Psychological Medicine

cambridge.org/psm

Frequency-dependent alterations of global signal topography in patients with major depressive disorder

Chengxiao Yang[1], Bharat Biswal[2], Qian Cui[3], Xiujuan Jing[1], Yujia Ao[4] and Yifeng Wang[1]

[1]Institute of Brain and Psychological Sciences, Sichuan Normal University, Chengdu 610066, China; [2]The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 611731, China; [3]School of Public Affairs and Administration, University of Electronic Science and Technology of China, Chengdu 611731, China and [4]Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Original Article

Cite this article: Yang C, Biswal B, Cui Q, Jing X, Ao Y, Wang Y (2024). Frequency-dependent alterations of global signal topography in patients with major depressive disorder. *Psychological Medicine* **54**, 2152–2161. https://doi.org/10.1017/S0033291724000254

Received: 7 April 2023
Revised: 29 September 2023
Accepted: 22 January 2024
First published online: 16 February 2024

Keywords:
frequency-dependence; global signal; global topography; major depressive disorder; resting-state fMRI

Corresponding author:
Yifeng Wang;
Email: wyf@sicnu.edu.cn

Abstract

Background. Major depressive disorder (MDD) is associated not only with disorders in multiple brain networks but also with frequency-specific brain activities. The abnormality of spatiotemporal networks in patients with MDD remains largely unclear.

Methods. We investigated the alterations of the global spatiotemporal network in MDD patients using a large-sample multicenter resting-state functional magnetic resonance imaging dataset. The spatiotemporal characteristics were measured by the variability of global signal (GS) and its correlation with local signals (GSCORR) at multiple frequency bands. The association between these indicators and clinical scores was further assessed.

Results. The GS fluctuations were reduced in patients with MDD across the full frequency range (0–0.1852 Hz). The GSCORR was also reduced in the MDD group, especially in the relatively higher frequency range (0.0728–0.1852 Hz). Interestingly, these indicators showed positive correlations with depressive scores in the MDD group and relative negative correlations in the control group.

Conclusion. The GS and its spatiotemporal effects on local signals were weakened in patients with MDD, which may impair inter-regional synchronization and related functions. Patients with severe depression may use the compensatory mechanism to make up for the functional impairments.

Introduction

Major depressive disorder (MDD) is one of the most prevalent mental disorders in the world and is characterized by negative mood, cognitive dysfunction, and decreased interest (Collaborators, 2022). Given its adverse effects on individuals and society, a great deal of research is anticipated to develop effective intervention programs by providing insight into its brain mechanisms. Current research, usually using the functional magnetic resonance imaging (fMRI) technique, suggests that MDD is likely to be associated with the alteration of large-scale networks rather than specific brain regions (Hamilton, Farmer, Fogelman, & Gotlib, 2015; Stern, 2022; Thiebaut de Schotten & Forkel, 2022). Contrary to the spatial dimension, the time scale or frequency is a major determinant of brain functions, which is usually impaired in mental disorders including MDD (Buzsáki, 2006; He et al., 2016; Qiao, Wang, & Wang, 2022b). Converging evidence suggests that MDD is a brain-wide spatiotemporal disorder (Guo et al., 2013; Sheng et al., 2018; Wang et al., 2016).

The global signal (GS) of fMRI time series is the grand average of signals across all gray matter voxels, reflecting the overall state of brain activity (Ao, Ouyang, Yang, & Wang, 2021). Researchers have long debated whether to regress out GS in fMRI studies due to its extensive influence on the functional connectivity (FC) among all brain networks (Murphy & Fox, 2017) and its particular significance for physiological and pathological states (Scalabrini et al., 2020). The regression of GS usually induces negative FCs by modulating the phase of local signals (Anderson et al., 2011; Gutierrez-Barragan, Basson, Panzeri, & Gozzi, 2019; Zhang et al., 2019). The GS facilitates the synchronization of functional systems not solely through signal interactions, but also by fluctuated arousal (Orban, Kong, Li, Chee, & Yeo, 2020; Raut et al., 2021) or glucose metabolism (Thompson et al., 2016). Therefore, the examination of GS and its correlation (GSCORR) with local signals presents a promising avenue for reconciling the disparate findings in various networks that are affected by MDD. Additionally, this investigation may uncover novel mechanisms or biomarkers that can aid in the treatment of MDD.

Altered GS and GSCORR have been found in multiple mental disorders, such as schizophrenia (SCZ) (Wang et al., 2021; Yang et al., 2017; Yang et al., 2014), bipolar disorder (BD) (Zhang et al., 2019), and MDD (Han *et al.* 2019; Scalabrini *et al.* 2020; Zhu *et al.* 2018). The SCZ patients often exhibit increased GS variability and GSCORR, whereas the BD patients have increased and decreased GSCORRs in different regions and mental states. For MDD patients, an increased, decreased, and unchanged GS and GSCORR in different regions or states have also been reported. These findings suggest that GS and GSCORR may serve as disease-specific biomarkers. However, their alterations in MDD have not reached a consensus.

In terms of the temporal dimension, the GS has a unique temporal structure that evolves throughout the lifespan (Ao et al., 2022). The interaction between GS and local signals is also constrained by time scales (Wang et al., 2023). The temporal characteristics of GS and its interaction with local signals have been frequently observed to be disturbed by mental disorders. For instance, altered GSCORR has been found in adolescent-onset schizophrenia patients in slow-5 (0.01–0.027 Hz) but not slow-4 (0.027–0.073 Hz) (Wang et al., 2021). For MDD, decreased static and increased dynamic GSCORR were reported (Han et al., 2019). Frequency-dependent alterations in FC as well as local activity have also been demonstrated in various diseases (Ries et al., 2019; Yang et al., 2022; Yang et al., 2021; Zhang et al., 2015). Frequency-dependent abnormalities in MDD tend to appear in slow-4 and slow-5 (Li, Qiu, Hu, & Luo, 2022; Wang et al., 2016; Xue, Wang, Wang, Liu, & Qiu, 2016). These findings indicate that patients with MDD may exhibit a reduced GSCORR at particular frequencies.

In the current study, we investigated the altered frequency characteristics of GS variability and GSCORR in patients with MDD. To mitigate the effects of sampling and system biases, a multicenter resting-state fMRI dataset was utilized, resulting in a larger sample size and more generalizable results. Based on previous studies (Ries et al., 2019; Wang et al., 2016), we hypothesized that patients with MDD would exhibit a frequency-dependent reduction of GS variability and GSCORR.

Materials and methods

Participants

All subjects in this study were obtained from the Strategic Research Program for Brain Sciences (SRPBS) (Tanaka, 2020), which included 255 MDD patients and 524 healthy controls (HCs) from six sites (Tanaka et al., 2021). The severity of depression was assessed according to the Beck Depression Inventory, Second Edition (BDI-II). The written informed consent was obtained from each participant.

Imaging acquisition and preprocessing

All resting-state fMRI data were collected on 3.0-T MRI scanners, but from six locations, including Hiroshima University Hospital (HUH), Hiroshima Rehabilitation Center (HRC), Hiroshima Kajikawa Hospital (HKH), Center of Innovation at Hiroshima University (COI), Kyoto University TimTrio (KUT), and University of Tokyo Hospital (UTO). The participants were instructed to look at the fixation point, relax, stay awake, but not think about anything in particular, and not move their bodies. The details of scanner parameters for the six centers are shown in Table 1.

