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PERSPECTIVE

Why are cortical GABA neurons relevant to internal focus in depression? A cross-level model linking cellular, biochemical and neural network findings

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Major depression is a complex and severe psychiatric disorder whose symptomatology encompasses a critical shift in awareness, especially in the balance from external to internal mental focus. This is reflected by unspecific somatic symptoms and the predominance of the own cognitions manifested in increased self-focus and rumination. We posit here that sufficient empirical data has accumulated to build a coherent biologic model that links these psychologic concepts and symptom dimensions to observed biochemical, cellular, regional and neural network deficits. Specifically, deficits in inhibitory γ-aminobutyric acid regulating excitatory cell input/output and local cell circuit processing of information in key brain regions may underlie the shift that is observed in depressed subjects in resting-state activities between the perigenual anterior cingulate cortex and the dorsolateral prefrontal cortex. This regional dysbalance translates at the network level in a dysbalance between default-mode and executive networks, which psychopathologically surfaces as a shift in focus from external to internal mental content and associated symptoms. We focus here on primary evidence at each of those levels and on putative mechanistic links between those levels. Apart from its implications for neuropsychiatric disorders, our model provides for the first time a set of hypotheses for cross-level mechanisms of how internal and external mental contents may be constituted and balanced in healthy subjects, and thus also contributes to the neuroscientific debate on the neural correlates of consciousness.

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INTRODUCTION

Major depressive disorder (MDD) is a leading cause of disability worldwide.[1] It is also a complex psychiatric disorder characterized by various symptoms including low affect, anhedonia, sadness, ruminations, increased self-focus, loss of appetite and sleep disturbances.[2–6] Taking a more general view, the various symptoms in depression signal a shift in mental experience, or 'awareness', reflected in the balance between internal and external mental contents and their coupling with abnormally negative affect. Indeed, rather than focusing on external mental contents in the environment-like objects or events, the awareness in MDD patients is dominated by internal mental contents stemming either from the own body or thoughts. This is well reflected in the unspecific somatic symptoms (e.g., increased bodily focus) and the strong predominance of cognitive processes such as ruminations (e.g., increased self-focus) of these patients, with this shift toward internal contents (somatic and mental) being notably associated with abnormally negative affect (see refs 6–9); however, the physiologic mechanisms underlying this abnormal balance and its association with abnormally negative affect remain unclear.

Imaging studies in humans and animal models demonstrate increased resting-state activity in the perigenual anterior cingulate cortex (PACC) in depression, which may be related to abnormal γ-aminobutyric acid (GABA) function in this region (see refs 8,10,11). Interestingly, the dorsolateral prefrontal cortex (DLPFC), especially in the left hemisphere, is characterized by an opposite pattern of decreased resting-state activity.[10,12] This shift in resting-state balance seems to be closely related to the shift in internal and external mental contents in awareness; this will be the main focus of our paper while leaving aside the neural mechanisms related to the generation, association and cognitive regulation of the abnormally negative affect in MDD. Studies of the resting-state activity in both healthy[13] and MDD subjects[14,15] demonstrated that internal mental contents are associated with PACC and default-mode network (DMN) activity, whereas external mental contents induce increased activity in the DLPFC and the executive network (EN). Owing to reasons of clarity, space and focus, we set aside the potential role of other regions and networks such as the insula and salience network,[16–18] the mechanisms of affect generation as related to subcortical regions[19] and the neural mech-

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anisms of cognitive emotion regulation as associated with DLPFC–amygdala downmodulation and cognitive–behavioral therapy in MDD.[20,21]

The model we develop here relies on direct brain-based evidence in human subjects with major depression and extends previously articulated GABA hypotheses of emotion dysregulation in depression.[22,23] The GABA hypothesis of depression was originally proposed in 1980, based on the efficacy of sodium valproate, a GABAergic anticonvulsant, in the treatment of mania.[24] This indirect level of evidence was supported by reports of low GABA levels in the plasma and cerebrospinal fluid of depressed subjects,[25–28] of decreased GABA concentration in the PACC and occipital cortex in MDD, as observed by proton magnetic resonance spectroscopy (MRS) or by transcranial magnetic stimulation (TMS),[11,29–31] and later by the association between GABAergic transmission and control of stress,[23] the effect of monoaminergic antidepressants on GABAergic transmission[32] and genetic manipulation studies in rodents.[33] However, the exact cellular, biochemical, physiologic and regional mechanisms of how GABA dysregulations affect various nested and bottom-up biologic levels and ultimately the different symptoms at the psychopathologic level in MDD remain unclear. Furthermore, how those GABA-related cellular and biochemical changes relate to broader neural network hypotheses of depression,[9,34] including pathophysiologic mechanisms underlying the abnormal balance between PACC/DMN and DLPFC/EN, in MDD has not been addressed.

Here we hypothesize that the abnormal balance between PACC/anterior DMN and DLPFC/EN (and subsequently the abnormal balance between internal and external mental contents in awareness) in MDD may be traced back to regional and cellular distribution of changes in GABA interneurons and to their specific organization in regulating the input, output and integrity of information processing as it transits through cortical layers. More specifically, we hypothesize the following bottom-up cross-level mechanisms (see Figure 1 for an overview): (i) there are robust MDD deficits in somatostatin (SST)-positive interneurons that mostly regulate excitatory input on the dendrites of pyramidal cells (as observed in post-mortem brain); (ii) there are sparser MDD deficits in parvalbumin (PV)-positive GABAergic interneurons that regulate the excitatory output of pyramidal cells, especially in the DLPFC; (iii) these cell-specific deficits may translate into a dysbalance between input and output of pyramidal cells, which, on a regional level, may translate into altered activity and a shift of the resting-state balance between PACC (and the DMN) and DLPFC (and the EN) in MDD (as it can be observed); (iv) the abnormal resting state between PACC/DMN and DLPFC/EN may be biochemically mediated by abnormal GABA function at the regional level (as supported by reduced biochemical levels and cell-specific changes) and (v) this translates at the network level into a dysbalance between DMN and EN, which psychopathologically surfaces in an abnormal balance between internal and external mental contents in awareness (as it is clinically evidenced).

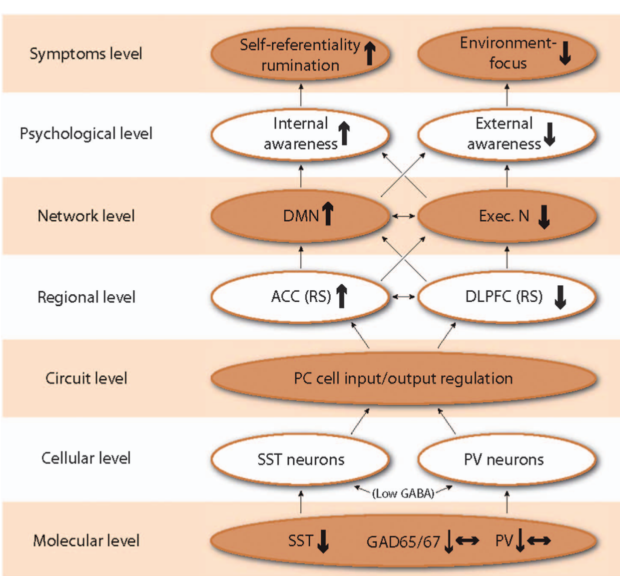

Figure 1. Overview of biologic levels and associated evidence of dysregulation related to depression. This document describes how deficits in inhibitory γ-aminobutyric acid (GABA) regulating excitatory cell input/output and local cell circuit processing of information in key brain regions may underlie the shift in resting-state activities between the perigenual anterior cingulate cortex (PACC) and the dorsolateral prefrontal cortex (DLPFC). This regional dysbalance translates at the network level in a dysbalance between default-mode and executive networks, which psychopathologically surfaces as a shift from external to internal mental content in awareness. This shift in mental content is reflected by unspecific somatic symptoms and the predominance of the own cognitions manifested in increased self-focus and rumination.

