SYSTEMATIC REVIEW

Brain-wide changes in excitation-inhibition balance of major depressive disorder: a systematic review of topographic patterns of GABA- and glutamatergic alterations

Yu-Ting Hu[1,2]✉, Zhong-Lin Tan[1], Dusan Hirjak[3] and Georg Northoff[1,2]✉

The excitation-inhibition (E/I) imbalance is an important molecular pathological feature of major depressive disorder (MDD) as altered GABA and glutamate levels have been found in multiple brain regions in patients. Healthy subjects show topographic organization of the E/I balance (EIB) across various brain regions. We here raise the question of whether such EIB topography is altered in MDD. Therefore, we systematically review the gene and protein expressions of inhibitory GABAergic and excitatory glutamatergic signaling-related molecules in postmortem MDD brain studies as proxies for EIB topography. Searches were conducted through PubMed and 45 research articles were finally included. We found: i) brain-wide GABA- and glutamatergic alterations; ii) attenuated GABAergic with enhanced glutamatergic signaling in the cortical-subcortical limbic system; iii) that GABAergic signaling is decreased in regions comprising the default mode network (DMN) while it is increased in lateral prefrontal cortex (LPFC). These together demonstrate abnormal GABA- and glutamatergic signaling-based EIB topographies in MDD. This enhances our pathophysiological understanding of MDD and carries important therapeutic implications for stimulation treatment.

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INTRODUCTION

Major depressive disorder (MDD) is a mental disorder that features a variety of different symptoms including affective, cognitive, sensory-perceptual, motor, and vegetative [1]. The symptomatic complexity of MDD is mirrored by an almost analogous complexity on the level of the brain regions, including limbic regions [2, 3], regions that comprise default mode network (DMN) and lateral prefrontal cortex (LPFC) [4–6], as well as lower-order regions like motor cortex [7] and visual cortex [8, 9]. The hierarchical architecture of functional brain networks in the healthy brains is altered in MDD and linked with gene expression profiles [10]. Excitation-inhibition (E/I) imbalance is an important molecular pathological feature of MDD as alterations in GABA and glutamate levels have been found in multiple brain regions in MDD patients [11, 12]. For instance, increases in glutamate concentrations in the medial prefrontal cortex positively correlate with the anxiety levels in women with MDD [13]. Yet another study observed inverse correlation between glutamate levels in the dorsal anterior cingulate cortex (ACC) and anhedonia ratings [14]. Together, these observations raise the question whether there are brain-wide changes in E/I balance (EIB) pattern in MDD following a particular topographic pattern in comparison to healthy brains. Addressing this yet to be answered question is the main goal of our paper.

For that purpose, we hereby review the changes in the expression levels of molecules associated with the inhibitory GABA and excitatory glutamate systems throughout the whole brain relying on postmortem brain studies of MDD patients compared to healthy controls. Following recent results on the topographic distribution of EIB in healthy subjects [15], we focus on three key topographic features in the present study: i) general view of whole brain involvement considering all regions; ii) cortical and subcortical limbic regions; iii) comparison between DMN regions and LPFC as they are known to stand in a negative relationship [16]. Accordingly, unlike most of the postmortem and imaging studies that focus on specific regions or networks, we here pursue an explicit whole-brain topographic approach. This contributes to a better understanding of the pathophysiological mechanisms of MDD, and moreover to future therapeutic stimulation interventions as for instance transcranial magnetic stimulation or deep brain stimulation, as they operate through modifying the EIB [17].

METHODS

Retrieval strategies

This study was conducted in accordance with the 2020 PRISMA guidelines (see Fig. 1 for schematic representation). Journal articles written in English on human brain research were systematically searched in PubMed from the earliest record to 05th November 2022. The following terms were searched as keywords in the title and abstract sections: (Major-depressive-disorder OR depression) AND (GABA* OR glutam*) AND (postmortem OR post-mortem). Articles other than original research, such as review and

[1]Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou, China. [2]Institute of Mental Health Research, University of Ottawa, Ottawa, Canada. [3]Central Institute of Mental Health, Heidelberg University, Mannheim, Germany. ✉email: yt.hu@zju.edu.cn; georg.northoff@theroyal.ca

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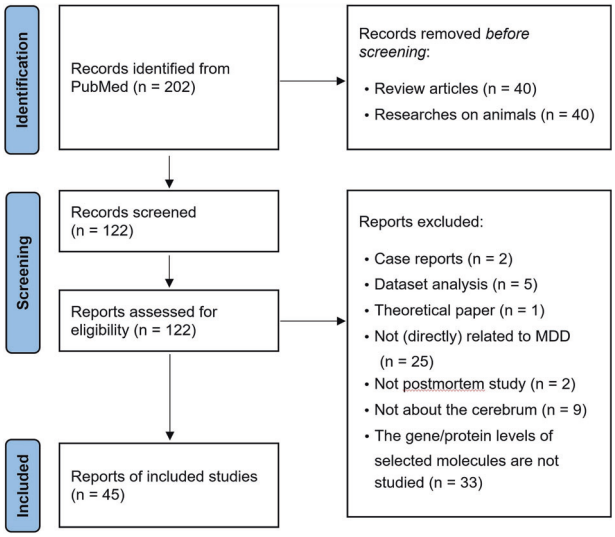

Fig. 1 PRISMA flow chart. PRISMA flow chart for the inclusion of studies.

case report, were excluded. Included studies quantified gene or protein expression levels of the following molecules in postmortem MDD brains by comparison with the healthy postmortem brains: i) glutamic acid decarboxylase (GAD) and glutaminase (GLS); ii) calcium-binding proteins parvalbumin (PV), calbindin (CB), calretinin (CR), and neuropeptide somatostatin (SST); iii) subunits of GABA-A and -B receptors, and of ionotropic glutamate receptor AMPA, NMDA, and kainite; iv) GABA transporter 1 (GAT1), vesicular glutamate transporter (VGLUT), and excitatory amino acid transporter (EAAT). Molecules were summarized in Supplementary Table 1. Search and selection were done by two independent reviewers.

