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Research paper

Altered task modulation of global signal topography in the default-mode network of unmedicated major depressive disorder

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ABSTRACT

Background: Altered global signal (GS) topography features in the resting-state fMRI of major depressive disorder (MDD), showing abnormally strong global signal representation in the default-mode network (DMN). Whether the abnormal local to global change also shapes activity during task states, and how it relates to psychopathological symptoms, e.g., abnormally slow time speed of motor, cognitive, and affective symptoms, remains unknown.

Methods: We investigated fMRI-based GS with its topographical representation during task states in unmedicated 51 MDD subjects and 28 healthy subjects. Task-related global signal correlation (GSCORR) was probed by a novel paradigm testing the processing of negative/neutral emotions during different time speeds, i.e., slow and fast.

Results: We observed a significant interaction between time speed and emotion of GSCORR in various DMN regions in healthy subjects. Next, we showed that MDD exhibits reduced task-related GSCORR in various DMN regions during specifically the fast processing of negative emotions. Finally, we demonstrated that GSCORR in DMN and other brain regions (motor-related regions, inferior frontal cortex) correlated with the degree of psychomotor retardation especially during the fast emotional stimuli.

Limitations: The measurement of interoceptive variables like respiration rate or heart rate were not included in our fMRI acquisition.

Conclusion: Together, we demonstrated the functional relevance of GS topography by showing reduced GSCORR in DMN during specifically the fast processing of negative emotions in MDD, suggesting the abnormal slowness, i.e., reduced time speed, to be a key feature of both brain and symptoms in MDD.

1. Introduction

Major depressive disorder (MDD) is a multidimensional disorder that, besides the extremely negative emotions, also includes abnormal slowing of time (Fuchs, 2013; Northoff et al., 2017; Stanghellini et al., 2017) as in psychomotor retardation (Handke et al., 2020; Hirjak et al., 2018; Northoff et al., 2021). Clinically as well as in classic factor analysis of the Hamilton Depression Rating Scale (HDRS), negative emotion, and

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psychomotor slowing/retardation are found to co-occur in MDD patients (Brody et al., 2001; Cleary and Guy, 1977). The abnormally negative emotions are supposedly mediated by local-regional task-related changes in the anterior and posterior midline regions of the default-mode network (DMN) (Broyd et al., 2009; Kaiser et al., 2015; Raichle et al., 2001; Scalabrini et al., 2020; Yan et al., 2019) as probed during task states (Anticevic et al., 2012; Davey et al., 2012; Grimm et al., 2009; Hamilton et al., 2015). Moreover, studies demonstrate that psychomotor slowing/retardation may also be related to dysfunction in DMN as well as to changes in motor regions (Hirjak et al., 2018; Krus Hansson, 2018; Northoff et al., 2021; Yin et al., 2018).

In general, psychomotor slowing was not only being observed in movements but also in affect and thought of acute MDD (Northoff, 2016, 2018; Rostami et al., 2021), just like abnormal perception of time (Northoff et al., 2017; Stanghellini et al., 2017). Hence, psychomotor slowing or retardation may be a more fundamental or basic dimension cutting across the different functions (cognition, affect, movements) including their respective brain regions/ networks. Probing that requires a more global approach to the brain where the focus is on the degree to which global activity is represented in specific networks such as the DMN or others.

The global to local relationship in fMRI is investigated by global signal (GS). Previously, GS is often considered to reflect a non-neuronal source of noise, such that its regression in fMRI data analysis is a controversial issue (Chen et al., 2012; Power et al., 2014, 2017). However, GS has been shown recently to reflect a physiological basis (Li et al., 2019b; Schölvinck et al., 2010; Zhang et al., 2020, 2019). Measured by global signal correlation (GSCORR) or global functional connectivity, recent fMRI studies demonstrate GS topography changes across the whole brain during the resting state in MDD, involving a variety of different regions in DMN (Abdallah et al., 2017; Han et al., 2019; Scheinost et al., 2018; Zhang et al., 2018). A recent study (Scalabrini et al., 2020) demonstrated that an abnormal increase in functional connectivity of DMN to non-DMN networks is accompanied by increased within-DMN resting-state functional connectivity most notably among the anterior and posterior cortical midline regions. However, these findings leave open several issues. First, they do not address how DMN changes relative to the brain's global activity are modulated during task states in MDD. Secondly, they leave open how such task-related changes in DMN relative to the global activity are related to symptoms like psychomotor slowing as typically coupled with negative emotions.

