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Disturbed hierarchy and mediation in reward-related circuits in depression

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A B S T R A C T

Backgrounds/Objective: Deep brain stimulation (DBS) has proved the viability of alleviating depression symptoms by stimulating deep reward-related nuclei. This study aims to investigate the abnormal connectivity profiles among superficial, intermediate, and deep brain regions within the reward circuit in major depressive disorder (MDD) and therefore provides references for identifying potential superficial cortical targets for non-invasive neuromodulation.

Methods: Resting-state functional magnetic resonance imaging data were collected from a cohort of depression patients (N = 52) and demographically matched healthy controls (N = 60). Utilizing existing DBS targets as seeds, we conducted step-wise functional connectivity (sFC) analyses to delineate hierarchical pathways linking to cerebral cortices. Subsequently, the mediation effects of cortical regions on the interaction within reward-related circuits were further explored by constructing mediation models.

Results: In both cohorts, sFC analysis revealed two reward-related pathways from the deepest DBS targets to intermediate regions including the thalamus, insula, and anterior cingulate cortex (ACC), then to the superficial cortical cortex including medial frontal cortex, posterior default mode network (pDMN), and right dorsolateral prefrontal cortex (DLPFC). Patients exhibited reduced sFC in bilateral thalamus and medial frontal cortex in short and long steps respectively compared to healthy controls. We also discovered the disappearance of the mediation effects of superficial cortical regions on the interaction between DBS targets and intermediate regions in reward-related pathways in patients with MDD.

Conclusion: Our findings support abnormal hierarchical connectivity and mediation effects in reward-related brain regions at different depth levels in MDD, which might elucidate the underlying pathophysiological mechanisms and inspire novel targets for non-invasive interventions.

1. Introduction

Major depressive disorder (MDD), a heterogeneous mental disorder with a high prevalence among the population (Filatova et al., 2021), is characterized by symptoms such as depressed mood, anhedonia, and fatigue, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Schulz & Arora, 2015). Medication has been the mainstream treatment for depression (Cipriani et al., 2018), but it is often slow-acting and associated with common side effects (Marwaha et al., 2023). Neuromodulation therapy has gradually emerged as a therapeutic tool due to its high safety and maneuverability (George et al., 1995).

As a brain network disorder, MDD involves multiple brain regions and circuits (Li et al., 2017). Among the circuits, the reward circuit is of great significance in MDD and demonstrates hierarchical connectivity. It originates in the ventral tegmental area (VTA) and extends to the nucleus accumbens (NAcc), the striatum, as well as the orbitofrontal cortex (OFC), the anterior cingulate gyrus (ACC), the thalamus, the lateral habenula (LHb), and other areas that project from the striatum (Höflich et al., 2019; Nestler & Carlezon, 2006). Additionally, the medial frontal cortex (MFC) has also been implicated in the processing of reward-related information (Amarante & Laubach, 2021; Cohen et al., 2012). Evidence found in humans and animals suggests that the reward system is responsible for directing organisms to accept reward information from the environment, prioritizing the allocation of attentional resources to those behaviors that bring rewards (Russo & Nestler, 2013). Abnormalities in the reward circuit have long been recognized to be related to multiple symptoms of depression, (Nestler & Carlezon, 2006). Geugies et al. also reported decreased functional connectivity (FC) between the insula and VTA in MDD during reward anticipation (Geugies et al., 2022).

Given the significance of the reward circuit in MDD pathogenesis,

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numerous studies have targeted key nodes of this circuit for deep brain stimulation (DBS) to alleviate depressive symptoms, according to a recent review. (Figee et al., 2022). However, the necessity of craniotomy for DBS limits its generalizability. According to several important studies that targeted the superficial cortical regions, stimulating superficial cortical areas can modulate the activity of themselves or subcortical and deeper cortical regions as well as their broader cortical networks, and then alleviate specific depressive symptoms (Philip et al., 2018). For instance, stimulation of the dorsal lateral prefrontal cortex (DLPFC) enhances its global connectivity while simultaneously reducing its connectivity with the amygdala (Eshel et al., 2020). Moreover, DLPFC stimulation significantly influences the function of the orbitofrontal cortex and hippocampus, as well as their connectivity, with such effects being strongly correlated with symptom improvement (Han et al., 2023). Therefore, understanding the impact of superficial cortical stimulation on subcortical and deeper cortical activity is crucial for the development of effective physical interventions.

It has been pointed out that damage to the reward circuit in MDD is primarily triggered by altered connectivity within the circuits, rather than local damage in separate brain regions (Geugies et al., 2022). Therefore, a method to probe MDD abnormalities at a circuit level is required. Stepwise functional connectivity (sFC), based on the graphic theory properties of the brain, addresses this need. Unlike traditional FC, sFC focuses on hierarchical connections among brain regions and elucidates the connections among the beginning, middle, and end of the circuit by calculating the distribution of nodes for different connection steps (Sepulcre et al., 2012). This method enables the exploration of neural circuits within the brain at the mesoscopic level, starting from pre-given seeds, in a data-driven manner. Lin et al. used the sFC method to identify disrupted information transmission from unimodal to multimodal networks in depressed patients without suicidal intent (Shiwei et al., n.d.). Previous research on the reward circuit in MDD has predominantly focused on interactions within the circuit itself, with relatively less attention given to the interaction between the reward circuit and other cortical regions, especially superficial cortical regions (Fan et al., 2021; Fischer et al., 2019). By investigating the interaction patterns between the reward circuit and the whole brain, it is possible to identify key cortical regions involved in MDD, which can further contribute to a deeper understanding of its neurobiological mechanisms.

Thus, we hypothesized that hierarchical connectivity between DBS targets and reward-related brain regions would exhibit abnormal alterations in patients with depression. To verify this hypothesis and explore new targets for NIBS, we employed the sFC approach to elaborate the pathways linking DBS targets to superficial cortical regions. Moreover, we further constructed mediation models to characterize the mediation effects within the reward circuit, providing stronger evidence to identify new targets for NIBS.

2. Methods

2.1. Participants

In this study, 52 patients with depression diagnosed by specialized psychiatrists (mean age = 29.04±9.62, 38 females) and 60 healthy controls (mean age = 26.85±9.48, 41 females) were recruited from the Clinical Hospital of Chengdu Brain Science Institute. In this study, patients with MDD were diagnosed by professional psychiatrists based on the primary criterion of a score greater than 7 on the Hamilton Depression Scale (HAMD) (Hamilton, 1960). No significant psychiatric or major medical comorbidities were reported among the patients in the MDD group. All study methods and the process design were approved by the local Ethics Committee of University of Electronic Science and Technology of China and followed the declaration of Helsinki. Subjects with a history of epilepsy or severe traumatic brain injury, a history of substance abuse, electronic or metal implantations, and other contraindications to MRI will be excluded. Detailed demographic information is shown in Table 1. Written informed consent was obtained from the subjects for this study.

Table 1
Demographics of the subjects.