Brain region grouping

The cortical regions investigated were defined by the Brodmann area (BA) as it is the basis for defining postmortem anatomical human brain structures. For grouping the brain regions, we followed the seven-network parcellation [18, 19]. Among which, three profiles, i.e., the limbic regions, regions that comprise DMN and LPFC were highlighted. In brief, limbic regions include BA11, 24, 25 and 28, as well as the hippocampus and amygdala [20, 21]; DMN regions includes the medial part of BA8~10, BA21, 24 and 28 [22]; LPFC includes BA44, 46 and 47. Involved brain regions and grouping details are shown in Supplementary Table 2.

Semi-quantification

Each study that reveals a significant increase in MDD patients compared with healthy controls in the expression level of one or more GABA and glutamate neurotransmission-related molecules will be counted as one entry and represented by a red rectangle in the figures, indicating an activation in the corresponding system; instead, studies that found a significant decrease in expression will be indicated in blue. Results for those molecules whose expression was not significantly different between MDD patients and healthy controls will not be shown in the figures while will be listed in Table 1. Of note, for studies measuring transporters that remove neurotransmitters from the synaptic cleft, namely GAT1 and EAAT1~3 in this review, lower levels of transporters imply higher neurotransmitter retention in the synaptic cleft, this would be seen as an increase in corresponding neurotransmission (red rectangle); conversely, an increase in the transporter level would be considered as a reduction in the transmission.

RESULTS

Search results

Searching identified a total of 202 records from PubMed, of which 40 review articles and 40 articles on animals were removed before screening. Of these, 77 records that didn't meet the inclusion criteria were excluded. See the PRISMA flow chart of review process presented in Fig. 1 for details. Characteristics and main findings of the included studies are shown in Table 1.

Global whole brain EIB alterations in postmortem MDD brains

We first provide a global overview of GABA- and glutamatergic changes throughout the whole brain in MDD. Despite the disparity in the number of studies across different cortical regions, this overview shows a brain-wide variation in EIB-related markers (Fig. 2). This suggests a more global rather than localized changes in the EIB related to glutamatergic excitation and GABAergic inhibition in MDD brain. We next raise the question whether there are specific topographic patterns in the EIB changes of MDD, that is, balances between different set of regions, within such global change.

E/I imbalance within cortical-subcortical limbic regions

GABAergic alterations. Higher mRNA levels of GAD65 and -67 were found in BA24 [23]; GAD65/67-ir neuronal density was increased in both the orbitofrontal cortex (BAs not specified) and the hippocampus [24]. However, studies have also reported that both mRNA [25] and protein levels of GAD67 [26] were reduced in BA25; lower GAD67 mRNA was also found in the hippocampus [27]. Lower PV mRNA levels were identified in BA25 [25]. The mRNA [25, 28, 29] and protein [28] levels of SST were also reduced in BA25. Decreased SST gene expression [30] and density of SST-ir neurons [31] were also observed in the amygdala. Gene expression of many GABA-A receptor subunits has been found elevated in BA24 [23, 32], namely α1, α2, α4, α5, β1~3, δ, ε, γ2, and θ; while diminished α1 expression has also been reported [32]. Higher levels of GABA-B receptor subunits 1 and 2 were observed in BA24 [23]. In sum, evidence points strongly towards reduced GABAergic signaling in MDD in the limbic regions (Fig. 3).

Glutamatergic alterations. GLS gene expression levels were increased in BA24 [23]. Higher gene expression of AMPA 1 [23, 33], 2~4 [23], NMDA 1~2C [23], kainate 1 [23], 5 [33]; and elevated [3H] AMPA binding density were observed in BA24 [34]. The mRNA level of AMPA 1, 3, 4 was found lower in the hippocampus [35]; while AMPA 4 levels were higher in the amygdala [32]. NMDA 2A protein levels were increased in amygdala [36]. VGLUT1~2 mRNA levels were higher in BA24 [23]; and VGLUT1 was also higher in the hippocampus [37]; while VGLUT1 was lower in BA28 [38]. Diminished levels of EAAT1~2 gene expression was reported in both BA24 [33] and hippocampus [37]; higher levels of EAAT3 [39] were found in BA24; whereas decreased EAAT3 protein levels were validated in BA25 [26]. In sum, there is strong evidence for increased glutamatergic signaling in the limbic regions of MDD (Fig. 3).

Together, this opposing change between the levels of molecules associated with GABA and glutamate neurotransmission supposedly leads to E/I imbalance with abnormally increased excitation and reduced inhibition in the cortical-subcortical limbic regions (Fig. 3).

