Research Paper

Aberrant functional connectivity of the globus pallidus in the modulation of the relationship between childhood trauma and major depressive disorder

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Background: Childhood trauma plays a crucial role in the dysfunctional reward circuitry in major depressive disorder (MDD). We sought to explore the effect of abnormalities in the globus pallidus (GP)–centric reward circuitry on the relationship between childhood trauma and MDD. **Methods:** We conducted seed-based dynamic functional connectivity (dFC) analysis among people with or without MDD and with or without childhood trauma. We explored the relationship between abnormal reward circuitry, childhood trauma, and MDD. **Results:** We included 48 people with MDD and childhood trauma, 30 people with MDD without childhood trauma, 57 controls with childhood trauma, and 46 controls without childhood trauma. We found that GP subregions exhibited abnormal dFC with several regions, including the inferior parietal lobe, thalamus, superior frontal gyrus (SFG), and precuneus. Abnormal dFC in these GP subregions showed a significant correlation with childhood trauma. Moderation analysis revealed that the dFC between the anterior GP and SFG, as well as between the anterior GP and the precentral gyrus, modulated the relationship between childhood abuse and MDD severity. We observed a negative correlation between childhood trauma and MDD severity among patients with lower dFC between the anterior GP and SFG, as well as higher dFC between the anterior GP and precentral gyrus. This suggests that reduced dFC between the anterior GP and SFG, along with increased dFC between the anterior GP and precentral gyrus, may attenuate the effect of childhood trauma on MDD severity. **Limitations:** Cross-sectional designs cannot be used to infer causality. **Conclusion:** Our findings underscore the pivotal role of reward circuitry abnormalities in MDD with childhood trauma. These abnormalities involve various brain regions, including the postcentral gyrus, precentral gyrus, inferior parietal lobe, precuneus, superior frontal gyrus, thalamus, and middle frontal gyrus. **Clinical trial registration:** ChiCTR2300078193

Introduction

Childhood trauma refers to distressing experiences that occur during the formative years, typically from 0–16 years of age.[1] Childhood trauma can be classified into 5 distinct categories, namely emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse.[1–3] Childhood trauma is a well-known risk factor for major depressive disorder (MDD),[4] with a notable linkage with high prevalence of depression,[2] low remission rates,[5] and protracted convalescence.[2] Patients with MDD exhibit abnormalities in the brain's reward circuitry, including diminished reward sensitivity,[6] issues with reward and risk decision-making,[7,8] emotional negativity bias,[9] and reward-dependence behaviours.[10] Previous studies have demonstrated that childhood trauma exerts discernible effects on cerebral developmental trajectories,[11–13] particularly by perturbing the customary operation of the brain's reward circuits.[1,14] Consequently, elucidating abnormalities in the reward circuitry among patients with MDD and childhood trauma is crucial for understanding underlying neurobiological mechanisms.

The basal ganglia play a crucial role in regulating various neurologic functions in the brain, including motor control, memory, emotion, reward processing, habit formation, and motor learning.[15,16] In the context of MDD with childhood trauma, the basal ganglia are believed to be implicated in the emotional and cognitive disturbances involving the different ways of emotion generation, as well as regulation from the bottom–up (in response to inherently emotional perceptual properties of the stimulus) or from the top–down (in response to cognitive evaluations),[15] which may contribute to the development of depression and related symptoms (e.g.,

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emotional dysregulation, cognitive impairment, social dysfunction).[16] Studying the basal ganglia can lead to a deeper understanding of how this region is affected by childhood trauma and how it contributes to the pathogenesis of depression.

Recent research has emphasized the central role of the globus pallidus in the reward circuitry. For instance, Ottenheimer and colleagues[17] observed a higher number of reward-sensitive neurons in the globus pallidus than in the nucleus accumbens when measuring electrophysiological activity in rats performing reward-related tasks. Moreover, a reward-related signal associated with preferences was found in the globus pallidus, which could flexibly report the relative value of reward outcomes under various conditions.[17] Stevenson and colleagues[18] discovered that the ability to discriminate potential rewards and punishments and respond to them depends on the activation of the ventral pallidum. Maintaining a balance between the inhibition and stimulation of neurons in the ventral pallidum contributes to the regulation of behavioural motivation.[18] These findings effectively establish the globus pallidus is not merely a relay station for downstream signals from reward neurons but a central brain region in the reward circuitry.

However, the globus pallidus is not a singular, homogeneous entity, but rather comprises functionally and structurally heterogeneous nuclei. Traditional investigations have anatomically divided the globus pallidus along the medial–lateral axis into inner and outer components.[19–21] In a groundbreaking study, Tian and colleagues[22] used a sample of more than 1000 healthy adults to establish a novel brain atlas applicable to subcortical nuclei. This innovative work diverged from conventional methods that relied on structural magnetic resonance imaging (MRI) to map brain anatomy.[22] Instead, they employed functional MRI to elucidate the intricate organizational patterns of the human subcortex, ultimately creating the most detailed subcortical gradient map to date.[22] Based on their atlas, the globus pallidus was divided into 4 subregions, namely the bilateral anterior globus pallidus and the bilateral posterior globus pallidus (Figure 1).[22] The anterior globus pallidus primarily serves motivational and cognitive functions, while the posterior globus pallidus is mainly involved in the regulation of motor functions, particularly precise grip motor parameters.[23]

Numerous studies have discovered the temporal correlation of low-frequency fluctuations across the resting human brain, which is measured as functional connectivity by resting-state functional MRI (rs-fMRI).[24,25] Building on the assumption of the enduring spatial and temporal stability of functional connectivity, Biswal and colleagues[24] unveiled functional associations among disparate cortical domains through the assessment of blood oxygen level–dependent (BOLD) signals during the quiescent state of cerebral activity. Accordingly, static functional connectivity has emerged as a prevalent approach employed to investigate the temporal covariation of BOLD signals across diverse enclaves of the brain. With the development of analysis strategies exploring brain functional networks, researchers have put forward dynamic functional connectivity to describe the time-varying nature of functional connectivity by applying the sliding window approach.[26] Although traditional static functional connectivity could represent the average functional connectivity in a short time and provide valuable information about functional communication within our brain,[25] dynamic functional connectivity may find more sensitive and specific markers of brain disease.[27] However, dynamic functional connectivity has the drawback of its sensitivity to noise, and the triggering mechanism behind the temporal variability of functional connectivity remains unclear.[28] In this work, we decided to use both static and dynamic functional connectivity analysis.[27]

The methods of static and dynamic functional connectivity analysis have been extensively employed to investigate anomalous brain functionality among people experiencing depression. For example, Sato and colleagues[29] found aberrant static functional connectivity between the left and right globus pallidus among people with subthreshold depression, alongside its associated dysfunctions such as dysphoria and diminished responsiveness to rewarding stimuli.

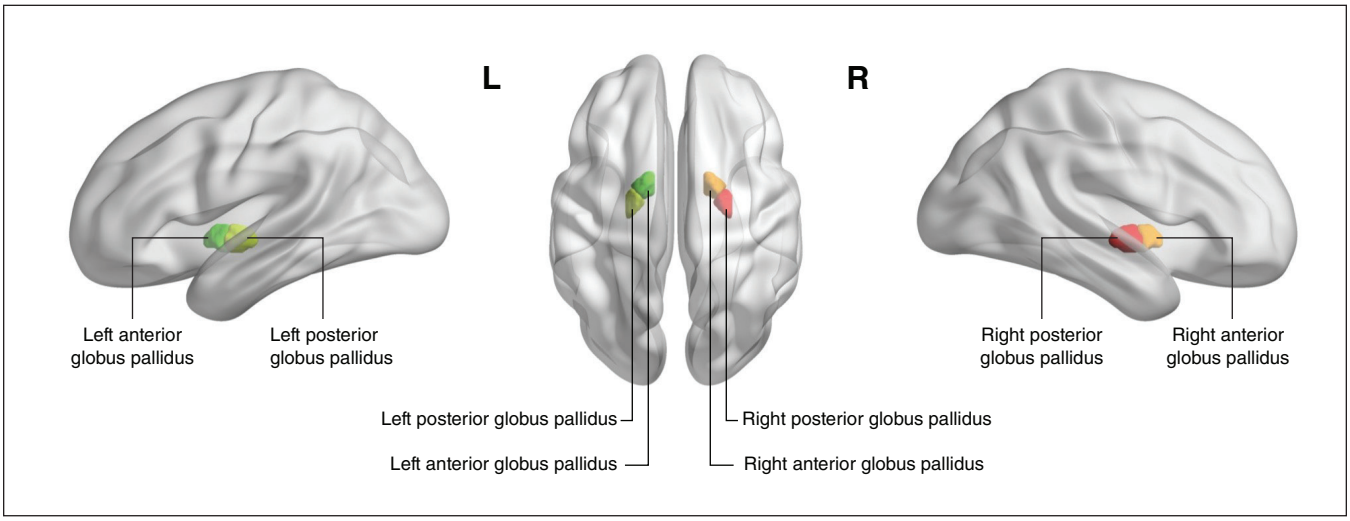


Figure 1: Visualization of the globus pallidus subregions. L = left; R = right.

Furthermore, Shunkai and colleagues[30] delved into abnormal hippocampal subregions using seed-based dynamic functional connectivity and revealed that dysfunctional connectivity was linked to deficits in working memory in melancholic depression. Similarly, Luo and colleagues[31] examined deviations in brain functionality among patients with MDD and childhood trauma; they observed abnormal static and dynamic functional connectivity between the amygdala subregions and cerebral regions associated with theory of mind. We sought to investigate abnormalities in static and dynamic functional connectivity within the reward circuitry, centred on the globus pallidus, among patients with MDD and childhood trauma.