	MDD(N = 52)	HC(N = 60)	p-value
Age(years), mean ± SD[a]	29.04 ± 9.62	26.85 ± 9.48	0.229
Education(years)[a]	14.86 ± 2.63	15.68 ± 2.33	0.087
Gender (M/F)[b]	14/38	19/41	0.583
HAMD[a]	21.25 ± 8.27	1.61 ± 1.94	<1e-5*
HAMA[a]	23.37 ± 10.95	1.64 ± 1.88	<1e-5*
SAS[a]	61.47 ± 21.01	40.48 ± 11.44	<1e-5*
SDS[a]	59.33 ± 13.54	35.50 ± 7.02	<1e-5*
mFD[a]	0.11 ± 0.05	0.11 ± 0.04	0.329

[a]p-value was obtained by two-sample t-tests; [b]p-value was obtained by Chi square test;
* Statistically significant
Abbreviations: MDD: major depressive disorder; HC: healthy control; M: Male; F: Female;
HAMD: Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale;
SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale;
mFD: mean frame-wise displacement.

2.2. Data Acquisition and preprocessing

All subjects underwent MRI scanning in a SIEMENS 3T scanner. The resting-state fMRI (rs-fMRI) data were collected using an echo-planar imaging sequence with the following parameters: repetition time (TR) = 2s, echo time (TE) = 30ms, flip angle (FA) = 90°, matric = 64×64, slice thickness = 4.4 mm, and slice gap = 4.4 mm. All subjects were scanned for a total of 510 s, yielding 255 functional images, each containing 34 slices. Subjects were asked to keep their eyes closed and relaxed throughout the whole scanning.

All functional image data were preprocessed in MATLAB 2021a, employing the DPABI toolbox (Yan et al., 2016). We discarded the first 5 volumes for each subject to account for equilibration effects. The remaining 250 volumes were processed with the following steps: (1) slice timing correction, (2) realign correction, (3) spatial normalization according to Montreal Neurological Institute (MNI) space. (4) head motion (the estimated motion parameters based on the Friston-24 model (Friston et al., 1996)),the mean of white matter (WM), and cerebrospinal fluid (CSF) signals were regressed as nuisance covariates. (5) bandpass filtering (0.01–0.08 Hz). All subjects with a maximum translation of more than 3 mm or a maximum rotation of more than 3° in any of the cardinal directions during the scanning process were excluded from subsequent analyses.

2.3. Step-wise functional connectivity analysis

The sFC analysis allows us to calculate the hierarchical connection between the seed region and every other voxel in the brain at each "link distance". Under the i^{th} link step, the value of each voxel is assigned by the number of pathways with i consecutive connectivity steps to the seed, which in turn constructs the sFC map of the whole brain (Pretus

Table 2
MNI coordinates of the seed regions.

	MNI Coordinates		
	x	y	z
SGC	5.9	16.3	−9.8
NAcc	−9	9	−8
rVS	12	10	−6
lLHb	−4	−26	2
rLHb	6	−26	2

Abbreviations: SGC: subgenual cingulate; NAcc: nucleus accumben;
rVS: right ventral striatum;lLHb: left lateral habenula; rLHb: right lateral habenula

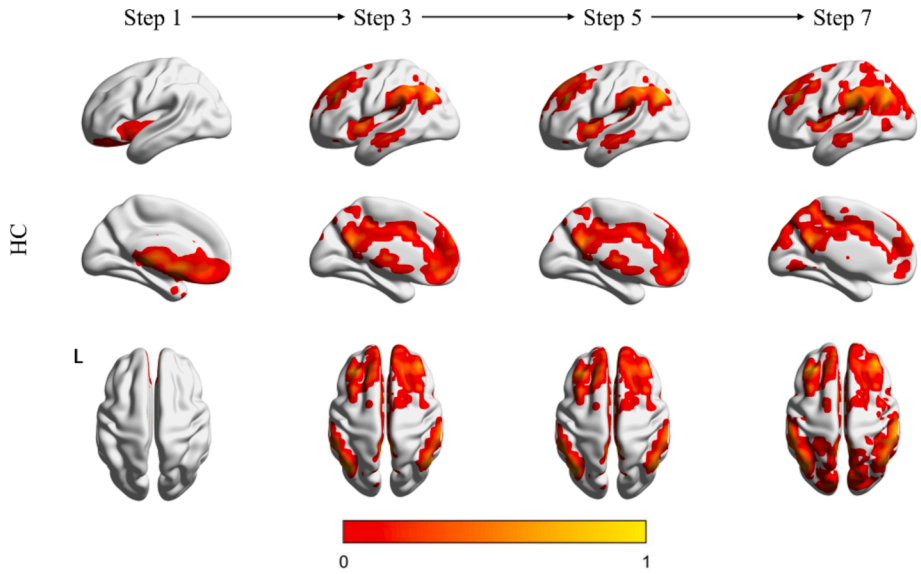

Fig. 1. Surface projections of the one-sample *t*-test results ($p < 0.05$, FDR corrected) reflecting the distribution of sFC at different connectivity steps in the healthy control group. Images display normalized T values. Abbreviation: HC: healthy control.

et al., 2019; Sepulcre et al., 2012). To relieve the computational burden, all images were down-sampled to a voxel size of $6\times6\times6mm^3$ before entering the sFC analysis. The Pearson correlation coefficients between each pair of voxel time series in the brain were calculated in the first step and Fisher-z transformation was conducted. To determine which voxel pairs exhibited significant connectivity, a multiple comparison correction ($p<0.001$ FDR) was applied to the significance of the correlation coefficients between each voxel pair. Afterwards, we retained the surviving correlation coefficients.

In this study, five regions of interest (ROI) were selected as seed regions (Table 2) based on key nodes in the reward circuit as well as previously identified DBS targets in the literature for the treatment of MDD(Scangos et al., 2021), including subgenual cingulate (SGC), nucleus accumben (NAcc), right ventral striatum (rVS), left lateral habenula (lLHb), and right lateral habenula (rLHb) (Fox et al., 2012; Du et al., 2018; P. M. Pan et al., 2017; Zhang et al., 2017). Spherical masks of a 3mm radius centered on each of these five seeds were made. In addition, a merged DBS target that synthesized all five DBS targets was generated. The averaged time course from five individual seeds and the merged DBS target was extracted, and these time courses were used in parallel for the subsequent sFC analyses.

One-sample t-tests ($p<0.05$, FDR corrected) were used to detect significantly positive connectivity at each step within each group. Two-sample t-tests were performed between groups at each step ($p<0.05$, cluster size >20 voxels). Age, gender, and years of education were included as nuisance covariates during two-sample t-tests. The two-sample *t*-test was conducted on the regions that were significant in the union of the results from the one-sample t-tests in both groups.

