitatory signals from thalamocortical (TC) and corticocortical (CC) projections converge on PYC dendrites (TC and CC) or the soma (TC). Somatostatin (SST) neurons (Martinotti cells) in L2/3 and deeper layers (L5 here) regulate gating and integration of dendritic input, through PYC feedback recruitment. VIP neurons inhibit L2/3 SST neurons to facilitate excitatory TC and CC input. PV neurons inhibit the soma of PYCs (L4 shown), axon initial segment (L6 shown), and other PV neurons (not shown). L4 TC input targets PYCs and PV neurons simultaneously, generating low-frequency PYC output that is regulated by PV feed-forward inhibition. In L4 (see asterisk [*]), a population of non-Martinotti SST neurons target PV interneurons, facilitating somatic disinhibition of PYC output. Integration of superficial and deeper inhibitory and excitatory activity combines to drive PYC output, which is propagated across cortical layers and brain regions. *(Adapted from Fee et al. [23].)*

intrinsic balance between excitation and inhibition [4]. Maintenance of the EIB is critical for proper brain functioning, as uncontrolled excitation leads to seizure and excessive inhibition (e.g., propofol overdose) leads to silencing of brain activity which can result in respiratory depression and death [6, 7]. Aside from these life-threatening instances, changes in EIB have been reported across a number of psychiatric and neurodevelopmental disorders including autism, Rett syndrome, Dravet syndrome, schizophrenia (SCZ), bipolar disorder (BD), and MDD [8–14]. EIB changes do not refer to simply an imbalance of excitation and inhibition, but can be conceptualized as changes in the threshold of cellular activation, or in the level of activity at which the balance is maintained (analogous to changing a homoeostatic set-point to a greater or lower level). Measures of EIB changes vary across these studies, though the shared substrate among measures is ultimately an alteration in GABA or glutamate signaling. Directionality of these changes varies between disorders, wherein MDD patients are generally characterized as having deficits in inhibition [15–18].

Relevance of EIB Changes to Network Activity of the Depressed Brain

Although changes in EIB have been widely reported in MDD, the functional implications of these changes for brain function and, ultimately, MDD symptomatology are not fully understood. Some evidence comes from investigations utilizing resting-state functional magnetic resonance imaging (fMRI) to investigate default mode network (DMN) activity [19, 20]. The DMN is a collection of brain regions that show correlated co-activation at resting-state (i.e., internal focus or in the absence of a cognitive task), including the anterior cingulate cortex (ACC), posterior cingulate cortex, hippocampus, and amygdala [20, 21]. Conversely, the executive network (EN), of which the dorsolateral prefrontal cortex (dlPFC) is a key member, is recruited in an opposite manner during internal/external focus. Thus, in healthy individuals, the ACC and dlPFC show reciprocal patterns of activation—greater ACC activity is associated with decreased dlFPC activity and vice versa. At the network level, a similar reciprocal pattern of activity is observed between the DMN and EN.

Consistent with MDD symptoms such as decreased external focus, increased self-reference, and rumination, the dlPFC shows decreased resting-state activity and the ACC shows increased activity [21, 22]. These changes in resting-state activity result in a disruption in the normal reciprocal activity between these two regions. Furthermore, there is evidence to suggest that these alterations may be mediated by deficits in inhibitory neurotransmission in the DMN and alterations in EIB at the cellular and microcircuit levels [21, 23]. The notion that deficits in individual neuron populations can lead to alterations in EIB, leading to brain activity alterations and then to depressive symptoms, is the basis of this chapter.

In this chapter, we will outline the historical and recent evidence regarding EIB changes in MDD and explore their potential cellular bases. In doing so, we will follow a "top-down" approach in which we present supporting evidence from clinical studies in humans, then postmortem investigations of MDD subjects, followed by insights from relevant rodent models, culminating with implications for the development of novel treatments targeting EIB changes in MDD.

EVIDENCE OF GABA DEFICITS FROM CLINICAL STUDIES

Clinical studies measuring *in vivo* GABA levels or function have done so using four modalities: (1) measuring GABA concentrations in the cerebrospinal fluid (CSF) of MDD and control patients, (2) measuring plasma concentrations of GABA, (3) utilizing proton magnetic resonance spectrometry (^{1}H-MRS) to examine GABA levels *in vivo*, (4) using transcranial magnetic stimulation (TMS) paired with electromyography (EMG) to measure *in vivo* functionality of GABA neurotransmission.

CSF GABA Levels in MDD

The first evidence of GABA deficits in MDD came from a study published in 1980 by Barry Gold and colleagues. CSF GABA levels were decreased in a heterogeneous group of depressed subjects (2/3 MDD, 1/3 SCZ) compared to a heterogeneous "control group," including cerebrovascular disease patients and true healthy controls (HC) [24]. Subjects were AD-abstinent for 2 weeks, not AD antidepressant-naïve—the gold-standard for controlling against medication effects. Subsequently, decreased CSF GABA levels were reported in three independent samples of MDD patients ($N = 26$–41) [25–27]. Interestingly, no GABA alterations were observed in manic BD or SCZ patients in two of these studies, though sample sizes were limited [25, 27]. Lastly, supporting a theory of persistent deficits, decreased GABA is reported in euthymic, medication-free BD and MDD patients [28]. These CSF studies are presented mainly for historical context as they are limited in number, are generally powered to observe only large effects, and involve considerable patient heterogeneity—though such limitations seem to be perennial and still impact current research. Despite this, CSF GABA levels are generally decreased in MDD, with weaker evidence of reductions in other disorders. The persistence of such deficits across mood episodes and bouts of treatment is suggestive of a trait marker for MDD.