Within the present study, we undertook analyses involving static and dynamic functional connectivity, employing each of the 4 subregions of the globus pallidus as the seed. The primary objective of this study was to unveil the abnormal characteristics pertaining to the functioning of the reward circuitry among patients with MDD and childhood trauma. Furthermore, we directed our efforts toward disentangling the distinct effects arising from the traumatic consequences of childhood trauma and the pathophysiological manifestations of depression on abnormal patterns of functional connectivity. Drawing on the foundation of previous functional connectivity investigations involving patients with MDD and childhood trauma,[31–34] we formulated a hypothesis positing that this population would manifest anomalous functional connectivity within the globus pallidus–centred reward circuitry, distinguishing them from their counterparts who contend solely with MDD.[29,35,36] This study offers a perspective on the potential neurobiological mechanisms of patients with MDD and childhood trauma by investigating the role of globus pallidus dysfunction in this context.

Methods

Participants

In our previous research, we explored alterations in the functionality of amygdala subregions among patients with MDD and childhood trauma using the same database as used here.[31] However, this study diverges from the previous one in that the primary focus of the earlier research was to observe abnormalities in the limbic system, particularly in the amygdala, associated with negative emotion regulation. In contrast, the present study sought to examine anomalies in the reward circuitry, specifically centred around the globus pallidus, linked to abnormalities in regulating positive emotions. Discovering putamen-related functional abnormalities associated with reward among patients with MDD and childhood trauma is critical for understanding their lack of motivation, heightened reward anticipation, and difficulty experiencing reward satisfaction.[34,37,38]

We rigorously analyzed our sample size estimation by using PASS software to ensure scientific accuracy. First, considering how the interaction effect between degree of depression and trauma experience factors can significantly influence 2-way analysis of variance (ANOVA), we conducted factorial ANOVA with preset parameters ($\alpha = 0.05$, $1\text{-}\beta = 0.8$, $k = 4$), and an expected main effect size of 0.25, along with the interaction effect size of 0.3. We calculated the initial target sample size for each group to be 23 and the total sample size to be 92. Furthermore, we determined the dropout-inflated enrolment sample size to be 29 for each group (116 total).

We recruited patients with MDD from the Affiliated Brain Hospital of Guangzhou Medical University, along with healthy controls recruited from the nearby community. We matched controls for age, sex, and education, and ensured they exhibited no psychiatric disorders by psychiatric screening. The diagnostic process for MDD adhered to the DSM-5 criteria and was administered by 2 psychiatrists. To gauge the severity of both depression and anxiety, we employed the Hamilton Depression Rating Scale (HAMD)[39,40] and the Hamilton Anxiety Rating Scale (HAMA),[41] respectively. To quantify the severity of childhood trauma, we employed the Childhood Trauma Questionnaire (CTQ).[3,42,43] The CTQ is regarded as an authoritative and foundational tool for quantifying the enduring effects of early-life adversity before the age of 16 years on an individual.[44,45] It encompasses 5 distinct dimensions, namely emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect.[42,43] The CTQ subscales are evaluated based on predefined threshold scores (emotional abuse score ≥ 13, physical abuse score ≥ 10, sexual abuse score ≥ 8, emotional neglect score ≥ 15, and physical neglect score ≥ 10).[3,42,43] We employed the CTQ subscale scores to ascertain the occurrence of childhood trauma and used the CTQ total score to quantify the severity of childhood trauma. We also used neglect (sum of emotional and physical neglect) and abuse (sum of emotional, physical, and sexual abuse) scores.

Organized according to their respective histories of early-life adversity, we categorized participants into those with MDD and childhood trauma, those with MDD without childhood trauma, controls with childhood trauma, and controls without childhood trauma. We excluded patients with profound mental disorders, such as posttraumatic stress disorder, bipolar disorder, and anxiety disorders; patients who had previously undergone electroconvulsive therapy or who had taken psychotropic medications; and patients with contraindications pertinent to rs-fMRI, including those with conditions such as claustrophobia.

MRI data acquisition

We acquired MRI data with a 3.0 T Philips scanner at the radiology department of The Affiliated Brain Hospital of Guangzhou Medical University in China. We instructed study participants to maintain a state of stillness and calmness while closing their eyes during the 8-minute scanning procedure. The functional scans of the resting state were recorded using a gradient-echo echoplanar imaging sequence, which consisted of 33 slices with a total of 240 time points. The repetition time was set at 2000 ms, with an echo time of 30 ms, a flip angle of 90°, a field of view of 220 × 220 mm^2, and a slice thickness and interslice gap of 4 mm and 0.6 mm, respectively. The acquisition matrix was set at 64 × 64.

MRI data preprocessing

The rs-fMRI data underwent preprocessing using Data Processing & Analysis for Brain Imaging (DPABI) software (version 5.2).[46] We discarded the initial 10 volumes to eliminate steady-state longitudinal magnetization, leaving 230 volumes, which were subsequently corrected for slice time and head motion. Based on the report of Jenkinson and colleagues,[47] head motion correction was executed by using the Friston 24-parameter model. We gathered the mean framewise displacement, computed from each time point for every participant; we included only those with a mean framewise displacement value of less than 0.2 mm in our analysis.[47] Subsequently, the images were normalized to the standard Montreal Neurological Institute's echo-planar imaging template and resampled to $3 \times 3 \times 3$ mm^3. After spatial normalization, we applied a 4 mm full-width at half maximum (FWHM) Gaussian kernel to smooth the images. To mitigate the effect of physiologic artifacts, white matter and cerebrospinal fluid signals were regarded as nuisance covariates and ruled out. The preprocessed images were ultimately subjected to a temporal band-pass filter between 0.01 and 0.08 Hz for further analysis. We chose not to use global signal regression in this study, given our interest in exploring differences in brain function between different groups, including people with MDD who had experienced childhood trauma, those with MDD who had not experienced childhood trauma, and healthy people with and without traumatic childhood experiences. Global signal regression could potentially distort the results of between-group analysis.[48] In addition, whole-brain signals are important in the context of psychiatric disorders, and not considering them could result in a loss of valuable representation.[48] Current and widely cited studies have also avoided regressing global signals during preprocessing analyses.[49,50]

Definition of regions of interest

Tian and colleagues[22] used functional MRI to map the intricate subcortical organization of the human brain. This atlas, which can be integrated with existing cortical maps, is designed to characterize the connections between the cortex and subcortical regions. Based on this atlas, we identified 4 subregions within the globus pallidus, namely the bilateral anterior and posterior globus pallidus, which were used as regions of interest in seed-based static and dynamic functional connectivity analyses.[22]

Static functional connectivity analysis

We conducted static functional connectivity analysis of the bilateral anterior globus pallidus and posterior globus pallidus using DPABI software.[46] We extracted the time series from the regions of interest and subsequently performed voxel-wise correlation analyses, examining the connectivity patterns between subregions of the globus pallidus and other brain regions. The resultant maps of static functional connectivity were subsequently enhanced through the application of a z transformation, thereby augmenting the normality of the data distribution.

Dynamic functional connectivity analysis

For the dynamic functional connectivity analysis, we adopted the Hamming sliding window approach, employing the temporal dynamic analysis toolkit in DPABI software.[46] We chose a window length of 50 time points (TRs) and a step width of 1 TR for conducting the dynamic functional connectivity analysis. Previous research has shown that a window length of 50 TR strikes an optimal balance between the accuracy of functional connectivity calculations and the ability to capture swift dynamic alterations.[31,34,51] This choice minimizes the risk of introducing erroneous fluctuations, associated with shorter windows, and the risk of obscuring the temporal dynamics' characteristics, associated with longer windows. Furthermore, we employed additional window lengths (30 TR and 70 TR) to explore potential implications on dynamic functional connectivity outcomes.

For each sliding window, we acquired correlation maps by computing temporal correlation coefficients between the time series of globus pallidus subregions and those of all other brain voxels. Consequently, each individual had a total of 181 correlation maps derived from sliding windows. Each correlation map underwent Fisher z transformation to enhance the normal distribution of the data. We generated the dynamic functional connectivity maps by calculating the standard deviation of the 181 z-value maps obtained from the sliding windows. For improved comparability and interpretability among different individuals, these dynamic functional connectivity maps were z-standardized. Lastly, we applied a Gaussian kernel with a FWHM of 4 mm to all maps. We also executed analogous calculations of dynamic functional connectivity patterns using the sliding window lengths of 30 TR and 70 TR, aimed at corroborating the robustness of our findings (Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.240019/tab-related-content).

Statistical analysis

To explore between-group differences in demographic characteristics (e.g., age, sex, education), clinical features (HAMD and HAMA scores), and severity of childhood trauma (total and subscale scores of CTQ), we applied Student t tests, χ^2 tests, and 1-way ANOVA using SPSS version 27.0.

We employed 2-way ANOVA with Benjamini–Hochberg post hoc tests to examine the variations in dynamic and static functional connectivity between the 4 groups (corrected $p < 0.05$). During the 2-way ANOVA, demographics were regarded as nuisance covariates. With the use of 2-way ANOVA, we could identify which factor — etiological, traumatic, or interaction — was responsible for any abnormal dynamic and static functional connectivity of the globus pallidus subregions among patients with MDD and those with childhood trauma.

To investigate the relationships between abnormal dynamic functional connectivity and childhood trauma, we used partial correlation analyses with the Benjamini–Hochberg correction to calculate adjusted (adj) p values. The demographic factors were accounted for as nuisance covariates.