2.4. Mediation analysis

Based on the sFC analysis, at each connection step, significantly positive connections among brain regions were identified. For each seed, a connection pathway was discovered that begins at a DBS target and

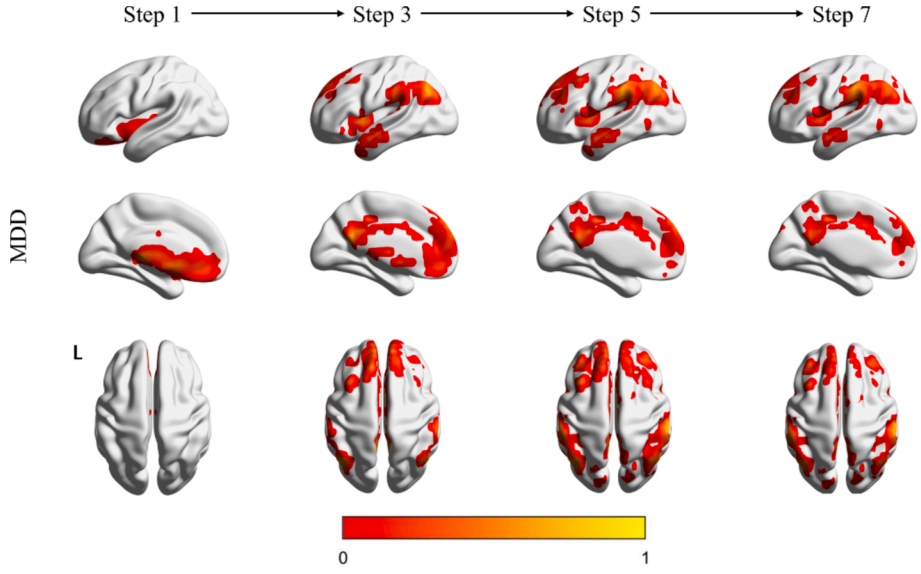

Fig. 2. Surface projections of the one-sample *t*-test results ($p < 0.05$, FDR corrected) reflecting the distribution of sFC at different connectivity steps in the depressed group. Images display normalized T values. Abbreviation: MDD: Major depressive disorder.

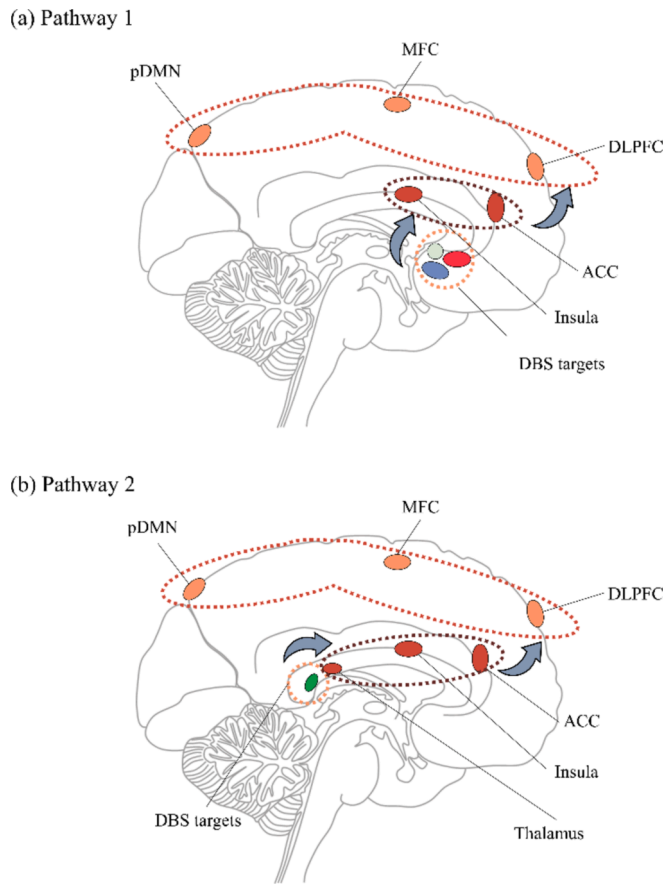

Fig. 3. Schematic diagrams of the two connectivity pathways obtained by the one-sample t results of the two groups of connection maps. Abbreviations: SGC: subgenual cingulate; NAcc: nucleus accumben; VS: ventral striatum; ACC: anterior cingulate cortex; MFC: medial frontal cortex; pDMN: posterior default mode network; DLPFC: dorsal lateral prefrontal cortex; LHb: lateral habenula.

ends at the superficial cortex. On this basis, two common sFC pathways were summarized for the two groups of subjects.

Considering that NIBS can directly act on superficial brain regions and further regulate the interaction among intermediate or deeper brain regions through functional circuits or networks, we constructed mediation models to further reveal the role of superficial regions in the interaction among intermediate or deep regions.

We used the BOLD signal of the superficial cortical regions of the network as the mediator variable (M), with the BOLD signal of the DBS target and the middle brain regions of the network as the independent variable (X) and dependent variable (Y), respectively. In this study, coefficient *a* represents the relationship between X and M, coefficient *b* represents the relationship between M and Y after controlling for X, and coefficient *c* represents the relationship between X and Y after controlling for M. One-sample t-tests were performed on the mediation coefficients obtained from the regression analysis to ascertain the significance of the mediation effect at the group level.

3. Results

3.1. sFC maps of MDD and Health controls

In HC, the DBS targets are mainly connected to the thalamus, and the ventral medial prefrontal cortex at the first step. In the third step, the DBS targets are predominantly connected with ACC, insula, posterior cingulate cortex (PCC), and angular gyrus. For five to seven steps, the sFC distribution pattern tends to converge to the default mode network

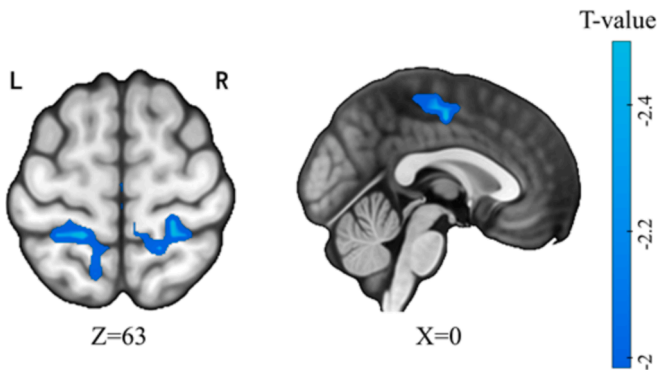

Fig. 4. Two-sample t-tests ($p < 0.05$, cluster size > 20) reveal differences in sFC of the merged DBS target in step 5. Images display T values. (MDD-HC). Abbreviations: MDD: Major depressive disorder; HC: Healthy control.

(DMN), the salience network (SN), and the MFC, which specifically, according to the AAL atlas (Tzourio-Mazoyer et al., 2002), is called the supplementary motor area (SMA).