The goal of our paper is to use such topographic representation of global brain activity to probe the impact of time speed (slow vs fast) on task-related activity during emotions. For that purpose, we designed a novel task paradigm by presenting the same emotional (and neutral) stimuli in different speeds, i.e., slow and fast. By investigating the task-related GSCORR, as probed for the first time in MDD, this allowed us to investigate the interaction between time speed (fast vs slow) and emotion (negative vs neutral) on the global neural level; moreover, we aimed to link that to symptoms like extreme slowness (psychomotor retardation), accompanying the negative emotion in MDD. We hypothesized that MDD shows abnormal changes in anterior and posterior midline DMN regions' global signal topography (GSCORR) during specifically negative emotions processed in fast time speed. Moreover, following previous findings (Northoff, 2018; Northoff et al., 2021), we hypothesized global changes in DMN to be related to psychomotor slowing coupled with negative emotion in this type of cognitive challenge in MDD.

2. Methods

2.1. Participants

The study was approved by the local ethics research committee of the Second Affiliated Hospital at Xinxiang Medical University and Affiliated Zhongda Hospital of Southeast University. We initially recruited a cohort of drug-free adult acute MDD subjects ($n = 74$) and age- and gender-matched health control (HC) subjects ($n = 30$) (Zhang et al., 2021). Written informed consent was obtained from all of the participants. The inclusion and exclusion criteria of the subjects with MDD in this study are as follows: a) confirmed by two chief psychiatrists through standardized structured clinical interviews for DSM-IV Axis I disorders (SCID-I), b) HDRS-24 scores ≥ 18; c) 'Drug-free' was defined as no antidepressant treatment at least 2 weeks prior to inclusion. Exclusion criteria were: (i) Any other psychiatric disorders or mental disorders caused by physical diseases or drug abuse or personality disorders; (ii) History of central nervous system organic diseases, such as traumatic brain injury, epilepsy, etc.; (iii) Presence of psychotic symptoms during the depressive episodes;(iv) presence of active suicide behavior; (v) history of internal medicine discords such as endocrine disease or blood, heart, liver, kidney dysfunction, diabetes, or pregnancy; (vi) Having contraindication to MRI or less than six months of ECT or rTMS therapy, (vii) The dozes of the treatment with lorazepam greater than 2 mg (or equivalent), any mood stabilizer or anticonvulsant.

Considering the large influence of head movement on the calculation of GS, in this study, we adopted stringent head motion correction (subjects with translations greater than 1.5 mm or rotations greater than 1.5 ° in each direction were excluded: exclusion of 2 HC subjects and 23 MDD subjects). Finally, 51 MDD subjects (32 females, age range 18– 54 years) and 28 HC subjects (17 females, age range 18 – 54 years) remained in our present study sample (Table 1). No differences were observed in clinical characteristics among patients who were excluded due to excessive motion and those patients with MDD included in the final analyses; this suggests the generalizability of the present finding (supplementary Table S1).

2.2. Task procedure in fMRI

A 2 × 2 factorial design was employed for eliciting task-evoked activity (Fig. 1A). The first factor consisted of emotional pictures, including "neutral" and "negative" pictures, which are selected from the International Affective Picture System (IAPS) based on standard scores for emotional arousal and emotional valence (Constantinescu et al., 2017). 20 independent healthy subjects (e.g., college students) performed arousal and valence ratings on these images. Based on their data, 30 neutral images (mean valence: 4.75 ± 0.57; mean arousal: 4.91 ±

Table 1
Comparison of Clinical Characteristics between Healthy Controls and MDD Patients.