Considering the possibility of abnormal dynamic functional connectivity serving as a moderator factor in the relationship between childhood trauma and depression severity, we conducted a moderator analysis using the PROCESS 3.3 toolbox for SPSS software (https://processmacro.org/index.html). In the moderation analyses, childhood trauma was considered as the independent variable, aberrant dynamic functional connectivity as the moderating variable, and depression severity as the dependent variable. To eliminate problematic multicollinearity effects, the moderator and their interaction terms were both centred on the mean.[52] Such transformations do not affect the significance level of the interaction terms or the simple slopes of any plotted regression lines. In addition, we included demographic variables such as age, sex, and education in the first step of the analysis. In the second step, we added childhood trauma (measured by the CTQ total score, neglect total score, and abuse total score) and aberrant variability in dynamic functional connectivity. Finally, in the third step, we added the interaction between childhood trauma and aberrant variability in dynamic functional connectivity. If the interaction had a significant effect, this would represent how aberrant variability in dynamic functional connectivity moderated the relationship between childhood trauma and HAMD score. We used 3 levels of the moderating variable, grouped as high (above mean + 0.5 standard deviation [SD]), moderate (mean – 0.5 SD to mean + 0.5 SD), and low (below mean – 0.5 SD) dynamic functional connectivity; we selected these thresholds to have similar numbers of participants in each subgroup. We considered a conventional 5% (2-tailed) threshold to be statistically significant.

Ethics approval

This study was approved by the Ethics Committee of the Affiliated Brain Hospital of Guangzhou Medical University. All participants provided written informed consent.

Results

Demographics and clinical features

We enrolled 181 participants, including patients with MDD and childhood trauma (n = 48), patients with MDD without childhood trauma (n = 30), controls with childhood trauma (n = 57), and controls without childhood trauma (n = 46). Demographics are presented in Table 1. Physical neglect (37.4%) represented the highest proportion of all forms of childhood trauma, while sexual abuse (6.6%) represented the lowest proportion among participants with childhood trauma (n = 105). We found no significant differences in age, sex, education, or framewise displacement across groups ($p > 0.05$). Similarly, HAMD and HAMA scores did not differ between patients with and without childhood trauma ($p > 0.05$). We found significant differences across the 4 groups in CTQ total scores, neglect total scores, abuse total

Table 1: Demographics and clinical features among patients with major depressive disorder (MDD) and healthy controls with or without childhood trauma

	Mean ± SD*					
Characteristic	MDD with childhood trauma n = 48	MDD without childhood trauma n = 30	Controls with childhood trauma n = 57	Controls without childhood trauma n = 46	$F/t/\chi^2$	p value
Age, yr	28.1 ± 6.524	29.07 ± 7.913	26.82 ± 7.033	27.28 ± 6.065	0.824	0.5
Sex, no. (%) of participants					2.436	0.1
Male	25 (52.1)	11 (36.7)	27 (47.4)	17 (37.0)		
Female	23 (47.9)	19 (63.3)	30 (52.6)	29 (63.0)		
Education, yr	12.92 ± 3.32	13.73 ± 3.35	14.14 ± 2.80	14.54 ± 2.34	2.671	0.05
HAMD score	29.46 ± 8.54	29.73 ± 5.46	NA	NA	0.081	1.0
HAMA score	24.09 ± 6.69	6.70 ± 4.28	NA	NA	3.910	0.05
Onset age, yr	27.80 ± 4.23	28.30 ± 5.66	NA	NA	0.673	0.5
Illness duration, yr	0.46 ± 0.23	0.55 ± 0.16	NA	NA	2.732	0.07
FD, mm	0.46 ± 0.21	0.56 ± 0.18	0.53 ± 0.12	0.52 ± 0.12	0.069	0.89
CTQ total score	55.33 ± 12.58	29.70 ± 4.54	43.60 ± 8.25	31.26 ± 4.23	85.943	< 0.001
Abuse total score	25.10 ± 9.06	16.50 ± 2.13	20.07 ± 4.78	16.85 ± 2.00	22.493	< 0.001
Neglect total score	30.23 ± 6.47	13.20 ± 3.67	23.52 ± 6.11	14.41 ± 3.17	99.317	< 0.001
Emotional abuse score	11.02 ± 4.99	5.73 ± 1.46	7.81 ± 3.17	6.13 ± 1.47	23.490	< 0.001
Physical abuse score	8.06 ± 4.50	5.57 ± 1.16	6.60 ± 2.14	5.41 ± 0.78	9.170	< 0.001
Sexual abuse score	6.02 ± 2.69	5.20 ± 0.41	5.67 ± 1.29	5.30 ± 0.66	2.271	0.04
Emotional neglect score	18.04 ± 3.98	7.43 ± 2.92	13.51 ± 4.82	8.22 ± 2.43	72.382	< 0.001
Physical neglect score	12.19 ± 3.49	5.77 ± 1.04	10.02 ± 2.78	6.20 ± 1.24	65.192	< 0.001

CTQ = Childhood Trauma Questionnaire, FD = framewise displacement, HAMA = Hamilton Anxiety Scale, HAMD = Hamilton Depression Scale, NA = not applicable, SD = standard deviation.
*Unless indicated otherwise.

scores, and each of the subscales of emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect ($p < 0.05$).

Static functional connectivity

We did not observe significant differences in the static functional connectivity of the globus pallidus subregions.

Dynamic functional connectivity

Using 2-way ANOVA, we detected significant group differences of abnormal dynamic functional connectivity in subregions of the globus pallidus. We identified the different effects attributed to the abnormal dynamic functional connectivity in pallidum subregions (i.e., the etiological effect of depression, the traumatic effect of childhood trauma, or interaction effect of depression plus childhood trauma). We then applied multiple comparisons with Benjamini–Hochberg correction (Table 2 and Figure 2).

Anterior globus pallidus

As shown in Table 2, significant group differences in dynamic functional connectivity were exhibited between the right anterior globus pallidus and right precuneus (traumatic effect), the right anterior globus pallidus and right superior frontal gyrus (interaction effect), the left anterior globus pallidus and right middle frontal gyrus (interaction effect), the left anterior globus pallidus and right postcentral gyrus (interaction effect), and the left anterior globus pallidus and right precentral gyrus (interaction effect).

As shown in Figure 2, we observed higher dynamic functional connectivity between the right anterior globus pallidus and right precuneus among control participants with childhood trauma compared with those without childhood trauma. We detected lower dynamic functional connectivity between the right anterior globus pallidus and right superior frontal gyrus among patients with MDD and childhood trauma relative to controls with childhood trauma, but higher dynamic functional connectivity between these areas among controls with childhood trauma relative to controls without childhood trauma. We observed higher dynamic functional connectivity between the left anterior globus pallidus and right middle frontal gyrus among patients with MDD and childhood trauma than among patients with MDD without childhood trauma, but lower dynamic functional connectivity between these areas among patients with MDD without childhood trauma than among controls without childhood trauma. We observed higher dynamic functional connectivity between the left anterior globus pallidus and right postcentral gyrus among patients with MDD without childhood trauma relative to controls without childhood trauma, and among controls with childhood trauma relative to controls without childhood trauma. We observed lower dynamic functional connectivity between the left anterior globus pallidus and right precentral gyrus among patients with MDD and childhood trauma relative to those without childhood trauma, and higher dynamic functional connectivity between these areas among patients with MDD without childhood trauma than among controls without childhood trauma.

