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The thalamus is the causal hub of intervention in patients with major depressive disorder: Evidence from the Granger causality analysis

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ABSTRACT

Major depressive disorder (MDD) is the leading mental disorder and afflicts more than 350 million people worldwide. The underlying neural mechanisms of MDD remain unclear, hindering the accurate treatment. Recent brain imaging studies have observed functional abnormalities in multiple brain regions in patients with MDD, identifying core brain regions is the key to locating potential therapeutic targets for MDD. The Granger causality analysis (GCA) measures directional effects between brain regions and, therefore, can track causal hubs as potential intervention targets for MDD. We reviewed literature employing GCA to investigate abnormal brain connections in patients with MDD. The total degree of effective connections in the thalamus (THA) is more than twice that in traditional targets such as the superior frontal gyrus and anterior cingulate cortex. Altered causal connections in patients with MDD mainly included enhanced bottom-up connections from the thalamus to various cortical and subcortical regions and reduced top-down connections from these regions to the THA, indicating excessive uplink sensory information and insufficient downlink suppression information for negative emotions. We suggest that the thalamus is the most crucial causal hub for MDD, which may serve as the downstream target for non-invasive brain stimulation and medication approaches in MDD treatment.

1. Introduction

Major depressive disorder (MDD), one of the most prevalent mental disorders, is characterized by abnormal symptoms in mood, cognition, and physical activities. MDD impairs multiple psychological functions in most brain regions and affects more than 350 million people worldwide. Moreover, it is the leading cause of disability and a primary factor in the global burden of disease (Santomauro et al., 2021). Thus, it is urgent to find key intervention targets for the treatment of MDD.

A consensus has been reached that patients with MDD suffer from dysfunctions in extensively connected brain regions via axonal pathways (Gong and He, 2015). However, these brain regions are not equally affected by depressive symptoms. For instance, dysfunctions in the dorsal lateral prefrontal cortex, anterior cingulate cortex, and insular are more frequently reported in patients with MDD (Connolly et al., 2013; Du et al., 2018; Sridharan et al., 2008; Wang et al., 2016). These regions are considered functional hubs due to their heavy connections with others and critical roles in MDD. Since pathological changes tend to occur in network hub regions of the brain (Crossley et al., 2014), while hub regions have a more widespread effect on network dynamics and cognitive impairment (Honey and Sporns, 2008; Warren et al., 2014), hub-based intervention would effectively improve the treatment efficiency of MDD.

Compared with functional hubs, effective hubs reflect the regions with heavily directional influences on multiple regions (Ishida et al., 2020; Rao et al., 2018). Several causal models were put forward to measure effective connections among brain regions, such as the dynamic causal modeling (DCM) (Friston et al., 2010), structural equation modeling (SEM) (Anderson et al., 1988), and Granger causality model (GCM) (Granger, 1969). The first two are hypothesis-driven models, whereas the latter is a data-driven approach. Granger causality analysis (GCA) is a method based on a linear regression model, and its principle was briefly described as follows. Suppose there are two time-series X and Y. If the past value of X is helpful to predict the current value of Y, it can be said that × Granger causes y and the effect can be measured by the F test on mean squared error prediction of Y with and without X. The GC approach is suitable for a systematic study of the whole brain, especially during resting-state brain activity. The GC approach is nonparametric

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and computationally straightforward (Roebroeck et al., 2005; Seth et al., 2013), thus providing a unique, unbiased solution for effective connection (Bielczyk et al., 2019). In recent years, the GC approach has been widely used to investigate the intrinsic effective connectivity (EC) network in resting-state functional magnetic resonance imaging (rs-fMRI) data (Bi et al., 2019; Iwabuchi et al., 2017; Jiang et al., 2017). The alteration of EC networks in MDD patients is viewed as an important aspect of pathogenesis and potential intervention targets of MDD (Feng et al., 2016; Hamilton et al., 2011; Yang et al., 2021a).

This article, therefore, aimed to provide the potential intervention target for MDD by reviewing the abnormal EC patterns in MDD patients based on GC studies and locating the hub region in the abnormal EC patterns. We discussed how these abnormalities affect MDD patients and the potential of the hub region as an effective target for the treatment of MDD.

2. Methods

We searched PubMed, ProQuest, Web of Science, EBSCO, Google Scholar, ScienceDirect, and PsycInfo using the query *(depression OR depressive OR MDD) AND (fMRI OR functional MRI OR functional magnetic resonance imaging) AND ("Granger")* to find out literature that studies abnormal ECs of fMRI using the GC approach in patients with MDD. We repeated the search twice during the review to track the latest publications, and the most recent search was performed on March 16, 2022. In addition, we checked the references of the studies we reviewed in case any relevant studies were not retrieved.

We only had one inclusion criterion: these pieces of literature reported abnormal Granger causality in MDD patients compared with normal controls. Based on this criterion, we screened out 19 articles, but for some reason, several studies were not included in the subsequent

Table 1
Literature summary.

Study	Sample Size	Age, mean (s.e.)	% Female	Study design	Decreased Connectivity		Increased Connectivity	
					From	To	From	To
(Hamilton et al., 2011)	16 (MDD),14 (Controls)	34.6 (1.6),30.4 (2.4)	62 %, 43 %	Rest state	HIP MPFC, DLPFC DMPFC	vACC, DLPFC vACC vSTR		
(Iwabuchi et al., 2014)	16 (MDD),16 (Controls)	34.4 (6.7), 33.8 (6.4)	56 %, 56 %	Rest state	CAU, THA SFGdor THA	INS ORBsupmed, INS PUT, INS, PAL, CAU, ORBsupmed, AMYG, IFGtriang, HIP	INS, ACG, PUT, IFGtriang CAL, LING, CUN, PUT, INS, PAL, CAU, AMYG, HIP, ORBmid, ORBsupmed, CRBL6, CRBLCrus1, IOG, FFG	SFGdor THA
(Grant et al., 2014)	19 (MDD),20 (Controls)	34.5 (10.7),31.2 (9.2)	55 %, 53 %	Eriksen flanker task	DOG	AMYG, ACC, MFG	MFG	AMYG, ACC
(Guo et al., 2015)	44 (MDD),44 (Controls)	27.5 (8.6), 29.4 (6.7)	50 %, 55 %	Rest state	ITG	INS	ANG ITG	STG, IFGoperc CRBL6
(Tadayonnejad et al., 2016)	19 (MDD),20 (Controls)	27.4 (7.8),31.8 (10.2)	63 %, 65 %	Rest state			THA	ANG, PreCG
(Gao et al., 2016)	22 (MDD), 22 (Controls)	38.4 (11.1), 36.7 (10.9)	59 %, 29 %	Rest state	PreCG, ORBsup ORBsup MFG, IFGtriang, ORBinf ORBmid SFGdor, ORBsupmed, IFGtriang, IFGoperc, TPOmid, DCG, DOG ORBinf	SFGdor MFG PreCG, ACG ORBsup ORBsupmed, ACG ORBmid SFGdor, PreCG, FFG, MOG, CAL	STG, MTG, HES, INS, CRBL45, Vermis45	CAU
(Feng et al., 2016)	23 (MDD), 20 (Controls)	31.5 (6.9), 30.1(7.5)	70 %, 70 %	Rest state	INS, PUT	ACC	IFGtriang, ORBmid ACC	ACC PUT
(Jiang et al., 2017)	20 (MDD), 20 (Controls)	41.8 (14.2), 41.6 (13.6)	55 %, 65 %	Rest state	PCG	INS, STG		
(Wang et al., 2017a)	23 (MDD), 25 (Controls)	38.7 (11.0), 39.5 (8.1)	52 %, 52 %	Rest state			FFG	AMYG
(Jiang et al., 2019)	20 (MDD), 20 (Controls)	41.8 (14.2), 41.6 (13.6)	65 %, 65 %	Rest state	CRBL45	THA, SFGmed		
(Wang et al., 2020)	23 (MDD), 25 (Controls)	38.7 (11.0), 39.5 (8.1)	52 %, 52 %	Rest state			MFG	ANG
(Luo et al., 2021)	27 (MDD), 54 (Controls)	29.7 (7.3), 29.4 (6.3)	63 %, 63 %	Rest state	FFG	CUN, CRBL6		
(Gao et al., 2021)	23 (MDD), 25 (Controls)	38.7 (11.0), 39.5 (8.1)	52 %, 52 %	Rest state	ANG	THA		