FROM GENES TO CELLS AND LOCAL CELL CIRCUIT REGULATION

Recent findings from preclinical, clinical and human post-mortem studies point toward an altered balance of excitatory (i.e., glutamatergic) and inhibitory (i.e., GABAergic) components of local cell circuits in cortical structures of the brain (see next section). Here we review briefly the cellular structure and connectivity of canonical local cell circuits that form the basic functional units of input/output regulation of excitatory pyramidal cells and cortical structures. The primary molecular evidence collected in post-mortem subjects with depression suggests reduced expression of the inhibitory GABAergic components of those local units that regulate incoming signaling, or information input. Hence, we focus on the inhibitory GABA component, but recognize that associated changes in the glutamatergic system need to occur to maintain the excitation–inhibition balance (see, for instance, Sanacora *et al.*[35]).

From inhibitory neuron identity to local circuit regulation of excitatory pyramidal cell function

Excitatory pyramidal cells use glutamate as the main neurotransmitter to propagate excitatory signals across cortical layers and brain regions.[36] Those excitatory neurons are under negative inhibitory control that is exerted mostly by local neurons that use GABA as their main inhibitory neurotransmitter.[37,38] GABAergic neurons are divided into subgroups based on the molecular markers they express, the cellular compartment they target and their electrophysiologic properties.[37,38] For the purpose of this report, we can describe GABA neurons in relation to a simplified pyramidal neuron two-compartment model, corresponding to their input and output functions (Figure 2a).[37,39]

The input function consists of incoming excitatory signals onto the dendritic tree of pyramidal cells, and it is targeted/inhibited by GABA neurons that are characterized by the expression of the neuropeptide SST. The output function of pyramidal cells consists of excitatory signals generated at the level of the cell body and axon, which are targeted/inhibited by GABA neurons that mainly express the calcium-binding peptide PV (Figure 2a).[37] Additional GABA neuron subtypes exist, including some that target and regulate the function of SST and PV neurons,[40] but they are omitted here for simplicity and because of sparse evidence for dysregulations in MDD (see next section). To better understand the implications of selective changes in MDD, we first provide a

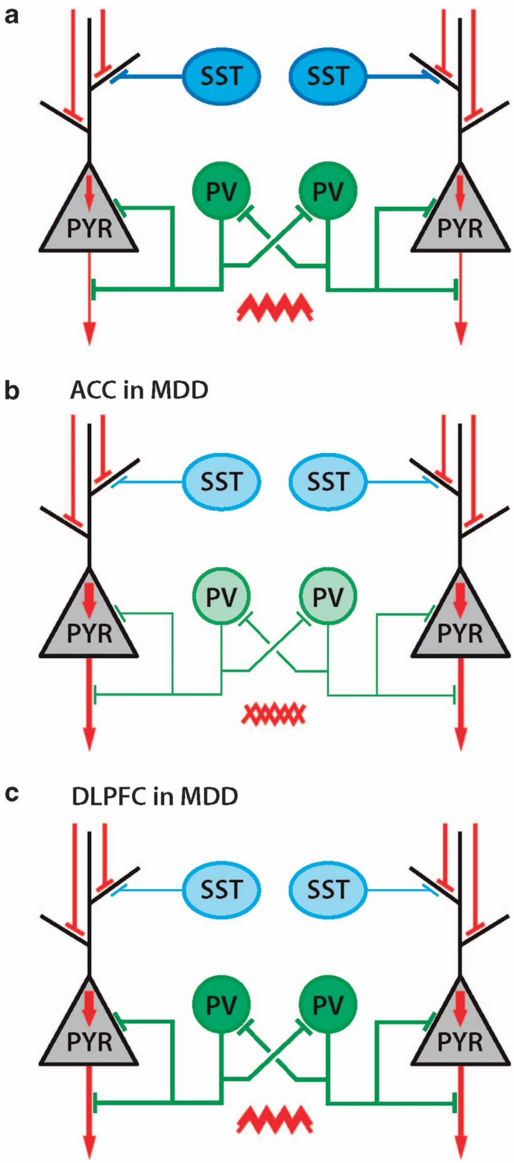

Figure 2. Inhibitory neuron identity and local circuit regulation of excitatory pyramidal cell function in controls and major depression. (**a**) Pyramidal neurons (PYR) receive inhibitory input on dendrites from somatostatin (SST)-positive γ-aminobutyric acid (GABA) neurons, and in the perisomatic region from parvalbumin (PV)-positive GABA neurons. Excitatory signal input is therefore regulated by SST neurons, whereas PV neurons regulate excitatory signal output. Furthermore, PV neurons are reciprocally connected by inhibitory input, and are critical in the generation of synchronous firing in the γ-range (sawtooth symbols), mediating propagation of information across ensembles of neurons. (**b**) In the perigenual anterior cingulate cortex (PACC), reduced expression of markers for SST and PV neurons and of GABA synthesis genes suggests reduced inhibition of input and output of information (and potentially less synchronous) in major depressive disorder (MDD). (**c**) In the dorsolateral prefrontal cortex (DLPFC), selective reduction in the expression of markers for SST neurons suggests reduced inhibition of input, but intact output, potentially resulting in overall increased information transfer (however, see section PACC and DLPFC reciprocal inhibition for a putative overriding effect of increased PACC activity on DLPFC activity under resting-state condition). Red codes represent excitatory signal, and blue and green codes represent inhibitory signals.

more detailed description of the respective functions and characteristics of SST and PV neurons.

SST neurons target and inhibit nonspecifically all distal dendrites of pyramidal neurons with a probability that is inversely related to their distance from pyramidal neurons.[41,42] They are recruited in a feedforward manner by activated pyramidal neurons for which they also provide feedback inhibition. SST neurons are characterized by delayed, sustained and adapting firing properties.[43] They also display low synchrony (owing to the absence of SST–SST feedback inhibition).[40] Taken together, SST neurons are specialized in customized and targeted local regulation of incoming excitatory signals, and are thus critical in maintaining the integrity of information input.[37] Recent findings (albeit in rodent visual cortex) suggest that SST neurons may also provide significant inhibition to most other GABA neuron subtypes,[40,44] and may thus regulate the overall inhibitory tone within local circuits in addition to regulating dendritic inhibition.