Plasma Levels of GABA in MDD

Circulating GABA levels show similar patterns as CSF. Plasma GABA investigations have primarily been conducted by Frederick Petty and colleagues over nearly 15 years. Shortly after initial CSF findings, decreased GABA levels in plasma were reported, though early studies were inconsistent. One report found decreased GABA in 34 medicated, depressed patients [28], whereas no significant changes were observed in a combined bipolar/unipolar depression sample of 9 patients [29]. Subsequent studies achieved greater homogeneity in diagnostic groups and observed significantly lower plasma GABA in MDD patients across numerous replication studies ($n = 48$–107) [30–34]. Plasma GABA deficits are also present in BD, particularly in depressive episodes and euthymia, with weaker evidence during mania [32, 35].

Interestingly, MDD patients with melancholic depression, of which anhedonia is a core symptom, showed particularly robust plasma GABA deficits [33, 36]. Furthermore, in a 4-year longitudinal study of male MDD patients, initial GABA levels were decreased, and this difference remained stable at follow-up, suggestive of persistent deficits [31, 33]. In summary, plasma GABA is most robustly decreased in MDD patients, in a trait-like manner, with some evidence of similar deficits in BD. In keeping with the NIMH Research Domain Criteria (RDoc) conceptualization of symptom dimensions [37], rather than DSM-based disorder classifications, anhedonia may be a particularly salient construct to which GABA deficits may contribute.

The publication bias towards male populations in the plasma GABA literature is a notable limitation, given the 2:1 prevalence of MDD in females versus males [38]. Future longitudinal studies of plasma GABA should endeavor to recruit sufficient samples to examine potential sex-based differences. Another primary limitation of both plasma and CSF GABA studies is the question of their relation to GABA levels in the brain. CSF and brain GABA levels are correlated in neurodegenerative diseases, but this association has not been established in neurologically intact subjects [39, 40]. Active transport systems facilitate CSF GABA movement to the plasma, and reports generally support a correlation between CSF and plasma levels [32]. As such, plasma and CSF levels may be relevant as diagnostic aids or a risk marker of MDD.

GABA Measured by ^{1}H-MRS: A Window into the Living Brain

The use of ^{1}H-MRS to determine GABA levels bypasses the limitations of peripheral measures by allowing measurement of GABA in particular brain regions *in vivo*. As discussed above, the regions of the DMN are particularly relevant to the neurobiology of MDD and these have been among the most studied regions. In initial investigations, the occipital cortex (OC) was primarily studied due to the technical ease of measurement in this region [41–45]. Decreased GABA has been observed in the OC, and this appears to be persistent across treated and untreated currently depressed patients [44, 46].

Interestingly, although the OC is not part of the DMN, studies of DMN regions have shown similar reductions—suggesting more pervasive GABAergic deficits. Specifically, GABA is decreased in the dlPFC and dorsomedial PFC of currently depressed patients [47], glutamate/GABA ratio is increased in the dlPFC of remitted MDD patients [48], and GABA is decreased in the ACC generally [41, 47, 49, 50].

Secondary analyses of DMN studies reveal interesting findings beyond simply decreased GABA. First, elevated glutamate/GABA ratio was correlated with an earlier age of MDD onset, suggestive of either a potential risk factor or co-occurring change over time. Second, GABA deficits in ACC and OC are most robust in MDD patients presenting with anhedonia [44, 49]. Third, reduced GABA in the ACC has been reported across psychiatric disorders with shared symptoms, most notably panic disorder [42, 51]. When taken together, these studies provide further support for decreased GABA as a trait marker.

Although the field is somewhat limited by a publication bias in early studies toward the OC, deficits are reported across MDD-relevant regions. There is remarkable consistency in GABA deficits across investigational approaches, despite the unclear relationship between brain-CSF-plasma findings. GABA deficits have been reported across the brain and, in the DMN, were most robust in the ACC, though not always reported [41, 47, 49, 50, 52]. However, the functional significance of these deficits cannot be inferred from ^{1}H-MRS alone, since tissue GABA levels reflect a combination of both intra- and extracellular GABA, not vesicular GABA levels or magnitude of GABA release [53].

To address these limitations, a handful of combined MRS-fMRI studies have provided partial insight into the relationship between GABA changes and region-level activity. Specifically, in HC subjects, resting-state blood-oxygen-level-dependent (BOLD) signal in the ACC is predicted by ACC GABA levels, but not glutamate [54]. In MDD, glutamate, but not GABA levels, significantly predict ACC BOLD signal [55]. This suggests EIB changes in the ACC, with an increased regulatory role for glutamate signaling, consistent with expected functional consequences in the context of GABA deficits. How regional neurotransmitter changes directly relate to EIB changes is unclear however, and although BOLD signal is generally regarded as reflecting neuronal activity, this is not always the case [56]. Even if one assumes that it is reflective of such activity, GABAergic and glutamatergic neurons cannot be dissociated solely on the basis of BOLD signal alone. Thus, measures more proximal to neuronal function are required.