This table lists the main findings of the studies discussed in this review, and a full representation of the brain regions involved in the table can be found in Table 2. Abbreviation list.

analysis of abnormally effective connectivity. Among them, some authors reported the different dynamic GC connectivity patterns between the patients with depression and normal subjects, but the dynamic connectivity cannot be analyzed in the same framework as the static connectivity (Lu et al., 2013). A study showed abnormal connections at the brain network level but did not report specific brain area information (Wei et al., 2015). Research has shown that decreased flexibility of the salience network (SN) compared with the controls rather than the abnormal connectivity (Wei et al., 2017). Two studies investigated the abnormal connection patterns between MDD patients and patients with amnestic mild cognitive impairment disease or Parkinson's disease, which lacked results compared with normal controls (Liang et al., 2016; Zheng et al., 2017). The study of Yang et al. only reported the connectivities that had changed but did not indicate whether the changes were enhanced or weakened (Yang et al., 2021a).

It is worth mentioning that two studies have reported changes in brain connectivities before and after treatment. Since we are interested in MDD-specific connectivity patterns rather than treatment effects, if some effective connectivities of patients are enhanced after therapy, and these changes are related to improving disease symptoms, we assumed that such weakened connections are pathological. In this way, we also incorporate these connections into the subsequent analysis (Gao et al., 2021; Wang et al., 2020). Thirteen articles were included in the following analysis. See Table 1 for details.

We extracted abnormal ECs in patients with MDD relative to healthy controls in each study and divided them into enhanced ECs and weakened ECs. Because the coordinate system and naming of brain regions were inconsistent in different studies, we converted the Talairach coordinates to the MNI coordinates with the tal2cbm toolkit https://www.brainmap.org/ale/index.html (Lancaster et al., 2007) and renamed brain regions with the AAL116 template (Tzourio-Mazoyer et al., 2002).

Table 2
This table explains the abbreviations for all brain regions referred to in the text and Table 1.

Abbreviation	
SFGdor	Superior frontal gyrus, dorsolateral
SFGmed	Superior frontal gyrus, medial
MFG	Middle frontal gyrus
PreCG	Precental gyrus
ORBsup	Superior frontal gyrus, orbital part
ORBmid	Middle frontal gyrus, orbital part
ORBsupmed	Superior frontal gyrus, medial orbital
IFGtriang	Inferior frontal gyrus, triangular part
IFGoperc	Inferior frontal gyrus, opercular part
STG	Superior temporal gyrus
MTG	Middle temporal gyrus
ITG	Inferior temporal gyrus
TPOmid	Temporal pole: middle temporal gyrus
FFG	Fusiform gyrus
HES	Heschl gyrus
SPG	Superior parietal gyrus
ANG	Angular gyrus
CUN	Cuneus
INS	Insula
ACG	Anterior cingulate and paracingulate gyri
DCG	Median cingulate and paracingulate gyri
PCG	Posterior cingulate gyrus
IOG	Inferior occipital gyrus
MOG	Middle occipital gyrus
CAL	Calcarine fissure and surrounding cortex
LING	Lingual gyrus
CAU	Caudate nucleus
PUT	Lenticular nucleus, putamen
PAL	Lenticular nucleus, pallidum
THA	Thalamus
HIP	Hippocampus
AMYG	Amygdala
CRBL	Cerebellum superior

The template has been registered along with the MRI and PET images so that using it as a mask can effectively extract information from different brain regions. In addition, it is also one of the most widely used templates, which facilitates communication. It is worth noting that if there are N studies reporting the same edge, we assign a weight value of N to this connectivity. Then, we used the BrainNet Viewer toolbox (Xia et al., 2013) to draw extracted ECs into a directed connectivity graph and counted the total degree (sum of input degree and output degree) of each node (Mrvar and Batagelj, 2016). In this research, we use graph theory's index "total degree" to define hubs, which are defined as several brain regions with an enormous total degree in abnormal ECs patterns. Moreover, Grubbs' test is used to detect outliers, i.e., whether there is a node whose total degree deviates abnormally from the mean (>three standard deviations) among all the nodes' total degrees (Grubbs, 1950).

3. Results

The extracted abnormal ECs were summarized (abnormal ECs in each study were shown in Table 1) and the connection map was obtained. As shown in Fig. 1A, the abnormal EC network in patients with MDD is composed of 37 nodes, where green lines and red lines represent weakened and enhanced ECs in the MDD group than in the control group, respectively. Among these nodes, the total degree of THA was the largest (see Fig. 1B). According to the elbow principle and the Grubbs' test ($G = 5.47 > G_{0.01} = 3.20$, $df = 37$), THA was the only outlier; we believe that THA plays a crucial role in the abnormal EC network of MDD. Fig. 1C shows abnormal ECs between the THA and other nodes, primarily including enhanced ECs from the THA to SFGdor, INS, basal ganglia (PAL, PUT, CAU), and limbic system (e.g., ORBsupmed, AMYG, and HIP) and weakened ECs from the INS, limbic system (e.g., ORBmid, AMYG, HIP), and visual cortex (e.g., CAL, CUN, LING, IOG, and FFG) to the THA.