E/I imbalance between default mode network (DMN) and lateral prefrontal cortex (LPFC)

GABAergic alterations. DMN regions: GAD67 protein levels were significantly reduced in BA9 [40], while higher mRNA levels of GAD65 and -67 were found in BA24 [23]. The mRNA levels of SST [41], and the density of CB- [42] and CR-ir [43] neurons were decreased in BA9. Diminished gene expression of GABA-A receptor subunits was found, including α1 (BA10 [44] and 24

Table 1. Studies included.

Year	Author	Brain regions	(referred BAs)	Analysis	Main findings
2000	Guidotti et al.	PFC	BA 9	Western blot	Unchanged GAD65 and 67
2005	Choudary et al.	DLPFC ACC	BA 9, 46 BA 24	Microarray	DLPFC: reduced EAAT1~2; increased AMPA3, kainite1 and 5, GABA-A-β3, -δ and γ2 ACC: reduced EAAT1~2; increased AMPA1 and kainite2
2005	Toro et al.	OFC hippocampus	BA 11 /	Immunoautoradiography	Both areas: unchanged NMDA1
2005	Torrey et al.	PFC superior TC ACC hippocampus	BA 9, 46 BA 22 BA 24 /	Microarray	All areas: unchanged GAD65 and 67, PV, CB, CR, AMPA1~4, kainate1~5, NMDA1 and 2A~2 C, and EAAT1~3
2007	Bielau et al.	DLPFC OFC superior TC ACC hippocampus	BA 9, 46 BA 11, 47 BA 22 BA 24 /	Immunohistochemistry	GAD65/67-ir neuronal density was increased in DLPFC, OFC, superior TC, and hippocampus; while was unchanged in ACC
2007	Rajkowska et al.	DLPFC OFC	BA 9 BA 47	Immunohistochemistry	CB-ir neuron density and size were reduced DLPFC, while unchanged in OFC; PV-ir neuron density and size were unchanged in DLPFC and OFC
2008	Beneyto et al.	DLPFC	BA 9, 46	In situ hybridization	Reduced NMDA1 and 2 A, unchanged NMDA2B, 2 C and 2D
2009	Feyissa et al.	PFC	BA 10	Western blot	Reduced NMDA2A and 2B; unchanged NMDA1
2009	Karolewicz et al.	amygdala	/	Western blot	Increased NMDA2A; unchanged NMDA1 and GAD67
2009	Klempan et al.	PFC	BA 44~47	Microarray	BA44: increased GABA-A-δ, GABA-B-2 BA46: decreased AMPA3
2009	Sequeira et al.	BA 4, 6, 8~10, 20, 21, 24, 38, 44, 46 amygdala		Microarray	BA4: decreased GAT1 BA6: increased GABA-A-δ, -β3; reduced kainate1 BA8~9: reduced GABA-A-α4 BA10: increased GABA-A-β3, AMPA2 and 4 BA20: increased GABA-A-α5, -γ2, GLS, and NMDA2A BA21: reduced GABA-A-γ1; reduced AMPA1 BA24: increased GABA-A-β1, with reduced α1 BA38: increased GABA-A-β3 BA44: increased GABA-A-δ BA46: increased GABA-A-α5 and -δ; reduced GABA-A-γ1, GAT1, and AMPA3 Amygdala: higher AMPA4
2009	Uezato et al.	inferior TC middle TC entorhinal cortex hippocampus	BA 20 BA 21 BA 28 /	In situ hybridization	Inferior TC: unchanged VGLUT1~3 Middle TC: reduced VGLUT2, unchanged VGLUT1 and 3 entorhinal cortex: reduced VGLUT1, unchanged VGLUT2 and 3 Hippocampus: unchanged VGLUT1~3
2010	Karolewicz et al.	DLPFC	BA 9	Western blot	Reduced GAD67, with unchanged GAD65
2010	Maciag et al.	occipital cortex	BA 17	Immunohistochemistry	CB-ir neuronal density was decreased, while the neuronal size was unchanged
2010	Miguel-Hidalgo et al.	OFC	BA 47	Immunohistochemistry	Reduced EAAT1 and 2
2011	Sibille et al.	DLPFC	BA 9	Q-PCR	Reduced SST; unchanged PV, CR, GAD65 and 67
2011	Thompson Ray et al.	entorhinal cortex hippocampus subiculum	BA 28 / /	In situ hybridization	GAD67 was reduced in hippocampus, while was unchanged in entorhinal cortex and subiculum
2011	Tripp et al.	sgACC	BA 25	Q-PCR, Western blot	Reduced SST
2011	Khundakar et al.	DLPFC	BA 9	Immunohistochemistry	Unchanged PV- and CR-ir percentage of area