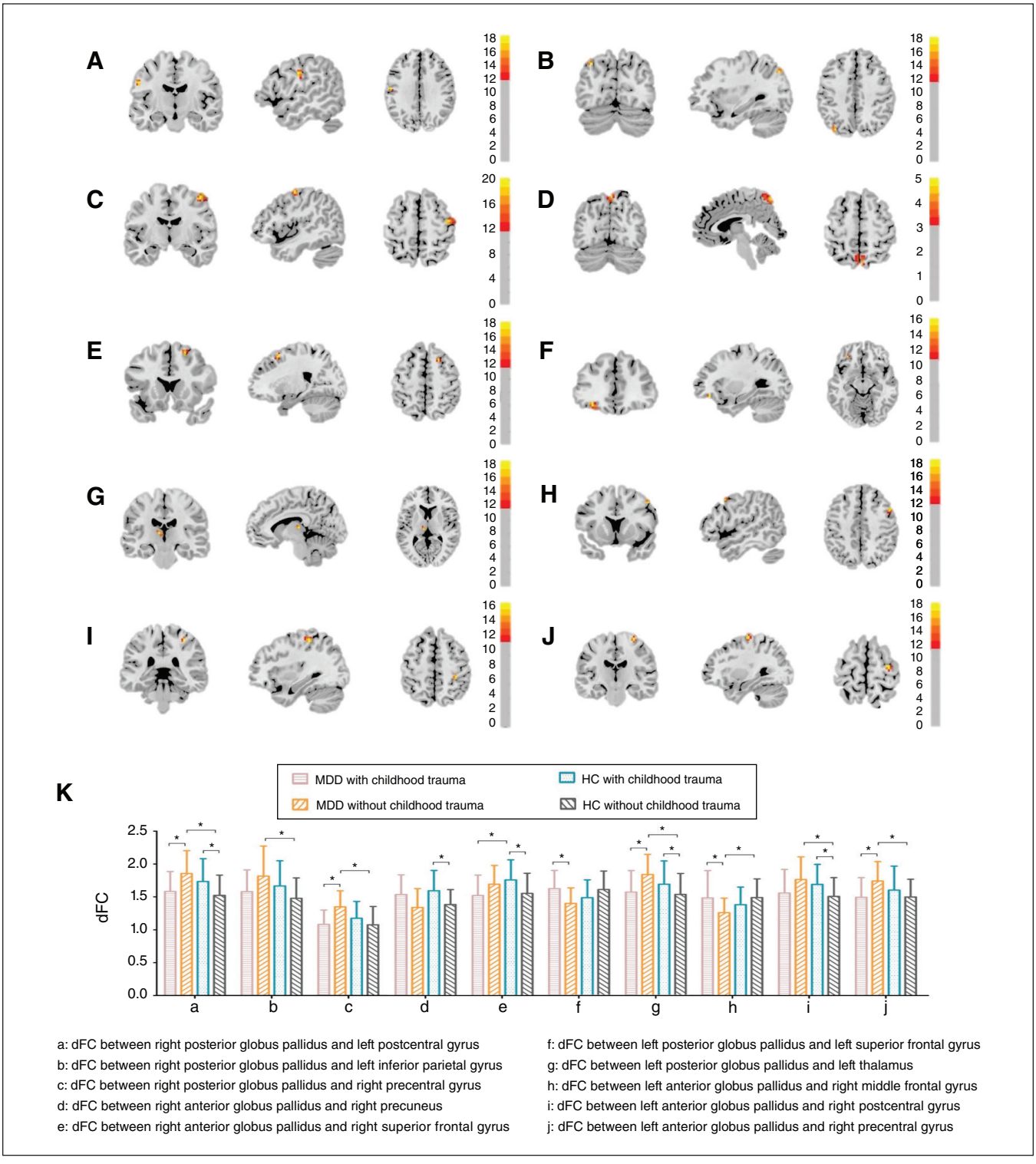
Posterior globus pallidus

As shown in Table 2, we found significant group differences in dynamic functional connectivity between the right posterior globus pallidus and left postcentral gyrus (interaction effect); the right posterior globus pallidus and left inferior parietal but supramarginal and angular gyri (interaction effect); the right posterior globus pallidus and right precentral gyrus (interaction effect); the left posterior globus pallidus and left superior frontal gyrus, medial orbital (interaction effect); and the left posterior globus pallidus and left thalamus (interaction effect).

As shown in Figure 2, we observed lower dynamic functional connectivity between the right posterior globus pallidus and left postcentral gyrus among patients with MDD and childhood trauma than among those with MDD without childhood trauma. We detected higher dynamic functional connectivity between these areas among patients MDD without childhood trauma relative to controls without childhood trauma, and among controls with childhood trauma compared with those without childhood trauma. We found higher dynamic functional connectivity between the right posterior globus pallidus and left inferior parietal

Table 2: Two-way analysis of variance of seed-based dynamic functional connectivity in the globus pallidus

Seed	Effect	Brain region	Cluster size	X	Y	Z	*F*
Right posterior globus pallidus	Interaction effect	Left postcentral gyrus	13	–54	–12	33	18.194
		Left inferior parietal lobe	12	–33	–75	42	18.428
		Right precentral gyrus	32	45	–9	57	20.350
Right anterior globus pallidus	Traumatic effect	Right precuneus	115	3	–72	57	5.208
	Interaction effect	Right superior frontal gyrus	16	21	18	54	18.894
Left posterior globus pallidus	Interaction effect	Left superior frontal gyrus, medial orbital	10	–30	39	–12	17.617
		Left thalamus	11	–9	–21	9	18.971
Left anterior globus pallidus	Interaction effect	Right middle frontal gyrus	19	51	12	45	18.181
		Right postcentral gyrus	21	33	–33	54	17.238
		Right precentral gyrus	16	30	–18	66	18.722



a: dFC between right posterior globus pallidus and left postcentral gyrus
b: dFC between right posterior globus pallidus and left inferior parietal gyrus
c: dFC between right posterior globus pallidus and right precentral gyrus
d: dFC between right anterior globus pallidus and right precuneus
e: dFC between right anterior globus pallidus and right superior frontal gyrus
f: dFC between left posterior globus pallidus and left superior frontal gyrus
g: dFC between left posterior globus pallidus and left thalamus
h: dFC between left anterior globus pallidus and right middle frontal gyrus
i: dFC between left anterior globus pallidus and right postcentral gyrus
j: dFC between left anterior globus pallidus and right precentral gyrus

Figure 2: Significant differences in dynamic functional connectivity (dFC) among patients with major depressive disorder (MDD) and childhood trauma, patients with MDD without childhood trauma, healthy controls (HC) with childhood trauma, and HC without childhood trauma, including between (A) the right posterior globus pallidus and left postcentral gyrus, (B) the right posterior globus pallidus and left inferior parietal gyrus, (C) the right posterior globus pallidus and right precentral gyrus, (D) the right anterior globus pallidus and right precuneus, (E) the right anterior globus pallidus and right superior frontal gyrus, (F) the left posterior globus pallidus and left superior frontal gyrus, (G) the left posterior globus pallidus and left thalamus, (H) the left anterior globus pallidus and right middle frontal gyrus, (I) the left anterior globus pallidus and right postcentral gyrus, and (J) the left anterior globus pallidus and right precentral gyrus. (K) Results of multiple comparisons of dFC. See Related Content tab for accessible version.

lobe among patients with MDD without childhood trauma than among controls without childhood trauma. We observed lower dynamic functional connectivity between the right posterior globus pallidus and right precentral gyrus among patients with MDD and childhood trauma compared with patients with MDD without childhood trauma, and higher dynamic functional connectivity between these areas among patients with MDD without childhood trauma than among controls without childhood trauma. We found higher dynamic functional connectivity between the left posterior globus pallidus and left superior frontal gyrus (medial orbital) among patients with MDD and childhood trauma than among patients without childhood trauma. We observed lower dynamic functional connectivity between the left posterior globus pallidus and left thalamus among patients with MDD and childhood trauma relative to patients without childhood trauma, and higher dynamic functional connectivity between these areas among patients with MDD without childhood trauma compared with controls without childhood trauma, and among controls with childhood trauma than among those without childhood trauma.

Table 3: Correlation analyses of Childhood Trauma Questionnaire (CTQ) scores and the variability in dynamic functional connectivity among patients with major depressive disorder

			r					
Seed	Effect	Brain region	Emotional abuse	Physical abuse	Sexual abuse	Emotional neglect	Physical neglect	CTQ total score
Right anterior globus pallidus	Traumatic effect	Right precuneus	0.155*	0.093	0.034	0.185*	0.234†	0.213†
	Interaction effect	Right superior frontal gyrus	–0.056	–0.024	–0.063	–0.176*	–0.02	–0.11

*Adjusted $p < 0.05$.
†Adjusted $p < 0.001$.

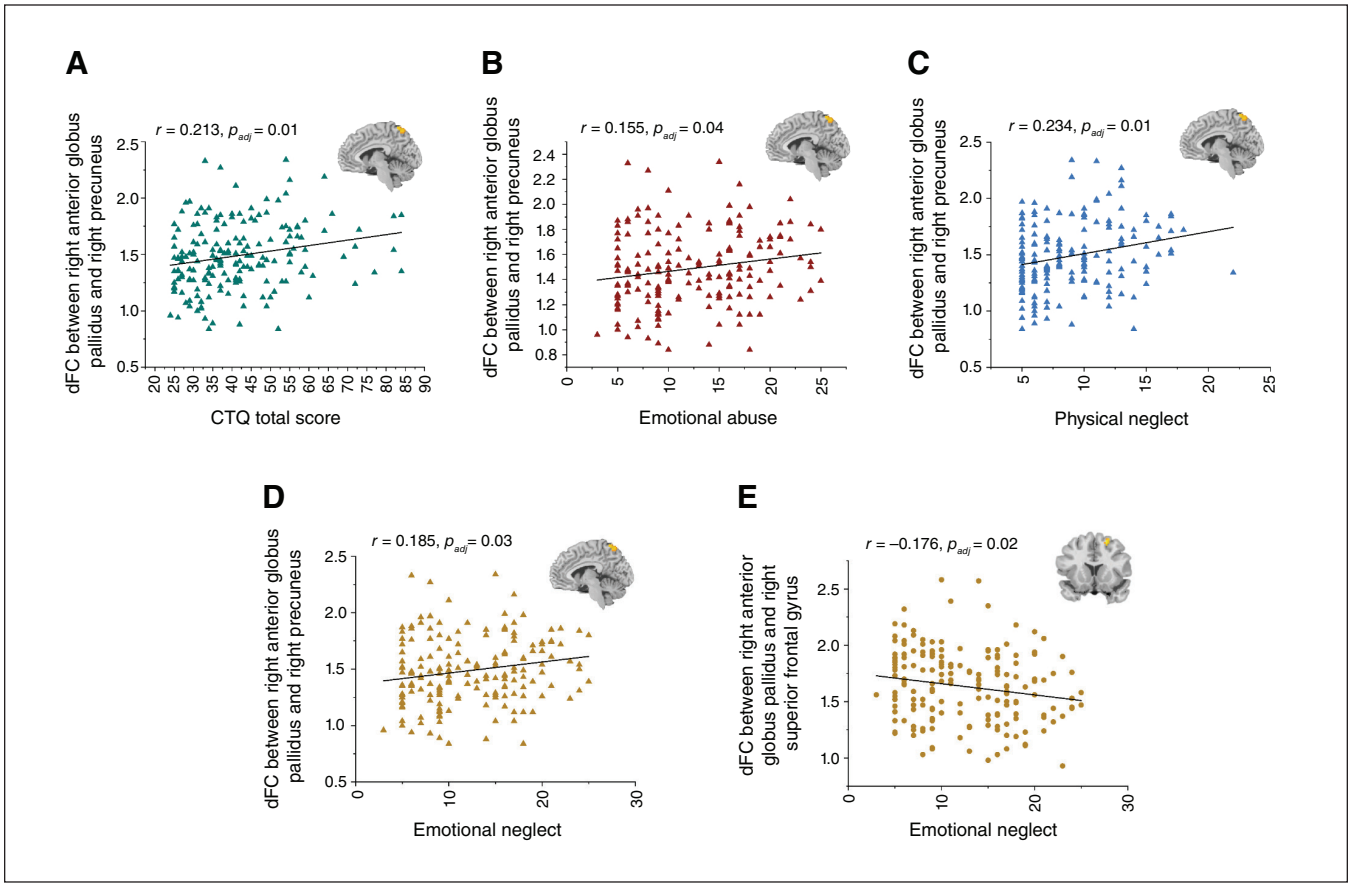


Figure 3: Correlation analyses of childhood trauma and the variability in dynamic functional connectivity (dFC), depicting the positive correlations between the dFC of the right anterior globus pallidus and right precuneus with the (A) Childhood Trauma Questionnaire (CTQ) total score, (B) emotional abuse score, (C) physical neglect score, and (D) emotional neglect (score), as well as (E) the negative correlation between the dFC of the right anterior globus pallidus and the right superior frontal gyrus with the emotional neglect score. adj = adjusted.