Resting-state fMRI image processing was performed using the DPARSF toolbox (http://www.restfmri.net) (Yan & Zang, 2010). Preprocessing steps consisted of removing the first ten time points, slice-timing, realignment, coregistration, normalization to the Montreal Neurological Institute (MNI) space, spatial smoothing with an isotropic Gaussian kernel of 6 mm full-width at half-maximum, and nuisance regression. The linear trend, white matter, cerebrospinal fluid, and 24 rigid body motion parameters were regressed out in the last step. Subjects whose head

Table 1. Imaging protocols for resting-state fMRI

Site	HUH	HRC	HKH	COI	KUT	UTO
MRI scanner	GE Signa HDxt	GE Signa HDxt	Siemens Spectra	Siemens Verio. Dot	Siemens TimTrio	GE MR750w
No. of channels per coil	8	8	12	12	32	24
FoV (mm)	256	256	192	212	212	212
Matrix	64 × 64	64 × 64	64 × 64	64 × 64	64 × 64	64 × 64
No. of slices	32	32	38	40	40	40
No. of volumes	143	143	107	240	240	240
In-plane resolution (mm)	4.0 × 4.0	4.0 × 4.0	3.0 × 3.0	3.3 × 3.3	3.3125 × 3.3125	3.3 × 3.3
Slice thickness (mm)	4	4	3	3.2	3.2	3.2
Slice gap (mm)	0	0	0	0.8	0.8	0.8
TR (ms)	2000	2000	2700	2500	2500	2500
TE (ms)	27	27	31	30	30	30
Total scan time	4:46	4:46	4:49	10:00	10:00	10:00
Flip angle (deg)	90	90	80	80	80	80

Abbreviations: FoV, field of view; TR, repetition time; TE, echo time; HUH, Hiroshima University Hospital; HRC, Hiroshima Rehabilitation Center; HKH, Hiroshima Kajikawa Hospital; COI, Center of Innovation at Hiroshima University; KUT, Kyoto University TimTrio; UTO, University of Tokyo Hospital. Data link: https://doi.org/10.7303/syn22317081.

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

motion of rotation >2.0° or translation >2.0 mm were excluded. The mean frame-wise displacement (FD) of each subject was further calculated to screen out participants whose mean FD was outside the range of the overall group mean plus three standard deviations (S.D.) (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Participants without BDI-II scores were also not included in the analysis. To minimize potential bias in clinical diagnoses resulting from differences in centers, we excluded HC with BDI-II scores exceeding 16 and MDD subjects with scores below 16. Finally, Given the acknowledged correlation between depression and gender, we meticulously screened the HC individuals to ensure that the gender ratio closely resembled that of the MDD group. There remained 171 MDD patients and 165 HCs, whose demographic information is shown in Table 2.

For structural scans, we segmented the whole brain into gray matter (GM), white matter, and cerebrospinal fluid maps using the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) of SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Then we normalized the GM images to MNI space (voxel size $1.5 \times 1.5 \times 1.5$ mm^3) and smoothed them using a Gaussian kernel (4 mm full width at half maximum). The total gray matter volume (GMV) was obtained by summing the normalized, smoothed GM maps and used for subsequent analysis.

GS_{sd} and GS_{power}

The GS of each subject at each time point was the mean signal of all gray matter voxels constrained by the binary Human Brainnetome Atlas (Fan et al., 2016; Wang et al., 2023). We measured the GS variability in the entire frequency range with two indices: GS_{sd} and GS_{power}. The GS_{sd} was the time standard deviation value of the GS series, and the power spectrum of GS (GS_{power}) was obtained by transforming the GS time series into frequency domain using the Welch method with a Hamming window (window length = 16 TR, overlap = 50%) (Baria, Baliki, Parrish, & Apkarian, 2011). Since the TR varies from site to site, we opted to limit the frequency range from 0.0012 to 0.1852 Hz based on the sampling theory, which ensures consistency in the bandwidth across sites (Proakis & Manolakis, 1988).

We regressed out age, gender, and site to control for demographic and environmental factors, as well as the total GMV to eliminate the effect of anatomical difference. The normalized residuals were used for subsequent statistical analysis. Two-sample *t* tests were performed to detect whether there were any group differences in GS_{sd} and GS_{power}.

Table 2. Demographic and clinical variables

Subjects	MDD (n = 171) Mean (S.D.)	Normal controls (n = 165) Mean (S.D.)	p value
Gender	44.44% female	45.45% female	0.85a
Hand	97.66% right-handed	95.76% right-handed	0.33a
Age	43.08 (12.05)	42.14 (13.34)	0.50b
BDI-II	29.95 (8.27)	5.50 (4.19)	< 0.001b

[a]Chi-squared test.
[b]Two-sample *t* test.
Abbreviations: MDD, major depressive disorder; HC, healthy control; BDI-II, Beck Depression Inventory- II.

GSCORR

Aiming to alleviate any potential limitations of the slow5–slow2 filtering method based on electrophysiological signals for fMRI signals (Buzsaki & Draguhn, 2004), we applied the k-means clustering analysis to classify frequency bands. The *t*-value of the two-sample *t* test for GS_{power} in each frequency bin was used to distinguish frequency-specific effects of GSCORR. The optimal clustering number was determined as three using the Davies Bouldin evaluation (Tibshirani, Walther, & Hastie, 2001). For each frequency band, we divided the gray matter into 246 regions-of-interest (ROI) using the Human Brainnetome Atlas and obtained the signal of each ROI by averaging all voxel signals in that region. The GSCORR was obtained by calculating the Pearson's correlation between GS and each ROI signal. *R* values were then transformed to z-scores using the Fisher's *Z* transformation (Fisher, 1915; Just, Cherkassky, Keller, Kana, & Minshew, 2007). Normalized residuals of GSCORR after regressing out age, gender, site, and total GMV were used for subsequent statistical analysis. At each band, two-sample *t* tests were used to detect differences between the two groups. Furthermore, we have employed commonly used slow 5–slow 3 and 0.01–0.08 Hz filtering methods to complement our findings.

Correlation analysis

If there were significant differences in GS_{sd}, GS_{power}, and GSCORR between MDD patients and HCs, their associations with clinical symptoms (BDI-II scores) were further evaluated by Pearson's correlation analysis for each group.

Multiple comparison corrections were performed for both *t* test and correlation analyses ($q < 0.05$, FDR corrected) (Wilks, 2006).

Control analysis

In our data analysis, we considered the influence of age, gender, site, and total GMV, and we included them as covariates in our assessment of GS. To delve further into these variables, we conducted separate analyses exploring their associations with GS. For the MDD and HC groups, we used two-sample *t* tests to examine gender differences in GS_{sd}, GS_{power}, and GSCORR. Additionally, Pearson's correlation coefficients were used to weigh age/total GMV correlations for both groups' GS_{sd}, GS_{power}, and GSCORR. To enhance the robustness of our utilization of multicenter data, we conducted similar analysis steps at each collection site. Subsequently, in order to mitigate the impact of time series duration on GSCORR due to variability in collection times across the multicenters, we performed a separate analysis utilizing data collected from the COI site. The analysis was conducted with two different time lengths: one encompassing all time points from the site (230 in total), and the other using a subset of 110 time points. Finally, in light of the debate surrounding the information contained in the GS (Liu, Nalci, & Falahpour, 2017; Power, Plitt, Laumann, & Martin, 2017), we have taken outcomes derived from the GS regression analyses, which use the same rigorous data analysis process, to supplement our findings. The outcomes of control analysis can be found in the Supplementary Material.

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

Results

Demographics and clinical variables

Table 2 shows the demographic and clinical variable data for all subjects. The two groups exhibit no significant difference in terms of gender ($\chi^2 = 0.03$, $p = 0.85$, df = 334), hand ($\chi^2 = 0.96$, $p = 0.33$, df = 334), and age (t = 0.68, $p = 0.50$, df = 334). Likewise, the disparity in age distribution shows no statistical significance. The BDI-II scores were significantly higher in the MDD group (t = 34.00, $p < 0.0001$, df = 334).