Table 1. continued

Year	Author	Brain regions	(referred BAs)	Analysis	Main findings
2012	Gibbons et al.	DLPFC ACC	BA 46 BA 24	In situ radioligand binding with autoradiography	DLPFC: unchanged binding density of [^{3}H]AMPA and [^{3}H]kainate ACC: increased [^{3}H]AMPA binding density, unchanged [^{3}H]kainate binding density
2012	Gilabert-Juan et al.	DLPFC	BA 9	Immunohistochemistry	Reduced VGLUT1, unchanged GAD67
2012	Guilloux et al.	amygdala	/	Microarray	Reduced SST
2012	Oh et al.	DLPFC	BA 9	Immunohistochemistry	Reduced CR-ir neuronal density
2012	Tripp et al.	subgenual ACC	BA 25	Q-PCR	Decreased PV, SST, GAD65 and 67; unchanged GAT1, CR, GABA-A-α1
2013	Duric et al.	hippocampus	/	Microarray	Reduced AMPA1, 3, and 4; unchanged NMDA1 and 2A~2D
2013	Goswami et al.	PFC	BA 10	NanoString nCounter gene expression analysis	Unchanged EAAT1-3, and VGLUT1
2013	Medina et al.	hippocampus	/	In situ hybridization	Decreased EAAT1 and 2; increased VGLUT1
2014	Chandley et al.	PFC	BA 10	Q-PCR	Unchanged AMPA1, 2, 4, NMDA1 and 2A~2D, and kainate1, 3, 5
2014	Gottschalk et al.	PFC	BA 10	LC-MS	Increased VGULT1; unchanged GAD65
2014	Wesseling et al.	PFC	BA 10	SRM-MS	Unchanged AMPA1~3 and NMDA1
2015	Gray et al.	DLPFC	BA 9, 46	Q-PCR	Increased AMPA2 and kainite2
2015	Seney et al.	subgenual ACC	BA 25	In situ hybridization	Reduced SST
2016	Darby	OFC	BA 11, 47	RNA sequencing	Molecules interested were unchanged
2016	Rafalo-Ulinska et al.	PFC	BA 10	Western blot	Decreased AMPA1 and NMDA2A
2016	Smiley et al.	primary auditory cortex	BA 41~42	Immunohistochemistry	CR- and CB-ir neuronal density was reduced; PV-ir neuronal density was unchanged
2016	Yin et al.	DLPFC	BA 9	RNA sequencing	Molecules interested were unchanged
2016	Zhao et al.	DLPFC, ACC	BA 46, BA 24	Q-PCR	EAAT1~3 were increased in DLPFC, while were unchanged in ACC
2016	Pantazatos et al.	DLPFC	BA 9	RNA sequencing	Molecules interested were unchanged
2017	Ramaker et al.	DLPFC, ACC	BA 9, BA 24	RNA sequencing	Molecules interested were unchanged
2017	Douillard-Guilloux et al.	amygdala	/	In situ hybridization	Reduced SST-ir neuronal density
2018	Scifo et al.	subgenual ACC	BA 25	MS-based proteomics	Decreased GAD67 and EAAT3
2018	Xiong et al.	parietal cortex	BA 7	Western blot	Increased GABA-A-α5
2018	Zhao et al.	DLPFC, ACC	BA 46, BA 24	Q-PCR	GAD65 and 67, GABA-A-α1~4, -β1~3, -δ, -ε and -γ2, GABA-B1 and 2, GLS, AMPA1~4, kainite1, NMDA1 and 2A~2B, VGLUT1 were increased in DLPFC and ACC; GABA-A-α5, -θ, and VGLUT2 were unchanged in DLPFC while increased in ACC (Note: changes in ACC were diminished in nonsuicidal MDD patients)
2019	Xiong et al.	parietal cortex	BA 7	Western blot	Increased GABA-B-1
2021	Matas et al.	frontal cortex	BA 6	Western blot	Decreased NMDA2A

ACC anterior cingulate cortex, *BA* Brodmann areas, *DLPFC* dorsolateral prefrontal cortex, *LC-MS* liquid chromatography-mass spectrometry, *OFC* orbitofrontal cortex, *SRM-MS* selected reaction monitoring-mass spectrometry, *TC* temporal cortex.