Demographic	HC Group ($n = 28$)	MDD Group ($n = 51$)	Significance		
			T Value / Chi-Square	*P* Value	SE
Age, years	32.36 (12.14)	30.27 (11.78)	0.744	0.459	2.800
Female	17 (60.71)	32 (62.75)	0.032	0.859	NA
Education, years	12.88 (3.67)	12.63 (3.19)	0.290	0.772	0.791
Age of onset,	NA	28.39 (11.69)	NA	NA	NA
Family history of mental disease (%)	1 (3.57)	20(39.2)	10.012	0.002*	NA
HDRS-24 scores	2.36 (2.48)	36.14 (7.98)	−21.779	<0.001*	1.551
#Retardation factor score	0.57 (0.74)	9.24 (2.02)	−21.890	<0.001*	0.396

Data represent means (standard deviation) or numbers of participants in each group (% of total). Abbreviations: HC, health control; MDD, Major Depressive Disorder; HDRS-24, 24-item Hamilton Depression Scale. #Retardation factor score was calculated as a sum of the item1, item7.item8 and item14 in HDRS-24.

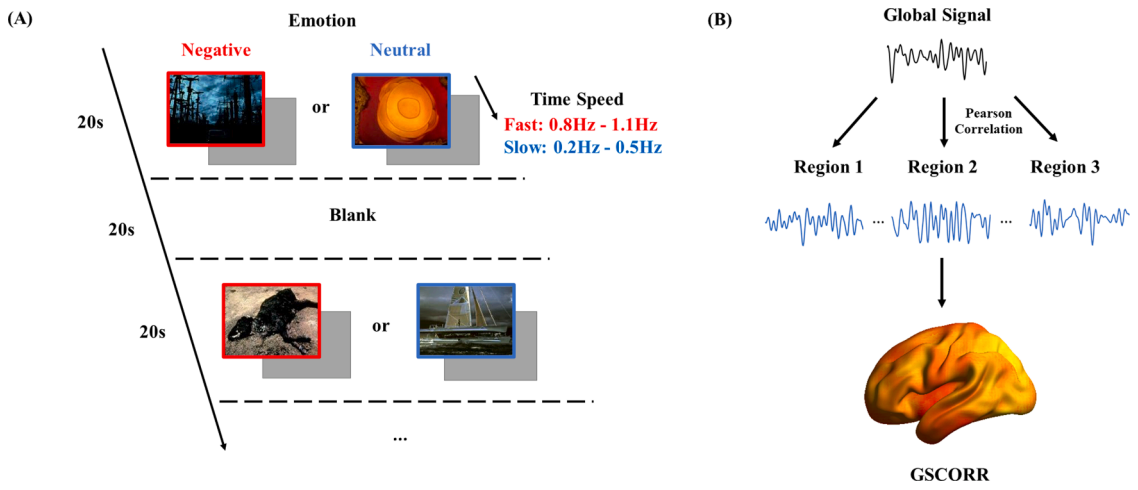

Fig. 1. (A) The schematic illustration of GSCORR correlation: the correlation between global signals and time series in each region of gray matter. (B) Experimental paradigm. The process for the task consisted of a 2 × 2 factorial design. The first factor consisted of emotional pictures, which included "neutral" and "negative" and were selected from the International Affective Picture System (IAPS). The second factor was time speed operationalized as the frequency of image flipping. Each participant was instructed to complete all sessions that were fast (changing between the picture and blank screen at around 1 Hz) and slow (changing between picture and blank screen at approximately 0.3 Hz) occurring in a random sequence. Each session consisted of 10 blocks, all trials within one session are presented in the same way.

0.64) and 30 negative images (mean valence: 2.88 ± 0.65; mean arousal: 4.77 ± 0.51) were selected for inclusion in the task. Through the paired-sample *t*-test, the emotional valence of negative pictures was found significantly lower than neutral pictures ($t = -11.006$, df = 29, $P < 0.001$), and there was no significant difference in arousal between them ($t = -0.978$, df = 29, $P = 0.336$). The second factor is the speed of time, expressed by the frequency of the image presentation. During the fast session, each emotional picture and blank screen were presented with an inter-stimulus interval of 910–1250 ms (0.8–1.1 Hz), repeating for 20 s. During the slow session, each emotional image and blank screen were presented with an inter-stimulus interval of 2000–5000 ms (0.2–0.5 Hz), still repeating for 20 s. Because it was a 2 × 2 factor design, four conditions (sessions) were performed in our experiment. They were negative × fast, negative × slow, neutral × fast, or neutral × slow, respectively. Each session contains 10 blocks, and all trials within one session presented the same stimuli, i.e., condition. During the experiment, the four conditions (sessions) were randomly presented for each subject. This long inter-stimulus interval of 9 s was used at the end of each session to allow the fMRI signal to return to baseline and avoid elevated baseline activity prior to the onset of the next session. Other details of the stimuli and task procedure can be found in supplementary materials.