The normalized t-map of sFC mappings of the merged DBS target in the HC and MDD groups are shown in Figs. 1, 2. The normalized t-value is obtained using the following formula:

$$t_{normalized} = \frac{t_{raw} - t_{min}}{t_{max} - t_{min}}$$

where $t_{normalized}$ is the normalized t-value of a certain voxel, t_{raw} is the raw t-value of the voxel, t_{max} is the maximum t-value across all brain voxels and t_{min} is the minimum t-value across all brain voxels. This standardization process scales the T-values to a range of [0, 1]. Similar connectivity patterns were observed in MDD groups.

Additionally, we also performed sFC analysis for five seeds individually and conducted group-level one-sample t-tests (Supplementary Figs. 1-10). Eventually, we identified two common sFC connection pathways in both groups of subjects. Steps 1–3 represent short-step connections, while steps 4–7 represent long-step connections. One pathway originates from the SGC/NAcc/rVS, connecting to the ACC/insula in short steps, and ultimately reaching the MFC/posterior default mode network (pDMN, i.e. bilateral angular gyrus and posterior cingulate cortex)/DLPFC in long steps (Fig. 3 (a)). Another pathway begins at the bilateral LHbs, connecting to the thalamus and ACC/insula in short steps, and similarly reaching the MFC/pDMN/DLPFC in long steps (Fig. 3 (b)). The MNI coordinates of these regions are shown in the Supplementary Table 1. According to the location and connection step of these regions in the brain, MFC, DLPFC and pDMN were classified as the superficial cortex, and the thalamus, ACC and insula as the intermediate regions.

3.2. Between-group sFC differences

For between-group differences in the sFC of all five DBS targets as well as the merged DBS target, the MDD group demonstrated reduced sFC compared with HC at steps 4–7 ($p < 0.05$), located in the right postcentral gyrus as well as in the MFC (Fig. 4). Bilateral LHb exhibited reduced sFC bilateral thalamus at step 2 (Fig. 5, (a), (b)). We performed repeat group difference tests for each individual seed point and found similar differential results at steps 4–7.

3.3. Mediation analysis

Compared to HC group, we discovered that four mediation effect were absent in the MDD group ($p<0.05$). Of note, the mediation effect of the rLHb-thalamus connection mediated by the DLPFC was lost (Fig. 6, (a)). In addition to this, we found that in the MDD group, the MFC has

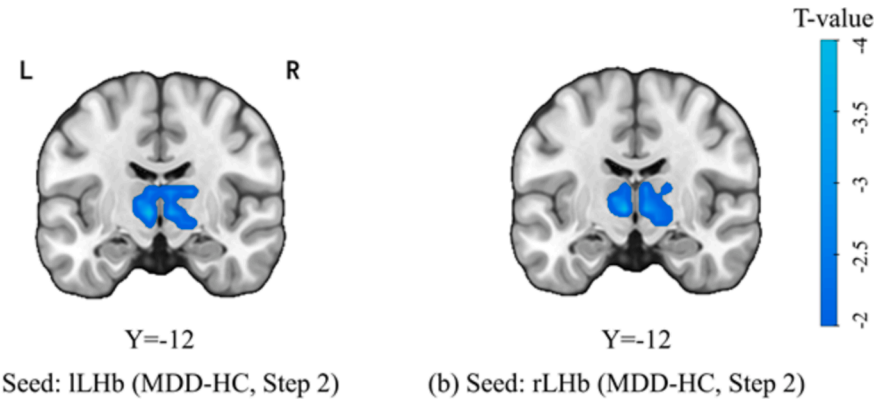

Fig. 5. Two-sample *t*-test reveals differences in the sFC seeding at (a)lLHb ($p < 0.05$, cluster size > 20); (b) and rLHb ($p < 0.05$, cluster size > 20). Images display T values. Abbreviations: lLHb: left lateral habenula; rLHb: right lateral habenula. MDD: Major depressive disorder; HC: Healthy control.

lost the mediation effect on NAcc-ACC and SGC-insula connections (Fig. 6, (b), (c)). Finally, the mediation of the interaction between SGC and the insula by pDMN (specifically bilateral angular gyrus) was not observed in the MDD group (Fig. 6, (d)).

4. Discussion

In this study, we aim to investigate abnormal hierarchical connectivity patterns between reward-related brain regions at multi-level depths in patients with depression. Hence, we employed the sFC method with DBS targets as seeds and revealed two pathways starting from deep brain regions to superficial regions. In MDD, the connectivity between SGC/NAcc/rVS and MFC decreased in long steps compared to HC. The sFC between the bilateral LHbs and the bilateral thalamus is reduced with short-step connections. Additionally, we constructed mediation models to investigate the mediation effect of superficial brain regions on the interactions between intermediate and deep brain regions in the sFC pathways. In the MDD cohort, the DLPFC failed to mediate the interaction between rLHb and the thalamus, and the MFC lost its mediation effect on the NAcc-ACC and SGC-insula connections. Furthermore, the mediation effect of pDMN on the connection between the SGC and insula was absent in patients. These findings bolster our current understanding of dysfunction within the reward circuit in MDD and further propose the possibility of novel targets of NIBS for the treatment of such a disorder.

We found decreased sFC between the bilateral LHbs and thalamus sFC in the second step in MDD. The LHb is a small nucleus located between the medial thalamus and the third ventricle (Lawson et al., 2013). It is potentially receiving reward information from the limbic system and is associated with negative reward processing, which is crucial for survival (Matsumoto & Hikosaka, 2007). Experimental results in mice showed that artificial inhibition of projections from the thalamic sensory reticular nucleus to the LHb induced depressive-like behavior whereas enhancement of this circuit alleviated depressive symptoms (Wang et al., 2023). Our results align with these previous findings. The reduction in the short-range sFC from the LHb to the thalamus suggests a potential disjunction between the LHb with thalamic regions, which in turn leads to the failure of reward information to be transmitted normally along the pathway to brain regions further downstream. This abnormality may be linked to neurotransmitter delivery. Inputs of GABA (inhibitory) and glutamate (excitatory) from the entopeduncular nucleus to the habenula affect its excitability to some extent. In a depression model, reduced GABA inputs were observed, resulting in increased excitability of the habenula and subsequent aversive symptoms (Shabel et al., 2014). This finding may enlighten our understanding of the causative factors of depression and the emergence of its symptoms.

Our findings indicate that DLPFC has lost its mediating effect on the interaction between the rLHb and the thalamus. The DLPFC is well-established as a crucial cognitive control region associated with reward processing (Huskey et al., 2018), and its dysfunction in depressed patients has been well-documented (Biver et al., 1994). Anatomical studies have confirmed the existence of frontal-subcortical circuits that connect the frontal cortex to the striatum, thalamus, etc., and are responsible for executive function, motivation, etc (Tekin & Cummings, 2002). It is believed that the DLPFC interrogates reward signals and subsequently transmits them to mesolimbic and mesocortical dopamine circuits, initiating reward-motivated behavior (Weinstein, 2023). Zhao et al. reported that the FC between DLPFC and insula was highly correlated with social anxiety and this correlation was mediated by the degree of depression (Zhao et al., 2022). The missing mediation effect observed in this study agrees with these previous findings, which may explain the neuropathological causes of symptoms of depression: disassociation of the cortico-striatal-thalamic circuits. Additionally, from the perspective of neuromodulatory, the DLPFC region is the dominant target for intervention with rTMS, which ameliorates depressive symptoms by enhancing the integrity of cortico-striatal-thalamic circuits (Dunlop et al., 2017). These findings in the current study strengthen the understanding of DLPFC in the reward system, and therefore enlightening insights into the reward-related etiology of depression.