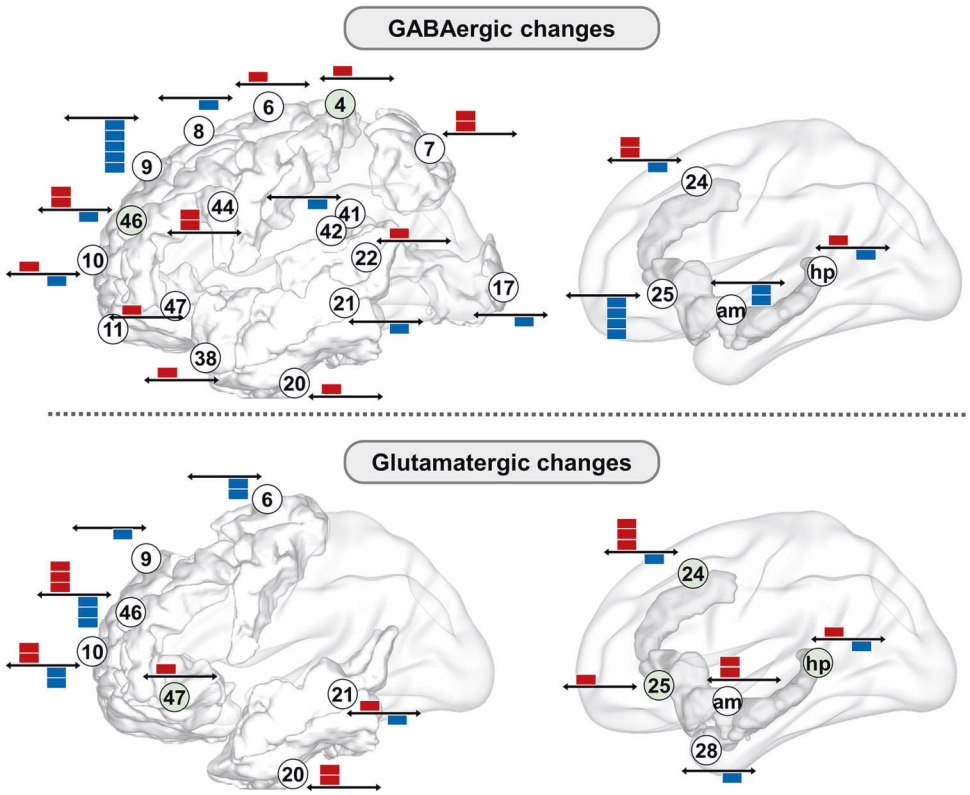

Fig. 2 Global excitation-inhibition balance changes in the postmortem MDD brain. Global GABAergic (upper) and glutamatergic (lower) signaling changes. Each rectangle represents a study, with red indicating an increase in the system activity and blue a decrease. The numbers in the circles represent the corresponding Brodmann areas. Circles with light green background indicate that there were studies measuring the transporters which remove the neurotransmitters from the synaptic cleft, namely GAT1 or EAAT1~3. am = amygdala, hp = hippocampus.

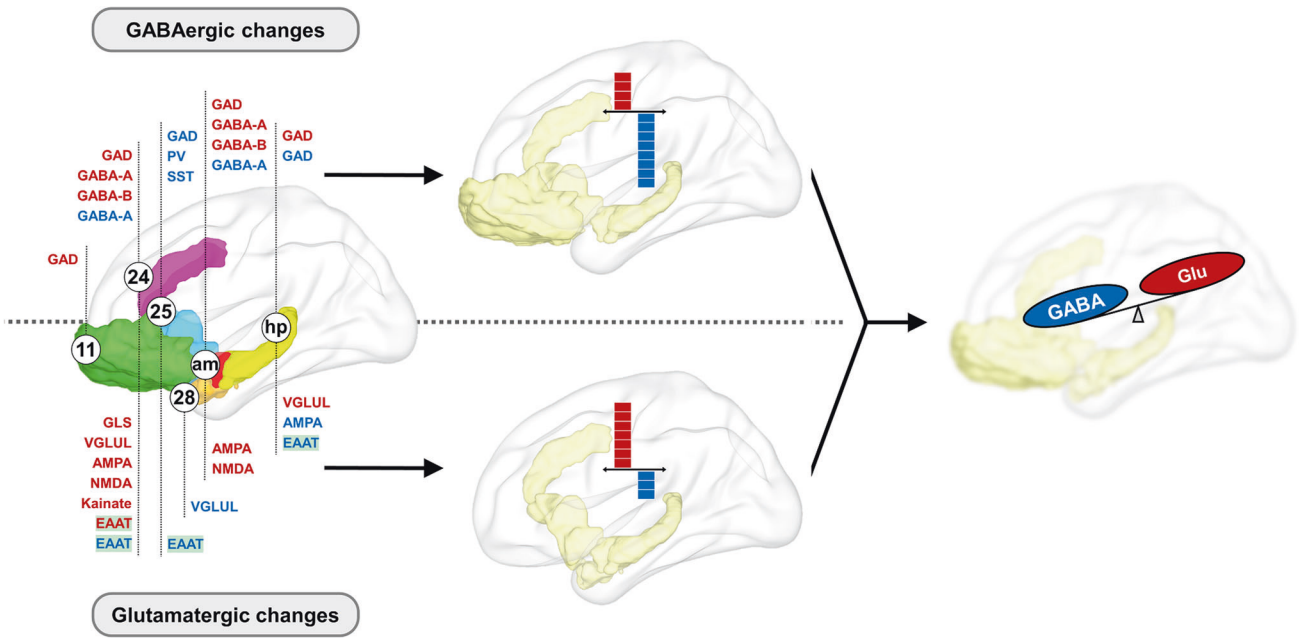

Fig. 3 Excitation-inhibition imbalance in cortical-subcortical limbic regions of the postmortem MDD brain. GABAergic signaling (upper) is decreased, whereas glutamatergic signaling (lower) is increased. am=amygdala, hp=hippocampus.

[32]), α3 in BA10 [44], α4 (BA8 [32], 9 [32], and 10 [44]); γ1 in BA21 [32], and δ in BA10 [44]. Elevated gene expression of GABA-A receptor subunits has also been reported, including β3 in BA10 [32], and α1, α2, α4, α5, β1~3, δ, ε, γ2, and θ in BA24 [23, 32]. Higher levels of GABA-B receptor subunits 1 and 2 were observed in BA24 [23]. In sum, strong evidence shows reductions in the levels of various molecules associated with GABA neurotransmission in the DMN regions of MDD patients (Fig. 4).