Correlation analysis

As shown in Table 3 and Figure 3, partial correlation analysis with Benjamini–Hochberg correction showed that dynamic functional connectivity between the right anterior globus pallidus and right precuneus was positively correlated with emotional abuse (r = 0.155, p_{adj} = 0.04), emotional neglect (r = 0.185, p_{adj} = 0.03), physical neglect (r = 0.234, p_{adj} = 0.01), and CTQ total scores (r = 0.213, p_{adj} = 0.01). In addition, dynamic functional connectivity between the right anterior globus pallidus and right superior frontal gyrus was negatively correlated with emotional neglect scores (r = –0.176, p_{adj} = 0.02).

Moderation analysis

We conducted moderation analyses to explore whether abnormal dynamic functional connectivity influenced the relationship between childhood trauma and depression severity. In the multiple linear regression model, abnormal dynamic functional connectivity was considered as the moderator variable, childhood trauma (including CTQ scores, neglect total scores, abuse total scores, and emotional abuse, physical abuse, sexual abuse, physical neglect, and emotional neglect scores) was considered as the independent variable, and depression severity (HAMD scores) was considered as the dependent variable. In the moderation analysis, we used data only from patients with MDD. Figure 4 depicts the outcomes of the moderating effect for the high, medium, and low dynamic functional connectivity groups. Table 4 details the results of the multilevel models of MDD severity by childhood trauma. We found that the dynamic functional connectivity between the right anterior globus pallidus and right superior frontal gyrus, as well as between the left anterior globus pallidus and right precentral gyrus, both played a moderating role in the relationship between childhood trauma and the severity of MDD.

To further explore the interaction effect of childhood trauma and abnormalities in dynamic functional connectivity on MDD severity, we performed multiple linear regressions in each of the 3 subgroups of dynamic functional connectivity. In multilevel models, MDD severity was the dependent variable and childhood trauma was the independent variable, with sex, age, and education as covariates. In a model with dynamic functional connectivity between the right anterior globus pallidus and the right superior frontal gyrus as the moderating variable, the

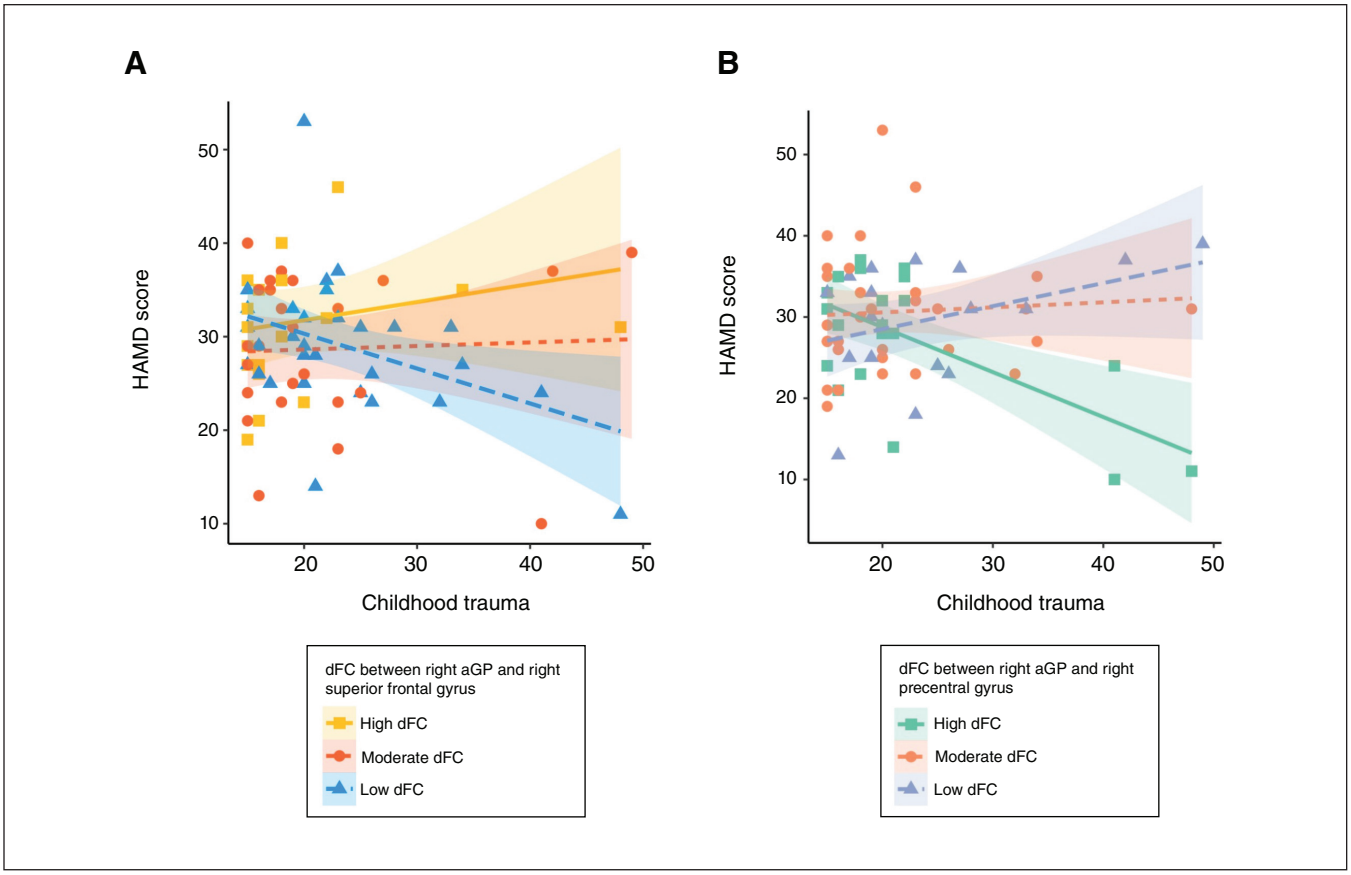


Figure 4: Abnormal dynamic functional connectivity (dFC) as a moderator of the relationship between childhood abuse (independent variable) and depression severity (dependent variable), at 3 levels of the moderating variable (high: above mean dFC + 0.5 standard deviation [SD], medium: mean dFC – 0.5 SD to mean dFC + 0.5 SD, low: below mean – 0.5 SD) for (A) dFC between the right anterior globus pallidus (aGP) and the right superior frontal gyrus and (B) dFC between the left aGP and right precentral gyrus. Full model results are presented in Table 5.

Table 4: Variability in dynamic functional connectivity (dFC) as a moderator in the relationship between childhood trauma and the severity of depression

Model	Variable	Estimate	SE	*t*	*p* value	η^2p	Power
Model A	Intercept	29.573	5.250	5.633	< 0.001	0.002	0.064
	Childhood trauma	–0.052	0.102	–0.510	0.6	0.010	0.133
	dFC between right anterior globus pallidus and right superior frontal gyrus	0.937	2.746	0.341	0.7	0.009	0.132
	Interaction of childhood trauma × dFC between right anterior globus pallidus and right superior frontal gyrus	0.754	0.358	2.106	0.04	0.057	0.547
Model B	Intercept	30.488	4.893	6.231	< 0.001	0.003	0.074
	Childhood trauma	–0.086	0.097	–0.890	0.4	0.017	0.196
	dFC between left anterior globus pallidus and right precentral gyrus	0.394	2.560	0.154	0.9	0.006	0.101
	Interaction of childhood trauma × dFC between left anterior globus pallidus and right precentral gyrus	–1.165	0.345	–3.381	0.001	0.134	0.916

SE = standard error.

group with low dynamic functional connectivity included patients with dynamic functional connectivity below 1.435, the moderate group included patients with dynamic functional connectivity between 1.435 and 1.747, and the group with high dynamic functional connectivity included patients with dynamic functional connectivity greater than 1.747. As shown in Model A of Table 5, childhood trauma was significantly associated with MDD severity only in the group with low dynamic functional connectivity, which showed that severity of childhood trauma was negatively associated with MDD severity.

Model B used the dynamic functional connectivity between the left anterior globus pallidus and right precentral gyrus as the moderating variable (low: dynamic functional connectivity < 1.429; moderate: dynamic functional connectivity 1.429–1.749; high: dynamic functional connectivity > 1.749). Childhood trauma was significantly positively associated with the severity of MDD in the high dynamic functional connectivity group only.

Results from univariate ANOVAs are provided in Appendix 1, Table S4 and Table S5.