TMS-EMG: Measuring the Functionality of the GABA System

TMS temporarily and non-invasively activates cortical regions using directed magnetic fields. Single and paired-pulse TMS-EMG testing paradigms can be used to measure GABA neurotransmission *in vivo* in the motor cortex. Short-interval cortical inhibition (SICI) and long-interval cortical inhibition (LICI) are paired-pulse paradigms involving a submotor-threshold conditioning pulse (CP)-administered 1–4 ms (SICI) or 50–200 ms (LICI) before a supra-threshold test pulse (TP). The decrease in the resultant motor-evoked potential (MEP) caused by the CP, compared to the TP alone, partly reflects $GABA_A$(SICI)- or $GABA_B$(LICI)-mediated inhibition [17]. The application of a single pulse during voluntary muscle activation results in the cortical silent period (CSP), during which no EMG background activity is observed [17]. CSP duration is reflective of both $GABA_A$- and $GABA_B$-mediated inhibition [57]. EMG outputs limit inhibitory measures to the motor cortex, though EEG paradigms have been developed which allow measurement from any cortical region. In a treatment-resistant MDD (TRD) population undergoing magnetic seizure therapy it was found that greater baseline N100 responses (EEG correlate of CSP) in the dlPFC correlated with greater treatment response [58]. However, the study contained no HC group, and thus, N100 deficits could not be confirmed.

The first evidence of altered cortical inhibition came from a study of 16 medicated, currently depressed MDD and 19 HC subjects, in which the CSP was significantly longer in MDD subjects [59]. This was not replicated in later studies and, indeed, the opposite directionality has been well-replicated. The first study showing shortened CSP, and thus deficient inhibitory signaling, investigated 20 unmedicated, depressed MDD patients [60]. This study also reported reduced SICI and a negative correlation between SICI and depressive symptom severity. A study of 35 medicated, depressed MDD patients and 35 HC replicated the CSP and SICI deficits, and negative correlation between SICI and symptom severity [61]. The presence of CSP deficits in both medicated and unmedicated subjects suggests that these deficits are not reversed by AD treatments. As shown in recent studies, SICI deficits appear more specific to TRD.

In a landmark TMS-EMG study of 25 depressed TRD, 19 unmedicated euthymic MDD, 16 unmedicated depressed MDD, and 25 HC subjects, CSP duration was decreased across all MDD groups compared to HC [17]. Substantial SICI deficits were observed in the TRD group only. No relationship between medication status and inhibitory measures was observed. A recent meta-analysis found that, across all TMS-EMG studies in MDD, CSP is shortened and SICI is decreased, though SICI deficits have almost exclusively been found in TRD subjects [62]. There is evidence of inhibitory deficits across psychiatric disorders, with SCZ showing the most consistent deficits (in SICI specifically) [9, 62]. Lastly, the fact

that TMS-EMG studies assess motor cortex-specific inhibition does not mean that the observed deficits are confined to the motor cortex, but rather reflects an inherent limitation of the available techniques. Future studies examining cortical inhibitory deficits in key regions of interest (e.g., DMN and EN regions) using EEG paradigms will be of great value.

Summary of Clinical Evidence

These clinical studies provided some of the initial findings of GABA deficits in MDD, and their potential implications for brain EIB. Decreased GABA has been identified in the plasma, CSF, and several brain regions of interest (via ^{1}H-MRS) and has been well-replicated in each setting. On a functional level, cortical inhibitory deficits reported in MDD subjects are consistent with an EIB shift toward decreased inhibitory function. It is important to note that *GABA deficits are not ubiquitous across all MDD subjects*, and that groups of *MDD patients tend to have lower GABA* than HC subjects on average. Nevertheless, this GABA deficit appears to be trait-like and is present in symptomatic and euthymic patients regardless of medication status. Furthermore, although there is evidence of GABA levels (across all four investigational levels) normalizing with *successful* AD treatment, the vast majority of studies that include both medicated and unmedicated MDD subjects find no significant differences in their particular index of GABA levels. This question has not been definitively answered, but may only be relevant in patients who exhibit a certain severity of GABA deficit.

Finally, GABA deficits are present across multiple psychiatric disorders with shared symptomatology and etiology (i.e., SCZ, BD, panic disorder). These deficits also seem to associate more strongly with anhedonia than other distinct symptom dimensions. The observation of a similar pathology across different disorders raises the possibility that different (mal)adaptations to decreased GABA occur in each disorder, or that decreased GABA in the context of different comorbid pathologies has distinct impacts on symptomatology. Alternatively, GABA may be decreased through different mechanisms across disorders and these upstream factors may lead to differential symptom emergence. In either case, a deeper understanding of the nature of GABA deficits in MDD is required to develop ADs targeting these deficits.