PV neurons target nonspecifically the perisomatic compartment of pyramidal cells in a cell distance-dependent manner.[41] PV neurons are directly activated by thalamic projections and corticocortical projections, and are characterized by fast spiking and non-adapting properties. Unlike SST neurons, PV neurons are highly synchronized through dense PV–PV reciprocal inhibition.[45,46] Taken together, PV neurons are specialized in regulating the output of targeted neurons and in the synchronization of firing of ensembles of pyramidal neurons, and thus contribute to maintaining the integrity and propagation of information output.[37,45,46] This intricate local cell circuit connectivity and distribution of tasks demonstrates the close links between excitatory and inhibitory functions, highlights the necessity of simultaneously maintaining proper regulation of input and output functions to preserve the integrity of transferred information and also suggests multiple sites of putative deregulations in the context of brain disorders. This latter point is well illustrated by the fact that many forward-genetic and pharmacologic studies in rodent systems or drug studies in humans can affect the excitatory/inhibition balance and lead to altered information transfer and related behaviors, including antidepressant activity.[35,47]

Taken together, this evidence demonstrates various ways in which the glutamatergic or GABAergic components of local circuits can be dysregulated; however, it does not necessarily address the question as to which changes actually occur in the context of depression. Knowing the true pathogenic mechanisms occurring at the level of the local cell circuits has consequences for understanding and modeling its bottom-up contribution to dysregulated functions in upper biologic scales, including neural network activity and potential symptom dimension. Note that this manuscript is on purpose focused solely on results from human studies. Studies in rodents have provided supporting evidence for the local circuit basic neuroscience described here (i.e., wiring, cell types), but have with few exceptions[48] so far not directly tested aspects of the neurobiology of disease hypotheses described in this report.

From the local cell circuit MDD-related pathology to ACC and DLPFC regional specificity

Surveys of the expression of genes implicated in the function and identification of the GABA/glutamate components of local cell circuits suggest primary deficits affecting the GABA system, especially SST neurons targeting the dendritic compartment and regulating information input.[49] Human post-mortem studies have reported a downregulation of *SST* gene expression in the DLPFC, PACC and amygdala of MDD patients compared with healthy comparison subjects.[50–53] These findings are consistent with earlier post-mortem studies showing reduced calbindin-positive GABA interneuron numbers in the frontal cortex of MDD patients,[54,55] as SST is mostly expressed in calbindin-positive interneurons (reviewed in Viollet *et al.*[56]). In addition, neuropeptide Y and cortistatin, two peptides partly colocalized with SST, were found to be similarly downregulated in the PACC and amygdala,[50,53] but not in the DLPFC in MDD patients. These three neuropeptides (SST, neuropeptide Y and cortistatin) are markers of the GABAergic neuron subtype described above that specifically regulate incoming excitatory signals or information input onto pyramidal cells.[56,57]

Regarding markers of other GABA neuron subtypes, results have been mostly negative across several brain regions investigated.[50–52] In a study comprising post-mortem samples from over 50 pairs of MDD and psychiatric control subjects, Tripp *et al.*[50] reported downregulation of PV and enzymes necessary for the production of GABA (GAD65 and GAD67), in addition to reduced SST, NPY and CORT expression. Reduced GAD67 was also reported in the DLPFC and amygdala in different studies.[52,58] Zhao *et al.*[59] observed that the transcripts for the genes for GABA-A receptors (β-subunit) were significantly reduced in the PACC in MDD, whereas the DLPFC did not show any abnormalities. Post-mortem findings suggest complex changes in the expression of GABA receptors and subunits in MDD (described in refs 60–62 and summarized in refs 10,23). These findings are important in that they suggest multiple changes in mediators of GABA signaling, although those GABA genes are expressed across different cell types and do not identify a specific cellular focus of pathology, as is the case for PV and SST markers. Finally, owing to the close functional balance exerted between GABA and glutamate, it is not surprising that changes in markers of glutamatergic functions have been reported in post-mortem subjects with MDD, although results on glutamate-related genes and gene products are more variable across studies and not consistent.[63,64]

These recent studies on neuron subtypes point to the necessity of refining the low GABA hypothesis of depression in terms of cellular origin and impact on information transfer. Specifically, the converging evidence now suggests that the low GABA phenotype observed in MDD may originate from the selective downregulation of SST-positive GABA neurons, at least across the cortico-limbic areas investigated so far. Given the specialized function of these cells, the GABA dysregulation may concern deficits in information input regulation in brain regions that largely process emotionally salient information (amygdala, PACC) and integrate it with cognitive processing (DLPFC). These post-mortem studies also suggest greater changes in the PACC that extend to altered PV-mediated output regulation and reduced GABA synthesis, consistent with reduced GABA levels measured in that area by MRS (see below). Figure 2 summarizes these primary findings and predicted impact on input/output regulation and information transfer in the DLPFC and PACC, respectively.

FROM THE CIRCUIT LEVEL TO THE REGIONAL LEVEL OF NEURAL ACTIVITY

How do specific changes in GABA neuron subtypes affecting input (SST) and output (PV) translate into neural activity at the regional level in MDD? Changes in GABA neuron subtypes affecting input and output are permanent and may therefore affect the generation of the ongoing neural activity and the resting state, as well as subsequent stimulus-induced or task-evoked activity. More specifically, these cellular changes should provide the most direct link to resting-state activity on a regional level as the impact of the endogenous changes in excitatory (glutamatergic) and inhibitory (GABAergic) balance should be the strongest in the absence of modulation by specific tasks or stimuli. Moreover, following the cellular–biochemical findings (see above and below), we here focus on the resting-state activity in the PACC and DLPFC, as two key regions consistently implicated in MDD in recent imaging studies, and on the abnormal shift from external to internal mental contents in awareness (see refs 8–10,65–67). In contrast, we here leave aside other regions and networks such as insula, salience network, amygdala and subcortical regions that may be implicated in the generation, and cognitive regulation of affect and its subsequent association with the internal (and external) mental contents.[17,19–21]

From local cell circuits to regional input/output structure in the PACC and DLPFC

Canonical cortical circuitry. A typical cortical input structure, as apparent in the DLPFC, is characterized by corticocortical