LPFC: Increased GAD65 and -67 mRNA levels were found in mainly dorsolateral prefrontal BA46 [23]. GAD65/67-ir neuronal

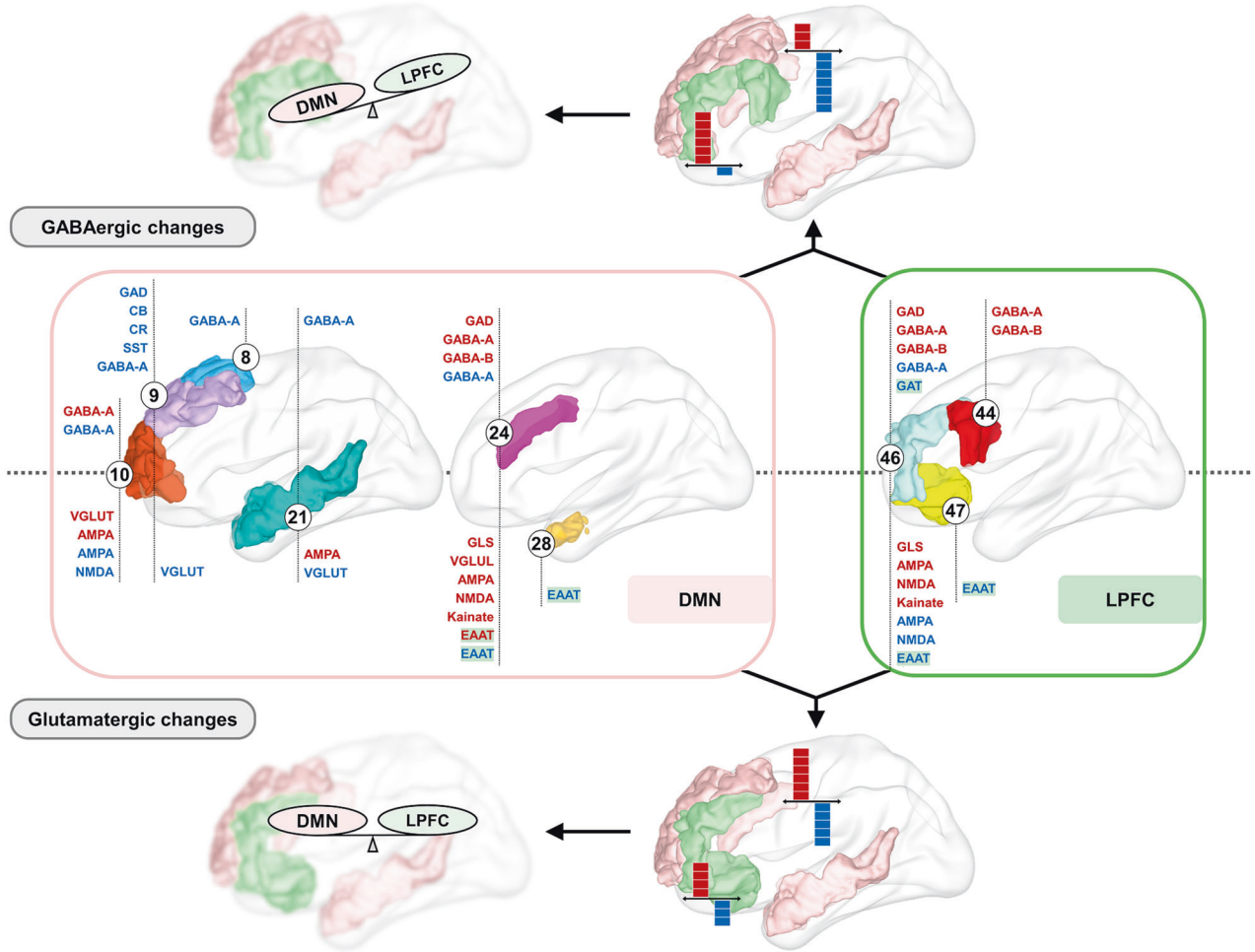

Fig. 4 Excitation-inhibition imbalance in default mode and lateral prefrontal regions of the postmortem MDD brain. GABAergic signaling (upper) is decreased in the default mode regions while increased in the lateral prefrontal regions; whereas glutamatergic signaling (lower) remains balanced between these two regions. DMN=default mode network, LPFC=lateral prefrontal cortex.

densities have been reported to be higher in the dorsolateral prefrontal cortex (BAs not specified) [24]. Higher levels of gene expression levels were observed for GABA-A receptor subunits, including α1~5, β1~3, δ, γ2, and ε in BA46 [23, 32]; β3, δ, and γ2 in the dorsal-LPFC [33]; as well as δ in BA44 [32, 45]. Whereas reduced levels of subunit γ1 were found in BA46 [32]. In addition, higher GABA-B receptor subunit 1 was identified in BA46 [23]; higher subunit 2 was seen in both BA44 [45] and 46 [23]. Gene expression level of GAT1 was decreased in BA46 [32]. In sum, there is strong evidence for the increased level of GABA neurotransmission-related molecules in the LPFC of MDD patients (Fig. 4).

Glutamatergic alterations. DMN regions: GLS gene expression levels were increased in BA24 [23]. Higher gene expression of AMPA 1 [23, 33], 2~4 [23], NMDA 1~2C [23], kainate 1 [23], 5 [33]; and elevated [3H] AMPA binding density were observed in BA24 [34]. Gene expression levels of AMPA subunits 2 and 4 were also increased in BA10 [32], so was the level of subunit 1 in BA21 [32]. While there were studies that found a significant decrease in the protein level of AMPA 1 [46] and NMDA 2A~2B [46, 47] in BA10. The gene expression of VGULT1 was found elevated in BA10 [48] and BA24 [23], while was found decreased in BA28 [38]; its protein level was observed to reduce in BA9 [49]. VGLUT2 gene expression was higher in BA24 [23] but lower in BA21 [38]. Diminished gene expression level of EAAT1~2 [33] and higher EAAT3 levels [39] were reported in BA24. In sum, there is some evidence for increase in glutamatergic molecules in DMN of MDD albeit, unlike in the case of GABAergic decrease in DMN, the evidence is not as uniform across all measures (Fig. 4).