Postmortem EVIDENCE OF GABA DEFICITS

Investigations of human postmortem brains provide multiple advantages over clinical studies, in addition to unique challenges and limitations. Most clearly, postmortem studies allow for direct measurement of neurotransmitters, proteins, and gene expression (mRNA) in distinct brain regions with the ability to observe such changes with a high degree of spatial resolution via microscopy techniques. However, these studies are limited by sample availability (typically small samples), a general lack of detailed symptom information beyond diagnostic category, variability in sample integrity measures across cases (e.g., postmortem interval, RNA integrity, brain pH), and varying causes of death, particularly with respect to suicide.

GABA Deficits in Postmortem MDD Brains: Replication and Extension of Clinical Findings

Postmortem investigations of GABA, GABA receptors, and glutamate decarboxylase (GAD) 65 and GAD67, enzymes which synthesize GABA, have identified GABA deficits albeit with some contradictory findings across studies. Early research, using heterogeneous depressed populations, found decreased GAD levels across the brain [63], though this finding was not replicated in a study of the PFC [64]. More recently, dlPFC protein levels of GAD67 (expressed throughout the cell), but not GAD65 (expressed in nerve terminals), were found to be significantly lower in unmedicated MDD subjects [65]. Medicated subjects had no GAD67 changes compared to HC, suggesting normalization with treatment, whereas GAD65 showed no differences between MDD and HC. However, GAD65 and GAD67 were significantly increased in the dlPFC, orbitofrontal cortex, and hippocampus of BD and MDD subjects in a separate study [66]. Aside from methodological heterogeneity across studies, a main limitation in understanding the nature of this GABA pathology is the ubiquity of GAD across interneuron types, given their diversity.

Initial interneuron-specific investigations did not use non-overlapping markers to distinguish cell types, presumably due to limited knowledge about the coexpression of these markers. For instance, a study examining the density of PV-, calbindin-, and calretinin-neurons in MDD, SCZ, BD, and HC subjects in the ACC found no significant differences in cell density in MDD, but decreased density of L2 calbindin-neurons in BD and SCZ [67]. Calbindin is expressed in subsets of PV and SST neurons, and calretinin is expressed in subsets of SST and VIP neurons, thus limiting precise conclusions [4]. Further work in the dlPFC found decreased CB-neurons in MDD, decreased L6 PV expression, and replicated the lack of change in calretinin [68, 69]. These studies indicate changes in GABAergic interneuron density in MDD, though methods of determining cell density are inconsistent and often simply measure overall expression. Considering this, these findings may reflect dysfunctional neurons instead of neuron loss, but are still generally suggestive of GABA deficits.

Studies employing large-scale transcriptomic analyses via oligonucleotide-based microarrays, and more recently, whole-transcriptome RNA sequencing have been able to simultaneously measure the expression of thousands of genes. Although space constraints limit a thorough summary of the extant literature, and statistical/analytical methods vary widely, it is almost universally reported that gene expression is disrupted in the ACC and PFC of MDD subjects. In both regions, altered expression of GABA and glutamate signaling-related genes is well-replicated, with GABA and glutamate receptors being consistently altered [70–73]. GABA receptors are generally downregulated in the ACC and upregulated in the PFC, consistent with fMRI findings discussed earlier. An investigation integrating information from multiple MDD microarray (across multiple regions) and genomics studies found that a core "module" of genes differentially coexpressed in MDD subjects was enriched in glutamate receptor, GABA receptor, and neurotrophic factor genes [74]. The finding that glutamate receptors and other measures of glutamate signaling are altered alongside GABA signaling in MDD is unsurprising given the functional relationship between these neurotransmitters in maintaining EIB.

SST-Neuron Dysfunction as a Key Contributing Pathological Substrate of MDD and Other Psychiatric Disorders

In addressing the limitations of interneuron investigations, our research group has identified SST neurons as a vulnerable interneuron subtype in psychiatric disorders. Initially, in a study of 19 matched triads of HC-MDD-BD subjects, it was observed that SST expression (mRNA) was significantly reduced in the dlPFC of MDD subjects and trended toward a reduction in BD subjects [75]. This reduction was further confirmed by a decrease in the precursor protein, prepro-SST, as assessed via western blot. Decreased SST mRNA was also found in the amygdala [76], and decreases in both SST and prepro-SST were identified in the subgenual ACC (sgACC) [77]. Further study in the sgACC replicated these findings in both males and females [78]. This decrease was present across all cortical layers in the sgACC, suggesting a widespread SST neuron-selective deficit, and has been identified as a decrease in SST expression *per cell*, rather than a loss of SST neurons [77]. However, recent evidence from the amygdala shows decreased SST neuron density in the lateral, basolateral, and basomedial amygdala and decreased SST cell density in the basomedial amygdala of female MDD subjects [79]. Although clearly decreased in MDD, SST deficits may occur differently across brain regions in MDD. Interestingly, given the high prevalence of MDD in females, SST reductions are observed in both sexes across studies, but are more robust in females.

SST deficits are also observed in large-scale transcriptomic studies in MDD, with SST and genes coexpressed with SST (e.g., cortistatin, neuropeptide Y) showing robust downregulation, even in the context of thousands of measured genes [76]. Interestingly, the patterns of altered gene expression are reminiscent of those observed in two mouse models of reduced brain-derived neurotrophic factor (BDNF) function [76]. BDNF is reduced in MDD and is a known regulator of SST, cortistatin, neuropeptide Y, and GAD65 expression, suggesting that SST deficits and reduced GABA function may occur downstream of BDNF deficits [80].