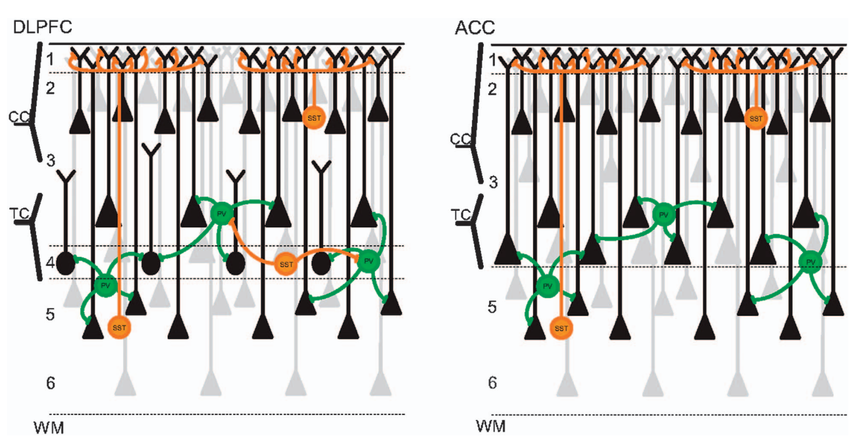

Figure 3. Local cell circuits and input/output regulation structure in the dorsolateral prefrontal cortex (DLPFC) and perigenual anterior cingulate cortex (PACC). (**a**) The DLPFC cortical input structure is characterized by corticocortical (CC) projections to pyramidal neurons located in layers 2/3 and by thalamocortical (TC) projections to deep layer 3 and layer 4. Inputs to layers 2 and 3 are characterized by robust inhibitory regulation by somatostatin (SST) neurons that occur mostly in distal dendrites located in layer 1. The layer 4 granular neurons have reduced dendritic arbors that do not extend to layer 1 and are less sensitive to corticocortical processing and SST-mediated input regulation. Layer 4 neurons are densely targeted and inhibited by parvalbumin (PV) neurons, thereby showing a predominance of output regulation. Deep layer 3 neurons that are also targeted by thalamic projections display more typical pyramidal cell structure, extend dendrites to layer 1 and thus show more balanced input and output regulation, and corticocortical processing (through dendritic extensions to layer 1) compared with layer 4 neurons. (**b**) The PACC departs from the canonical layer structure described in (**a**) owing to its absence of layer 4 (i.e., agranular cortex). All thalamic projections terminate in deep layer 3 and are submitted to greater processing through SST-mediated input regulation compared with DLPFC, notably by including corticocortical processing through layer 1 extension.

projections to pyramidal neurons located in layers 2/3 and by thalamic projections to deep layer 3 and layer 4.[36] Input to layers 2 and 3 is characterized by robust inhibitory regulation by SST neurons that occur mostly in distal dendrites located in layer 1 (Figure 3a), and thus shows a predominance of input regulation. In contrast, the layer 4 granular neurons have smaller dendritic arbors that do not extend to layer 1 and are less sensitive to corticocortical processing and SST-mediated input regulation; these layer 4 neurons are densely targeted and inhibited by PV neurons, and thereby show a predominance of output regulation. Deep layer 3 neurons that are also targeted by thalamic projections display more typical pyramidal cell structure, extend dendrites to layer 1 and thus show more balanced input and output regulation, and corticocortical processing (through extensions to layer 1) compared with layer 4 neurons (Figure 3).[68]

PACC. The PACC is a part of the limbic system that extends from the subcortical midline regions such as raphe nucleus, locus coeruleus, ventral tegmental area, amygdala, hypothalamus, periaqueductal gray and ventral striatum (and many others) to the PACC and the insula at the cortical level.[69–72] The PACC consequently receives inputs from these subcortical limbic regions stemming mostly from proprioceptive and, especially, interoceptive vegetative inputs, as well as from other cortical regions that are not directly implicated in exteroceptive stimulus processing. In addition to the predominantly internal input, the PACC also receives direct external inputs from all five exteroceptive sensory modalities and can therefore be considered a convergence zone between internal and external inputs.[72,73]

Notably, the PACC departs from the canonical layer structure described above in an important way, owing to its absence of layer 4 (i.e., agranular cortex).[74] This indicates a structure-based difference in how information is processed in the PACC; it implies that all thalamic projections terminate in deep layer 3 and are submitted to greater processing through SST-mediated input regulation compared with DLPFC, notably by including corticocortical processing through layer 1 extension (Figure 3b). These structural–organizational peculiarities in the PACC (when compared with DLPFC) are accompanied by specific biochemical features. The subgenual subdivision of the ACC shows high GABA-A and GABA-B receptor expression, as well as benzodiazepine, 5HT1a and α1 receptors,[75,76] which has been confirmed in mice,[77] monkeys[78] and humans using MRS-based measurement of GABA, glutamate and glutamine.[79] A recent imaging study observed that the highest concentration of GABA and glutamate was found in the PACC. Concentrations for both neurotransmitters were lower in supragenual and posterior cingulate regions, following the distribution of GABA-B receptors (see Dou *et al.*[79]). Analogous regional biochemical data are not yet available for the DLPFC, thus we currently remain unable to compare directly both regions with regard to GABA and glutamate (and ultimately in their excitation––inhibition balance).

DLPFC. The DLPFC is located more laterally and is part of what is described as the EN.[16] The DLPFC receives strong inputs from all five exteroceptive sensory modalities and their respective sensory cortices and from the midline regions via especially the supragenual anterior cortex.[72,80] Such predominance of external input is corroborated by the major input from the thalamus via thalamocortical loops.[8,73] This robust thalamic input terminates in deep layers 3 and 4, which is paralleled by dense PV neurons in those layers in DLPFC. The combination of strong development of layer 4, thalamic input and predominance of external input distinguishes the DLPFC from the PACC (Figure 3) and has implications for how that information is processed in those two regions, and that may become apparent and relevant in the context of pathologic changes in MDD.

Regional specificities and putative impact of MDD cellular pathology in ACC and DLPFC. What does such input/output structure and its biochemical modulation imply for neural activity at the regional level in the PACC and DLPFC and how do the MDD-related changes in GABA markers described in the previous section interact with this regional cellular and layer specificity? First, one would predict that the PACC is activated by predominantly internally generated contents stemming from internal inputs such as the strong subcortical vegetative–interoceptive input, its convergence with external inputs and the continuous input from other cortical regions unrelated to exteroceptive processing. Second, given the integrated SST- and PV-GABA neuron-mediated input/output regulation (i.e., agranular cortex; Figure 3) and the biochemical structure of the PACC with the strong concentration of GABA-A/B receptors and benzodiazepines receptors, one would expect that the internal inputs into PACC may be strongly related to GABA. Third, one would expect a different pattern in the DLPFC. Owing to its extended cortical connections, especially those with sensory modalities and presence of a clearly delineated layer 4 with direct and less processed external input via the thalamus (Figure 3), one would expect externally generated contents stemming from exteroceptive inputs of the environment to predominate here. Fourth, changes in the excitation–inhibition balance in either PACC or DLPFC should lead to an abnormal balance between internally and externally generated contents.

Based on the MDD-related reported changes described above in markers of GABA-mediated input/output regulation, these structural differences including the differences in relative intero- and exteroceptive input processing, suggest a specific pattern of changes differentially affecting the DLFPC and PACC. In the DLPFC, the prediction is of reduced inhibition and processing of corticocortical and thalamic input but normal (or putatively increased) output of the processed information, as mediated by reduced SST-, but intact PV-, related inhibition (Figure 3). In the PACC, the prediction is of more profound deregulations encompassing reduced inhibition and fine-tuning of input (due to reduced SST neuron function) and reduced output inhibition (due to reduced PV neuron function). These PACC changes would occur in a context of a general decrease in GABA concentration (due to lower GAD65/67-mediated synthesis[50]) together leading to increased regional activation. Such increased regional activation, however, is not necessarily associated with greater synchronized output toward other regions as reduced PV cell function may also lead to reduced efficacy in synchronization of firing of ensembles of pyramidal neurons (see, for instance, refs 10,81) (Figure 3b).