The MFC region is also identified as the SMA, according to the AAL atlas (Tzourio-Mazoyer et al., 2002). Depression, as a multi-network disorder, also exhibits abnormal changes in the sensorimotor network (SMN), including a decrease in degree centrality (H. Yang, 2021). In previous studies, SMA has also been found to be involved in multiple stages of emotion regulation, including cognition and executive functioning (Kohn et al., 2014). Rodent studies have shown that stress or negative reward prediction errors lead to motor activity inhibition, interpreted as a self-protective mechanism (Seligman, 1972). Studies have reported a significantly positive correlation between functional abnormalities in the postcentral gyrus and HAMD scores, as well as the severity of somatic symptoms (P. Liu, 2021). In patients with MDD, we observed an abnormal reduction in long-step sFC between the MFC, postcentral gyrus, and the SGC, NAcc, rVS, reflecting alterations specific to MDD. Given the involvement of the primary sensory region, SMN, in the perception of external information and somatosensory processes, damage to this system may explain the vegetative symptoms observed in patients with MDD. In addition, it has been reported in the literature that FC between the SMA and the whole brain is reduced in patients with MDD and that such a reduction is positively correlated with the HAMA score (P. Pan et al., 2022). Our results suggest that MDD may cause hierarchical damage to the brain from primary sensorimotor to advanced cognitive functions and further lead to a series of depressive symptoms.

Furthermore, we found that the MFC no longer mediated the NAcc-ACC and SGC-insula connections in MDD. It is worth noticing that

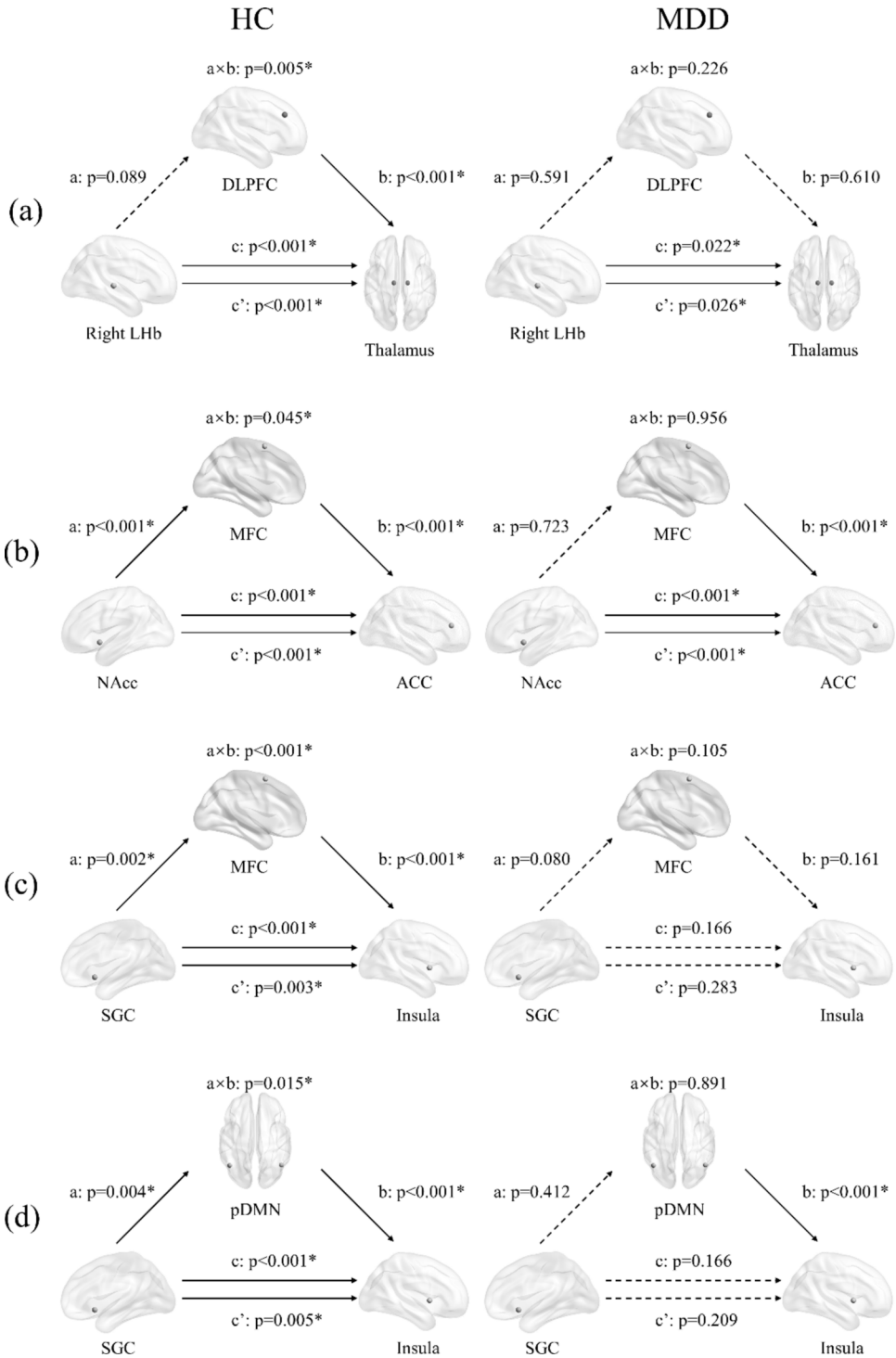

Fig. 6. Altered mediation pathways in MDD: (a) originates from right LHb, to thalamus via DLPFC; (b) originates from NAcc, to ACC via MFC; (c) originates from SGC, to insula via MFC; (d) originates from SGC, to insula via pDMN. Abbreviations: HC: healthy control; MDD: major depressive disorder; DLPFC: dorsal lateral prefrontal cortex; NAcc: nucleus accumbens; MFC: medial frontal cortex; lLHb: left lateral habenula; rLHb: right lateral habenula; ACC: anterior cingulate cortex; SGC: subgenual cingulate; pDMN: posterior default mode network.