SST deficits, as with GABA deficits more generally, have been reported in other psychiatric disorders. Although not examined in the same detail as in MDD, decreased SST in the dlPFC of BD subjects was noted above, and other studies have found decreased SST expression and cell density in the hippocampus [81] and caudal entorhinal cortex [82]. Similarly, in SCZ subjects, studies have found decreased expression of SST in the dlPFC [83, 84] and decreased SST neuron number and density in the hippocampus [85] and caudal entorhinal cortex [82]. The fact that SST deficits are present across disorders and serve as a potential origin for GABA deficits observed in other research methodologies begs the question—are these SST deficits causally involved in depression?

INSIGHTS FROM ANIMAL MODELS

Studies in mice are well-suited to answering questions posed in the previous section, given the large host of transgenic tools available to manipulate the expression of individual genes of interest in regional and temporal manners.

SST Neurons Are Causally Involved in Depressive-Like Behavior and Are Selectively Vulnerable to Dysfunction

Mice lacking the *Sst* gene (Sst^{KO}) show significantly elevated baseline (in the absence of stress) depressive-like behavior across multiple tests measuring anxiety-, helplessness-, and anhedonia-like behaviors (collectively referred to as

"emotionality") compared to wild-type (WT) mice [86]. This increased emotionality persists after exposure to unpredictable chronic mild stress (UCMS). UCMS consists of a 4- to 6-week series of 1–3 daily social-environmental stressors, which causes progressive physiological (increased corticosterone, fur quality deterioration) and behavioral (increased emotionality) changes that are reminiscent of MDD [86, 87]. Interestingly, Sst^{KO} and Sst^{Het} (50% of WT *Sst* expression) mice both show reduced BDNF in the cingulate cortex, despite conventional descriptions of *Sst* as a BDNF-dependent gene, suggesting a bi-directional regulation of these genes. Sst^{KO} mice also show decreased *Gad67* and cortistatin. Taken together, *Sst* ablation demonstrably results in increased emotionality and MDD-like changes in the expression of GABA-related genes. Other work has shown that acute, but not chronic, chemogenetic inhibition of SST neurons in the PFC is sufficient to induce elevated emotionality in mice [88]. This further supports a role for SST neurons in depressive-like behavior, but suggests that other brain regions or cell types may contribute to the long-term adaptations involved in depression.

Microarray profiling of SST neurons and PYCs from UCMS-exposed and control mice demonstrates that SST neurons undergo a wide range of gene expression changes in response to stress, whereas PYCs show relatively few. This suggests that SST neurons are intrinsically vulnerable to stress, a well-known precipitating factor for major depressive episodes [89, 90]. Bioinformatics analyses revealed that the most disrupted biological pathway in SST neurons was eukaryotic initiation factor 2 (*eIF2*) signaling, which is involved in protein synthesis. A key member of this pathway, *eIF2a*, was decreased in SST neurons of UCMS-exposed mice and was highly correlated with *Sst* expression. Cellular stress can result in increased numbers of unfolded or misfolded proteins which activate the unfolded protein response, leading to phosphorylation and deactivation of eIF2a. Most interestingly, chronic administration of an inhibitor of the primary eIF2a kinase (PKR-like endoplasmic reticulum kinase—PERK), i.e., pharmacological blockade of the SST-specific and UCMS-induced eIF2a dysregulation, showed AD-like effects by blocking the development of emotionality in UCMS-exposed mice. SST neurons appear to have an intrinsic vulnerability in their response to stress involving downregulation of genes involved in GABA signaling, which is not shared by PYCs and is necessary for the development of stress-induced emotionality.

FUNCTIONAL EFFECTS OF SST PATHOLOGY

We have recently put forward two models, using different scale perspectives, to conceptualize how SST deficits (1) affect microcircuit function and (2) translate into altered neural network activity and ultimately MDD symptoms (see [23] and [21], respectively, for comprehensive reviews).

At the microcircuit level, decreased SST neuron function can be conceptualized as a change in the regulation of PYC activity at baseline and during excitatory input. Recalling the microcircuit connectivity from the beginning of this chapter, excitatory TC and CC inputs in upper layers are integrated by SST neuron inhibition of PYC dendrites (and upstream modulation by VIP neurons), which is summated with TC inputs in L4 (modulated by PV and SST neurons) to yield PYC output patterns. The change in PYC output between baseline and activated states, referred to as the signal-to-noise ratio (SNR), contributes to "code" neural information [91]. The effects of decreased SST neuron function are manifold (Fig. 2A). First, baseline PYC activity will be increased, due to reduced dendritic inhibition and tonic firing of SST neurons, which is corroborated by experimental evidence showing that acute optogenetic inhibition of SST neurons increases PYC activity [92]. Second, reduced feedback inhibition of PYCs via SST neurons may result in altered stimulus-induced PYC activation. Third, the increased baseline and altered stimulus-induced PYC activation will lead to a decreased SNR, resulting in disruptions in the neural code, which is then transmitted through the brain. These functional changes in the microcircuitry are predicted to (1) impair the integrity of CC (internal) information processing and (2) reduce TC (external) information input and integration due to decreased L4 non-Martinotti cell-mediated inhibition of PV neurons.