From input structure to resting-state activity in the PACC and DLPFC

Imaging findings in healthy subjects show a reciprocal pattern of neural activity between PACC and DLPFC (Figure 4). Increased activity in the DLPFC is accompanied by decreased activity levels in the PACC and *vice versa* (see, for instance, refs 82,83). This however must be further specified in both neural and psychologic regard; let us focus, in the following, mainly on the neural mechanisms, such as the processing of the input on the regional levels of PACC and DLPFC, while leaving aside for the moment psychological issues such as the balance between internal and external mental contents and their association with abnormally negative affect.

Most imaging studies are conducted in functional magnetic resonance imaging (fMRI) that yields blood-oxygen-level-dependent (BOLD) signal. The BOLD signal has been shown to be based predominantly on the input to a certain region and its local field potentials rather than its output.[84,85] Most importantly,

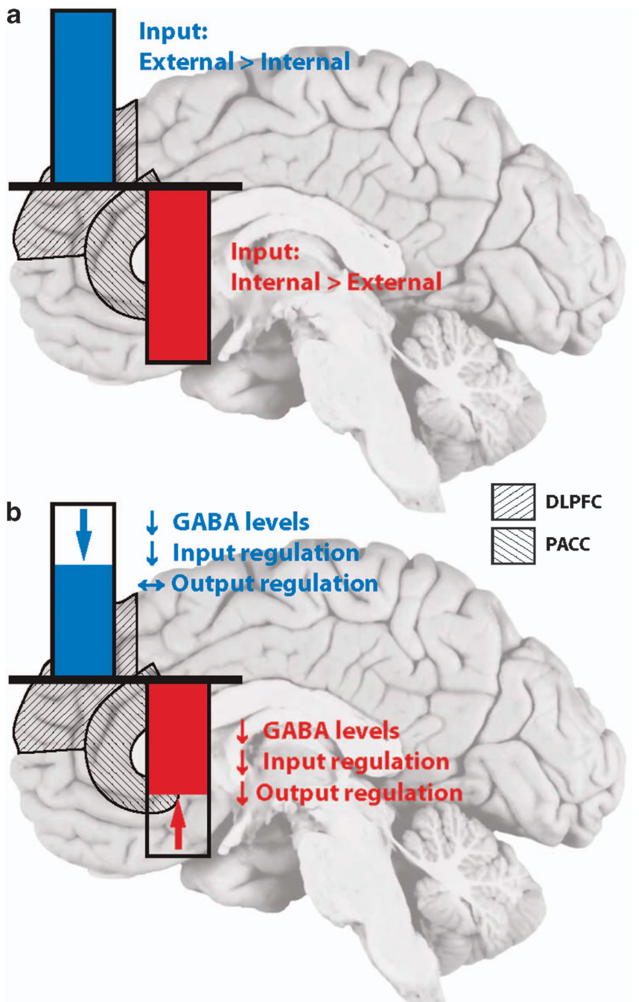

Figure 4. Resting-state activity in the perigenual anterior cingulate cortex (PACC) and the dorsolateral prefrontal cortex (DLPFC) in controls and major depression. (**a**) Imaging findings in healthy subjects show a reciprocal pattern of neural activity between PACC and DLPFC. Increased activity in the DLPFC is accompanied by decreased activity levels in the PACC and *vice versa*. The relative ratio of information content (internal versus external) is depicted for both areas. (**b**) In major depressive disorder (MDD), the resting-state activity of the DLPFC is reduced. In contrast the PACC shows increased resting-state activity in MDD (i.e., less negative activity), resulting in an abnormal reciprocal modulation between the two regions. Underlying cellular and biochemical changes are highlighted and described in Figures 2 and 3.

the BOLD signal shows positive signal changes, the so-called activation, and negative ones, that is, deactivation. While the physiologic basis of the activation has been relatively well investigated, the physiologic underpinnings of the deactivation remain unclear (see refs 86,87).

Why is that important for PACC and DLPFC? Interestingly, the PACC shows predominantly negative BOLD response, that is, deactivation in fMRI (see refs 83,88). This contrasts with the DLPFC that shows positive BOLD signals, that is, activation. Independent and separate analyses of both regions' neural activities reveal that both activation and deactivation seem to be reciprocally modulated between PACC and DLPFC: greater deactivation in the PACC entails increased activation in the DLPFC, whereas lower deactivation in the PACC leads to low activation in the DLPFC (Figure 4). This has been demonstrated in several studies in healthy subjects (see refs 8,82,83).

Most interestingly, this pattern of reciprocal modulation seems to be related to the processing of internally and externally generated contents. Cognitive tasks, such as working memory or executive tasks that focus strongly on external stimuli from the environment, strongly recruit neural activity and more specifically activation in the DLPFC. This contrasts with the PACC where the deactivation is rather modulated by vegetative and emotional processing.[2,89] The differential pattern of neural activity, activation versus deactivation, in the PACC and DLPFC consequently suggests relation to the processing of different kinds of contents, internally versus externally generated, that stem from different origins, interoceptive and somatic from the own body (and/or cortically from other cortical regions' ongoing activity) or exteroceptive from the external environment.

What about the findings in both regions in MDD? The PACC (and the adjacent ventromedial prefrontal cortex (VMPFC)) shows increased resting-state activity in MDD (see refs 4,8,10,12,90 for recent reviews). In contrast, resting-state activity in, especially, the left DLPFC is reduced in MDD (Figure 4). Such opposite change in the resting-state activity level in MDD is well compatible with their reciprocal modulation where changes in the activity level of one region are accompanied by opposite changes in the respective other region. See also Bermpohl *et al.*[91] for a confirmation of abnormal reciprocal modulation between PACC and DLPFC in MDD during task-evoked activity.

How is such reciprocal pattern between PACC and DLPFC in the resting state related to their different input structure and cellular/biochemical modulation? This remains unclear at this point in time, however. One may be puzzled at first glance that such question about the relationship between input structure on a cellular level and resting-state activity on a regional level can be raised at all. Intuitively, one would associate the resting-state activity with the absence of any input. However, this concerns only the absence of specific external inputs such as particular goals or tasks as related to exteroceptive input. In contrast, the unspecific input coming from other cortical and subcortical regions, the interoceptive input from the body and the unspecific exteroceptive input from the senses are still processed even in the resting state (which therefore can be coined resting state only in an operational sense of the term but not in a physiologic meaning).[92,93]

Given this, one may indeed raise the question whether the opposite and thus reciprocal pattern of PACC and DLPFC resting-state activity in MDD is related to a dysbalance in the unspecific inputs: even in the resting state the interoceptive input from the own body and the input from the other cortical regions' ongoing resting-state activity are processed and, owing to the alleged cellular–biochemical abnormalities (see above), may predominate. Such predominance of internal inputs may, hypothetically, be caused by the decreased gating of these inputs onto excitatory neurons by the disturbed SST interneurons as well as by reduced inhibitory regulation of excitatory output by the disturbed PV interneurons in the PACC in MDD (Figure 2), which, in turn, may ultimately lead to increased resting-state activity in the PACC.