Validation analysis

We conducted supplementary analyses that employed different sliding window lengths (70 TR and 30 TR) to validate the robustness of our findings. Most results were consistent with our main analyses. This congruence serves to emphasize the reliability and stability of our findings. Compared with patients with MDD without childhood trauma, those with both MDD and childhood trauma had lower dynamic functional connectivity between the right posterior globus pallidus and right precentral gyrus with window lengths of 30 TR, 50 TR, and 70 TR, and between the left posterior globus pallidus and left thalamus with window lengths of 50 TR and 70 TR. Conversely, there was higher dynamic functional connectivity between the left anterior globus pallidus and right middle frontal gyrus among patients with MDD and childhood trauma than among those without childhood trauma with window lengths of 30 TR and 50 TR. We observed lower dynamic functional connectivity between the left anterior globus pallidus and right precentral gyrus among patients with MDD and childhood trauma than among those without childhood trauma with window lengths of 30 TR and 50 TR. Detailed results with window lengths of 30 TR and 70 TR are provided in Appendix 1.

Discussion

We employed analyses involving static and dynamic functional connectivity, using subregions of the globus pallidus as the seeds, to investigate abnormal functional connectivity patterns between patients with MDD with or without childhood trauma and healthy controls with or without childhood trauma. This study provides insights into the relationship between MDD, childhood trauma, and dysfunction in specific globus pallidus subregions, shedding light on the neurobiological basis of MDD susceptibility. Among patients with MDD and childhood trauma, dynamic functional connectivity decreased between the posterior globus pallidus and several brain regions, including the postcentral gyrus, precentral gyrus, and thalamus. Conversely, dynamic functional connectivity increased between the anterior globus pallidus and the middle frontal gyrus (medial orbital). Furthermore, among controls with childhood trauma, dynamic functional connectivity increased between the anterior globus pallidus and the precuneus, superior frontal gyrus, and postcentral gyrus. Similarly, dynamic functional connectivity increased between the posterior globus pallidus and the postcentral gyrus and thalamus. Moreover, abnormal dynamic functional connectivity between the anterior globus pallidus and several brain regions (such as the precuneus and the superior frontal gyrus) was significantly associated with childhood trauma. Abnormal dynamic functional connectivity between the anterior globus pallidus and the superior frontal gyrus, and between the anterior globus pallidus and the precentral gyrus, moderated the relationship between childhood abuse and the severity of depression. This further elucidates the intricate relationship between childhood trauma, dysfunction in subregions of the globus pallidus, and MDD.

Table 5: Multilevel models of severity of major depressive disorder by childhood abuse by degree of abnormal dynamic functional connectivity (dFC)

Model	Variable	No. of patients	Estimate	SE	*t*	*p* value	η^2p	Power
Model A	Model 1: dFC variability < 1.435	32						
	Intercept		29.594	10.047	2.945	0.007	< 0.001	0.050
	Age		–0.032	0.218	–0.145	0.9	< 0.001	0.050
	Sex		3.985	2.575	1.548	0.1	0.111	0.310
	Education		0.132	0.384	0.343	0.7	< 0.001	0.050
	Childhood trauma		–0.327	0.156	–2.101	0.04	0.139	0.384
	Model 2: dFC variability 1.435–1.747	27						
	Intercept		36.923	9.400	3.928	0.001	0.001	0.051
	Age		–0.159	0.238	–0.666	0.5	0.021	0.100
	Sex		–3.181	3.399	–0.936	0.4	0.010	0.075
	Education		–0.101	0.543	–0.186	0.8	0.013	0.080
	Childhood trauma		0.110	0.197	0.557	0.6	< 0.001	0.050
	Model 3: dFC variability > 1.747	19						
	Intercept		27.409	13.298	2.061	0.06	< 0.001	0.050
	Age		–0.176	0.204	–0.862	0.4	0.005	0.058
	Sex		–5.022	3.492	–1.438	0.2	0.086	0.210
	Education		0.649	0.622	1.043	0.3	0.008	0.064
	Childhood trauma		0.423	0.272	1.557	0.1	0.048	0.136
Model B	Model 1: dFC variability < 1.429	20						
	Intercept		16.810	12.492	1.346	0.2	0.006	0.060
	Age		–0.031	0.284	–0.108	0.9	0.003	0.055
	Sex		2.385	3.418	0.698	0.5	< 0.001	0.050
	Education		0.270	0.437	0.618	0.5	0.051	0.140
	Childhood trauma		0.251	0.182	1.377	0.2	0.080	0.200
	Model 2: dFC variability 1.429–1.749	36						
	Intercept		30.716	8.782	3.498	< 0.001	0.005	0.063
	Age		–0.038	0.180	–0.214	0.8	0.001	0.052
	Sex		–2.960	2.739	–1.081	0.3	< 0.001	0.050
	Education		0.239	0.436	0.548	0.6	0.018	0.101
	Childhood trauma		0.111	0.188	0.589	0.6	0.170	0.275
	Model 3: dFC variability > 1.749	22						
	Intercept		37.628	10.403	3.617	0.002	0.001	0.052
	Age		0.142	0.203	0.700	0.5	0.096	0.22
	Sex		–0.064	2.910	–0.022	1.0	< 0.001	0.05
	Education		–0.092	0.523	–0.176	0.9	0.002	0.053
	Childhood trauma		–0.589	0.169	–3.477	0.003	0.336	0.730

SE = standard error.

Altered dynamic functional connectivity with the anterior globus pallidus

We observed alterations in the functional connectivity of the anterior globus pallidus with several brain regions, including the precuneus, superior frontal gyrus, middle frontal gyrus, postcentral gyrus, and precentral gyrus. The anterior globus pallidus is considered to play a crucial role in motivation (i.e., reward-seeking and aversive avoidance) and cognitive processing (i.e., goal decisions and action selection).[23,53,54] The anterior part of the precuneus is a central hub of the default mode network and is believed to facilitate theory of mind and self-referential thinking.[55,56] On the other hand, the posterior default mode network, which includes the superior frontal gyrus and the posterior cingulate cortex, is associated with episodic memory and visual–spatial imagery processing.[55,57] We speculate that abnormal dynamic functional connectivity in these areas is linked to motivation deficits, reduced reward processing, and aberrant episodic memory processing among patients with MDD and childhood trauma. In alignment with our speculation, Tozzi and colleagues[58] illustrated that high severity of childhood trauma, represented by concurrent childhood neglect and abuse, was strongly associated with reduced thickness in the precuneus, and that patients with MDD had lower activation of the right precuneus compared with

controls, impairing the procession of episodic memory. Zhang and colleagues[55] also found that increased spontaneous neural activity in the right precuneus in subclinical depression may cause cognition and sensory dysfunction. Our findings confirm the important role of the anterior globus pallidus–precuneus in MDD with childhood trauma.

Previous research has shown that childhood trauma exerts profound influences on motivation and reward systems.[5,34,59] This effect manifests in several distinct ways. People with childhood trauma often have anhedonia, with difficulty in deriving satisfaction from pleasurable experiences, which is highly associated with dysfunction in the brain's reward circuitry.[60] Fan and colleagues[34] reported that physical, social, and anticipatory (but not consummatory) anhedonia of the reward system could be persistently affected by childhood traumatic experiences. Childhood trauma frequently hampers motivation, making it challenging to establish goals, pursue happiness, and actively seek rewards.[59] Finally, people with childhood trauma may resort to self-punishing behaviours — such as substance abuse, self-harm, or other self-destructive actions — as a means of coping with their traumatic past.[5] Paradoxically, these behaviours can be interpreted as a form of reward as they serve to alleviate emotional distress. Our findings support the idea that childhood trauma can have profound effects on motivation and reward systems.

We observed abnormal functional connectivity between the anterior globus pallidus and the precentral gyrus and postcentral gyrus. This could be related to the motor and emotional regulatory functions, as well as the sensory and emotional regulatory functions, of these brain regions.[61–63] The precentral gyrus is primarily associated with muscle movement and motor execution.[61] Although not directly related to emotional regulation, it has been shown that physical activity and sports can have a positive impact on emotional states.[64,65] Physical activity promotes the release of neurotransmitters in the brain, such as dopamine and endorphins, which are associated with emotional regulation.[66] Therefore, the precentral gyrus may be indirectly involved in emotional regulation through exercise and physical activities. In addition, patients with somatic symptom disorder involving demonstrated pain symptoms have shown abnormal regional homogeneity in the left precentral gyrus, indicating the role of the precentral gyrus in the perception of pain, similar to symptoms of unexplained physical pain among people with depression.[62] The postcentral gyrus is part of the somatosensory cortex and is mainly related to the reception and processing of sensory information. Emotional regulation often involves interpretation and response to sensory information from both the self and the external environment.[63] Consistent with our findings, the rs-fMRI study conducted by Liu and colleagues[67] revealed that abnormalities in brain regions associated with somatic symptoms (precentral gyrus and paracentral gyrus) were also significantly associated with depressive symptoms. Furthermore, depressive symptoms may influence somatic symptoms, just as depression may influence or amplify somatic sensations associated with depression.[67] Therefore, the postcentral gyrus may play a role in emotional perception and emotional regulation by interpreting and replying to specific sensory information.

Altered dynamic functional connectivity with the posterior globus pallidus

We detected alterations in dynamic functional connectivity between the posterior globus pallidus and several brain regions, including the superior frontal gyrus, thalamus, postcentral gyrus, and inferior parietal lobe. The posterior globus pallidus is primarily involved in regulating motor functions (i.e., action preparation and execution),[53] especially precise grasping movements.[23,68] The superior frontal gyrus plays a crucial role in emotion regulation, cognitive control, and decision-making.[69,70] The abnormal dynamic functional connectivity between the posterior globus pallidus and the superior frontal gyrus may lead to decreased cognitive flexibility, making it challenging for patients to adapt to changes and adversities in life. In their study of people with subclinical depression, Zhang and colleagues[55] found that increased spontaneous neural activity in both the left middle frontal gyrus (especially in the inferior frontal junction) and the left superior frontal gyrus may serve as neuroimaging markers for the diagnosis of depressive disorder. Moreover, the close association of the superior frontal gyrus with emotion regulation suggests that its dysfunction may contribute to emotional instability, increased negative emotions, and decreased positive emotions leading by negative bias, which are typical symptoms of depression. Noll-Hussong and colleagues[71] found that higher activation of the lateral and medial superior frontal gyrus among patients with childhood experiences of sexual abuse may reflect an increased negativity bias.