Reduced GS_{sd} in patients with MDD and its correlation with clinical scores

As shown in Fig. 1A, the GS_{sd} was significantly reduced in patients with MDD compared with the HCs ($t = -4.015$, $p < 0.0001$, df = 334). Neither the MDD group ($r = 0.044$, $p = 0.824$) nor the HC group ($r = 0.017$, $p = 0.566$) exhibited a significant correlation between GS_{sd} and BDI-II scores (see Fig. 1B). The findings of the subsamples COI (including 230 time points and 110 time points), HKH, HRC, and HUH were shown in online Supplementary Figures S1 – S5 consistently demonstrated lower GS_{sd} in MDD compared to HC. Additionally, there was no significant correlation found between GS_{sd} and BDI-II scores.

Reduced GS_{power} in patients with MDD and its correlation with clinical scores

The GS_{power} was significantly lower in the MDD group than in the HC group at all frequency points (Fig. 2A). The correlation between GS_{power} and BDI-II scores appeared positive in MDD and negative in HC (see Fig. 2B). Similar patterns were observed in the subsamples, with lower GS_{power} observed in MDD. Furthermore, the MDD showed a positive correlation between GS_{power} and BDI-II scores, whereas the HC group showed a negative trend (online Supplementary Figures S6 – S10).

Frequency-dependent alteration of GSCORR in patients with MDD and its correlation with clinical scores

Based on the outcomes of the clustering process, we segregated the preprocessed image data into three distinct frequency bands: low frequency (LF: 0.0012–0.0728 Hz), medium frequency (MF: 0.0728–0.1383 Hz), and high frequency (HF: 0.1383–0.1852 Hz). The GSCORR was comparable between the two groups at the LF, but it was significantly reduced in almost the entire brain in the MDD group at MF band. Additionally, it was reduced in the default mode network (DMN: including the medial frontal cortex, medial temporal lobe, parahippocampal gyrus, lateral temporal lobe, and parietal lobe), salience network (SN: including the dorsal anterior cingulate cortex, anterior insula, amygdala, and thalamus), and sensorimotor network (SMN: including the precentral gyrus, postcentral gyrus, superior occipital gyrus, posterior inferior temporal gyrus, posterior insula, and superior temporal gyrus) at the HF (see Fig. 3A).

At the LF, there was no significant correlation between GSCORR and BDI-II score. However, at MF and HF bands, the correlations between GSCORR and clinical score were mainly observed in specific brain regions such as the middle frontal gyrus, inferior temporal gyrus, and occipital lobe. This observation, as depicted in Fig. 3B and Table 3, suggests that the brain-symptom association is expressed in different functional systems in patients and HCs. The results of subsamples COI, HKH, HRC and HUH are shown in online Supplementary Figures S11 – S15. The predominant differences in GSCORR were primarily observed at MF band, exhibiting a significant correlation with BDI-II scores in the frontal gyrus and occipital lobe. As a complement to our GS_{power} intergroup difference-based filtering approach, results with traditional frequency division of 0.01–0.08 Hz revealed that the GSCORR was comparable between the two groups and not significantly correlated with the BDI-II scores. However, applying slow5–slow3 filtering revealed a significant reduction in GSCORR in the MDD group at slow 3 band, which was further correlated with BDI-II scores. The MDD group showed a significant positive correlation between GSCORR and scores in the middle frontal gyrus, while the HC group showed a significant negative correlation between GSCORR and scores in the middle occipital gyrus and inferior temporal gyrus. These results were illustrated in online Supplementary Figures S16 and S17. Finally, results of the GS regression as a control analysis provided valuable insights. When controlling for GS, the significant difference in GSCORR between the MDD and HC groups at MF and HF bands were no longer observed. Additionally, GSCORR was not found to be

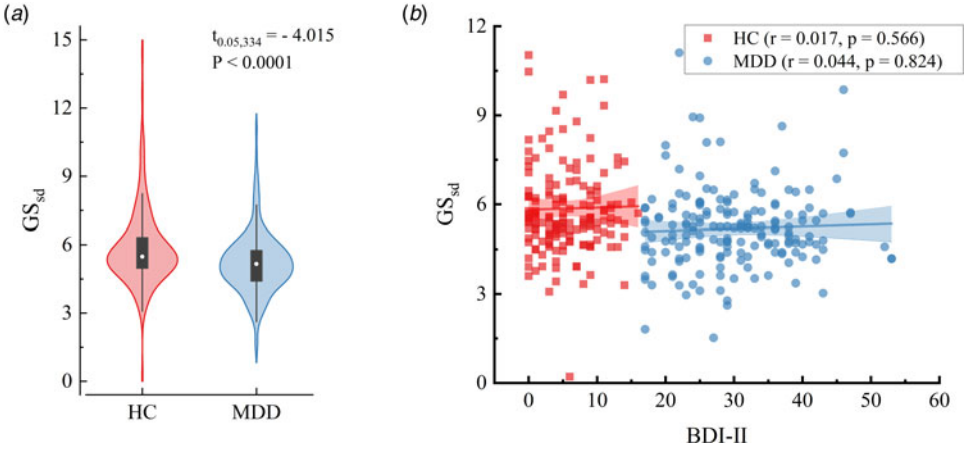

Figure 1. Altered GS_{sd} in patients with MDD. (a). The violin figure shows the distribution of GS_{sd} in HC and MDD groups, respectively. (b). The Pearson correlation between GS_{sd} and BDI-II scores.

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

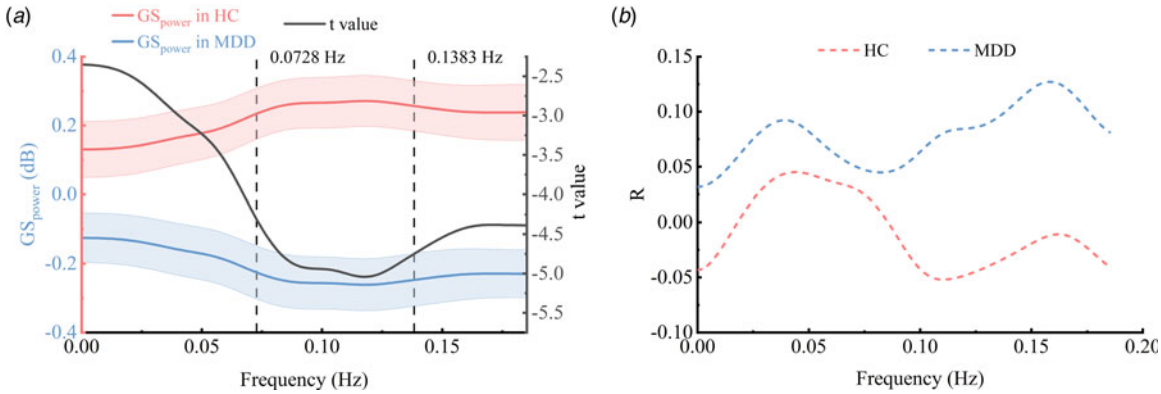

Figure 2. Altered GS_{power} in patients with MDD. (a). The GS_{power} was reduced in patients with MDD at the full frequency range. FDR correction, $q < 0.05$. Red and blue shadows represent standard errors. (b). The Pearson's correlation between GS_{power} and BDI-II scores in the two groups.

significantly correlated with BDI-II scores (online Supplementary Figure 18).

Relationships between GS and gender, age, and total GMV

For the gender effect, there was no significant difference ($p > 0.05$, FDR) in GS_{sd}, GS_{power}, and GSCORR between males and females in either the MDD or the HC group (also see online Supplementary Figure S19). Regarding the age effect, GS_{sd} and GS_{power} were negatively correlated with age in both the MDD and HC groups. Furthermore, we observed distinct patterns of significant correlation between GSCORR and age in the two groups, as seen in online Supplementary Figure S20. Lastly, our analysis of the relationship between total GMV and GS revealed that GS_{sd} and GSCORR did not have a significant correlation with total GMV in either group. By contrast, GS_{power} in the MDD group showed a significant positive correlation with GMV, as shown in online Supplementary Figure S21.