4. Discussion

MDD is a mental disorder characterized by widespread network abnormalities. To shed light on the effective intervention target for MDD, we reviewed abnormal ECs in patients with MDD compared to healthy controls. As shown in Fig. 1, the total degree of abnormal ECs was the largest in the THA among all reported brain nodes, which may serve as a causal intervention target for the treatment of MDD.

The THA, as a relay station, transmits most of the sensory information to appropriate parts of the cerebral cortex (Levin et al., 1991). It has been shown that the THA is involved in emotion, arousal, and self-referential processing (Taber et al., 2004; Young et al., 2017) and participates in the emotional salience network and the emotional regulation network (Yamamura et al., 2016). Peters et al. suggested that the cortico-striatal-thalamic-cortical (CSTC) loop of the salience network is a cross-diagnostic feature of a variety of neuropsychiatric diseases, including MDD (Peters et al., 2016). In this loop, the mediodorsal nucleus of the thalamus (MDT), as a relay nucleus, integrates information from cortical, limbic, and striatal to help with flexible action selection (Delevich et al., 2015). At the same time, it serves as a part of the reward circuit to help project information from the ventral striatum to the prefrontal cortex (Haber and Knutson, 2010), which was found to cause deficits in MDD patients (Kim et al., 2019; Sachs-Ericsson et al., 2018). Our summary showed abnormalities of ECs in the circuits and abnormal information flowing between the limbic system and THA in patients with MDD, arguing for the critical role of THA as a causal hub in patients with MDD.

Abnormal bidirectional ECs between the basal ganglia and THA were discovered. The basal ganglia are subcortical structures that include the striatum (CAU and PUT) and PAL. In patients with MDD, ECs from the striatum and PAL to THA were weakened, and ECs in the opposite direction were strengthened. Collected evidence shows that the striatum is involved in the reward circuit, and its dysfunction will affect the coding

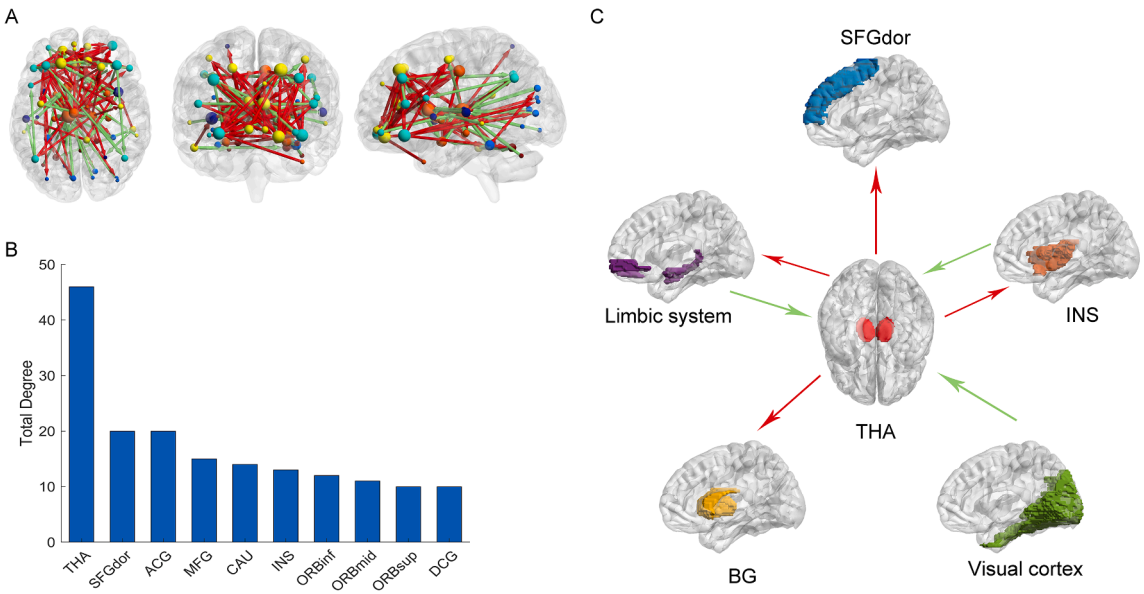

Fig. 1. Abnormal ECs in patients with MDD. (A) Abnormal ECs among 37 nodes. Red lines represent increased ECs, while green lines represent weakened ECs in patients with MDD. (B) Ten nodes with the highest total degree. (C) Abnormal ECs between the THA and other brain areas in patients with MDD. Red lines represent increased ECs, while green lines represent weakened ECs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of reward information (Der-Avakian and Markou, 2012), which may lead to one of the core symptoms of MDD, that is, anhedonia (Gabbay et al., 2013; Takamura et al., 2017). There are bidirectional anatomical connections between the striatum and THA (Alexander et al., 1991). The activity of the striatum is driven by glutamatergic input from the thalamus and cortical regions (Alloway et al., 2017), while increased blood flow and hyperactivity in the THA would increase the information flow from THA to the striatum (Hamilton et al., 2012; Iwabuchi et al., 2014). The prominent sensory stimulation and environmental information transmitted through the thalamostriatal pathway are involved in regulating attention shift and behavioral flexibility (Kato et al., 2018). In the opposite direction, reduced responses in the striatum caused by lower dopamine transporter would reduce information flow from the striatum to THA (Meyer et al., 2001). Convergent evidence has shown that the striatum is involved in reward expectations, reward-based learning, and goal-oriented behavior besides processing input sensory information (Haruno et al., 2004; Robinson et al., 2012). The striatum dysfunction may lead to one of the core symptoms of MDD, that is, anhedonia (a psychopathological state of inability to experience happiness) (Gabbay et al., 2013; Takamura et al., 2017; Yang et al., 2021b). The relationship between PAL and MDD has also been studied. PAL is involved in the reward circuits of the ventral striatum (Haber and Knutson, 2010). Compared with healthy controls, the asymmetry of PAL in MDD patients is reduced, and the grey volume of PAL is directly related to the number of prior depressive episodes (Lacerda et al., 2003), and post-mortem studies also found smaller PAL volume in MDD (Bielau et al., 2005; Drevets, 2022; Sheline, 2003). These findings suggest that basal ganglia may play a role in the pathophysiology of MDD. Increased sensory information from the THA to basal ganglia and decreased reward information in the opposite direction potentially contribute to the anhedonia and negative attention bias of MDD patients (Chen et al., 2021).