2.3. MRI data acquisition

High-resolution T1-weighted anatomical images covering the whole brain were acquired using a 3D-magnetization-prepared rapid gradient-echo (MPRAGE) sequence: repetition time (TR) = 2530 ms; echo time (TE) = 2.43 ms; flip angle (FA) = 7°; resolution matrix = 256 × 256; slices = 192; slice thickness = 1.0 mm; gap = 0.5 mm; voxel size = 1.0 × 1.0 × 1.0 mm^3. Besides, routine T2-weighted images were obtained to rule out subjects with changes in their white matter, cerebral infarctions, or other lesions. fMRI images during the task were obtained using a gradient-recalled echo-planar imaging (GRE-EPI) sequence: TR = 1000 ms; TE = 25 ms; FA = 76°; acquisition matrix = 64 × 64; FOV = 210 × 210 mm^2; slices = 20; slice thickness = 6.0 mm; gap = 0 mm; voxel size = 3.3 × 3.3 × 6.0 mm^3. Four sessions were performed for each subject, each lasted for 410 s.

2.4. Data analysis

2.4.1. Preprocessing

MRI data preprocessing for each subject was performed using the Statistical Parametric Mapping 8 (SPM8) toolkit (http://www.fil.ion.ucl.ac.uk/spm) and the Data Processing & Analysis for Brain Imaging (DPABI V3.1) (Yan et al., 2016) toolbox operating on the MATLAB platform (The MathWorks, Inc., Natick, MA, USA). We discarded the first ten volumes of each run and corrected the remaining images for timing diversifications and motion effects. Six head motion parameters were estimated and visually inspected. Considering the large influence of head movement on the calculation of GS (Power et al., 2017), the motion parameters from the volume realignment step were used to exclude participants who exhibited translations greater than 1.5 mm or rotations greater than 1.5 ° in each direction in each session (total 23 MDD subjects and 2 HC subjects were removed).

Aaverage frame displacement (FD) was obtained as a covariate for the comparison between groups (Jenkinson et al., 2002). Polynomial trends were removed from the scans. Then, several nuisance variables including 24-dimensional temporal derivative head-motion parameters as well as mean time series from the white matter and cerebrospinal fluid were regressed from the gray matter. According to the Montreal Neurological Institute template, we normalized the obtained images in a spatial manner in the identical stereotactic space using 12 affine transformations and then resampled them to 3 × 3 × 3 mm^3 voxels.

2.5. Calculation of GSCORR

The GS was calculated for each participant using normalized (z-score) fMRI signals across all voxels in the gray matter. The GSCORR was calculated by Pearson correlation between the GS and the time series in each gray matter voxel (Power et al., 2017) (Fig. 1B). The correlation *r* values were then transformed through the Fisher z-transformation (Cole et al., 2016). Then, the GSCORR maps were smoothed with a Gaussian kernel of 6 × 6 × 6 mm.

2.6. Statistical analysis

2.6.1. Voxel-wise two-way repeated measurement ANOVA within-subject group analysis of GSCORR

Considering that our experimental paradigm is novel, the two-way

repeated measurement ANOVA was carried out by the flexible factorial design module of SPM8 (https://www.fil.ion.ucl.ac.uk/spm/doc/spm8_manual.pdf) in the HC group first (Gläscher and Gitelman, 2008; Song et al., 2014). Based on our factorial design, time speed and emotion were set as two main factors. The interaction between them was also set as a factor we explore. The threshold of voxel-wise comparison was set at $P < 0.05$ after Alphasim correction (1000-iteration monte carlo simulation) in the brain gray matter mask without cerebellum with cluster size > 4914 mm^3 (corrected $P < 0.05$). For illustration purposes, the GSCORR values were extracted from the significant brain area obtained by whole-brain voxel-wise analysis as the regions of interest (ROIs) of the HC group and the MDD group respectively. Then, two-sample t-tests were performed respectively in each ROI.