Discussion

Using a multicenter resting-state fMRI dataset, we explored the altered variability of GS and GSCORR in MDD patients. These

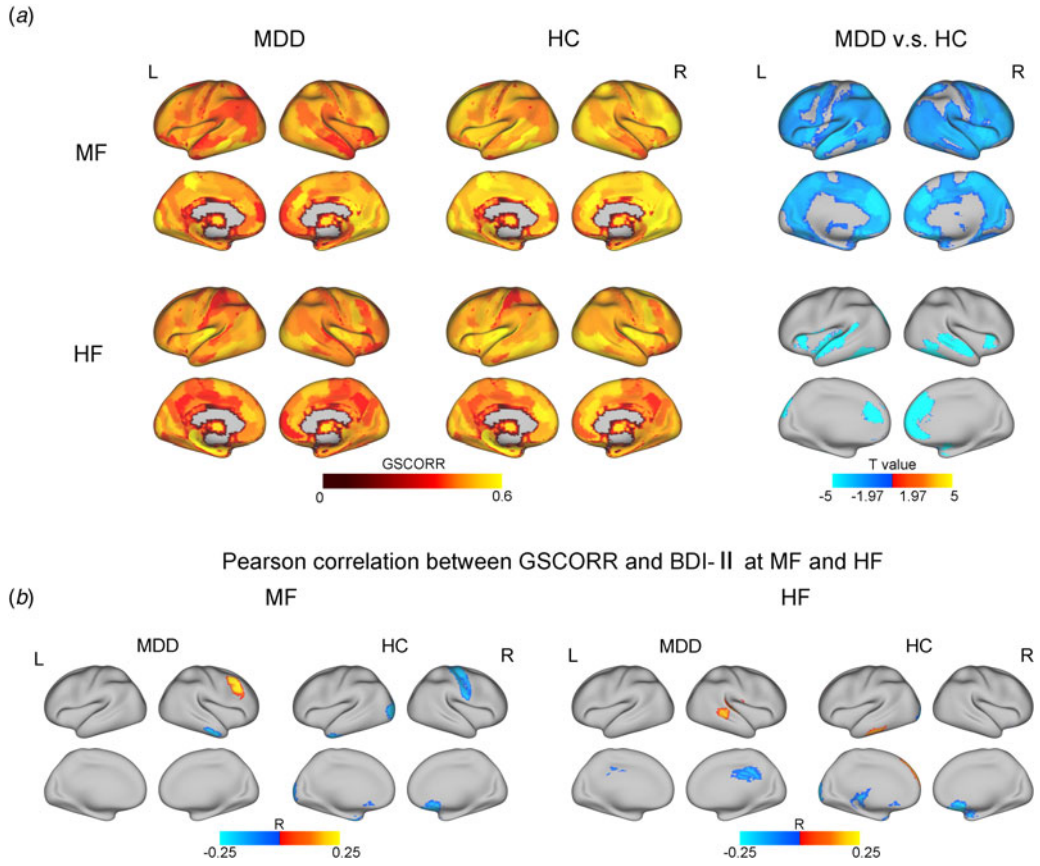

Figure 3. Frequency-dependent alteration of GSCORR in patients with MDD. (a). Reduced GSCORR in MDD patients at MF and HF bands, respectively. (b). The Pearson's correlation between GSCORR and BDI-II scores in the MDD and HC groups at MF and HF band, respectively. MF, medium frequency; HF, high frequency.

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

Table 3. Brain areas showing significant correlations between GSCORR and clinical scores

Frequency	Subjects	Areas	MNI (x,y,z)	*R*	*p*
MF	MDD				
		Middle frontal gyrus (MFG.R)	42, 11, 39	0.2127	0.0052
		Inferior temporal gyrus (ITG.R)	55, −11, −32	−0.1945	0.0108
	HC				
		Precental gyrus (PreCG.R)	34, −19, 59	−0.1835	0.0183
		Gyrus rectus (REC.R)	9, 20, −19	−0.1715	0.0277
		Parahippocampal gyrus (PHG.L)	−23, 2, −32	−0.1667	0.0323
		Middle occipital gyrus (MOG.L)	−18, −99, 2	−0.1794	0.0211
		Postcentral gyrus (PoCG.R)	50, −14, 44	−0.1359	0.0313
		Inferior temporal gyrus (ITG.L)	−43, −2, −41	−0.1642	0.0351
HF	MDD				
		Posterior cingulate gyrus (PCG.R)	4, −37, 32	0.1840	0.0160
		Superior temporal gyrus (STG.R)	54, −24, 11	0.1677	0.0283
		Middle temporal gyrus (MTG.R)	53, −37, 3	−0.1576	0.0395
	HC				
		Superior frontal gyrus, dorsolateral (SFGdor.L)	11, 49, 40	0.1677	0.0313
		Gyrus rectus (REC.R)	9, 20, −19	−0.2268	0.0034
		Parahippocampal gyrus (PHG.L)	−23, 2, −32	0.1609	0.0390
		Amygdala (AMYG.R)	28, −3, −20	−0.1829	0.0187
		Middle occipital gyrus (MOG.L)	−18, −99, 2	−0.2181	0.0049
		Thalamus (THA.L)	−15, −28, 4	−0.1621	0.0375
		Inferior temporal gyrus (ITG.L)	−55, −31, −27	−0.1751	0.0245

indicators were systematically reduced in MDD patients, especially at the medium frequency. As the brain signal variability (BSV) is indicative of the amount of kinetic energy that the brain can utilize to shift between various potential states (Garrett, McIntosh, & Grady, 2014; Wang et al., 2020), and the GSCORR reflects a global reconciliation for multiple functional systems (Zhang and Northoff, 2022), the reduced variability of GS and its interaction with local signals may indicate an impairment in the coordination among various functional systems in patients with MDD. Fortunately, the patients may invoke the association cortex to cope with the increase in depression, as shown by a positive correlation between GS indicators and depressive scores, primarily in the association cortex. In addition, we investigated a subset of data gathered from singular site and discovered that the outcomes from these centers paralleled the combined outcomes from multicenter effectively, validating the trustworthiness of utilizing data from multi-site. Moreover, the findings were consistent between the complete (230 time points) and the reduced (110 time points) subsets of data acquired from the COI site, indicating that the scanning duration minimally impacts GS. In addition to validating our findings through classical filtering methods and GS regression, we observed that gender, age, and total GMV show significant associations with GS. These variables should be controlled when assessing the clinical implications of GS.

Reduced GS variability in patients with MDD

We employed the GS_{sd} and GS_{power} to measure variabilities in the GS (Tolkunov, Rubin, & Mujica-Parodi, 2010). The BSV has been demonstrated to have a close relationship with brain functions and psychiatric disorders (Garrett et al., 2013; Li et al., 2019; Månsson et al., 2022). The GS variability, as an overall response of BSV, has been demonstrated to be negatively correlated to alertness or arousal (Falahpour, Wong, & Liu, 2016; Wong, Olafsson, Tal, & Liu, 2013; Zhang & Northoff, 2022). It decreases with the intake of caffeine (Wong et al., 2013) and increases during sleep deprivation (Nilsonne et al., 2017). Yang et al., found higher GS variability in patients with SCZ but not in those with BD (Yang et al., 2014). This difference may be due to variations in patients' alertness, which is impaired in patients with SCZ but not in those with BD (Elias et al., 2017; Klein, Shekels, McGuire, & Sponheim, 2020). Since the only confirmed role of GS is its inverse correlation with alertness, we hypothesized that the reduced GS variability in the MDD group may have responded to their abnormally increased arousal (Hegerl & Hensch, 2014; Hegerl, Wilk, Olbrich, Schoenknecht, & Sander, 2012; Schmidt et al., 2016). Evidence from sleep deprivation therapy in MDD patients supports this hypothesis. For instance, it has been found that depression symptoms were alleviated, and GS variability increased in MDD patients by sleep deprivation (Benedetti & Colombo, 2011; Nilsonne et al., 2017; Wolf et al., 2016). These findings seem to suggest that MDD patients have

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

lower GS variability and higher arousal, whereas sleep deprivation resulted in increased GS variability and reduced arousal, alleviating depression.