LPFC: GLS mRNA levels were elevated in BA46 [23]. In BA46, gene expression levels of AMPA 2~4, kainate 1, and NMDA 1~2B were reported to be increased [23], while AMPA 3 [32, 45] was decreased. Higher gene expression levels of AMPA 2, 3 [33, 50] and kainate 1, 2, 5 [33, 50] were detected in the dorsal-LPFC, while NMDA 1~2A reduced [51]. EAAT1~2 mRNA levels were diminished in dorsal-LPFC [33]; and their protein levels were lower in BA47 [52]. In sum, there is evidence for changes in glutamatergic molecules in LPFC of MDD (Fig. 4).

Together, GABAergic signaling seems to be abnormally strong in LPFC relative to DMN in MDD. In contrast, the glutamatergic evidence in both DMN and LPFC is mixed when considering all markers as they show both increases and decreases. Therefore, more research is needed to develop a clearer picture of the balance of glutamatergic changes between DMN and LPFC in MDD.

Other EIB alterations

GABAergic alterations. Motor-related regions: Higher gene expressions of GABA-A receptor subunit δ and β3 were observed in BA6 [32]; protein levels of GABA-A receptor subunit α5 [53] and GABA-B receptor subunit 1 [54] were both significantly increased

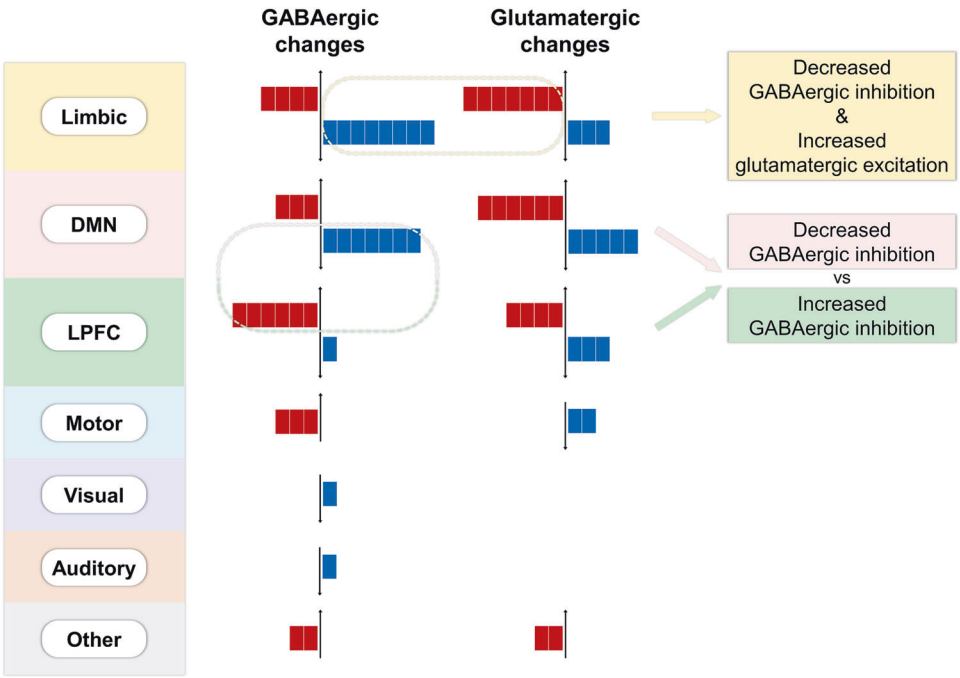

Fig. 5 Diagram of the key observations. Topography of excitation-inhibition balance changes in the postmortem MDD brain.

in BA7. The gene expression level of GAT1 was decreased in BA4 [32]. Figure not shown.

Primary sensory regions: CB-ir neuron densities were significantly decreased in the visual cortex (BA17) [55]; the densities of both CB- and CR-ir neurons were lower in the auditory cortex (BA41 and 42) [56]. Figure not shown.

Other regions: Increased GAD 65/67-ir neuronal density was observed in BA22 [24]. Gene expressions of the GABA-A receptor subunit α5 and -γ2 were elevated in BA20 [32]; and levels of subunit β3 were higher in BA38 [32]. Figure not shown.

Glutamatergic alterations. Motor-related regions: Decreased gene expression of kainate subunit 1 [32] and protein level of NMDA subunit 2A [57] were found in BA6. Figure not shown.

Other regions: Increased gene expressions of GLS and NMDA 2A were observed in BA20 [32]. Figure not shown.