Enhanced ECs were also observed from the THA to the limbic system [e.g., the ORBsupmed and ORBmid parts of the orbitofrontal cortex (OFC), AMYG, and HIP], whereas reduced ECs were found in the opposite direction. The OFC plays a crucial role in several psychiatric and neurological disorders because of its involvement in a wide range of psychological functions such as emotional processing and regulation (Gilbert et al., 2010), autobiographical memory (Liu et al., 2017), decision-making (Bechara et al., 2000), and integration of sensory information (Price, 1999). The gray matter volume of the OFC in MDD patients is reduced, which may lead to inefficient suppression of excessive negative emotions from the THA and reduced ECs to THA via anatomical connection (Kringelbach, 2005; Wagner et al., 2008). On the other hand, the thalamus connects to the OFC via the amygdala, a core structure of the limbic system (Timbie and Barbas, 2015). The activation of THA glutamatergic neurons terminated in the amygdala is associated with depression-related behaviors (Zhao et al., 2021). Compared with the normal population, the hyperactivity of THA in depressed patients increased the negative information projected to the AMYG, which may overflow the processing capacity of the AMYG, in turn leading to insufficient suppression of negative signals and reduced ECs from the AMYG to THA (Iwabuchi et al., 2014; Lau et al., 2009; Suslow et al., 2010; Yang et al., 2010). In addition, the overactivity of THA was associated with increased levels of glucocorticoids in MDD patients, leading to the atrophy of HIP via the glucocorticoid receptors in the HIP (Frodl and O'Keane, 2013; Yi et al., 2017). The variability of gray matter volume and activity in the HIP are fundamental causes of negative emotions and dysfunctions of cognitive processing, especially memory impairment in patients with depression (Iwabuchi et al., 2014; Price and Drevets, 2010; Štillová et al., 2015; Zhang et al., 2018). Of note, the OFC and limbic systems, including THA, HIP, and AMYG, are important parts of the affective network. Abnormal ECs in this network (Iwabuchi et al., 2014; Tadayonnejad et al., 2016) are closely related to the weakened top-down control of the limbic system in depressed patients (Carballedo et al., 2011; He et al., 2016; Long et al., 2015).

The THA (especially the lateral geniculate nucleus), INS, and visual cortex constitute a salience detection system for survival-related information (Georgiadis and Kringelbach, 2012; Shi and Davis, 1999; Tischler and Davis, 1983). The INS is involved in a variety of functions, including sensorimotor, pain, attention, decision-making, and socio-emotional processes (Gasquoine, 2014). Wang et al. found increased gray matter volume in the INS of MDD patients (Wang et al., 2017b), which may result in the discoordination of the salience network to integrate sensory information from THA (Gogolla, 2017). This is consistent with the view of Hamilton et al., who believe that the interruption of the THA-INS connection may cause the failure of sensory information to be transmitted along the CSTC circuit to SFGdor (Hamilton et al., 2012). In addition, structural and functional abnormalities

were widely reported in the visual cortex of MDD patients. For example, MDD individuals showed hypoactivity in CAL, CUN, IOG, and FFA (Li and Wang, 2021; Liu et al., 2013) and larger volumes in LING (Jung et al., 2014). These abnormalities may disrupt the information flow from the visual cortex to THA. Overall, increased information from the THA to INS, primarily through the AMYG, may cause more negative information perceived by patients with MDD (Peluso et al., 2009; Suslow et al., 2010). However, decreased information from the INS and visual cortex to THA may indicate that MDD patients cannot successfully inhibit these negative signals, thus falling into negative attention bias and pessimistic thinking (Jaworska et al., 2015; Piscopo et al., 2013).

The SFGdor is invariably involved in MDD because of its critical role in many cognitive and emotional processes, including self-awareness (Lutz et al., 2016), working memory (Seeley et al., 2007), and emotional regulation (Kuhn et al., 2011). Enhanced EC from the THA to SFGdor may increase the burden of SFGdor, even exceed its processing capacity due to the dysfunctions of SFGdor in patients with MDD (Bora et al., 2012; Tadayonnejad et al., 2016), which further leads to the defect of top-down regulation of negative emotions (Webb et al., 2014).

Overall, the abnormal EC patterns centered on the THA hub in patients with MDD are primarily associated with enhanced bottom-up information input from the THA to the cortex and limbic system and reduced top-down modulation from those regions to THA (Campus et al., 2019; Hirata et al., 2006). As a tightly connected “central core” of brain regions, the THA plays a crucial role in regulating emotion and cognition (Kang et al., 2018). There is evidence that the density of THA neurons is higher (Young et al., 2004), and the local cerebral blood flow is increased in patients with MDD (Hamilton et al., 2012). The fractional amplitude of low-frequency fluctuations in the right THA is positively correlated with depressive symptoms (Tadayonnejad et al., 2015). The strengthened THA functional connections (FC) are also related to the decline of cognitive function (Kang et al., 2018; Koenig et al., 2019). When depression patients received sertraline treatment, the resting-state FC between the medial thalamus and the dorsal anterior cingulate gyrus returned to normal (Anand et al., 2005), and the thalamic metabolism decreased with the remission of the disease (Holthoff et al., 2004). The GC analysis also found abnormal causal connections between THA and widespread brain regions (Iwabuchi et al., 2014; Tadayonnejad et al., 2016), indicating that THA is a promising target for the intervention of depression.

Finally, the THA consists of seven sub-regions connected to different cortical areas (Behrens et al., 2003), endowing it with the possibility of precise intervention for different symptoms. Depression-related symptoms are sensitive to deep brain stimulation (DBS) in the anterior thalamic nuclei (ANT) (Drane and Pedersen, 2019; Fisher et al., 2010), mediodorsal thalamus (MDT) (Young et al., 2004), and inferior thalamic peduncle (Jiménez et al., 2007). The mediodorsal thalamus is also a critical network node in studies with electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) on the SFGdor (George et al., 1994; Leaver et al., 2015; Li et al., 2004). However, systematic studies are still lacking on the intervention effect of different THA sub-regions as precise targets of different depressive symptoms.

Several limitations should be noted. The first is the methodological problem of GC, which may suffer from explanatory causality ambiguity and instability (Solo, 2016; Stokes and Purdon, 2017). The second limitation stems from the articles we reviewed. The limited number of studies reviewed in this study may lead to a biased result, and the fact that most studies used a ‘seed’ approach to explore EC and the lack of subdivision of brain regions (especially the THA we are concerned about) limits the discussion of our results. This is something that needs to be further explored in future studies.