The thalamus serves as a pivotal relay station for sensory information by receiving signals from sensory organs and transmitting them to other parts of the brain.[72] Patients with MDD and childhood trauma exhibit altered responses to sensory information, including overinterpretation of emotional cues or heightened sensory sensitivity.[73] This phenomenon may be linked to the role of the thalamus in sensory processing. Furthermore, the thalamus is closely associated with emotional processing and the regulation of emotional processing across psychiatric disorders, as confirmed by a meta-analysis.[74] Emotional disturbances — such as emotional dysregulation, depression, and anxiety — are serious concerns among people with childhood trauma–related depression, and the thalamus may play a vital role in the neural circuitry of emotional regulation.[74,75] In addition, dysfunction and structural disruptions in the thalamus can lead to an amnestic syndrome; impairments in recall and recognition may explain the phenomenon of memory loss among people with MDD.[76]

The inferior parietal lobe is involved in the perception and processing of self-identity and body image.[74] Patients with MDD and childhood trauma often report distorted perceptions of their self-image, as shown in a study from northeast India, which showed a strong association between body image and depression and anxiety among college students, which may be related to the dysfunction of the inferior parietal lobe.[77] People with childhood trauma–related depression may exhibit an attention bias toward negative emotional information in their cognitive processes; a dysfunctional inferior parietal lobe may contribute to this attention bias, increasing sensitivity to negative stimuli.[58,71] Skokauskas and colleagues[78] suggested

that, with the contrast judgment of emotion minus judgment of geometry following emotional negative stimuli, participants with MDD and sexual abuse showed significantly higher activation in the area of the left inferior parietal lobe, further unveiling how the dysfunction between the posterior globus pallidus and the inferior parietal lobe impaired cognitive processing, as well as the predisposition to a negative bias.

The postcentral gyrus is a part of the somatosensory cortex primarily associated with touch, pain, and proprioception (perception of body position).[62,63] Patients with MDD may show heightened sensory perception, particularly in terms of perceiving pain or discomfort, which may be related to dysfunction in the posterior postcentral gyrus.[62] Furthermore, those exposed to traumatic experiences in childhood may occasionally report alterations in their state of consciousness, including feeling sluggish, experiencing difficulty concentrating, a sense of detachment from reality, or depersonalization.[79] Dysfunction in the postcentral gyrus could influence these consciousness-related issues. Our findings highlight the role of abnormal functional connectivity in the posterior globus pallidus in the emotional and cognitive dysregulation of patients with MDD and childhood trauma.

The relationship between dynamic functional connectivity abnormalities and childhood trauma

We found a positive correlation between childhood trauma and dynamic functional connectivity with the anterior globus pallidus as the region of interest. Childhood trauma often leads to difficulties in emotional regulation and heightened stress responses.[80] The anterior portion of the globus pallidus plays a critical role in motivation processing involving reward-seeking and aversive avoidance, as well as cognitive processing, including goal decision-making and action selection.[23,53,54] Hence, functional abnormalities may result in reduced reward-seeking, more frequent avoidance behaviours, and tougher goal decision-making and action selection. The dynamic functional connectivity of the anterior globus pallidus modulated the relationship between childhood abuse and the severity of depression. This provides new evidence for the long-term effect of childhood trauma on the development of MDD via impairment of the reward system.[2,4]

Limitations

As the CTQ is a self-reported and retrospective questionnaire, the assessment of childhood trauma is susceptible to individual subjectivity and recall bias. Given the cross-sectional nature of the study, causal relationships between variables are challenging to infer. Future research should consider factors beyond sex, age, and education — such as family composition, household income, and social support — in understanding the effect of childhood trauma on depression outcomes. Future research could also investigate the effects of specific subtypes of childhood trauma on abnormal functional connectivity in MDD or other depressive subtypes. Compared with the large sample size of previous studies,[81,82] the limited sample size in our study undermines its statistical validity, necessitating a more extensive sample to either confirm or refute the present findings. Previous studies have indicated the basal ganglia play a crucial role in producing psychomotor symptoms.[83,84] We did not examine psychomotor abnormalities and will address this aspect in the future.

Conclusion

We explored the relationship between childhood trauma, MDD, and dysfunctional reward circuitry centred on subregions of the globus pallidus. Our findings support childhood trauma as a risk factor for MDD. Patients with MDD and childhood trauma exhibit pronounced abnormalities in the reward circuitry. These abnormalities involve various brain regions, including the postcentral gyrus, precentral gyrus, inferior parietal lobe, precuneus, superior frontal gyrus, thalamus, and middle frontal gyrus. Our findings offer new insights into identifying neurobiological markers for patients with MDD and childhood trauma.

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References

1. Lloyd A, Mckay RT, Furl N. Individuals with adverse childhood experiences explore less and underweight reward feedback. *Proc Natl Acad Sci U S A* 2022;119:e2109373119.
2. McKay MT, Cannon M, Chambers D, et al. Childhood trauma and adult mental disorder: a systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatr Scand* 2021;143:189-205.
3. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl* 2003;27:169-90.
4. LeMoult J, Humphreys KL, Tracy A, et al. Meta-analysis: exposure to early life stress and risk for depression in childhood and adolescence. *J Am Acad Child Adolesc Psychiatry* 2020;59:842-55.
5. Biscond M, Revranche M, Navarro-Mateu F, et al. The effect of childhood adversities on the persistence of suicidal ideation and plans among college students: a longitudinal study. *J Affect Disord* 2023;323:354-60.