Summary – Topographic structure of EIB changes

By summarizing the EIB changes, three key observations emerge in the brain topography of MDD patients (Fig. 5).

i. EIB reflected by glutamatergic excitation and GABAergic inhibition in MDD brains shows general brain-wide changes across the whole brain regions rather than regionally localized changes.
ii. Opposite alteration is found between GABAergic and glutamatergic signaling within the cortical-subcortical limbic regions: GABAergic signaling is attenuated, whereas glutamatergic signaling is elevated.
iii. Opposite GABAergic signaling is found between the DMN regions and LPFC: increased in the LPFC, while, on the contrary, diminished in the DMN regions. On the other hand, the glutamatergic signaling is relatively unchanged in both LPFC and DMN regions.

DISCUSSION

We here reviewed the brain-wide topographic pattern of E/I imbalances in MDD as operationalized by changes of inhibitory GABAergic and excitatory glutamatergic markers in postmortem tissue. Our findings of brain-wide E/I imbalance are further supported by in vivo magnetic resonance spectroscopy (MRS) studies in MDD patients. Reduction in GABA levels were observed in multiple brain regions, especially in the medial prefrontal regions including the ACC in MDD patients [11, 58–60]. These support our observation of decreased GABAergic signaling in especially cortical-subcortical limbic and DMN regions in postmortem studies as reviewed here.

One key system with changes in E/I imbalance in MDD are the regions of the cortical-subcortical limbic system with especially its anterior regions like the perigenual ACC (PACC). In MDD patients, significantly reduce negative BOLD responses during external emotional tasks have been demonstrated in PACC [61], together with enhanced resting-state activities [60, 62]; and increased functional connectivity of the rostral ACC with subcortical limbic regions has been reported [16]. These are in line with our observation of reduced GABAergic and elevated glutamatergic signaling in cortical-subcortical limbic regions.

Yet another key network is the default-mode network (DMN). Our current data suggest that increased DMN activity may be related to reduced GABAergic inhibition in DMN as suggested by our previous study [16]. In contrast, the LPFC in MDD patients is characterized by decreased activity [16], and our present data suggest such deficient LPFC activity to be related to increased GABAergic inhibition. These changes amount to an abnormal reciprocal balance of decreased-increased GABAergic inhibition in DMN-LPFC which well mirrors an analogous pattern of their reciprocal modulation on the more systemic-macroscopic level, e.g., hyperactivity in DMN and hypoactivity in LPFC [5, 16]. This is supported by a recent study that showed how deficits in inhibitory GABAergic interneurons, through modulating excitatory neuronal input/output and local cell circuit processing of information in key brain regions, may underlie the shift in the balance of DMN and LPFC [16]. Such switch in the supposedly GABAergic mediated reciprocal activity balance of DMN and LPFC in MDD patients is closely associated with a shift in awareness. Rather than focusing on the external environment, people with MDD show increased self-focused awareness of their own physical conditions or thoughts generally coupled with negative aspects [63, 64]. Increased self-awareness is related to increased neural activity in

DMN as has been revealed by functional imaging studies in MDD patients [5, 61, 65].

In addition to limbic and DMN-LPFC regions, we also demonstrate abnormal E/I imbalance in more primary regions. For instance, in the occipital cortex of MDD patients, GABA levels were found to be unchanged [66] or lower [11, 58, 59] compared to healthy controls; the latter is consistent with the reduced CB-ir neuron density that has been found in the postmortem study [55].

Beyond demonstrating global topographic pattern of EIB changes in MDD, our findings carry important therapeutic implications. The current practice mostly focuses on stimulating one region in isolation as for instance the dorsal LPFC with transcranial magnetic stimulation [67] or the ACC with deep brain stimulation [68, 69]. Our results show that we may need to extend our therapeutic approach beyond single regions: we need to change the topographic pattern of EIB rather than just targeting the EIB in one single region or network. Our previous clinical study demonstrated the therapeutic potential and good tolerance of transcranial magnetic stimulation in the visual cortex of patients with MDD [17]. Due to the co-occurrence of different symptoms with different balances or constellations among sensory, motor, cognitive, affective, social, and vegetative functions in MDD [1], one can thus speak of "symptom coupling" or "co-occurrence of symptom" which, as we assume, can be traced to the brain-wide topography changes in EIB across different regions and their respectively associated functions [70]. In that case topography, indexing the spatial relations between different regions' EIB, would also be manifest on the psychological or mental level in form of the relationship of the different symptoms – topography may then provide the "common currency" of cellular/E/I imbalance, neural and mental levels [71].

CONCLUSION

Recent studies of the healthy brain have shown global topographic patterns of EIB. We here ask the question whether there are abnormal topographic EIB patterns in MDD compared with healthy brains. We show that GABA- and glutamatergic changes in postmortem MDD brains exhibit i) brain-wide changes; ii) disbalance in cortical-subcortical limbic regions with decreased GABAergic signaling and increased glutamatergic signaling; iii) reciprocal modulation of GABA neurotransmission in DMN (reduced GABAergic signaling) and LPFC (elevated GABAergic signaling). Together, we demonstrate global-topographic E/I imbalances in MDD, supported by in vivo MRS findings of changes in especially inhibitory GABAergic system of MDD. Beyond providing novel insight into pathophysiological mechanisms, these findings carry important implications for stimulation therapy that may target topographic patterns of EIB rather than individual regions of EIB.

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AUTHOR CONTRIBUTIONS

Y.H. and G.N. designed the study. Y.H. and Z.T. contributed to the reference retrieval. Y.H. and G.N. made the figures. Y.H., Z.T., D.H., and G.N. wrote the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Yu-Ting Hu or Georg Northoff.