In conclusion, this article provides aggregated GC evidence for the hub role of THA in patients with MDD by showing heavily enhanced bottom-up ECs from the THA to cortical and subcortical regions and reduced top-down ECs from these regions to the THA. It is noteworthy that a large proportion of the GC studies on brain disorders focused on MDD. Although with different purposes and regions of interest, most literature revealed that the THA is a hub node responsible for MDD symptoms. Considering specific connections between sub-regions of the THA and various brain regions, we argue that the THA can serve as the target of precision intervention for different MDD symptoms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1991. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and “limbic” functions. Prog. Brain Res. 85, 119–146.
Alloway, K.D., Smith, J.B., Mowery, T.M., Watson, G.D.R., 2017. Sensory processing in the dorsolateral striatum: the contribution of thalamostriatal pathways. Front. Syst. Neurosci. 11, 53.
Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. Neuropsychopharmacology 30, 1334–1344.
Anderson, J., Gerbing, C., David, W., 1988. Structural equation modeling in practice: A review and recommended two-step approach. Psychol. Bull.
Bechara, A., Damasio, H., Damasio, A.R., 2000. Emotion, decision making and the orbitofrontal cortex. Cereb. Cortex 10, 295–307.
Behrens, T., Johansen-Berg, H., Woolrich, M.W., Smith, S.M., Wheeler-Kingshott, C., Boulby, P.A., Barker, G.J., Sillery, E.L., Sheehan, K., Ciccarelli, O., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat. Neurosci. 6, 750.
Bi, K., Luo, G., Tian, S., Zhang, S., Liu, X., Wang, Q., Lu, Q., Yao, Z., 2019. An enriched granger causal model allowing variable static anatomical constraints. NeuroImage: Clinical 21, 101592.
Bielau, H., Trübner, K., Krell, D., Agelink, M.W., Bernstein, H.G., Stauch, R., Mawrin, C., Danos, P., Gerhard, L., Bogerts, B., 2005. Volume deficits of subcortical nuclei in mood disorders. Eur. Arch. Psychiatry Clin. Neurosci. 255, 401–412.
Bielczyk, N.Z., Uithol, S., van Mourik, T., Anderson, P., Glennon, J.C., Buitelaar, J.K., 2019. Disentangling causal webs in the brain using functional magnetic resonance imaging: A review of current approaches. Network Neurosci. 3, 237–273.
Bora, E., Fornito, A., Pantelis, C., Yucel, M., 2012. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J. Affect. Disord. 138, 9–18.
Campus, P., Covelo, I.R., Kim, Y., Parsegian, A., Kuhn, B.N., Lopez, S.A., Neumaier, J.F., Ferguson, S.M., Woods, L.C.S., Sarter, M., 2019. The paraventricular thalamus is a critical mediator of top-down control of cue-motivated behavior in rats. Elife 8, e49041.
Carballedo, A., Scheuerecker, J., Meisenzahl, E., Schoepf, V., Bokde, A., Möller, H.-J., Doyle, M., Wiesmann, M., Frodl, T., 2011. Functional connectivity of emotional processing in depression. J. Affect. Disord. 134, 272–279.
Chen, F., Lv, X., Fang, J., Li, T., Xu, J., Wang, X., Hong, Y., Hong, L., Wang, J., Wang, W., 2021. Body–mind relaxation meditation modulates the thalamocortical functional connectivity in major depressive disorder: a preliminary resting-state fMRI study. Transl. Psychiatry 11, 1–9.
Connolly, C.G., Wu, J., Ho, T.C., Hoeft, F., Wolkowitz, O., Eisendrath, S., Frank, G., Hendren, R., Max, J.E., Paulus, M.P., Tapert, S.F., Banerjee, D., Simmons, A.N., Yang, T.T., 2013. Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. Biol. Psychiatry 74, 898–907.
Crossley, N.A., Mechelli, A., Scott, J., Carletti, F., Fox, P.T., McGuire, P., Bullmore, E.T., 2014. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 137, 2382–2395.
Delevich, K., Tucciarone, J., Huang, Z.J., Li, B., 2015. The mediodorsal thalamus drives feedforward inhibition in the anterior cingulate cortex via parvalbumin interneurons. J. Neurosci. 35, 5743–5753.
Der-Avakian, A., Markou, A., 2012. The neurobiology of anhedonia and other reward-related deficits. Trends Neurosci. 35, 68–77.
Drane, D.L., Pedersen, N.P., 2019. Finding the Sweet Spot: Fine-Tuning DBS Parameters to Cure Seizures While Avoiding Psychiatric Complications. Epilepsy currents 19, 174–176.
Drevets, W.C., 2022. Neuroplasticity in mood disorders. Dialogues Clinical Neurosci.