ACC, insula, and MFC are widely considered to participate in reward-related functions (Cho et al., 2013; Chudasama et al., 2013; Ramkumar et al., 2016). Given that NAcc and SGC are crucial nodes in the reward circuit, these abnormal changes stand with the opinion that the interaction between MFC and the reward circuit is damaged in MDD. Previous studies have shown that the FC between MFC and OFC is negatively correlated with the score of the Snaith-Hamilton Pleasure Scale (SHAPS) (Ma et al., 2024), which indicated that the disconnection between MFC and reward system contributes to anhedonia in depression. Since anhedonia in depression may stem from the inability to respond to reward information, our findings suggest that the loss of mediation effect of MFC on the reward system is likely one of the primary causes of the abnormal reward information processing function that manifests as anhedonia in patients with MDD. A *meta*-analysis pooling 45 studies highlighted that SMA specifically participates in multiple reward-related functions, especially in the anticipation process

of reward (Jauhar et al., 2021). An experiment based on primates suggested that the reward expectancy signal widely spread among the SMA and may promote learning in actions of the body in the direction of maximizing rewards (Campos et al., 2005). These findings strongly support the explanation of anhedonia symptoms in MDD based on reward circuit abnormalities. Additionally, they provide a neuropathological explanation for the manifestation of motor retardation and other overt symptoms in MDD patients.

Lastly, the pDMN lost its mediation effect between the SGC and the insula in depressed patients. The insula serves as a key node of the SN, which is responsible for switching between the DMN and the executive network such as CEN, enabling the brain to correctly process stimuli from both the internal and external environments (Menon & Uddin, 2010). The abnormalities in these three networks and their connections are widely regarded as one of the neuropathological mechanisms underlying MDD (Cha et al., 2024). The disjunction between DMN and SN was well-documented in previous literature (Shao et al., 2018). As reported by Yang et al., MDD patients are not able to exhibit salience responses to positive stimuli (Y. Yang et al., 2016). Our findings can be interpreted as indicating connectivity abnormalities in the reward circuit-DMN-SN brain networks in MDD patients. On one hand, this result likely suggests that MDD patients are unable to process information from both internal and external sources in a reward-oriented manner. On the other hand, the imbalance among these three networks further impairs the dynamic switching function from the DMN to the CEN network in MDD patients. This supports the explanation for the occurrence of rumination and emotional disinhibition symptoms in MDD patients (C.-H. Liu et al., 2015).

5. Limitation & Conclusion

There are some limitations. First, the limited computational power in this study resulted in the need to down-sample the data during the sFC analysis, which might lose some detailed information and affect our results. Second, the medication information of the subjects in this study is not clear due to the long time-span of data collection. Generally, medications used in patients with depression are neurotransmitter-based and thus affect the functional properties of nodes in the neural circuits. Whether the results observed in this study are affected by medication needs to be further verified. Finally, considering that this study is based on the abnormalities of hierarchical connectivity and mediating effects within the cortical reward circuitry in patients with depression, the mean WM signal was regressed as a nuisance covariate in preprocessing. However, recent studies have indicated that the white matter may also contain physiologically meaningful signals, and also show specific abnormal changes in several psychiatric disorders (G. Ji et al., 2019; G.-J. Ji et al., 2017). Whether the WM signals are involved in the construction of the brain's reward circuitry requires further investigation.

In the present study, we examined reward circuits in depressed patients by applying sFC and mediation models. Depressed patients exhibited reduced sFC between the DBS targets and MFC along with postcentral gyrus at long-step connections; as well as the presence of reduced sFC in the bilateral thalamus, with the bilateral LHbs as seeds. The mediation effects model was further constructed on the basis of the sFC pathway. We observed that several superficial cortical regions, including the DLPFC, MFC, and pDMN, have lost their mediation effect over the interaction between intermediate and deep reward-related brain areas. This may elucidate the emergence of certain symptoms in depression and support the exploration of novel NIBS targets for depression interventions.

6. Statement of ethics

This study was approved by the Ethics Committee of the University of Electronic Science and Technology of China and complies with the requirements of the Declaration of Helsinki. Patients and healthy control subjects provided written informed consent after fully understanding the purpose and process of the study.

CRediT authorship contribution statement

Ruikun Yang: Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation. **Junxia Chen:** Methodology, Formal analysis, Data curation. **Suping Yue:** Validation, Resources, Conceptualization. **Yue Yu:** Resources, Data curation, Conceptualization. **Jiamin Fan:** Software, Methodology, Formal analysis, Data curation. **Yuling Luo:** Visualization, Validation, Methodology, Conceptualization. **Hui He:** Visualization, Formal analysis, Data curation. **Mingjun Duan:** Visualization, Resources, Funding acquisition, Conceptualization. **Sisi Jiang:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Dezhong Yao:** Supervision, Project administration, Funding acquisition, Conceptualization. **Cheng Luo:** Supervision, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103739.

Data availability

Data will be made available on request.

References

Amarante, L. M., & Laubach, M. (2021). Coherent theta activity in the medial and orbital frontal cortices encodes reward value. *eLife*, *10*, e63372. Doi: 10.7554/eLife.63372.

Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P., Mendlewicz, J., Lotstra, F., 1994. Frontal and parietal metabolic disturbances in unipolar depression. *Biol. Psychiatry* 36 (6), 381–388. https://doi.org/10.1016/0006-3223(94)91213-0.

Campos, M., Breznen, B., Bernheim, K., Andersen, R.A., 2005. Supplementary motor area encodes reward expectancy in eye-movement tasks. *J. Neurophysiol.* 94 (2), 1325–1335. https://doi.org/10.1152/jn.00022.2005.

Cha, J., Choi, K.S., Rajendra, J.K., McGrath, C.L., Riva-Posse, P., Holtzheimer, P.E., Figee, M., Kopell, B.H., Mayberg, H.S., 2024. Whole brain network effects of subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Mol. Psychiatry* 29 (1), 112–120. https://doi.org/10.1038/s41380-023-02306-6.

Cho, Y.T., Fromm, S., Guyer, A.E., Detloff, A., Pine, D.S., Fudge, J.L., Ernst, M., 2013. Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *Neuroimage* 66, 508–521. https://doi.org/10.1016/j.neuroimage.2012.10.013.

Chudasama, Y., Daniels, T.E., Gorrin, D.P., Rhodes, S.E.V., Rudebeck, P.H., Murray, E.A., 2013. The role of the anterior cingulate cortex in choices based on reward value and reward contingency. *Cereb. Cortex* 23 (12), 2884–2898. https://doi.org/10.1093/cercor/bhs266.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A., Geddes, J.R., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 391 (10128), 1357–1366. https://doi.org/10.1016/S0140-6736(17)32802-7.

Cohen, M.X., Bour, L., Mantione, M., Figee, M., Vink, M., Tijssen, M.A.J., Rootselaar, A. V., Munckhof, P.V.D., Richard Schuurman, P., Denys, D., 2012. Top–down-directed synchrony from medial frontal cortex to nucleus accumbens during reward anticipation. *Hum. Brain Mapp.* 33 (1), 246–252. https://doi.org/10.1002/hbm.21195.

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 (11), 3. https://doi.org/10.1038/s41398-017-0005-6.