2.6.2. Voxel-wise comparison of HC vs MDD in GSCORR

The voxel-wise group comparison was carried out by the "Two-sample T-test" module of DPABI, controlling the age, sex, and gray matter volume (Xie et al., 2015) and mean FD factors as covariates. The threshold of voxel-wise comparison was set at $P < 0.05$ after Alphasim correction (1000-iteration monte carlo simulation). The cluster size was larger than 5668 mm^3, 4320 mm^3, 4401 mm^3, and 4104 mm^3 in negative-fast condition, negative-slow condition, neutral-fast condition, and neutral-slow condition, respectively, with corrected $P < 0.05$.

2.6.3. Voxel-wise correlation of GSCORR with psychopathological symptom severity

To investigate the correlation between GSCORR and psychopathological symptoms, the retardation factor score of HDRS (indexing the coupling of negative emotion and psychomotor slowness (Brody et al., 2001; Cleary and Guy, 1977)) and other factor scores (anxiety/somatization, cognitive disturbance, hopelessness, etc.,) were used to correlate with GSCORR in whole brain voxel way for the MDD group, controlling the age, sex, gray matter volume and mean FD factors as covariates. Since the condition of negative-fast was the main contrast yielding task-specific GSCORR decreases in MDD, here we only conducted whole-brain voxel-wise correlation of GSCORR during this condition. The threshold of voxel-wise comparison was set at $P < 0.05$ after Alphasim correction (1000-iteration Monte carlo simulation) with cluster size > 5184 mm^3 (corrected $P < 0.05$).

3. Results

3.1. Demographic and neuropsychological data

As shown in Table 1, the age, sex, and education levels between HC and MDD groups were matched. Significant differences in total HDRS scores ($P < 0.001$), retardation factor score ($P < 0.001$), and family history of mental disease ($P < 0.005$) between the two groups were observed (Two-sample *t*-test or chi-square test were performed).

3.2. Task-sensitive GSCORR changes in DMN and non-DMN of HC

To calculate the effect of the four task conditions on GSCORR in the healthy population, we first conducted two-way repeated measures ANOVA for investigating time- and emotion-related effects including their interaction in HC subjects alone (Fig. 2 and supplementary Fig. S1); the obtained brain regions serve then as ROIs for their comparison with MDD. First, we investigated time-effects in healthy subjects alone which yielded significant main-effect GSCORR voxels in various DMN regions including pregenual anterior cingulate cortex (pACC)/ventromedial prefrontal cortex (VMPFC), angular gyrus, and medial temporal/parahippocampal gyrus (supplementary Fig. S1A). While non-DMN voxels were obtained in the left temporal pole, left superior temporal gyrus, motor regions (precentral and postcentral), and occipital cortex (calcarine) (supplementary Fig. S1A). Besides, we did not observe these regions to be involved in emotion-related effects alone: only the lateral prefrontal cortex and mid-occipital cortex showing significant GSCORR voxels when focusing on emotion as the main effect (supplementary Fig. S1B). Most interestingly, for the interaction (time speed × emotion) whose regions may indicate the modulation from both conditions, the