Du, L., Liu, H., Du, W., Chao, F., Zhang, L., Wang, K., Huang, C., Gao, Y., Tang, Y., 2018. Stimulated left DLPFC-nucleus accumbens functional connectivity predicts the anti-depression and anti-anxiety effects of rTMS for depression. Transl. Psychiatry 7, 3.
Feng, Z., Xu, S., Huang, M., Shi, Y., Xiong, B., Yang, H., 2016. Disrupted causal connectivity anchored on the anterior cingulate cortex in first-episode medication-naive major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 124–130.
Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., DeSalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., McKhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R., Graves, N., Group, S.S., 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51, 899–908.
Friston, K.J., Harrison, L.M., Penny, W.D., 2010. Dynamic causal modeling. Neuroimage 19, 1273–1302.
Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol. Dis. 52, 24–37.
Gabbay, V., Ely, B.A., Li, Q., Bangaru, S.D., Panzer, A.M., Alonso, C.M., Castellanos, F.X., Milham, M.P., 2013. Striatum-based circuitry of adolescent depression and anhedonia. J. Am. Acad. Child Adolesc. Psychiatry 52 (628–641), e613.
Gao, J., Li, Y., Wei, Q., Li, X., Wang, K., Tian, Y., Wang, J., 2021. Habenula and left angular gyrus circuit contributes to response of electroconvulsive therapy in major depressive disorder. Brain Imaging Behav. 15, 2246–2253.
Gao, Q., Zou, K., He, Z., Sun, X., Chen, H., 2016. Causal connectivity alterations of cortical-subcortical circuit anchored on reduced hemodynamic response brain regions in first-episode drug-naive major depressive disorder. Sci. Rep. 6, 21861.
Gasquoine, P.G., 2014. Contributions of the insula to cognition and emotion. Neuropsychol Rev 24, 77–87.
George, M.S., Ketter, T.A., Post, R.M., 1994. Prefrontal cortex dysfunction in clinical depression. Depression 2, 59–72.
Georgiadis, J.R., Kringelbach, M.L., 2012. The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Prog. Neurobiol. 98, 49–81.
Gilbert, A.M., Prasad, K., Goradia, D., Nutche, J., Keshavan, M., Frank, E., 2010. Grey matter volume reductions in the emotion network of patients with depression and coronary artery disease. Psychiatry Res. Neuroimaging 181, 9–14.
Gogolla, N., 2017. The insular cortex. Curr Biol 27, R580–R586.
Gong, Q., He, Y., 2015. Depression, neuroimaging and connectomics: a selective overview. Biol. Psychiatry 77, 223–235.
Granger, C.W., 1969. Investigating causal relations by econometric models and cross-spectral methods. Econometrica 424–438.
Grant, M.M., White, D., Hadley, J., Hutcheson, N., Shelton, R., Sreenivasan, K., Deshpande, G., 2014. Early life trauma and directional brain connectivity within major depression. Hum. Brain Mapp. 35, 4815–4826.
Grubbs, F.E., 1950. Sample criteria for testing outlying observations. Ann. Math. Stat. 27–58.
Guo, W., Liu, F., Zhang, Z., Liu, J., Yu, M., Zhang, J., Xiao, C., Zhao, J., 2015. Unidirectionally affected causal connectivity of cortico-limbic-cerebellar circuit by structural deficits in drug-naive major depressive disorder. J Affect Disord 172, 410–416.
Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.
Hamilton, J.P., Chen, G., Thomason, M.E., Schwartz, M.E., Gotlib, I.H., 2011. Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Mol Psychiatry 16, 763–772.
Hamilton, J.P., Etkin, A., Furman, D.J., Lemus, M.G., Johnson, R.F., Gotlib, I.H., 2012. Functional Neuroimaging of Major Depressive Disorder: A Meta-Analysis and New Integration of Baseline Activation and Neural Response Data. Am. J. Psychiatry 169, 693–703.
Haruno, M., Kuroda, T., Doya, K., Toyama, K., Kimura, M., Samejima, K., Imamizu, H., Kawato, M., 2004. A neural correlate of reward-based behavioral learning in caudate nucleus: a functional magnetic resonance imaging study of a stochastic decision task. J. Neurosci. 24, 1660–1665.
He, Z., Cui, Q., Zheng, J., Duan, X., Pang, Y., Gao, Q., Han, S., Long, Z., Wang, Y., Li, J., 2016. Frequency-specific alterations in functional connectivity in treatment-resistant and-sensitive major depressive disorder. J. Psychiatr. Res. 82, 30–39.
Hirata, A., Aguilar, J., Castro-Alamancos, M.A., 2006. Noradrenergic activation amplifies bottom-up and top-down signal-to-noise ratios in sensory thalamus. J. Neurosci. 26, 4426–4436.
Holthoff, V.A., Beuthien-Baumann, B., Zundorf, G., Triemer, A., Ludecke, S., Winiecki, P., Koch, R., Fuchtner, F., Herholz, K., 2004. Changes in brain metabolism associated with remission in unipolar major depression. Acta Psychiatr. Scand. 110, 184–194.
Honey, C.J., Sporns, O., 2008. Dynamical consequences of lesions in cortical networks. Hum. Brain Mapp. 29, 802–809.
Ishida, T., Dierks, T., Strik, W., Morishima, Y., 2020. Converging Resting State Networks Unravels Potential Remote Effects of Transcranial Magnetic Stimulation for Major Depression. Front. Psych. 11, 836.
Iwabuchi, S.J., Peng, D., Fang, Y., Jiang, K., Liddle, E.B., Liddle, P.F., Palaniyappan, L., 2014. Alterations in effective connectivity anchored on the insula in major depressive disorder. Eur. Neuropsychopharmacol. 24, 1784–1792.
Iwabuchi, S.J., Raschke, F., Auer, D.P., Liddle, P.F., Lankappa, S.T., Palaniyappan, L., 2017. Targeted transcranial theta-burst stimulation alters fronto-insular network and prefrontal GABA. Neuroimage 146, 395–403.
Jaworska, N., Yang, X.-R., Knott, V., MacQueen, G., 2015. A review of fMRI studies during visual emotive processing in major depressive disorder. World J. Biol. Psychiatry 16, 448–471.