Dunlop, K., Hanlon, C.A., Downar, J., 2017. Noninvasive brain stimulation treatments for addiction and major depression. *Ann. N. Y. Acad. Sci.* 1394 (1), 31–54. https://doi.org/10.1111/nyas.12985.

Eshel, N., Keller, C.J., Wu, W., Jiang, J., Mills-Finnerty, C., Huemer, J., Wright, R., Fonzo, G.A., Ichikawa, N., Carreon, D., Wong, M., Yee, A., Shpigel, E., Guo, Y., McTeague, L., Maron-Katz, A., Etkin, A., 2020. Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. *Neuropsychopharmacology* 45 (6), 1018–1025. https://doi.org/10.1038/s41386-020-0633-z.

Fan, J., Liu, W., Xia, J., Li, S., Gao, F., Zhu, J., Han, Y., Zhou, H., Liao, H., Yi, J., Tan, C., Zhu, X., 2021. Childhood trauma is associated with elevated anhedonia and altered core reward circuitry in major depression patients and controls. *Hum. Brain Mapp.* 42 (2), 286–297. https://doi.org/10.1002/hbm.25222.

Figee, M., Riva-Posse, P., Choi, K.S., Bederson, L., Mayberg, H.S., Kopell, B.H., 2022. Deep brain stimulation for depression. *Neurotherapeutics* 19 (4), 1229–1245. https://doi.org/10.1007/s13311-022-01270-3.

Filatova, E.V., Shadrina, M.I., Slominsky, P.A., 2021. Major Depression: One Brain, One Disease. One Set of Intertwined Processes. *Cells* 10 (6), 1283. https://doi.org/10.3390/cells10061283.

Fischer, A.S., Ellwood-Lowe, M.E., Colich, N.L., Cichocki, A., Ho, T.C., Gotlib, I.H., 2019. Reward-circuit biomarkers of risk and resilience in adolescent depression. *J. Affect. Disord.* 246, 902–909. https://doi.org/10.1016/j.jad.2018.12.104.

Fox, M.D., Buckner, R.L., White, M.P., Greicius, M.D., Pascual-Leone, A., 2012. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol. Psychiatry* 72 (7), 595–603. https://doi.org/10.1016/j.biopsych.2012.04.028.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J., Turner, R., 1996. Movement-Related effects in fMRI time-series. *Magn. Reson. Med.* 35 (3), 346–355. https://doi.org/10.1002/mrm.1910350312.

George, M.S., Wassermann, E.M., Williams, W.A., Callahan, A., Ketter, T.A., Basser, P., Hallett, M., Post, R.M., 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport* 6 (14), 1853–1856. https://doi.org/10.1097/00001756-199510020-00008.

Geugies, H., Groenewold, N.A., Meurs, M., Doornbos, B., De Klerk-Sluis, J.M., Van Eijndhoven, P., Roest, A.M., Ruhé, H.G., 2022. Decreased reward circuit connectivity during reward anticipation in major depression. *NeuroImage: Clinical* 36, 103226. https://doi.org/10.1016/j.nicl.2022.103226.

Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23 (1), 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Han, S., Li, X.-X., Wei, S., Zhao, D., Ding, J., Xu, Y., Yu, C., Chen, Z., Zhou, D.-S., Yuan, T.-F., 2023. Orbitofrontal cortex-hippocampus potentiation mediates relief for depression: A randomized double-blind trial and TMS-EEG study. *Cell Rep. Med.* 4 (6), 101060. https://doi.org/10.1016/j.xcrm.2023.101060.

Höflich, A., Michenthaler, P., Kasper, S., Lanzenberger, R., 2019. Circuit mechanisms of reward, anhedonia, and depression. *Int. J. Neuropsychopharmacol.* 22 (2), 105–118. https://doi.org/10.1093/ijnp/pyy081.

Huskey, R., Craighead, B., Miller, M.B., Weber, R., 2018. Does intrinsic reward motivate cognitive control? A naturalistic-fMRI study based on the synchronization theory of flow. *Cogn. Affect. Behav. Neurosci.* 18 (5), 902–924. https://doi.org/10.3758/s13415-018-0612-6.

Jauhar, S., Fortea, L., Solanes, A., Albajes-Eizagirre, A., McKenna, P.J., Radua, J., 2021. Brain activations associated with anticipation and delivery of monetary reward: a systematic review and meta-analysis of fMRI studies. *PLoS One* 16 (8), e0255292. https://doi.org/10.1371/journal.pone.0255292.

Ji, G., Ren, C., Li, Y., Sun, J., Liu, T., Gao, Y., Xue, D., Shen, L., Cheng, W., Zhu, C., Tian, Y., Hu, P., Chen, X., Wang, K., 2019. Regional and network properties of white matter function in Parkinson's disease. *Hum. Brain Mapp.* 40 (4), 1253–1263. https://doi.org/10.1002/hbm.24444.

Ji, G.-J., Liao, W., Chen, F.-F., Zhang, L., Wang, K., 2017. Low-frequency blood oxygen level-dependent fluctuations in the brain white matter: more than just noise. *Sci. Bullet.* 62 (9), 656–657. https://doi.org/10.1016/j.scib.2017.03.021.

Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U., 2014. Neural network of cognitive emotion regulation—An ALE meta-analysis and MACM analysis. *Neuroimage* 87, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001.

Lawson, R.P., Drevets, W.C., Roiser, J.P., 2013. Defining the habenula in human neuroimaging studies. *Neuroimage* 64, 722–727. https://doi.org/10.1016/j.neuroimage.2012.08.076.

Li, W., Wang, Y., Ward, B.D., Antuono, P.G., Li, S.-J., Goveas, J.S., 2017. Intrinsic inter-network brain dysfunction correlates with symptom dimensions in late-life depression. *J. Psychiatr. Res.* 87, 71–80. https://doi.org/10.1016/j.jpsychires.2016.12.011.

Liu, C.-H., Ma, X., Song, L.-P., Tang, L.-R., Jing, B., Zhang, Y., Li, F., Zhou, Z., Fan, J., Wang, C.-Y., 2015. Alteration of spontaneous neuronal activity within the salience network in partially remitted depression. *Brain Res.* 1599, 93–102. https://doi.org/10.1016/j.brainres.2014.12.040.

Liu, P., 2021. Brain functional alterations in MDD patients with somatic symptoms: a resting-state fMRI study. *J. Affect. Disord.*.

Ma, Y., Guo, C., Luo, Y., Gao, S., Sun, J., Chen, Q., Lv, X., Cao, J., Lei, Z., Fang, J., 2024. Altered neural activity in the reward-related circuit associated with anhedonia in mild to moderate Major Depressive Disorder. *J. Affect. Disord.* 345, 216–225. https://doi.org/10.1016/j.jad.2023.10.085.

Marwaha, S., Palmer, E., Suppes, T., Cons, E., Young, A.H., Upthegrove, R., 2023. Novel and emerging treatments for major depression. *Lancet* 401 (10371), 141–153. https://doi.org/10.1016/S0140-6736(22)02080-3.