In contrast, in the DLPFC the integrity of the unspecific exteroceptive input that predominates may be affected because of reduced SST interneuron-mediated function in MDD. Although this may translate into increased regional activity, at least two mechanisms may suggest the opposite (i.e., reduced DPPFC activity as observed): (1) the unspecific exteroceptive input may increase which, in turn, would induce even stronger down-modulation by the reciprocal feedback inhibition of the PACC, or (2) increased input may induce stronger degrees of output inhibition by the preserved (and abundant) PV interneurons in the DLPFC. Future investigations are necessary to determine the exact neural mechanism of DLPFC downregulation in MDD, and also how the abnormal dysbalance between PACC and DLPFC may affect the control of the DLPFC in downmodulating amygdala activity, owing to the central role of cognitive emotion regulation in cognitive behavioral therapy.[20,21]

Taken together, the cellular and biochemical abnormalities in the input–output gating mechanisms in the PACC and DLPFC may lead to a dysbalance in the processing between internally and externally generated contents in the resting state in MDD. More specifically, the lack of input gating onto pyramidal neurons by the deficient SST neurons and the decreased inhibition by the deficient PV neurons may lead to an overflow of internally generated contents in the PACC, which, tentatively, may be reflected in its elevated resting-state activity. As PACC and DLPFC activity levels are reciprocally coupled with each other, resting-state hyperactivity in the PACC entails resting-state hypoactivity in the DLPFC, which is exactly what can be observed, especially, in the left DLPFC in MDD. Hence, even if the amount of externally generated input that is processed in the DLPFC remains within the 'normal' limits, resting-state activity in the DLPFC may nevertheless be downmodulated owing to its reciprocal coupling with the abnormally high resting-state activity in the PACC. Note that we have so far only accounted for the mere processing of inputs on the regional level of neural activity in the PACC and DLPFC while not touching upon how these inputs are converted into mental contents and associated with negative affect.

From GABA to resting-state activity in the PACC (and DLPFC)

GABA and glutamate resting-state concentrations can be investigated in humans using MRS. As alluded to earlier, findings show significant reductions of GABA in occipital cortex in MDD. Analogous findings (although not fully consistent) have been observed in the PACC (and/or adjacent regions) where especially GABA is reduced in MDD (see refs 29,31,94–96). A recent translational meta-analysis in MDD combining human imaging data and animal model-based data[10] confirmed the reduced GABA concentration in the PACC with further findings suggesting reduction in both GABA-A and GABA-B receptors, as well as in GAD-67, the enzyme that converts glutamate into GABA. In contrast to the PACC, MRS findings have not been as consistent in the DLPFC (see, for instance, Grimm *et al.*[15]) for which reason we focus on PACC in the following, consistent with the above-described decreases in SST- and PV-mediated input/output gating deficits.

How does such seemingly reduced GABAergic-mediated neural inhibition translate into the elevated resting-state activity level in the PACC? To test directly this association, it is necessary to combine MRS with fMRI. One of the first such studies in this regard combined fMRI with MRS in the PACC. Interestingly, the concentration of GABA in the PACC predicted the degree of negative BOLD signal, or deactivation, in the same region: the higher the GABA concentration, the stronger the degree of negative BOLD response.[7] In contrast, no such coupling was found for glutamate. These associations between resting-state neurotransmitter concentration and BOLD signal are different in MDD. In MDD patients, the negative BOLD signal in the PACC, which is reduced in MDD, is no longer predicted by resting-state GABA concentration.[97] Instead, the reduced negative BOLD signal in the PACC is now predicted by the concentration of glutamate, suggesting an abnormally strong role of glutamatergic-mediated neural excitation in parallel to a decreased GABAergic-mediated neural inhibition, potentially reflecting (mal)adaptive changes in excitation/inhibition balance in that region in MDD.

This is consistent with the earlier described deficit in expression of genes coding for PV-, SST- and GABA-synthesizing enzymes in the PACC in MDD, as the potential source of reduced GABA levels. However, it remains unclear how those GABA neuron deficits impact the intra- and extracellular concentration of GABA as it is measured with MRS. More specifically, we have to consider that MRS does not measure synaptic activity related to GABA (and glutamate) but only intra- and extracellular concentrations;[98] this means that direct inference from the cellular-synaptic changes reported above to the cellular–regional level as measured with MRS remains impossible. Moreover, one has to consider that most MRS studies do not provide a separate measurement of glutamate as distinguished from glutamine. Therefore, we can only point out intuitive correspondence and consistency between the findings on the different levels while abstaining from any causal assumptions.

Based on the above-described correspondences between cellular and regional level, we suggest the following. One would expect that SST-related deficits, as well as PV and GABA abnormalities, lead to an abnormal shift in the excitation–inhibition balance, which then abnormally upmodulates the level of resting-state activity in the PACC. This could be tested in electrophysiologic studies that also include measurements of SST, PV, glutamate and GABA, where one would expect the SST-related deficits to result in a shift of the excitation–inhibition balance toward abnormally elevated excitation and reduced inhibition in MDD. Initial testing of this hypothesis in animal models does indeed suggest long-term local and network adaptations in the excitation–inhibition balance.[48,99] In humans, first tentative and incomplete support for GABAergic modulation of the excitation––inhibition balance on the regional level comes from combined TMS-MRS studies that show changes in GABA concentration during TMS-induced increase or decrease in neural inhibition (over the motor cortex).[100,101] Future studies may want to extend such approach to the above-mentioned substances, which could lend further support to our hypothesis. Moreover, the initial fMRI-MRS combined studies point to differential effects of glutamate and GABA on fMRI BOLD signal, which is in line with their differences on the cellular level. How this impacts the excitation–inhibition balance remains unclear, however. As the excitation–inhibition balance results from the interaction between glutamate and GABA, one may want to relate a combined measure of their ratio (rather than single measures) in future fMRI-MRS or TMS-MRS studies.

FROM THE REGIONAL LEVEL OF NEURAL ACTIVITY TO THE NETWORK LEVEL AND THE SYMPTOMS

From regions to networks and psychologic functions

We already mentioned the DMN and the EN as two key networks in the resting state. The PACC is a key region in especially the anterior DMN[16,102,103] that is signified by low-frequency fluctuations,[16,97,98] whereas the DLPFC is crucial for the EN.[16] The DMN and ENs are anticorrelated, that is, they stand in a negative inhibitory relationship to each other: for example, increase in EN excitation (for instance, in DLPFC) decreases DMN PACC (and medial prefrontal) functional connectivity to the EN (and the salience network) (and *vice versa* with a decrease in EN excitation disinhibiting DMN functional connectivity)[104] (Figure 5). Taken together, this strongly suggests that the above-mentioned reciprocal modulation between PACC and DLPFC on the regional level resurfaces as negative relationship or anticorrelation between DMN and EN on the network level. Psychologically, we assume the balance between DMN and EN to be associated with the abnormal shift from external to internal mental contents in awareness in MDD, which, in turn, is coupled to an abnormally negative affect. We here focus on (1) the neural mechanisms underlying the balance between internal and external mental contents while leaving aside (2) the association of mental contents with negative affect (for which PACC and DLPFC and their connections to subcortical regions seems to have an essential role[9,19]).