Jiang, Y., Duan, M., Chen, X., Chang, X., He, H., Li, Y., Luo, C., Yao, D., 2017. Common and distinct dysfunctional patterns contribute to triple network model in schizophrenia and depression: A preliminary study. Prog. Neuropsychopharmacol. Biol. Psychiatry 79, 302–310.
Jiang, Y., Duan, M., Chen, X., Zhang, X., Gong, J., Dong, D., Li, H., Yi, Q., Wang, S., Wang, J., Luo, C., Yao, D., 2019. Aberrant Prefrontal-Thalamic-Cerebellar Circuit in Schizophrenia and Depression: Evidence From a Possible Causal Connectivity. Int. J. Neural Syst. 29, 1850032.
Jiménez, F., Velasco, F., Salin-Pascual, R., Velasco, M., Nicolini, H., Velasco, A.L., Castro, G., 2007. Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder. Operative Neuromodulation. Springer 393–398.
Jung, J., Kang, J., Won, E., Nam, K., Lee, M.-S., Tae, W.S., Ham, B.-J., 2014. Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in major depressive disorder: a voxel-based morphometry study. J. Affect. Disord. 169, 179–187.
Kang, L.J., Zhang, A.X., Sun, N., Liu, P.H., Yang, C.X., Li, G.Z., Liu, Z.F., Wang, Y.F., Zhang, K.R., 2018. Functional connectivity between the thalamus and the primary somatosensory cortex in major depressive disorder: a resting-state fMRI study. BMC Psychiatry 18, 1–8.
Kato, S., Fukabori, R., Nishizawa, K., Okada, K., Yoshioka, N., Sugawara, M., Maejima, Y., Shimomura, K., Okamoto, M., Eifuku, S., 2018. Action selection and flexible switching controlled by the intralaminar thalamic neurons. Cell Rep. 22, 2370–2382.
Kim, K., Shin, J.-H., Myung, W., Fava, M., Mischoulon, D., Papakostas, G.I., Choi, K.W., Na, E.J., Seo, S.W., Seong, J.-K., 2019. Deformities of the globus pallidus are associated with severity of suicidal ideation and impulsivity in patients with major depressive disorder. Sci. Rep. 9, 1–10.
Koenig, K.A., Rao, S.M., Lowe, M.J., Lin, J., Sakaie, K.E., Stone, L., Bermel, R.A., Trapp, B.D., Phillips, M.D., 2019. The role of the thalamus and hippocampus in episodic memory performance in patients with multiple sclerosis. Mult. Scler. J. 25, 574–584.
Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. Nat. Rev. Neurosci. 6, 691–702.
Kuhn, S., Gallinat, J., Brass, M., 2011. Keep calm and carry on": structural correlates of expressive suppression of emotions. PLoS One 6, e16569.
Lacerda, A.L.T., Nicoletti, M.A., Brambilla, P., Sassi, R.B., Mallinger, A.G., Frank, E., Kupfer, D.J., Keshavan, M.S., Soares, J.C., 2003. Anatomical MRI study of basal ganglia in major depressive disorder. Psychiatry Res. Neuroimaging 124, 129–140.
Lancaster, J.L., Tordesillas-Gutierrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., Mazziotta, J.C., Fox, P.T., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28, 1194–1205.
Lau, J.Y.F., Goldman, D., Buzas, B., Fromm, S.J., Guyer, A.E., Hodgkinson, C., Monk, C. S., Nelson, E.E., Shen, P.-H., Pine, D.S., 2009. Amygdala function and 5-HTT gene variants in adolescent anxiety and major depressive disorder. Biol. Psychiatry 65, 349–355.
Leaver, A.M., Espinoza, R., Pirnia, T., Joshi, S.H., Narr, K.L., 2015. Modulation of Intrinsic Brain Activity by Electroconvulsive Therapy in Major Depression. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 1, 77–86.
Levin, H.S., Eisenberg, H.M., Benton, A.L., 1991. Frontal lobe function and dysfunction. Oxford University Press, USA.
Li, X., Nahas, Z., Kozel, F.A., Anderson, B., Bohning, D.E., George, M.S., 2004. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biol. Psychiatry 55, 882–890.
Li, X., Wang, J., 2021. Abnormal neural activities in adults and youths with major depressive disorder during emotional processing: a meta-analysis. Brain Imaging Behav. 15, 1134–1154.
Liang, P., Deshpande, G., Zhao, S., Liu, J., Hu, X., Li, K., 2016. Altered directional connectivity between emotion network and motor network in Parkinson's disease with depression. Medicine 95, e4222.
Liu, F., Guo, W., Liu, L., Long, Z., Ma, C., Xue, Z., Wang, Y., Li, J., Hu, M., Zhang, J., Du, H., Zeng, L., Liu, Z., Wooderson, S.C., Tan, C., Zhao, J., Chen, H., 2013. Abnormal amplitude low-frequency oscillations in medication-naive, first-episode patients with major depressive disorder: A resting-state fMRI study. J. Affect. Disord. 146, 401–406.
Liu, Y., Zhao, X., Cheng, Z., Zhang, F., Chang, J., Wang, H., Xie, R., Wang, Z., Cao, L., Wang, G., 2017. Regional homogeneity associated with overgeneral autobiographical memory of first-episode treatment-naive patients with major depressive disorder in the orbitofrontal cortex: A resting-state fMRI study. J. Affect. Disord. 209, 163–168.
Long, Z., Duan, X., Wang, Y., Liu, F., Zeng, L., Zhao, J.-P., Chen, H., 2015. Disrupted structural connectivity network in treatment-naive depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 56, 18–26.
Lu, Q., Bi, K., Liu, C., Luo, G., Tang, H., Yao, Z., 2013. Predicting depression based on dynamic regional connectivity: a windowed Granger causality analysis of MEG recordings. Brain Res 1535, 52–60.
Luo, L., Wu, H., Xu, J., Chen, F., Wu, F., Wang, C., Wang, J., 2021. Abnormal large-scale resting-state functional networks in drug-free major depressive disorder. Brain Imaging Behav. 15, 96–106.
Lutz, J., Bruhl, A.B., Scheerer, H., Jancke, L., Herwig, U., 2016. Neural correlates of mindful self-awareness in mindfulness meditators and meditation-naive subjects revisited. Biol Psychol 119, 21–30.