Matsumoto, M., Hikosaka, O., 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature* 447 (7148), 1111–1115. https://doi.org/10.1038/nature05860.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214 (5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0.

Nestler, E.J., Carlezon, W.A., 2006. The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry* 59 (12), 1151–1159. https://doi.org/10.1016/j.biopsych.2005.09.018.

Pan, P.M., Sato, J.R., Salum, G.A., Rohde, L.A., Gadelha, A., Zugman, A., Mari, J., Jackowski, A., Picon, F., Miguel, E.C., Pine, D.S., Leibenluft, E., Bressan, R.A., Stringaris, A., 2017. Ventral striatum functional connectivity as a predictor of adolescent depressive disorder in a longitudinal community-based sample. *Am. J. Psychiatry* 174 (11), 1112–1119. https://doi.org/10.1176/appi.ajp.2017.17040430.

Pan, P., Wang, L., Wu, C., Jin, K., Cao, S., Qiu, Y., Teng, Z., Li, S., Shao, T., Huang, J., Wu, H., Xiang, H., Chen, J., Liu, F., Tang, H., Guo, W., 2022. Global functional connectivity analysis indicating dysconnectivity of the hate circuit in major depressive disorder. *Front. Aging Neurosci.* 13, 803080. https://doi.org/10.3389/fnagi.2021.803080.

Philip, N. S., Barredo, J., Van 'T Wout-Frank, M., Tyrka, A. R., Price, L. H., & Carpenter, L. L. (2018). Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. *Biol. Psychiat.*, *83*(3), 263–272. Doi: 10.1016/j.biopsych.2017.07.021.

Pretus, C., Marcos-Vidal, L., Martínez-García, M., Picado, M., Ramos-Quiroga, J.A., Richarte, V., Castellanos, F.X., Sepulcre, J., Desco, M., Vilarroya, Ó., Carmona, S., 2019. Stepwise functional connectivity reveals altered sensory-multimodal integration in medication-naïve adults with attention deficit hyperactivity disorder. *Hum. Brain Mapp.* 40 (16), 4645–4656. https://doi.org/10.1002/hbm.24727.

Ramkumar, P., Dekleva, B., Cooler, S., Miller, L., Kording, K., 2016. Premotor and motor cortices encode reward. *PLoS One* 11 (8), e0160851. https://doi.org/10.1371/journal.pone.0160851.

Russo, S.J., Nestler, E.J., 2013. The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 14 (9), 609–625. https://doi.org/10.1038/nrn3381.

Scangos, K.W., Makhoul, G.S., Sugrue, L.P., Chang, E.F., Krystal, A.D., 2021. State-dependent responses to intracranial brain stimulation in a patient with depression. *Nat. Med.* 27 (2), 229–231. https://doi.org/10.1038/s41591-020-01175-8.

Schulz, P.E., Arora, G., 2015. Depression: *CONTINUUM: Lifelong Learning. Neurology* 21, 756–771. https://doi.org/10.1212/01.CON.0000466664.35650.b4.

Seligman, M.E.P., 1972. Learned Helplessness. *Annu. Rev. Med.* 23 (1), 407–412. https://doi.org/10.1146/annurev.me.23.020172.002203.

Sepulcre, J., Sabuncu, M.R., Yeo, T.B., Liu, H., Johnson, K.A., 2012. Stepwise connectivity of the modal cortex reveals the multimodal organization of the human brain. *J. Neurosci.* 32 (31), 10649–10661. https://doi.org/10.1523/JNEUROSCI.0759-12.2012.

Shabel, S.J., Proulx, C.D., Piriz, J., Malinow, R., 2014. GABA/glutamate co-release controls habenula output and is modified by antidepressant treatment. *Science* 345 (6203), 1494–1498. https://doi.org/10.1126/science.1250469.

Shao, J., Meng, C., Tahmasian, M., Brandl, F., Yang, Q., Luo, G., Luo, C., Yao, D., Gao, L., Riedl, V., Wohlschläger, A., Sorg, C., 2018. Common and distinct changes of default mode and salience network in schizophrenia and major depression. *Brain Imaging Behav.* 12 (6), 1708–1719. https://doi.org/10.1007/s11682-018-9838-8.

Shiwei, L., Xiaojing, Z., Yingli, Z., Shengli, C., Xiaoshan, L., Ziyun, X., Gangqiang, H., & Yingwei, Q. (n.d.). Cortical hierarchy disorganization in major depressive disorder and its association with suicidality. *Front. Psychiat.*

Tekin, S., Cummings, J.L., 2002. Frontal–subcortical neuronal circuits and clinical neuropsychiatry. *J. Psychosom. Res.* 53 (2), 647–654. https://doi.org/10.1016/S0022-3999(02)00428-2.

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 (1), 273–289. https://doi.org/10.1006/nimg.2001.0978.

Wang, X.-Y., Xu, X., Chen, R., Jia, W.-B., Xu, P.-F., Liu, X.-Q., Zhang, Y., Liu, X.-F., Zhang, Y., 2023. The thalamic reticular nucleus-lateral habenula circuit regulates depressive-like behaviors in chronic stress and chronic pain. *Cell Rep.* 42 (10), 113170. https://doi.org/10.1016/j.celrep.2023.113170.

Weinstein, A.M., 2023. Reward, motivation and brain imaging in human healthy participants – A narrative review. *Front. Behav. Neurosci.* 17, 1123733. https://doi.org/10.3389/fnbeh.2023.1123733.

Yan, C.-G., Wang, X.-D., Zuo, X.-N., Zang, Y.-F., 2016. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics* 14 (3), 339–351. https://doi.org/10.1007/s12021-016-9299-4.

Yang, H., 2021. Disrupted intrinsic functional brain topology in patients with major depressive disorder. *Mol. Psychiatry*.

Yang, Y., Zhong, N., Imamura, K., Lu, S., Li, M., Zhou, H., Li, H., Yang, X., Wan, Z., Wang, G., Hu, B., Li, K., 2016. Task and resting-state fMRI reveal altered salience responses to positive stimuli in patients with major depressive disorder. *PLoS One* 11 (5), e0155092. https://doi.org/10.1371/journal.pone.0155092.

Zhang, L., Wang, H., Luan, S., Yang, S., Wang, Z., Wang, J., Zhao, H., 2017. Altered volume and functional connectivity of the Habenula in Schizophrenia. *Front. Hum. Neurosci.* 11, 636. https://doi.org/10.3389/fnhum.2017.00636.

Zhao, W., Zhang, X., Zhou, X., Song, X., Zhang, Z., Xu, L., Zhou, F., Kendrick, K.M., 2022. Depression mediates the association between insula-frontal functional connectivity

and social interaction anxiety. *Hum. Brain Mapp.* 43 (14), 4266–4273. https://doi.org/10.1002/hbm.25952.