Reduced GSCORR in patients with MDD

The GSCORR has an inherent structure that is marked by a decline in *r* values from sensorimotor areas to association areas (Zhang, Huang, Tumati, and Northoff, 2020). Such intrinsic structure is thought to reflect the sensorimotor-to-transmodal heterogeneity of neurodevelopmental order, functional connectivity, and gene expression (Huntenburg, Bazin, & Margulies, 2018). As suggested by the dual-layer model (Zhang and Northoff, 2022), the GS regulates arousal while the GSCORR coordinates different forms of cognition. Therefore, the reduced GSCORR in patients with MDD is plausibly linked to abnormalities in cognitive functions.

The GSCORR has been found to be impaired in patients with psychiatric disorders (Han et al., 2019; Yang et al., 2017; Zhang et al., 2019) as well as in epileptic patients (Li et al., 2021), usually associated with particular symptoms or cognitive/emotional functions. In patients with MDD, the reduction of GSCORR in almost the whole brain at the medium frequency and in both sensorimotor areas (e.g. SMN) and association areas (e.g. DMN and SN) at the high frequency suggests the systematic weakening of global-local interaction (Wang et al., 2023). This may indicate that MDD is in an abnormal cognitive/emotional state compared to HCs. This is in line with the global disorder hypothesis, which suggests the over-processing of bottom-up negative information from the sensory system and the failure of top-down negative emotion suppression from the higher-order system in patients with MDD (Xia et al., 2022). Coincidentally, Northoff et al. (Northoff, Wiebking, Feinberg, and Panksepp, 2011) proposed a 'resting-state hypothesis' for MDD, which posits that MDD is a widespread brain disorder that affects various functional brain networks. This hypothesis was supported by the findings that patients with MDD display abnormalities in the DMN, SN, central executive network, affective network, and the limbic system, which involve most areas of the brain (Dichter, Gibbs, & Smoski, 2015; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015; Wang, Hermens, Hickie, & Lagopoulos, 2012). The current results support these findings from the global-local interaction viewpoint. Earlier studies have observed both an increased and a decreased GS presentation in MDD (Han et al., 2019; Keskin, Eker, Gonul, & Northoff, 2023; Scalabrini et al., 2020). Our investigation has yielded partially consistent and partially contradictory results, which may be attributed to the different approaches in signal frequency manipulation. Specifically, the previous study employed classical filtering within the 0.01–0.08 Hz frequency range, whereas we utilized a distinct frequency band (0.0728–0.1383 Hz). This discrepancy in frequency bands may imply that the signal frequencies serve distinct functional roles (Buzsaki & Draguhn, 2004; Knyazev, 2007), which will be further explored in the forthcoming section. Alternatively, the inconsistencies across studies may be attributed to variations in the inclusion of covariates. Prior studies have discovered a correlation between GS and age (Ao et al., 2023; Nomi et al., 2022) and a significantly smaller total GMV in the MDD group (Lai & Wu, 2014; Tae, 2015), which aligns with our findings. Consequently, we conducted the regression analysis with these variables as covariates to ensure the accuracy and reliability of our results.

Frequency-dependent functional alteration in patients with MDD

Does the widespread decline of GSCORR result from the GS? A recent study found that altered intra- and inter-network connections of the DMN in patients with MDD were primarily contributed by the GS, highlighting the coordination of GS on various functional systems (Scalabrini et al., 2020). We have demonstrated in a previous study that the global–local interaction is dominated by the causal impact of the GS on local signals (i.e. functional separation) at higher frequency bands, whereas by the effect of local signals on the GS (e.g. functional integration) at lower frequency bands (Wang et al., 2023). The declined GSCORR in patients with MDD, mainly at higher frequency bands, is thus possibly determined by the reduced GS.

The brain is a complex system that encompasses multi-scale spatiotemporal structures. It seems that different frequencies are associated with different spatial organizations of brain activity (Qiao et al., 2022a), which further support specific cognitive processes (Siegel, Donner, & Engel, 2012). As a result, the frequency-dependent effect may serve as a valuable window for probing the pathological mechanism of mental disorders. Frequency-dependent alterations of brain activity have been extensively documented in MDD (Fingelkurts et al., 2007; He et al., 2016; Ries et al., 2019), as well as in other mental disorders (Newson & Thiagarajan, 2019; Qiao et al., 2022a; Yang et al., 2021), indicating that the pathological alteration of brain activity occurs at particular time scales. However, the association between altered spatiotemporal structures and impaired cognitions are largely unknown.

Here we attempt to explain the frequency-dependent decline of GSCORR within the dual-layer model of GS. First, the reduction of GS fluctuation in patients with MDD is associated with their hyper-alertness (see section 4.1). Second, the declined GSCORR is primarily attributed to the reduction in GS (see above). The decreased GSCORR throughout the brain, therefore, implies the modulation of slow oscillation of arousal on the entire brain (Raut et al., 2021). As heightened alertness is known to cause impaired cognitive control and irritable emotions (Baldi & Bucherelli, 2005; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999; Peifer, Schulz, Schächinger, Baumann, & Antoni, 2014), it is not surprising that patients suffering from MDD experience impairment in multiple cognitive and emotional domains.

Clinical relevance of GS indicators

The results showed that the correlations between GS_{power}/GSCORR and clinical scores were positive in the MDD group, whereas the correlations were mainly negative, although not significant, in the HCs. Because the GS topography is primarily located in sensory-motor areas (Ao et al., 2021), enhanced connectivity in higher control areas (e.g. the DMN, SN) suggests that patients with MDD may invoke executive control functions in response to depressive symptoms. Similarly, Zhu et al. 2018) reported a positive correlation between the variable coefficient of GS and depressive score, while the former can predict the effect of antidepressants in MDD patients. On the contrary, the negative correlation in HCs is mainly located in the sensory and motor areas, suggesting that the bottom-up depression-related information affects normal people, but their GSCORR remains intact. Therefore, we argue that positive correlations between depressive scores and GS_{power}/GSCORR in the current study reflect a compensatory mechanism. That is, patients with more serious

https://doi.org/10.1017/S0033291724000254 Published online by Cambridge University Press

symptoms tend to enhance the GS and its influence on local activities to compensate for impaired brain functions, whereas HCs do not need such a compensatory mechanism (e.g. no correlation).

Limitations

We present here several disadvantages of the current study. First, the dataset used for the analysis does not contain the medication status and disease history, which limits the interpretation of the clinical relevance of GS. Second, respiratory and cardiac noises were not eliminated as they were not involved in the dataset. However, the GS topography may be insensitive to these noises (Yan, Yang, Colcombe, Zuo, and Milham, 2017), which suggests that our results are still reliable. Third, all participants were recruited from Japan, which may reflect an East Asian-specific result and cannot be generalized to other samples. Finally, in the retained sample, the female-to-male ratio of the MDD group differs from that of the control group. Considering that MDD is more prevalent in women (Albert, 2015; Picco, Subramaniam, Abdin, Vaingankar, & Chong, 2017), further investigation is needed to understand the gender effect, which was regressed out in the current study.

Conclusion

Utilizing a multicenter dataset, we unveiled reduced GS fluctuations in MDD, suggesting a potential association with alertness. Furthermore, we noted a frequency-dependent reduction of GSCORR in MDD, which might indicate a weakened effect of GS on local activities through the arousal system in patients with MDD (Wang et al., 2023), impairs the coordination among various functional systems. However, the patients may invoke higher executive control functions to compensate for these deficits, shedding light on the antidepressant treatment. These results strongly indicate that temporal and spatial variations of GS play a pivotal role in interpreting and understanding depression, as outlined in 'Spatiotemporal Psychopathology' (Northoff, 2016; Northoff and Hirjak, 2022).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000254

Author contributions. Chengxiao Yang: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. Bharat Biswal: Methodology, Writing – review & editing. Qian Cui: Writing – review & editing, Funding acquisition. Xiujuan Jing: Writing – review & editing. Yujia Ao: Writing – review & editing, Yingfeng Wang: Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

Funding statement. This work was supported by the National Science Foundation of China (62177035, 82172059).