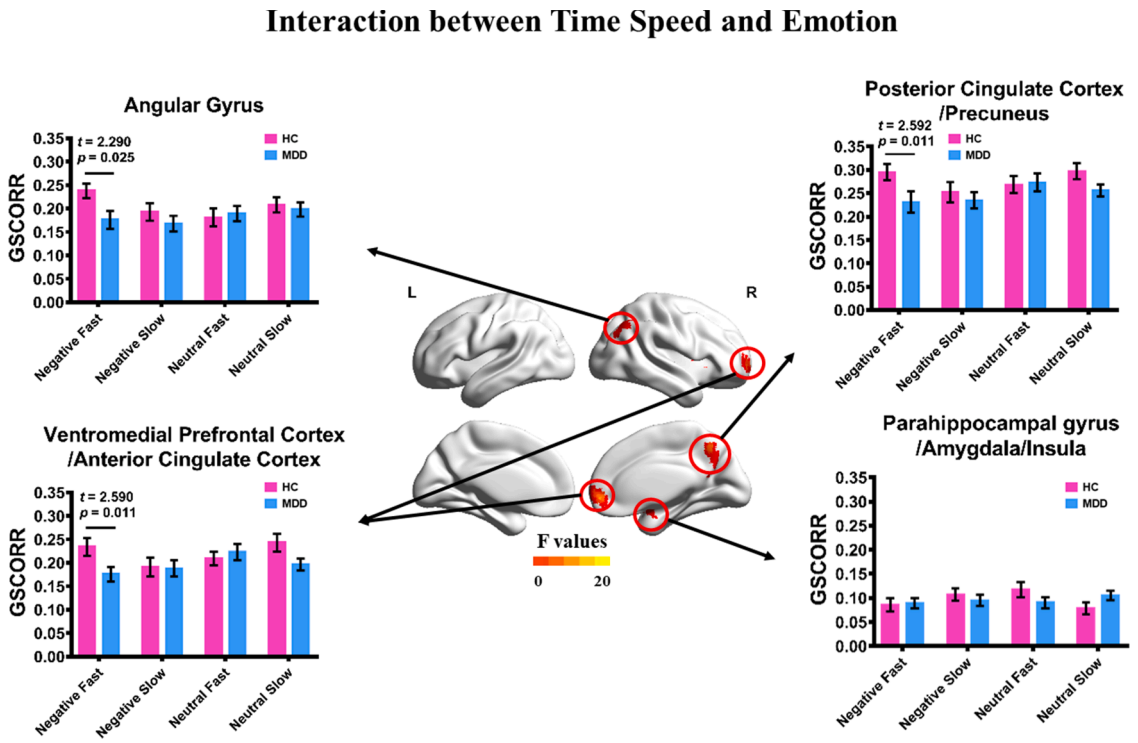

Fig. 2. The significant brain regions of the interaction between time speed × emotion (obtained by the Voxel-wise 2 × 2 repeated measured ANOVA, $P < 0.05$, Alphasim correction) in the HC group and the GSCORR values of both MDD and HC groups extracted from the significant brain regions obtained in HC. Error bars represent the standard error of the mean.

significant GSCORR voxels were mainly observed in DMN regions like midline pACC/VMPFC, angular gyrus, posterior cingulate cortex (PCC) as well as in insula (Fig. 2), The interaction suggest an important role of the DMN regions in modulating the interaction between time speed and emotion. Together, these data in healthy subjects demonstrate that GS topography in pACC/VMPFC, medial temporal (parahippocampus), and angular gyrus mediate time-related effects and the interaction between time speed and emotion. Furthermore, our findings suggest that GS topography is task-sensitive by mediating predominantly time-related effect and the time × emotion interaction as distinct from pure emotion-related effect.

3.3. MDD show task-specific GSCORR changes in task-sensitive regions of HC

Next, we took the regions obtained in HC subjects as ROIs and plotted their respective GSCORR values in MDD for comparing all four conditions (see bars in Fig. 2 and supplementary Fig. S1A). MDD showed significantly lower GSCORR values in DMN regions like pACC/VMPFC ($t = -2.590$, $P = 0.011$), PCC ($t = -2.592$, $P = 0.011$), and angular gyrus ($t = -2.290$, $P = 0.025$) as well as in the pre- and postcentral gyrus ($t = -2.443$, $P = 0.017$) during the interaction between time speed × emotion and/or time-related effects (Fig. 2 and supplementary Fig. S1A). MDD subjects showed GSCORR reductions in these regions during specifically the condition of negative-fast, i.e., the fast processing of negative emotions, but not in the other conditions.

Together, these findings demonstrate the task-specific nature of GSCORR reduction in MDD. Unlike HC subjects, MDD subjects are not able to increase their GSCORR in DMN and other brain regions when faster time speed is required during especially the processing of negative emotions, i.e., negative-fast (Fig. 2). Given that we analyze the topography of global activity, the lack of GSCORR increase in DMN during negative-fast must be considered relative to the whole brain. MDD subjects can no longer differentially modulate their DMN connectivity relative to other brain regions during specifically the fast processing of negative emotions.

3.4. MDD show task-specific GSCORR reduction in DMN and non-DMN during negative-fast

As the ROI-based findings may be biased by the selections of ROI from the healthy subjects, we next conducted direct whole-brain GSCORR comparisons of MDD vs HC subjects for each of the four different conditions. Among the four conditions, negative-fast yielded the most significant GSCORR differences ($P < 0.05$, Alphasim corrected;) between MDD and HC (Fig. 3A). GSCORR decreases were observed in DMN regions such as pACC/VMPFC and PCC (extending into medial prefrontal cortex) as well as in non-DMN regions such as premotor/motor cortex and superior temporal gyrus (Fig. 3A). GSCORR in another region, i.e., the insula was reduced in MDD during both negative-slow and neutral-fast (Fig. 3B and C). No significant brain regions were observed in neutral-slow (Fig. 3D).