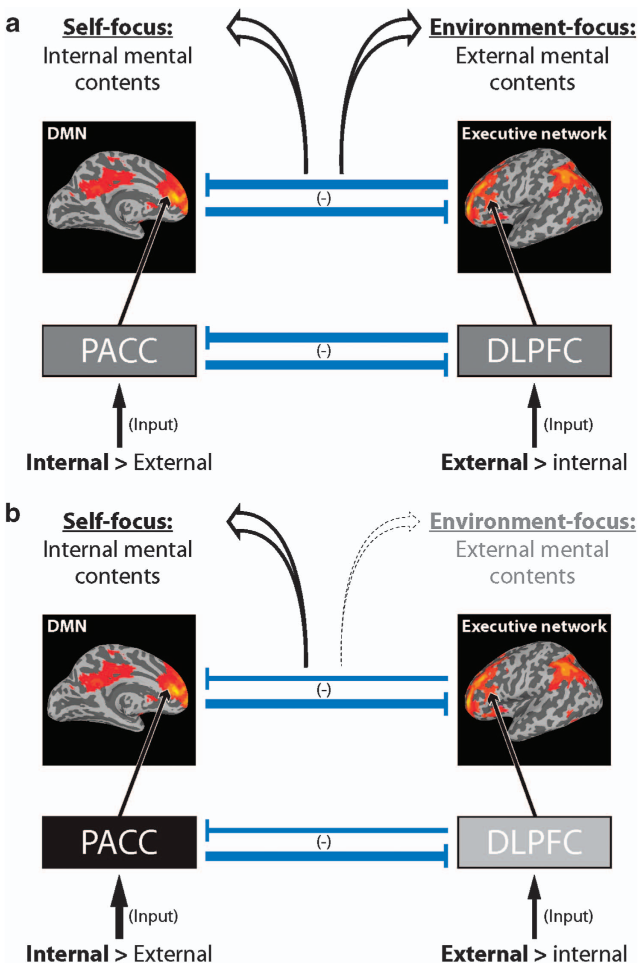

Figure 5. From input over regions and networks to contents in awareness. (**a**) 'Normal' balance between default-mode network (DMN) and executive network (EN) in healthy subjects. Lower level: The figure illustrates schematically the relationship between regions (PACC, perigenual anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex) and their respective input (PACC: stronger internal input from own body and thoughts; DLPFC: stronger external input from environment). Upper level: The PACC is the core region of the DMN as visualized in the brain on the left, whereas the DLPFC is the core region of the EN as visualized in the brain on the right. Similar to PACC and DLPFC, both networks, such as DMN and EN, stand in a reciprocal relationship to each other as signified by the negative sign symbol. The balance between DMN and EN mediates the balance between internal and external mental contents in our awareness, which can be described as self-focus and environment focus. (**b**) Dysbalance between DMN and EN in major depressive disorder (MDD). The mechanisms described in the healthy brain in (**a**) are altered in MDD. There is a dysbalance on the input level with decreased input to the DLPFC, which in turn implies (relatively) increased internal input in the PACC. This dysbalances PACC and DLPFC and subsequently alters the balance between DMN and EN, which, in turn, abnormally increases internal mental contents leading to an increased self-focus, whereas, at the same time, external mental contents are decreased with a decreased external environment focus.

What psychologic functions are associated with the DMN and the EN? As implied by its name, the EN is closely related to cognitive–executive functions including generation of goal orientation and planning and initiation of action and movements. As such, it processes predominantly external stimuli stemming from exteroceptive sensory inputs, which are cognitively elaborated and transformed into action in the EN (see Menon[16]). Hence, the input structure of the DLPFC where the thalamically mediated exteroceptive input predominates seems to be translated onto the network level of the EN. This clearly distinguishes it from the DMN that has been associated with various inner mental functions such as mind wandering,[105,106] random or undirected thoughts,[107] consciousness[108,109] and self-referential activity.[103,110,111] It remains to be explored whether the mental functions associated with the DMN originate in the internal input from other cortical and subcortical regions as it may be hypothesized on the basis of the input structure of the PACC.

From GABA to neural networks

What about the biochemical modulation of these networks? A recent fMRI-MRS study demonstrated that the resting-state functional connectivity within the DMN is modulated by the concentration of GABA in the posterior cingulate cortex (PCC):[112] the higher the concentration of GABA in PCC, the lower the functional connectivity from PCC to other regions within the DMN. In contrast to GABA, PCC glutamate correlated positively with functional connectivity in the DMN. Another study by Duncan *et al.*[113] demonstrated that PACC glutamate levels positively predicted the strength of functional connectivity from PACC to various limbic–subcortical regions such as the thalamus, ventral striatum and PAG. These initial results suggest that functional connectivity within the DMN is modulated by GABA and glutamate, and thus most likely dependent on the excitation–inhibition neuronal balance. This is further supported by challenge studies using benzodiazepines. A recent study by Flodin *et al.*[114] showed increase in functional connectivity within, particularly, the DMN during application of oxazepam, a benzodiazepine that modulates GABA-A receptors, and thus GABAergic neural inhibition. An earlier challenge study using the benzodiazepine lorazepam[115] demonstrated altered balance between PACC deactivation and DLPFC activation during lorazepam challenge, a finding that is well in accordance with the observations on the network level.

In addition to GABAergic challenges, recent studies have used ketamine, a glutamatergic agent, to challenge resting-state functional connectivity. Again, changes in functional connectivity in, particularly, the DMN and dysbalance with the EN were observed[116,117] (see also Anticevic *et al.*[118]). We have to be careful, however. While the results of these first studies demonstrate regionally and network-specific effects of ketamine and benzodiazepines, we have to consider that these effects may be nonspecific for several reasons. First, they are globally distributed throughout the whole brain, which, in most of the studies, is corrected for by global normalization when testing for region- and/or network-specific effects. Second, we cannot exclude vascular rather than neuronal effects of these substances, especially given the neurovascular nature of the BOLD signal in fMRI. Future investigations may consequently want to include measures of vascular blood flow, such as arterial spin labeling, in challenging studies with ketamine or benzodiazepines.

Taken together, considering methodologic caveats, these studies tentatively suggest that GABA and glutamate impact not only cellular and regional but also network-related activity that affects the balance between the DMN and EN. One may therefore suggest that the excitation–inhibition balance may be crucial in modulating the balance between these two networks. The central role of the excitation–inhibition balance on the network level is further supported by the recent study by Chen *et al.*,[104] who observed that (using TMS) increases and decreases in the degree of neural excitation in the DLPFC/EN lead to opposite changes in the PACC/DMN functional connectivity (see also refs 118,119).