Competing interests. The authors declare no conflict of interests.

References

Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience*, *40*(4), 219. doi:10.1503/jpn.150205

Anderson, J. S., Druzgal, T. J., Lopez-Larson, M., Jeong, E. K., Desai, K., & Yurgelun-Todd, D. (2011). Network anticorrelations, global regression, and phase-shifted soft tissue correction. *Human Brain Mapping*, *32*(6), 919–934. doi:10.1002/hbm.21079

Ao, Y., Kou, J., Yang, C., Wang, Y., Huang, L., Jing, X., … Chen, J. (2022). The temporal dedifferentiation of global brain signal fluctuations during human brain ageing. *Scientific reports*, *12*(1), 3616. doi:10.1038/s41598-022-07578-6

Ao, Y., Ouyang, Y., Yang, C., & Wang, Y. (2021). Global signal topography of the human brain: A novel framework of functional connectivity for psychological and pathological investigations. *Frontiers in Human Neuroscience*, *15*, 644892. doi:10.3389/fnhum.2021.644892

Ao, Y., Yang, C., Drewes, J., Jiang, M., Huang, L., Jing, X., … Wang, Y. (2023). Spatiotemporal dedifferentiation of the global brain signal topography along the adult lifespan. *Human Brain Mapping*, *44*(17), 5906–5918. doi:10.1002/hbm.26484

Baldi, E., & Bucherelli, C. (2005). The inverted "u-shaped" dose-effect relationships in learning and memory: Modulation of arousal and consolidation. *Nonlinearity in Biology, Toxicology, Medicine*, *3*(1), nonlin-003. doi:10.2201/nonlin.003.01.002

Baria, A. T., Baliki, M. N., Parrish, T., & Apkarian, A. V. (2011). Anatomical and functional assemblies of brain BOLD oscillations. *Journal of Neuroscience*, *31*(21), 7910–7919. doi:10.1523/JNEUROSCI.1296-11.2011

Benedetti, F., & Colombo, C. (2011). Sleep deprivation in mood disorders. *Neuropsychobiology*, *64*(3), 141–151. doi:10.1159/000328947

Buzsáki, G. (2006). *Rhythms of the brain*. New York: Oxford University Press.

Buzsaki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science (New York, N.Y.)*, *304*(5679), 1926–1929. doi:10.1126/science.1099745

Collaborators, G. B. D. M. D. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet. Psychiatry*, *9*(2), 137–150. doi:10.1016/S2215-0366(21)00395-3

Dichter, G. S., Gibbs, D., & Smoski, M. J. (2015). A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *Journal of Affective Disorders*, *172*, 8–17. doi:10.1016/j.jad.2014.09.028

Elias, L. R., Miskowiak, K. W., Vale, A. M., Kohler, C. A., Kjaerstad, H. L., Stubbs, B., … Carvalho, A. F. (2017). Cognitive impairment in euthymic pediatric bipolar disorder: A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(4), 286–296. doi:10.1016/j.jaac.2017.01.008

Falahpour, M., Wong, C. W., & Liu, T. T. (2016). The resting state fMRI global signal is negatively correlated with time-varying EEG vigilance. Paper presented at the Proceedings of the 24th Annual Meeting of the ISMRM.

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., … Jiang, T. (2016). The human brainnetome atlas: A New brain atlas based on connectional architecture. *Cerebral Cortex (New York, N.Y.: 1991)*, *26*(8), 3508–3526. doi:10.1093/cercor/bhw157

Fingelkurts, A. A., Fingelkurts, A. A., Rytsälä, H., Suominen, K., Isometsä, E., & Kähkönen, S. (2007). Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. *Human Brain Mapping*, *28*(3), 247–261. doi:10.1002/hbm.20275

Fisher, R. A. (1915). Frequency distribution of the values of the correlation coefficient in samples from an indefinitely large population. *Biometrika*, *10*(4), 507–521. doi:10.2307/2331838

Fredholm, B. B., Bättig, K., Holmén, J., Nehlig, A., & Zvartau, E. E. (1999). Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacological Reviews*, *51*(1), 83–133.

Garrett, D. D., McIntosh, A. R., & Grady, C. L. (2014). Brain signal variability is parametrically modifiable. *Cerebral cortex*, *24*(11), 2931–2940. doi:10.1093/cercor/bht150

Garrett, D. D., Samanez-Larkin, G. R., MacDonald, S. W. S., Lindenberger, U., McIntosh, A. R., & Grady, C. L. (2013). Moment-to-moment brain signal variability: A next frontier in human brain mapping? *Neuroscience & Biobehavioral Reviews*, *37*(4), 610–624. doi:10.1016/j.neubiorev.2013.02.015

Guo, W., Liu, F., Dai, Y., Jiang, M., Zhang, J., Yu, L., … Xiao, C. (2013). Decreased interhemispheric resting-state functional connectivity in first-episode, drug-naive major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *41*, 24–29. doi:10.1016/j.pnpbp.2012.11.003

Gutierrez-Barragan, D., Basson, M. A., Panzeri, S., & Gozzi, A. (2019). Infraslow state fluctuations govern spontaneous fMRI network dynamics. *Current Biology*, *29*(14), 2295–2306 e2295. doi:10.1016/j.cub.2019.06.017

Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive rumination, the default-mode network, and the dark matter of clinical neuroscience. *Biological Psychiatry*, *78*(4), 224–230. doi:10.1016/j.biopsych.2015.02.020

Han, S., Wang, X., He, Z., Sheng, W., Zou, Q., Li, L., … Chen, H. (2019). Decreased static and increased dynamic global signal topography in major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *94*, 109665. doi:10.1016/j.pnpbp.2019.109665

He, Z., Cui, Q., Zheng, J., Duan, X., Pang, Y., Gao, Q., … Chen, H. (2016). Frequency-specific alterations in functional connectivity in treatment-resistant and-sensitive major depressive disorder. *Journal of Psychiatric Research*, *82*, 30–39. doi:10.1016/j.jpsychires.2016.07.011

Hegerl, U., & Hensch, T. (2014). The vigilance regulation model of affective disorders and ADHD. *Neuroscience & Biobehavioral Reviews*, *44*, 45–57. doi:10.1016/j.neubiorev.2012.10.008

Hegerl, U., Wilk, K., Olbrich, S., Schoenknecht, P., & Sander, C. (2012). Hyperstable regulation of vigilance in patients with major depressive disorder. *The World Journal of Biological Psychiatry*, *13*(6), 436–446. doi:10.3109/15622975.2011.579164

Huntenburg, J. M., Bazin, P.-L., & Margulies, D. S. (2018). Large-scale gradients in human cortical organization. *Trends in Cognitive Sciences*, *22*(1), 21–31. doi:10.1016/j.tics.2017.11.002

Just, M. A., Cherkassky, V. L., Keller, T. A., Kana, R. K., & Minshew, N. J. (2007). Functional and anatomical cortical underconnectivity in autism: Evidence from an FMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex*, *17*(4), 951–961. doi:10.1093/cercor/bhl006

Keskin, K., Eker, M. C., Gonul, A. S., & Northoff, G. (2023). Abnormal global signal topography of self modulates emotion dysregulation in major depressive disorder. *Translational Psychiatry*, *13*(1), 107. doi:10.1038/s41398-023-02398-2