Meyer, J.H., Kruger, S., Wilson, A.A., Christensen, B.K., Goulding, V.S., Schaffer, A., Minifie, C., Houle, S., Hussey, D., Kennedy, S.H., 2001. Lower dopamine transporter binding potential in striatum during depression. Neuroreport 12, 4121–4125.
Mrvar, A., Batagelj, V., 2016. Analysis and visualization of large networks with program package Pajek. Complex Adaptive Systems Modeling 4, 6.
Peluso, M.A.M., Glahn, D.C., Matsuo, K., Monkul, E.S., Najt, P., Zamarripa, F., Li, J., Lancaster, J.L., Fox, P.T., Gao, J.-H., 2009. Amygdala hyperactivation in untreated depressed individuals. Psychiatry Res. Neuroimaging 173, 158–161.
Peters, S.K., Dunlop, K., Downar, J., 2016. Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. Front. Syst. Neurosci. 10, 104.
Piscopo, D.M., El-Danaf, R.N., Huberman, A.D., Niell, C.M., 2013. Diverse Visual Features Encoded in Mouse Lateral Geniculate Nucleus. J. Neurosci. 33, 4642.
Price, J.L., 1999. Prefrontal Cortical Networks Related to Visceral Function and Mood. Ann. N. Y. Acad. Sci. 877, 383–396.
Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. Neuropsychopharmacology 35, 192–216.
Rao, N.P., Deshpande, G., Gangadhar, K.B., Arasappa, R., Varambally, S., Venkatasubramanian, G., Ganagadhar, B.N., 2018. Directional brain networks underlying OM chanting. Asian J. Psychiatr. 37, 20–25.
Robinson, J.L., Laird, A.R., Glahn, D.C., Blangero, J., Sanghera, M.K., Pessoa, L., Fox, P. M., Uecker, A., Friehs, G., Young, K.A., Griffin, J.L., Lovallo, W.R., Fox, P.T., 2012. The functional connectivity of the human caudate: an application of meta-analytic connectivity modeling with behavioral filtering. Neuroimage 60, 117–129.
Roebroeck, A., Formisano, E., Goebel, R., 2005. Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 25, 230–242.
Sachs-Ericsson, N.J., Hajcak, G., Sheffler, J.L., Stanley, I.H., Selby, E.A., Potter, G.G., Steffens, D.C., 2018. Putamen volume differences among older adults: depression status, melancholia, and age. J. Geriatr. Psychiatry Neurol. 31, 39–49.
Santomauro, D.F., Herrera, A.M.M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D.M., Abbafati, C., Adolph, C., Amlag, J.O., Aravkin, A.Y.J.T.L., 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 398, 1700–1712.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.
Seth, A.K., Chorley, P., Barnett, L.C., 2013. Granger causality analysis of fMRI BOLD signals is invariant to hemodynamic convolution but not downsampling. Neuroimage 65, 540–555.
Sheline, Y.I., 2003. Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiatry 54, 338–352.
Shi, C., Davis, M., 1999. Pain pathways involved in fear conditioning measured with fear-potentiated startle: lesion studies. J. Neurosci. 19, 420–430.
Solo, V., 2016. State-space analysis of Granger-Geweke causality measures with application to fMRI. Neural Comput. 28, 914–949.
Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences 105, 12569-12574.
Štillová, K., Jurák, P., Chládek, J., Chrastina, J., Halámek, J., Bočková, M., Goldemundová, S., Říha, I., Rektor, I., 2015. The role of anterior nuclei of the thalamus: a subcortical gate in memory processing: an intracerebral recording study. PLoS One 10, e0140778.
Stokes, P.A., Purdon, P.L., 2017. A study of problems encountered in Granger causality analysis from a neuroscience perspective. Proceedings of the national academy of sciences 114, E7063-E7072.
Suslow, T., Konrad, C., Kugel, H., Rumstadt, D., Zwitserlood, P., Schöning, S., Ohrmann, P., Bauer, J., Pyka, M., Kersting, A., 2010. Automatic mood-congruent amygdala responses to masked facial expressions in major depression. Biol. Psychiatry 67, 155–160.
Taber, K.H., Wen, C., Khan, A., Hurley, R.A., 2004. The limbic thalamus. J. Neuropsychiatry Clin. Neurosci. 16, 127–132.
Tadayonnejad, R., Yang, S., Kumar, A., Ajilore, O., 2015. Clinical, cognitive, and functional connectivity correlations of resting-state intrinsic brain activity alterations in unmedicated depression. J. Affect. Disord. 172, 241–250.
Tadayonnejad, R., Ajilore, O., Mickey, B.J., Crane, N.A., Hsu, D.T., Kumar, A., Zubieta, J. K., Langenecker, S.A., 2016. Pharmacological modulation of pulvinar resting-state regional oscillations and network dynamics in major depression. Psychiatry Res. Neuroimaging 252, 10–18.
Takamura, M., Okamoto, Y., Okada, G., Toki, S., Yamamoto, T., Ichikawa, N., Mori, A., Minagawa, H., Takaishi, Y., Fujii, Y., Kaichi, Y., Akiyama, Y., Awai, K., Yamawaki, S., 2017. Patients with major depressive disorder exhibit reduced reward size coding in the striatum. Prog. Neuropsychopharmacol. Biol. Psychiatry 79, 317–323.
Timbie, C., Barbas, H., 2015. Pathways for Emotions: Specializations in the Amygdalar, Mediodorsal Thalamic, and Posterior Orbitofrontal Network. J. Neurosci. 35, 11976–11987.
Tischler, M.D., Davis, M., 1983. A visual pathway that mediates fear-conditioned enhancement of acoustic startle. Brain Res. 276, 55–71.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289.
Wagner, G., Koch, K., Schachtzabel, C., Reichenbach, J.R., Sauer, H., Schlösser, R.G.M., 2008. Enhanced rostral anterior cingulate cortex activation during cognitive control is related to orbitofrontal volume reduction in unipolar depression. Journal of psychiatry & neuroscience: JPN 33, 199.
Wang, J., Wei, Q., Bai, T., Zhou, X., Sun, H., Becker, B., Tian, Y., Wang, K., Kendrick, K., 2017a. Electroconvulsive therapy selectively enhanced feedforward connectivity from fusiform face area to amygdala in major depressive disorder. Soc. Cogn. Affect. Neurosci. 12, 1983–1992.
Wang, L., Wei, Q., Wang, C., Xu, J., Wang, K., Tian, Y., Wang, J., 2020. Altered functional connectivity patterns of insular subregions in major depressive disorder after electroconvulsive therapy. Brain Imaging Behav. 14, 753–761.
Wang, Y.-L., Yang, S.-Z., Sun, W.-L., Shi, Y.-Z., Duan, H.-F., 2016. Altered functional interaction hub between affective network and cognitive control network in patients with major depressive disorder. Behav. Brain Res. 298, 301–309.
Wang, W., Zhao, Y., Hu, X., Huang, X., Kuang, W., Lui, S., Kemp, G.J., Gong, Q., 2017b. Conjoint and dissociated structural and functional abnormalities in first-episode drug-naive patients with major depressive disorder: a multimodal meta-analysis. Sci Rep 7, 10401.
Warren, D.E., Power, J.D., Bruss, J., Denburg, N.L., Waldron, E.J., Sun, H., Petersen, S.E., Tranel, D., 2014. Network measures predict neuropsychological outcome after brain injury. Proc. Natl. Acad. Sci. 111, 14247–14252.
Webb, C.A., Weber, M., Mundy, E.A., Killgore, W.D., 2014. Reduced gray matter volume in the anterior cingulate, orbitofrontal cortex and thalamus as a function of mild depressive symptoms: a voxel-based morphometric analysis. Psychol. Med. 44, 2833–2843.
Wei, M., Qin, J., Yan, R., Bi, K., Liu, C., Yao, Z., Lu, Q., 2015. Association of resting-state network dysfunction with their dynamics of inter-network interactions in depression. J. Affect Disord. 174, 527–534.
Wei, M., Qin, J., Yan, R., Bi, K., Liu, C., Yao, Z., Lu, Q., 2017. Abnormal dynamic community structure of the salience network in depression. J Magn Reson Imaging 45, 1135–1143.
Xia, M., Wang, J., He, Y., 2013. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 8, e68910.
Yamamura, T., Okamoto, Y., Okada, G., Takaishi, Y., Takamura, M., Mantani, A., Kurata, A., Otagaki, Y., Yamashita, H., Yamawaki, S., 2016. Association of thalamic hyperactivity with treatment-resistant depression and poor response in early treatment for major depression: a resting-state fMRI study using fractional amplitude of low-frequency fluctuations. Transl. Psychiatry 6, e754.
Yang, Y., Cui, Q., Pang, Y., Chen, Y., Tang, Q., Guo, X., Han, S., Fateh, A.A., Lu, F., He, Z., 2021b. Frequency-specific alteration of functional connectivity density in bipolar disorder depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 104, 110026.
Yang, T.T., Simmons, A.N., Matthews, S.C., Tapert, S.F., Frank, G.K., Max, J.E., Bischoff-Grethe, A., Lansing, A.E., Brown, G., Strigo, I.A., 2010. Adolescents with major depression demonstrate increased amygdala activation. J. Am. Acad. Child Adolesc. Psychiatry 49, 42–51.
Yang, L., Wei, A.H., Ouyang, T.T., Cao, Z.Z., Duan, A.W., Zhang, H.H., 2021a. Functional plasticity abnormalities over the lifespan of first-episode patients with major depressive disorder: a resting state fMRI study. Annals of translational medicine 9, 349.
Yi, J.H., Brown, C., Whitehead, G., Piers, T., Lee, Y.S., Perez, C.M., Regan, P., Whitcomb, D.J., Cho, K., 2017. Glucocorticoids activate a synapse weakening pathway culminating in tau phosphorylation in the hippocampus. Pharmacol Res 121, 42–51.
Young, K.D., Bodurka, J., Drevets, W.C., 2017. Functional neuroimaging of sex differences in autobiographical memory recall in depression. Psychol. Med. 47, 2640–2652.
Young, K.A., Holcomb, L.A., Yazdani, U., Hicks, P.B., German, D.C., 2004. Elevated neuron number in the limbic thalamus in major depression. Am. J. Psychiatry 161, 1270–1277.
Zhang, F.F., Peng, W., Sweeney, J.A., Jia, Z.Y., Gong, Q.Y., 2018. Brain structure alterations in depression: Psychoradiological evidence. CNS Neurosci. Ther. 24, 994–1003.
Zhao, D., Liu, C., Cui, M., Liu, J., Meng, F., Lian, H., Wang, D., Hu, F., Liu, D., Li, C., 2021. The paraventricular thalamus input to central amygdala controls depression-related behaviors. Exp. Neurol. 342, 113744.
Zheng, L.J., Yang, G.F., Zhang, X.Y., Wang, Y.F., Liu, Y., Zheng, G., Lu, G.M., Zhang, L.J., Han, Y., 2017. Altered amygdala and hippocampus effective connectivity in mild cognitive impairment patients with depression: a resting-state functional MR imaging study with granger causality analysis. Oncotarget 8, 25021–25031.