What do these findings in healthy subjects let us predict for MDD? First, given that DMN and EN show a different input structure, one would suspect dysbalance between both networks in MDD. With the PACC as key region, the DMN network may predominate and thus be abnormally strong leading to the EN being downmodulated, so that one would expect anticorrelation between the internal DMN functional connectivity and the internal EN functional connectivity, reflecting network dysbalance. Second, one would expect that such network dysbalance may be accompanied by psychologic dysbalance between internal and external contents: the DMN-mediated internal contents such as self-referential activity, mind wandering and random thoughts may predominate over the rather suppressed external content as processed in the EN. Third, one would expect the biochemical dysbalance between GABA and glutamate to drive the network dysbalance; the excitation–inhibition balance in the DMN may tilt abnormally toward the excitatory pole, whereas in the EN it may be shifted more toward the inhibitory pole. There is, as we will see, strong empirical support for the first and second predictions, whereas evidence for the third remains to be provided.

From altered networks to depressive symptoms

Recent studies in MDD indeed show changes in resting-state functional connectivity. Although differing in their details and the exact regions, all studies have reported increased functional connectivity of the pre- and/or subgenual ACC with other regions of the DMN. This includes the VMPFC and other subcortical limbic regions (e.g., the amygdala), which may be central in cognitive emotion regulation and cognitive behavioral therapy in MDD.[120–124] Most interestingly, these studies report increased functional connectivity in the anterior part of the DMN that includes the PACC, the VMPFC and the DMPFC. This seems to be a trait marker of MDD that remains independent of the state, that is, depressed or non-depressed.[121–123]

Although not fully consistent, the data show that the functional connectivity between PACC and DLPFC is abnormally increased in MDD.[122,124,125] Does this mean that the abnormally increased functional connectivity, especially within the anterior DMN, enslaves the neural activity of the DLPFC? If so, one would expect decreased anticorrelation between DMN and ENs in MDD. Unfortunately, the degree of anticorrelation has not yet been measured as such in MDD. However, decreased anticorrelation between DMN and EN would be well in accordance with the decreased reciprocal modulation between PACC and DLPFC in MDD described previously. Finally, the psychopathologic specificity of the network findings for MDD may be questioned. Studies in, for instance, schizophrenia and bipolar disorder also report abnormalities in both DMN and EN (see, for instance, refs 126–128). However, the nature of changes seems to distinguish depression from both bipolar and schizophrenia: increased PACC functional connectivity to other regions both within and outside the DMN, which are specifically involved in emotion processing (e.g., subcortical limbic regions) and emotion regulation, such as EN, seems to be relatively specific for MDD and distinguishes it from bipolar disorder and schizophrenia (see, for instance, refs 129,130). More specifically, MDD patients show hyperactivity (and increased functional connectivity) in the PACC (and VMPFC), whereas the same regions are hypoactive in schizophrenia, which may be related to their opposite symptoms with regard to the self (see below).[90]

Are specific symptoms associated with the network dysbalance? Studies demonstrated that regions of the default-mode network, including the anterior regions, seem to be directly related to self-referential processing.[14,15,131,132] Behaviorally, MDD patients show increased degrees of self-referentiality, an increased self-focus as it has been termed,[7] which they attribute to negative emotional stimuli; this is directly related to decreased deactivation and functional connectivity in the anterior midline regions such as PACC, VMPFC and DMPFC. Berman *et al.*[133] demonstrated increased functional connectivity between PACC and PCC in MDD, which, most importantly, predicted especially the degree of rumination and brooding in these patients (see also refs 134–136 for more or less similar results) (Figure 5). These results support the assumption by Kuhn and Gallinat[90] who, based on meta-analysis (see above), associate increased PACC/anterior DMN activity with increased self-focus, whereas decreased activity in the same regions in schizophrenia is related to decreased self-focus (if not loss of self).

Taken together, these data suggest that symptoms such as rumination and increased self-referentiality, as characterized by abnormally strong internal contents, are associated with changes in the DMN and specifically its anterior regions including the PACC. This inclines one to assume that the input structure, with the predominance of internal input in the PACC and DMN, is also reflected at the network and most importantly at the symptom level in MDD. One may thus infer that the cellular and circuit abnormalities focusing on SST-and PV-positive GABA interneurons are integrated with regional structural specificities and together conveyed or translated into abnormal regional and network activity, where they manifest psychologically in dysbalance between internal and external contents. This manifest as increased rumination and abnormally elevated self-referentiality, and decreased external mental contents from the environment resulting in (subjective–experiential) detachment from the environment, that is, a decreased environment focus.[7,9,137] However, it remains unclear why and how internal mental contents such as ruminations or body changes are more strongly associated with negative rather than positive affect and emotions in MDD (see, for instance, Price and Drevets[8]). Finally, in addition to ruminations and internal self-focus, one may also want to consider other symptoms in MDD-like anhedonia. Anhedonia has been associated with resting-state hyperactivity and hyperconnectivity in the PACC and downstream subcortical regions such as the striatum (see refs 9,138). Most interestingly, anhedonia has also been associated with abnormal levels of GABA and glutamate, and thereby with an abnormal excitation–inhibition balance in these regions in both animal models and human MDD.[31,97,139]

CONCLUSION

Molecular studies in MDD demonstrate changes in specific GABA interneurons, namely SST-positive and to a lesser extent PV-positive neurons, affecting the regulation of input/output of excitatory signals from and onto pyramidal neurons. We here hypothesize that such dysbalance at the local cell circuit affects the processing of information as it transits through cortical layers, translating, through multiple steps described here, to a dysbalance between the PACC and DLPFC as core regions of the DMN and EN, and in turn leading to a dysbalance between internal and external mental contents in awareness in MDD as clinically observed. Accordingly, we propose a cross-level hypothesis ranging from cellular and biochemical levels to regional and neural network levels of activities and to their manifestation at the behavioral level within the gestalt of clinical symptoms (Figure 1). In addition to providing a putative molecular-based explanation of clinical symptoms, this model also supports novel opportunities to link directly molecularly based animal models of human MDD pathology with human imaging studies of regional and network-related activity changes. Finally, our hypotheses about the cellular, biochemical and regional mechanisms of internal and external awareness in MDD carry important implications beyond MDD. These concern other psychiatric and neurologic disorders such as schizophrenia, where partly overlapping neuronal changes are observed, and where the balance between internal and external (mental) contents including their association with the self is also abnormal or disrupted (although in ways that differ from MDD). While our hypothesis addresses mainly neuroscientific mechanisms, it may nevertheless be relevant in future diagnosis and therapy of MDD. For instance, it may allow developing more specific neuronal and biochemical markers for one of the central symptoms of MDD, that is, increased self-focus. In turn, this may enable the development of therapeutically more specific pharmacologic and psychotherapeutic interventions. Finally, apart from neurologic and psychiatric disorders, our hypotheses provide for the first time a set of hypotheses and suggestions for cross-level mechanisms of how internal and external contents may be constituted and balanced in awareness in healthy subjects. This can thus be seen as a contribution to the neuroscientific debate on the neural predispositions and correlates of consciousness.[92,137]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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