Klein, S. D., Shekels, L. L., McGuire, K. A., & Sponheim, S. R. (2020). Neural anomalies during vigilance in schizophrenia: Diagnostic specificity and genetic associations. *NeuroImage: Clinical*, *28*, 102414. doi:10.1016/j.nicl.2020.102414

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience & Biobehavioral Reviews*, *31*(3), 377–395. doi:10.1016/j.neubiorev.2006.10.004

Lai, C. H., & Wu, Y. T. (2014). Frontal-insula gray matter deficits in first-episode medication-naive patients with major depressive disorder. *Journal of Affective Disorders*, *160*, 74–79. doi:10.1016/j.jad.2013.12.036

Li, L., Wang, Y., Ye, L., Chen, W., Huang, X., Cui, Q., … Chen, H. (2019). Altered brain signal variability in patients with generalized anxiety disorder. *Frontiers in Psychiatry*, *10*, 84. doi:10.3389/fpsyt.2019.00084

Li, R., Wang, H., Wang, L., Zhang, L., Zou, T., Wang, X., … Chen, H. (2021). Shared and distinct global signal topography disturbances in subcortical and cortical networks in human epilepsy. *Human Brain Mapping*, *42*(2), 412–426. doi:10.1002/hbm.25231

Li, X. K., Qiu, H. T., Hu, J., & Luo, Q. H. (2022). Changes in the amplitude of low-frequency fluctuations in specific frequency bands in major depressive disorder after electroconvulsive therapy. *World Journal of Psychiatry*, *12*(5), 708. doi:10.5498/wjp.v12.i5.708

Liu, T. T., Nalci, A., & Falahpour, M. (2017). The global signal in fMRI: Nuisance or information? *Neuroimage*, *150*, 213–229. doi:10.1016/j.neuroimage.2017.02.036

Månsson, K. N. T., Waschke, L., Manzouri, A., Furmark, T., Fischer, H., & Garrett, D. D. (2022). Moment-to-moment brain signal variability reliably predicts psychiatric treatment outcome. *Biological Psychiatry*, *91*(7), 658–666. doi:10.1016/j.biopsych.2021.09.026

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015). Resting-state functional connectivity in major depressive disorder: A review. *Neuroscience & Biobehavioral Reviews*, *56*, 330–344. doi:10.1016/j.neubiorev.2015.07.014

Murphy, K., & Fox, M. D. (2017). Towards a consensus regarding global signal regression for resting state functional connectivity MRI. *Neuroimage*, *154*, 169–173. doi:10.1016/j.neuroimage.2016.11.052

Newson, J. J., & Thiagarajan, T. C. (2019). EEG Frequency bands in psychiatric disorders: A review of resting state studies. *Frontiers in Human Neuroscience*, *12*, 521. doi:10.3389/fnhum.2018.00521

Nilsonne, G., Tamm, S., Schwarz, J., Almeida, R., Fischer, H., Kecklund, G., … Akerstedt, T. (2017). Intrinsic brain connectivity after partial sleep deprivation in young and older adults: Results from the Stockholm sleepy brain study. *Scientific Reports*, *7*(1), 9422. doi:10.1038/s41598-017-09744-7

Nomi, J. S., Bzdok, D., Li, J., Bolt, T., Chang, C., Kornfeld, S., … Uddin, L. Q. (2022). Global fMRI signal topography differs systematically across the lifespan. *bioRxiv*, 2022.2007. 2027.501804. doi:10.1101/2022.07.27.501804.

Northoff, G. (2016). How do resting state changes in depression translate into psychopathological symptoms? From 'Spatiotemporal correspondence'to 'Spatiotemporal Psychopathology'. *Current Opinion in Psychiatry*, *29*(1), 18–24. doi:10.1097/YCO.0000000000000222

Northoff, G., & Hirjak, D. (2022). Spatiotemporal psychopathology–An integrated brain-mind approach and catatonia. *Schizophrenia Research*, *263*, 153–159. doi:10.1016/j.jad.2015.05.007

Northoff, G., Wiebking, C., Feinberg, T., & Panksepp, J. (2011). The 'resting-state hypothesis' of major depressive disorder—A translational subcortical–cortical framework for a system disorder. *Neuroscience & Biobehavioral Reviews*, *35*(9), 1929–1945. doi:10.1016/j.neubiorev.2010.12.007

Orban, C., Kong, R., Li, J., Chee, M. W. L., & Yeo, B. T. T. (2020). Time of day is associated with paradoxical reductions in global signal fluctuation and functional connectivity. *PLoS Biology*, *18*(2), e3000602. doi:10.1371/journal.pbio.3000602

Peifer, C., Schulz, A., Schächinger, H., Baumann, N., & Antoni, C. H. (2014). The relation of flow-experience and physiological arousal under stress—can u shape it? *Journal of Experimental Social Psychology*, *53*, 62–69. doi:10.1016/j.jesp.2014.01.009

Picco, L., Subramaniam, M., Abdin, E., Vaingankar, J. A., & Chong, S. A. (2017). Gender differences in major depressive disorder: Findings from the Singapore Mental Health Study. *Singapore Medical Journal*, *58*(11), 649–655. doi:10.11622/smedj.2016144

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*, *59*(3), 2142–2154. doi:10.1016/j.neuroimage.2011.10.018

Power, J. D., Plitt, M., Laumann, T. O., & Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. *Neuroimage*, *146*, 609–625. doi:10.1016/j.neuroimage.2016.09.038

Proakis, J. G., & Manolakis, D. G. (1988). Introduction to digital signal processing: Prentice Hall Professional Technical Reference.

Qiao, J., Li, X., Wang, Y., Wang, Y., Li, G., Lu, P., … Wang, S. (2022a). The infraslow frequency oscillatory transcranial direct current stimulation over the left dorsolateral prefrontal cortex enhances sustained attention. *Frontiers in Aging Neuroscience*, *14*, 879006. doi:10.3389/fnagi.2022.879006

Qiao, J., Wang, Y., & Wang, S. (2022b). Natural frequencies of neural activities and cognitions may serve as precise targets of rhythmic interventions to the aging brain. *Frontiers in Aging Neuroscience*, *14*, 988193. doi:10.3389/fnagi.2022.988193

Raut, R. V., Snyder, A. Z., Mitra, A., Yellin, D., Fujii, N., Malach, R., & Raichle, M. E. (2021). Global waves synchronize the brain's functional systems with fluctuating arousal. *Science Advances*, *7*(30), eabf2709. doi:10.1126/sciadv.abq3851

Ries, A., Hollander, M., Glim, S., Meng, C., Sorg, C., & Wohlschlager, A. (2019). Frequency-dependent spatial distribution of functional hubs in the human brain and alterations in major depressive disorder. *Frontiers in Human Neuroscience*, *13*, 146. doi:10.3389/fnhum.2019.00146

Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., … Northoff, G. (2020). All roads lead to the default-mode network-global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology*, *45*(12), 2058–2069. doi:10.1038/s41386-020-0785-x

Schmidt, F. M., Pschiebl, A., Sander, C., Kirkby, K. C., Thormann, J., Minkwitz, J., … Himmerich, H. (2016). Impact of serum cytokine levels on EEG-measured arousal regulation in patients with major depressive disorder and healthy controls. *Neuropsychobiology*, *73*(1), 1–9. doi:10.1159/000441190