These alterations in information processing may lead to different disruptions across brain regions and ultimately to the altered network activity alluded to earlier in this chapter (Fig. 2B). In the ACC, both SST [78] and PV [80] reductions have been reported in MDD, indicating decreased dendritic and perisomatic inhibition of PYCs. Additionally, in the absence of L4, TC input terminates on deep L3 PYCs, making the effect of these deficits on TC input integration unclear and such effects are not well-understood. Consistent with a role for thalamocortical input in internal focus, this provides a microcircuit basis for increased resting-state ACC and DMN activity and subsequently increased self-focus/rumination in MDD patients. Conversely, in the dlPFC, decreased SST, but not PV levels [75], have been reported. In this case, PYCs would still lack functional dendritic inhibition, but perisomatic inhibition would presumably remain relatively intact. Furthermore, increased PV neuron-mediated inhibition of PYCs, due to deficits in L4 non-Martinotti cells, would result in the disruption of TC inputs described above. The net effects on PYCs are consistent with decreased resting-state activity in the dlPFC and EN described above and a decreased external focus observed in MDD patients.

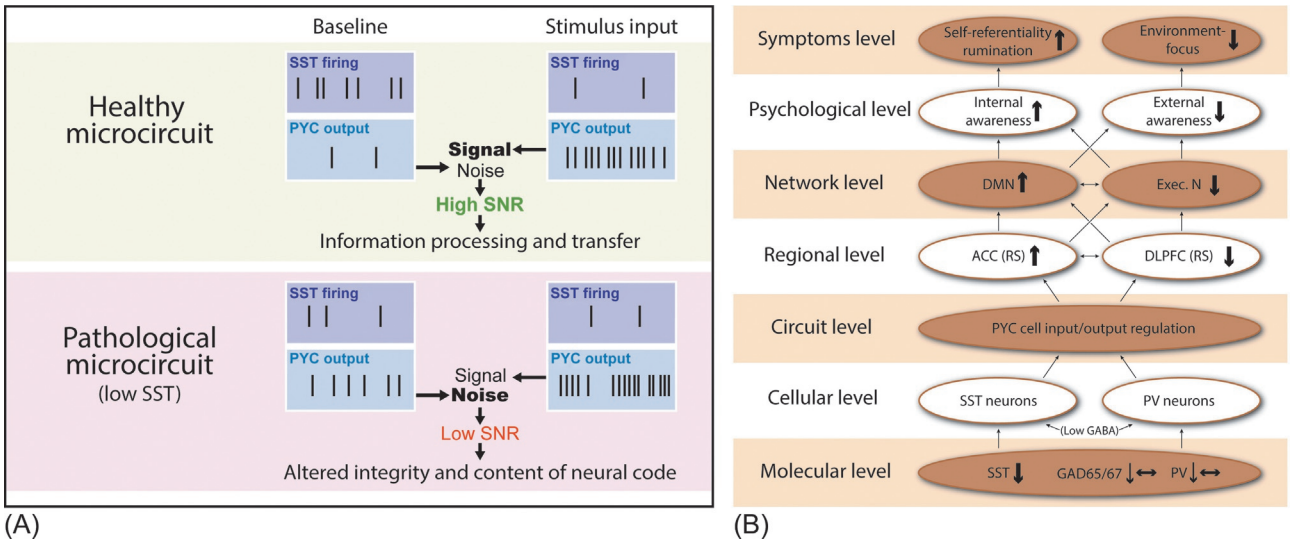

FIG. 2 Conceptual framework of the functional consequences of SST deficits at the microcircuit and other biological levels, ultimately resulting in depressive symptoms. (A) In a healthy microcircuit (top) at baseline, SST neurons have high tonic activity which contributes to sparse PYC activation. Upon stimulus input, VIP-mediated inhibition reduces SST neuron firing, resulting in sustained and ordered bursts of PYC output. The difference between the PYC activity in the presence and absence of SST neuron inhibition represents a signal-to-noise ratio (SNR) that contributes to encoding information. In a pathological microcircuit (bottom), reduced SST activity may increase baseline PYC activity, thus increasing background noise. Decreased SST neuron activity in response to stimuli similarly leads to increased PYC activity; however, the resulting lower SNR is predicted to translate into altered integrity and content of neural code. *(Adapted from Fee et al. [23].)* (B) SST, GAD, and PV deficits, along with decreased GABA, reflect dysfunction of SST and PV neurons. This manifests as altered PYC regulation and activity, differentially affecting the ACC and dlPFC, which show increased and decreased resting-state activity, respectively. This change in resting-state balance leads to changes in network activity, where DMN activity is increased and EN activity is decreased. Lastly, these changes are hypothesized to mediate increased internal and decreased external focus, manifesting as the ruminative symptoms often observed in MDD. *(Adapted from Northoff and Sibille [97].)*

Other Relevant Contributors to EIB

In addition to SST neuron dysfunction, glial cell deficits, particularly in astrocytes and oligodendrocytes, likely contribute to EIB changes in MDD. Astrocytes are closely associated with synapses and, among other functions, facilitate the clearance of glutamate from synapses and conversion of glutamate to glutamine. Glutamine is either recycled into glutamate or transported to GABAergic interneurons for synthesis into glutamate, then GABA (via GADs), referred to as glutamate/GABA cycling [93]. Astrocyte loss and decreased astrocyte markers (glial fibrillary acidic protein) have been reported in fronto-limbic regions of MDD, potentially contributing to EIB changes [94]. Oligodendrocyte deficits in MDD would impact myelination and may potentiality play a role in altered communication between brain regions through disruptions in the timing and synchrony of neuron firing [94, 95].