6. Potsch L, Rief W. Transdiagnostic considerations of the relationship between reward sensitivity and psychopathological symptoms - a cross-lagged panel analysis. *BMC Psychiatry* 2023;23:650.
7. Gao F, Fan J, Xia J, et al. Decreased sensitivity to risk levels in ventral stratum in major depressive disorder during risky decision-making. *J Affect Disord* 2021;282:187-93.
8. Ng TH, Alloy LB, Smith DV. Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. *Transl Psychiatry* 2019;9:293.
9. Hanson JL, Hariri AR, Williamson DE. Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. *Biol Psychiatry* 2015;78:598-605.
10. Cléry-Melin ML, Jollant F, Gorwood P. Reward systems and cognitions in Major Depressive Disorder. *CNS Spectr* 2019;24:64-77.
11. Ahn SJ, Kyeong S, Suh SH, et al. What is the impact of child abuse on gray matter abnormalities in individuals with major depressive disorder: a case control study. *BMC Psychiatry* 2016;16:397.
12. Antoniou G, Lambourg E, Steele JD, et al. The effect of adverse childhood experiences on chronic pain and major depression in adulthood: a systematic review and meta-analysis. *Br J Anaesth* 2023;130:729-46.
13. Petrican R, Fornito A. Adolescent neurodevelopment and psychopathology: the interplay between adversity exposure and genetic risk for accelerated brain ageing. *Dev Cogn Neurosci* 2023;60:101229.
14. Li G, Cao C, Fang R, et al. Neural correlates of posttraumatic anhedonia symptoms: decreased functional connectivity between ventral pallidum and default mode network regions. *J Psychiatr Res* 2021;140:30-4.
15. McRae K, Misra S, Prasad AK, et al. Bottom-up and top-down emotion generation: implications for emotion regulation. *Soc Cogn Affect Neurosci* 2012;7:253-62.
16. Lacerda ALT, Nicoletti MA, Brambilla P, et al. Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatry Res* 2003;124:129-40.
17. Ottenheimer D, Richard JM, Janak PH. Ventral pallidum encodes relative reward value earlier and more robustly than nucleus accumbens. *Nat Commun* 2018;9:4350.
18. Stephenson-Jones M, Bravo-Rivera C, Ahrens S, et al. Opposing contributions of GABAergic and glutamatergic ventral pallidal neurons to motivational behaviors. *Neuron* 2020;105:921-933.e5.
19. Griffiths KR, Lagopoulos J, Hermens DF, et al. Right external globus pallidus changes are associated with altered causal awareness in youth with depression. *Transl Psychiatry* 2015;5:e653.
20. Aristieta A, Gittis A. Distinct globus pallidus circuits regulate motor and cognitive functions. *Trends Neurosci* 2021;44:597-9.
21. Courtney CD, Pamukcu A, Chan CS. Cell and circuit complexity of the external globus pallidus. *Nat Neurosci* 2023;26:1147-59.
22. Tian Y, Margulies DS, Breakspear M, et al. Topographic organization of the human subcortex unveiled with functional connectivity gradients. *Nat Neurosci* 2020;23:1421-32.
23. Prodoehl J, Corcos DM, Vaillancourt DE. Basal ganglia mechanisms underlying precision grip force control. *Neurosci Biobehav Rev* 2009;33:900-8.
24. Biswal B, Yetkin FZ, Haughton VM, et al. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995;34:537-41.
25. van den Heuvel MP, Hulshoff PH. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol* 2010;20:519-34.
26. Allen EA, Damaraju E, Plis SM, et al. Tracking whole-brain connectivity dynamics in the resting state. *Cereb Cortex* 2014;24:663-76.
27. Calhoun VD, Miller R, Pearlson G, et al. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron* 2014;84:262-74.
28. Hutchison RM, Womelsdorf T, Allen EA, et al. Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage* 2013;80:360-78.
29. Sato Y, Okada G, Yokoyama S, et al. Resting-state functional connectivity disruption between the left and right pallidum as a biomarker for subthreshold depression. *Sci Rep* 2023;13:6349.
30. Shunkai L, Su T, Zhong S, et al. Abnormal dynamic functional connectivity of hippocampal subregions associated with working memory impairment in melancholic depression. *Psychol Med* 2023;53:2923-35.
31. Luo Q, Chen J, Li Y, et al. Aberrant static and dynamic functional connectivity of amygdala subregions in patients with major depressive disorder and childhood maltreatment. *Neuroimage Clin* 2022;36:103270.
32. Fan J, Gao F, Wang X, et al. Right amygdala-right precuneus connectivity is associated with childhood trauma in major depression patients and healthy controls. *Soc Cogn Affect Neurosci* 2023;18:nsac064.
33. Jones JS, Goldstein SJ, Wang J, et al. Evaluation of brain structure and metabolism in currently depressed adults with a history of childhood trauma. *Transl Psychiatry* 2022;12:392.
34. Fan J, Liu W, Xia J, et al. Childhood trauma is associated with elevated anhedonia and altered core reward circuitry in major depression patients and controls. *Hum Brain Mapp* 2021;42:286-97.
35. McAlonan GM, Robbins TW, Everitt BJ. Effects of medial dorsal thalamic and ventral pallidal lesions on the acquisition of a conditioned place preference: further evidence for the involvement of the ventral striatopallidal system in reward-related processes. *Neuroscience* 1993;52:605-20.
36. Smith KS, Tindell AJ, Aldridge JW, et al. Ventral pallidum roles in reward and motivation. *Behav Brain Res* 2009;196:155-67.
37. Guyer AE, Kaufman J, Hodgdon HB, et al. Behavioral alterations in reward system function: the role of childhood maltreatment and psychopathology. *J Am Acad Child Adolesc Psychiatry* 2006;45:1059-67.
38. Nagy SA, Kürtös Z, Németh N, et al. Childhood maltreatment results in altered deactivation of reward processing circuits in depressed patients: a functional magnetic resonance imaging study of a facial emotion recognition task. *Neurobiol Stress* 2021;15:100399.
39. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord* 2013;150:384-8.
40. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
41. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50-5.
42. Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry* 1994;151:1132-6.
43. Bernstein DP, Ahluvalia T, Pogge D, et al. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. *J Am Acad Child Adolesc Psychiatry* 1997;36:340-8.
44. Aloba O, Opakunle T, Ogunrinu O. Childhood Trauma Questionnaire-Short Form (CTQ-SF): Dimensionality, validity, reliability and gender invariance among Nigerian adolescents. *Child Abuse Negl* 2020;101:104357.
45. Kongerslev MT, Bach B, Rossi G, et al. Psychometric validation of the Childhood Trauma Questionnaire-Short Form (CTQ-SF) in a Danish clinical sample. *Child Abuse Negl* 2019;94:104026.
46. Yan CG, Wang XD, Zuo XN, et al. DPABI: Data processing & analysis for (resting-state) brain imaging. *Neuroinformatics* 2016;14:339-51.
47. Jenkinson M, Bannister P, Brady M, et al. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 2002;17:825-41.
48. Yang GJ, Murray JD, Repovs G, et al. Altered global brain signal in schizophrenia. *Proc Natl Acad Sci U S A* 2014;111:7438-43.
49. Stoodley CJ, D'Mello AM, Ellegood J, et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. *Nat Neurosci* 2017;20:1744-51.
50. Cole MW, Ito T, Bassett DS, et al. Activity flow over resting-state networks shapes cognitive task activations. *Nat Neurosci* 2016;19:1718-26.
51. Cui G, Wang Y, Wang X, et al. Static and dynamic functional connectivity of the prefrontal cortex during resting-state predicts self-serving bias in depression. *Behav Brain Res* 2020;379:112335.
52. Aiken LS, West SG, editors. *Multiple regression: testing and interpreting interactions*. New York (NY): Sage Publications Inc.; 1991.
53. Saga Y, Hoshi E, Tremblay L. Roles of multiple globus pallidus territories of monkeys and humans in motivation, cognition and action: an anatomical, physiological and pathophysiological review. *Front Neuroanat* 2017;11:30.
54. Pessiglione M, Schmidt L, Draganski B, et al. How the brain translates money into force: a neuroimaging study of subliminal motivation. *Science* 2007;316:904-6.

55. Zhang B, Qi S, Liu S, et al. Altered spontaneous neural activity in the precuneus, middle and superior frontal gyri, and hippocampus in college students with subclinical depression. *BMC Psychiatry* 2021;21:280.
56. Utevsky AV, Smith DV, Huettel SA. Precuneus is a functional core of the default-mode network. *J Neurosci* 2014;34:932-40.
57. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 2006;129:564-83.
58. Tozzi L, Garczarek L, Janowitz D, et al. Interactive impact of childhood maltreatment, depression, and age on cortical brain structure: mega-analytic findings from a large multi-site cohort. *Psychol Med* 2020;50:1020-31.
59. DelDonno SR, Mickey BJ, Pruitt PJ, et al. Influence of childhood adversity, approach motivation traits, and depression on individual differences in brain activation during reward anticipation. *Biol Psychol* 2019;146:107709.
60. Stringaris A, Vidal-Ribas BP, Artiges E, et al. the brain's response to reward anticipation and depression in adolescence: dimensionality, specificity, and longitudinal predictions in a community-based sample. *Am J Psychiatry* 2015;172:1215-23.
61. Zhao K, Liu H, Yan R, et al. Cortical thickness and subcortical structure volume abnormalities in patients with major depression with and without anxious symptoms. *Brain Behav* 2017;7:e00754.
62. Yoshino A, Okamoto Y, Kunisato Y, et al. Distinctive spontaneous regional neural activity in patients with somatoform pain disorder: a preliminary resting-state fMRI study. *Psychiatry Res* 2014;221:246-8.
63. Nelson AJ, Chen R. Digit somatotopy within cortical areas of the postcentral gyrus in humans. *Cereb Cortex* 2008;18:2341-51.
64. Gorham LS, Jernigan T, Hudziak J, et al. Involvement in sports, hippocampal volume, and depressive symptoms in children. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2019;4:484-92.
65. Jackson M, Kang M, Furness J, et al. Aquatic exercise and mental health: a scoping review. *Complement Ther Med* 2022;66:102820.
66. Kandola A, Ashdown-Franks G, Hendrikse J, et al. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. *Neurosci Biobehav Rev* 2019;107:525-39.
67. Liu P, Tu H, Zhang A, et al. Brain functional alterations in MDD patients with somatic symptoms: A resting-state fMRI study. *J Affect Disord* 2021;295:788-96.
68. Boecker H, Dagher A, Ceballos-Baumann AO, et al. Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with H2 15O PET. *J Neurophysiol* 1998;79:1070-80.
69. Niendam TA, Laird AR, Ray KL, et al. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn Affect Behav Neurosci* 2012;12:241-68.
70. Frank DW, Dewitt M, Hudgens-Haney M, et al. Emotion regulation: quantitative meta-analysis of functional activation and deactivation. *Neurosci Biobehav Rev* 2014;45:202-11.
71. Noll-Hussong M, Otti A, Laeer L, et al. Aftermath of sexual abuse history on adult patients suffering from chronic functional pain syndromes: an fMRI pilot study. *J Psychosom Res* 2010;68:483-7.
72. Taber KH, Wen C, Khan A, et al. The limbic thalamus. *J Neuropsychiatry Clin Neurosci* 2004;16:127-32.
73. Kropf E, Syan SK, Minuzzi L, et al. From anatomy to function: the role of the somatosensory cortex in emotional regulation. *Braz J Psychiatry* 2019;41:261-9.
74. McTeague LM, Rosenberg BM, Lopez JW, et al. Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *Am J Psychiatry* 2020;177:411-21.
75. Pozzi E, Vijayakumar N, Rakesh D, et al. Neural correlates of emotion regulation in adolescents and emerging adults: a meta-analytic study. *Biol Psychiatry* 2021;89:194-204.
76. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 2002; 53:647-54.
77. Diengdoh I, Ali A. Body image and its association with depression, anxiety, and self-esteem among college going students: a study from Northeast India. *Indian J Community Med* 2022;47:218-22.
78. Skokauskas N, Carballedo A, Fagan A, et al. The role of sexual abuse on functional neuroimaging markers associated with major depressive disorder. *World J Biol Psychiatry* 2015;16:513-20.
79. Laoide AO, Egan J, Osborn K, et al. What was once essential, may become detrimental: the mediating role of depersonalization in the relationship between childhood emotional maltreatment and psychological distress in adults. *J Trauma Dissociation* 2018;19:514-34.
80. Loveday S, Hall T, Constable L, et al. Screening for adverse childhood experiences in children: a systematic review. *Pediatrics* 2022;149:e2021051884.
81. Marek S, Tervo-Clemmens B, Calabro FJ, et al. Reproducible brain-wide association studies require thousands of individuals. *Nature* 2022;603:654-60.
82. Goltermann J, Winter NR, Meinert S, et al. Resting-state functional connectivity patterns associated with childhood maltreatment in a large bicentric cohort of adults with and without major depression. *Psychol Med* 2023;53:4720-31.
83. Scalabrini A, Vai B, Poletti S, et al. All roads lead to the default-mode network-global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology* 2020;45:2058-69.
84. Northoff G, Hirjak D, Wolf RC, et al. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. *Mol Psychiatry* 2021;26:92-102.