Sheng, J., Shen, Y., Qin, Y., Zhang, L., Jiang, B., Li, Y., … Wang, J. (2018). Spatiotemporal, metabolic, and therapeutic characterization of altered

functional connectivity in major depressive disorder. *Human Brain Mapping*, *39*(5), 1957–1971. doi:10.1002/hbm.23976
Siegel, M., Donner, T. H., & Engel, A. K. (2012). Spectral fingerprints of large-scale neuronal interactions. *Nature Reviews Neuroscience*, *13*(2), 121–134. doi:10.1038/nrn3137
Stern, P. (2022). No neuron is an island. *Science (New York, N.Y.)*, *378*, 486–487. doi:10.1126/science.adf4275
Tae, W.-S. (2015). Regional gray matter volume reduction associated with major depressive disorder: A voxel-based morphometry. *Investigative Magnetic Resonance Imaging*, *19*(1), 10–18. doi:10.13104/imri.2015.19.1.10
Tanaka, S. C. (2020). SRPBS Multi-disorder MRI dataset (unrestricted). *Synapse (New York, N.Y.)*. doi:10.7303/syn22317081
Tanaka, S. C., Yamashita, A., Yahata, N., Itahashi, T., Lisi, G., Yamada, T., … Imamizu, H. (2021). A multi-site, multi-disorder resting-state magnetic resonance image database. *Scientific Data*, *8*(1), 227. doi:10.1038/s41597-021-01004-8
Thiebaut de Schotten, M., & Forkel, S. J. (2022). The emergent properties of the connected brain. *Science (New York, N.Y.)*, *378*(6619), 505–510. doi:10.1126/science.abq2591
Thompson, G. J., Riedl, V., Grimmer, T., Drzezga, A., Herman, P., & Hyder, F. (2016). The whole-brain "global" signal from resting state fMRI as a potential biomarker of quantitative state changes in glucose metabolism. *Brain Connectivity*, *6*(6), 435–447. doi:10.1089/brain.2015.0394
Tibshirani, R., Walther, G., & Hastie, T. (2001). Estimating the number of clusters in a data set via the gap statistic. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *63*(2), 411–423. doi:10.1111/1467-9868.00293
Tolkunov, D., Rubin, D., & Mujica-Parodi, L. (2010). Power spectrum scale invariance quantifies limbic dysregulation in trait anxious adults using fMRI: Adapting methods optimized for characterizing autonomic dysregulation to neural dynamic time series. *Neuroimage*, *50*(1), 72–80. doi:10.1016/j.neuroimage.2009.12.021
Wang, L., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2012). A systematic review of resting-state functional-MRI studies in major depression. *Journal of Affective Disorders*, *142*(1–3), 6–12. doi:10.1016/j.jad.2012.04.013
Wang, L., Kong, Q., Li, K., Su, Y., Zeng, Y., Zhang, Q., … Si, T. (2016). Frequency-dependent changes in amplitude of low-frequency oscillations in depression: A resting-state fMRI study. *Neuroscience Letters*, *614*, 105–111. doi:10.1016/j.neulet.2016.01.012
Wang, X., Liao, W., Han, S., Li, J., Wang, Y., Zhang, Y., … Chen, H. (2021). Frequency-specific altered global signal topography in drug-naive first-episode patients with adolescent-onset schizophrenia. *Brain Imaging and Behavior*, *15*(4), 1876–1885. doi:10.1007/s11682-020-00381-9
Wang, Y., Ao, Y., Yang, Q., Liu, Y., Ouyang, Y., Jing, X., … Chen, H. (2020). Spatial variability of low frequency brain signal differentiates brain states. *PLoS One*, *15*(11), e0242330. doi:10.1371/journal.pone.0242330
Wang, Y., Yang, C., Li, G., Ao, Y., Jiang, M., Cui, Q., … Jing, X. (2023). Frequency-dependent effective connections between local signals and the global brain signal during resting-state. *Cognitive Neurodynamics*, *17*(2), 555–560. doi:10.1007/s11571-022-09831-0
Wilks, D. S. (2006). On "field significance" and the false discovery rate. *Journal of Applied Meteorology and Climatology*, *45*(9), 1181–1189. doi:10.1175/Jam2404.1
Wolf, E., Kuhn, M., Normann, C., Mainberger, F., Maier, J. G., Maywald, S., … Nissen, C. (2016). Synaptic plasticity model of therapeutic sleep deprivation in major depression. *Sleep Medicine Reviews*, *30*, 53–62. doi:10.1016/j.smrv.2015.11.003
Wong, C. W., Olafsson, V., Tal, O., & Liu, T. T. (2013). The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. *Neuroimage*, *83*, 983–990. doi:10.1016/j.neuroimage.2013.07.057
Xia, M., Liu, J., Mechelli, A., Sun, X., Ma, Q., Wang, X., … He, Y. (2022). Connectome gradient dysfunction in major depression and its association with gene expression profiles and treatment outcomes. *Molecular Psychiatry*, *27*(3), 1384–1393. doi:10.1038/s41380-022-01519-5
Xue, S., Wang, X., Wang, W., Liu, J., & Qiu, J. (2016). Frequency-dependent alterations in regional homogeneity in major depression. *Behavioural Brain Research*, *306*, 13–19. doi:10.1016/j.bbr.2016.03.012
Yan, C., & Zang, Y. (2010). DPARSF: A MATLAB toolbox for" pipeline" data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience*, *4*, 1377. doi:10.3389/fnsys.2010.00013
Yan, C. G., Yang, Z., Colcombe, S. J., Zuo, X. N., & Milham, M. P. (2017). Concordance among indices of intrinsic brain function: Insights from inter-individual variation and temporal dynamics. *Science Bulletin*, *62*(23), 1572–1584. doi:10.1016/j.scib.2017.09.015
Yang, G. J., Murray, J. D., Glasser, M., Pearlson, G. D., Krystal, J. H., Schleifer, C., … Anticevic, A. (2017). Altered global signal topography in schizophrenia. *Cerebral Cortex (New York, N.Y.: 1991)*, *27*(11), 5156–5169. doi:10.1093/cercor/bhw297
Yang, G. J., Murray, J. D., Repovs, G., Cole, M. W., Savic, A., Glasser, M. F., … Pearlson, G. D. (2014). Altered global brain signal in schizophrenia. *Proceedings of the National Academy of Sciences*, *111*(20), 7438–7443. doi:10.1073/pnas.1405289111
Yang, H., Zhang, H., Meng, C., Wohlschlager, A., Brandl, F., Di, X., … Biswal, B. (2022). Frequency-specific coactivation patterns in resting-state and their alterations in schizophrenia: An fMRI study. *Human Brain Mapping*, *43*(12), 3792–3808. doi:10.1002/hbm.25884
Yang, Y., Cui, Q., Pang, Y., Chen, Y., Tang, Q., Guo, X., … Chen, H. (2021). Frequency-specific alteration of functional connectivity density in bipolar disorder depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *104*, 110026. doi:10.1016/j.pnpbp.2020.110026
Zhang, J., Huang, Z., Tumati, S., & Northoff, G. (2020). Rest-task modulation of fMRI-derived global signal topography is mediated by transient coactivation patterns. *PLoS Biology*, *18*(7), e3000733. doi:10.1371/journal.pbio.3000733
Zhang, J., Magioncalda, P., Huang, Z., Tan, Z., Hu, X., Hu, Z., … Northoff, G. (2019). Altered global signal topography and Its different regional localization in motor cortex and hippocampus in mania and depression. *Schizophrenia Bulletin*, *45*(4), 902–910. doi:10.1093/schbul/sby138
Zhang, J., & Northoff, G. (2022). Beyond noise to function: Reframing the global brain activity and its dynamic topography. *Communications Biology*, *5*(1), 1350. doi:10.1038/s42003-022-04297-6
Zhang, Y., Zhu, C., Chen, H., Duan, X., Lu, F., Li, M., … Chen, H. (2015). Frequency-dependent alterations in the amplitude of low-frequency fluctuations in social anxiety disorder. *Journal of Affective Disorders*, *174*, 329–335. doi:10.1016/j.jad.2014.12.001
Zhu, J., Cai, H., Yuan, Y., Yue, Y., Jiang, D., Chen, C., … Yu, Y. (2018). Variance of the global signal as a pretreatment predictor of antidepressant treatment response in drug-naïve major depressive disorder. *Brain Imaging and Behavior*, *12*, 1768–1774. doi:10.1007/s11682-018-9845-9