The SST-neuron deficits described above contrast with the general lack of deficits observed in other interneuron classes. PV and, more so, VIP levels are not consistently altered nor are among the most dysregulated changes in postmortem transcriptomic MDD studies, especially when compared to SST neurons [74–76, 80, 96]. However, as mentioned above, PV is decreased in the ACC, but not dlPFC, of MDD subjects and may be important in how changes in EIB homeostasis interact between brain regions [75, 97]. PV neuron deficits are well-studied and robust in SCZ patients, perhaps suggestive of shared pathologies across disorders, but reflecting differing magnitudes of change [98]. VIP neuron deficits have not been directly observed in MDD, though there is some historical evidence of VIP reductions in CSF of MDD patients [99, 100]. The paucity of studies investigating VIP neuron deficits limits our interpretation of these findings. Unbiased cell-type-specific molecular surveys of the distinct cellular components of cortical microcircuits are still missing in MDD (and other brain disorders). The short-term effects of altering the activity of individual interneuron subtypes has been investigated using optogenetic techniques, though notable limitations have been regional constraints and the absence of investigations using MDD-relevant animal models [101–104]. Hypothesis-driven studies investigating VIP and PV neuron deficits and behavioral effects in the context of MDD-relevant mouse models are warranted, especially if able to be performed in the further context of overt SST deficits.

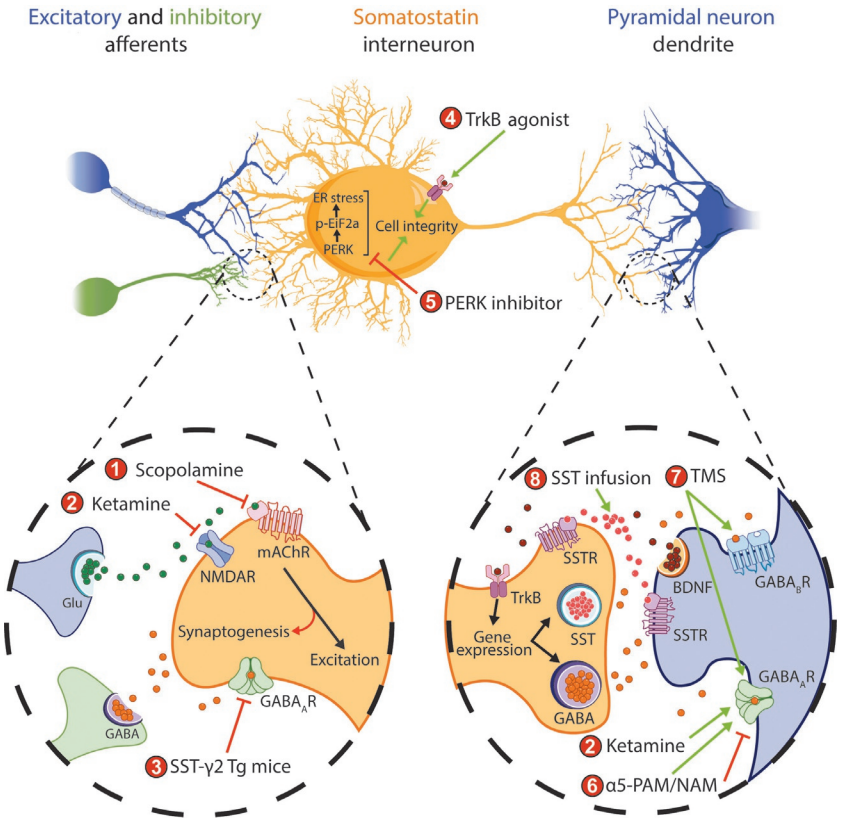

FIG. 3 Potential treatment modalities to target SST neuron deficits. (1) Preclinical and human studies show AD-like effects of scopolamine mediated by M1 muscarinic acetylcholine receptors [105–108]. (2) NR2B subunit-containing *N*-methyl-D-aspartate receptors are responsible for the AD-like effects of ketamine [107, 109]. Ketamine may also act postsynaptically by indirectly facilitating GABA signaling from SST neurons [109]. (3) Mice lacking γ2 subunit-containing $GABA_A$ receptors demonstrate AD- and anxiolytic-like behaviors [110]. (4) Supporting brain-derived neurotrophic signaling via tropomyosin receptor kinase B agonists has been shown to have AD-like effects and increased BDNF-dependent gene expression which is reduced in MDD [111]. (5) Decreasing ER stress signaling via inhibition of PKR-like endoplasmic reticulum kinase has AD-like effects in UCMS-exposed mice [111]. (6) Facilitating normal SST neuron signaling through α5 subunit-containing $GABA_A$Rs has shown AD-like effects in female mice [114]. (7) rTMS is used as an AD treatment, primarily in TRD patients, and has been shown to activate L1-L2/3 neurons targeting PYC dendrites [118]. (8) Direct SST infusions into cortico-limbic brain regions show AD-like effects in mice [119]. *(Adapted from Fee et al. [23].)*

IMPLICATIONS FOR NOVEL TREATMENTS

Given the multiple sites at which SST neuron activity can be influenced, many novel therapeutic approaches emerge for treating SST deficits, grouped broadly into presynaptic, cell integrity, and postsynaptic targets (Fig. 3). See detailed summary in [23]. Presynaptically, antagonism of NR2B subunit-containing *N*-methyl-D-aspartate receptors (NMDAR) by ketamine or muscarinic acetylcholine receptors (mAChR) by scopolamine shows rapid-onset AD-like effects in animals and humans [105–108]. Although having inhibitory effects on SST neurons, AD effects may arise through feedback signaling from PYCs after a spike in glutamatergic signaling and subsequent synaptogenesis [107]. Ketamine may also act postsynaptically by indirectly facilitating GABA signaling from SST neurons [109]. Deletion of the γ2-subunit of $GABA_A$ receptors in SST neurons reduces inhibitory input, and thus has a disinhibitory effect on SST neurons which results in robust AD-like effects in mice, confirming the therapeutic potential of increasing SST cell signaling [110]. Supporting SST neuron integrity comes from two primary mechanisms, tropomyosin receptor kinase B (TrkB—the primary BDNF receptor) agonism and PERK inhibition. The AD-like effects of PERK inhibition have been described above, and TrkB agonists reverse UCMS-induced emotionality and increase expression of BDNF-dependent genes (e.g., SST) [111].

Postsynaptic targets primarily act through facilitating normal SST neuron inhibition on PYC dendritic targets. GABA released from SST neurons preferentially activates α5-$GABA_A$Rs and (to a lesser extent) $GABA_B$Rs expressed on PYC dendrites [112, 113]. α5-$GABA_A$R-selective positive allosteric modulators act through increasing the sensitivity of these receptors to GABA and have shown AD-like effects in female UCMS-exposed mice [114]. Interestingly, α5-$GABA_A$R-selective negative allosteric modulators have also shown AD-like effects in animals, potentially through a similar feedback mechanism as with ketamine/scopolamine [115]. Lastly, SST peptide infusions into cortico-limbic areas have shown AD-like effects in mice, though multiple peripheral effects and a poor blood-brain barrier penetration of SST analogues may limit clinical applicability [116, 117]. Finally, TMS has been shown to inhibit L5 PYC dendritic activity via activation of L1-L2/3 neurons targeting PYC dendrites, acting through $GABA_A$ and $GABA_B$ mechanisms [118]. SST neurons are the only interneuron type with this morphology which shows deficits in MDD, hence suggesting that repetitive TMS may impinge on a common downstream SST cell-related mechanism.

SUMMARY AND FUTURE DIRECTIONS

In this chapter, we have established that MDD is characterized by decreased GABA levels and function across multiple levels of investigation, and that this is related to EIB changes in MDD. Plasma, CSF, ^{1}H-MRS, and TMS studies show a large concordance of findings, with GABA reductions and decreased inhibitory function present across depressive and euthymic periods. Reduced GABA is observed in other psychiatric disorders with shared symptomatology with MDD (namely BD and SCZ), and GABA reductions are more robust in patients with anhedonia and related symptoms. Regions of the DMN, and dlPFC, show the most robust decreases and/or the most concordance with changes in resting-state fMRI activity. In human postmortem studies, confirmation of these clinical findings is observed with decreased GABA, GADs, or GABA receptors in the ACC, dlPFC, amygdala, and other DMN regions. Deficits in SST neurons may underlie these general GABA deficits, as SST expression is decreased per cell, across all examined layers in the ACC, dlPFC, and amygdala. Animal studies provide evidence that SST neurons are selectively vulnerable to stress, and that Sst^{KO} mice have increased emotionality, suggesting that SST neuron deficits are causally involved in depression.

Despite the depth of knowledge about SST neuron deficits in psychiatric disorders which has arisen in the past decade, there is still much we do not know about the nature and impact of these deficits. First, although SST deficits are well-characterized, the adaptations of other interneuron types in the context of reduced SST neuron activity have not been well-explored. Transcriptomic, chemogenetic, optogenetic, and neurophysiological studies examining the changes in gene expression and neuronal activity patterns of the whole microcircuit in the context of MDD are warranted. Such studies will improve understanding about how information processing is altered, and how differences across brain regions result in the emergence of specific symptoms. Second, though many treatment options theoretically exist, there are no targeted treatments for SST deficits, with the arguable exception of rTMS. The treatment opportunities outlined above require translation from preclinical rodent models to human clinical trials for this research to have a real-world impact for MDD patients. Lastly, in parallel to the development of these treatments, tools for target engagement and patient stratification are required. A major limitation of current treatments is the "black box" nature of response, and clinicians lack response biomarkers and screening tools to optimize treatment for each patient. The development of tools to assess efficacy of SST neuron-targeted interventions *in vivo* and to stratify patients based on response to various treatments would be a boon to psychiatry.

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