Together, these results support and confirm the key involvement of DMN regions in mediating task-specific effects of abnormal GS topography in MDD. As in the previous analyses, MDD subjects exhibit a reduced increase in their DMN GS topography during specifically the fast processing of negative emotions. This suggests the task-specific reduction in DMN GS topography in MDD, that is, these subjects remain unable to modulate their DMN functional connectivity relative to the other brain regions (as indicated by GSCORR) during the fast and most challenging condition, i.e., negative-fast stimuli presentation.

3.5. Relation of task-related GSCORR to psychopathological symptom severity

Finally, we relate GSCORR changes during the fast processing of negative emotion to psychomotor retardation in MDD as obtained from the subscales of HDRS. This yielded significant negative correlation of GSCORR with the retardation factor score ($P < 0.05$, Alphasim corrected) in various DMN regions including posterior midline regions such as PCC ($r = -0.346$, $P = 0.013$) extending into premotor regions ($r = -0.371$, $P = 0.007$) as well as in left inferior frontal gyrus ($r = -0.0.375$, $P = 0.007$) with the lower GSCORR in these regions during the condition of negative-fast, and the higher the degree of psychomotor retardation (Fig. 4). Besides, these findings were not obtained with other factor scores (supplementary Fig. S2).

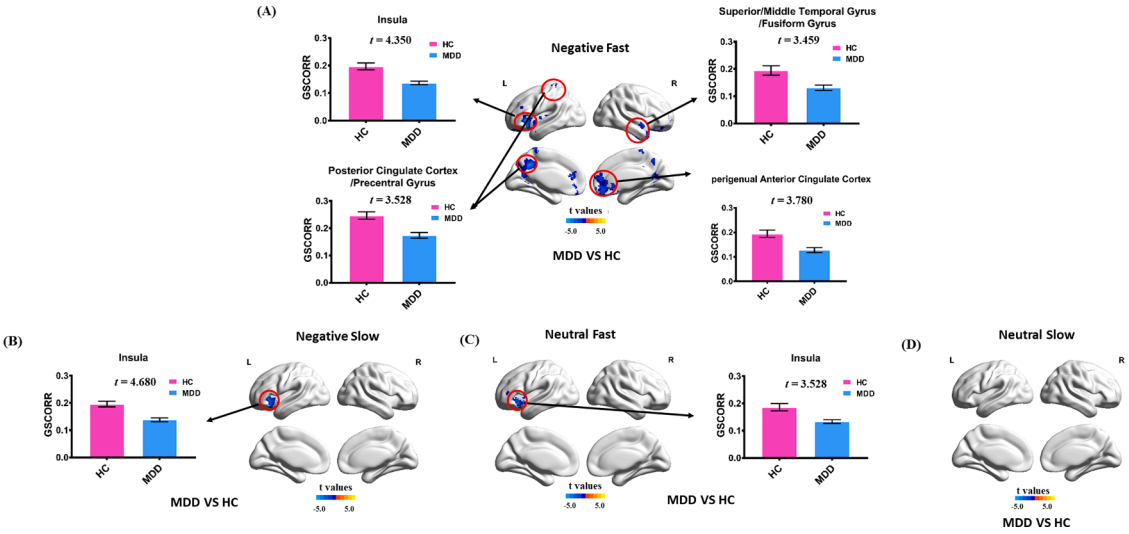

Fig. 3. Voxel-wise group comparison of GSCORR between MDD and HC groups in each condition of emotion × time speed tasks ($P < 0.05$, Alphasim correction). (A) Voxel-wise group comparison of GSCORR between MDD and HC groups in the condition of Negative Fast. (B) Voxel-wise group comparison of GSCORR between MDD and HC groups in the condition of Negative Slow. (C) Voxel-wise group comparison of GSCORR between MDD and HC groups in the condition of Neutral Fast. (D) There was no significant difference in GSCORR between MDD and HC groups in the condition of Neutral Slow. Error bars represent the standard error of the mean.

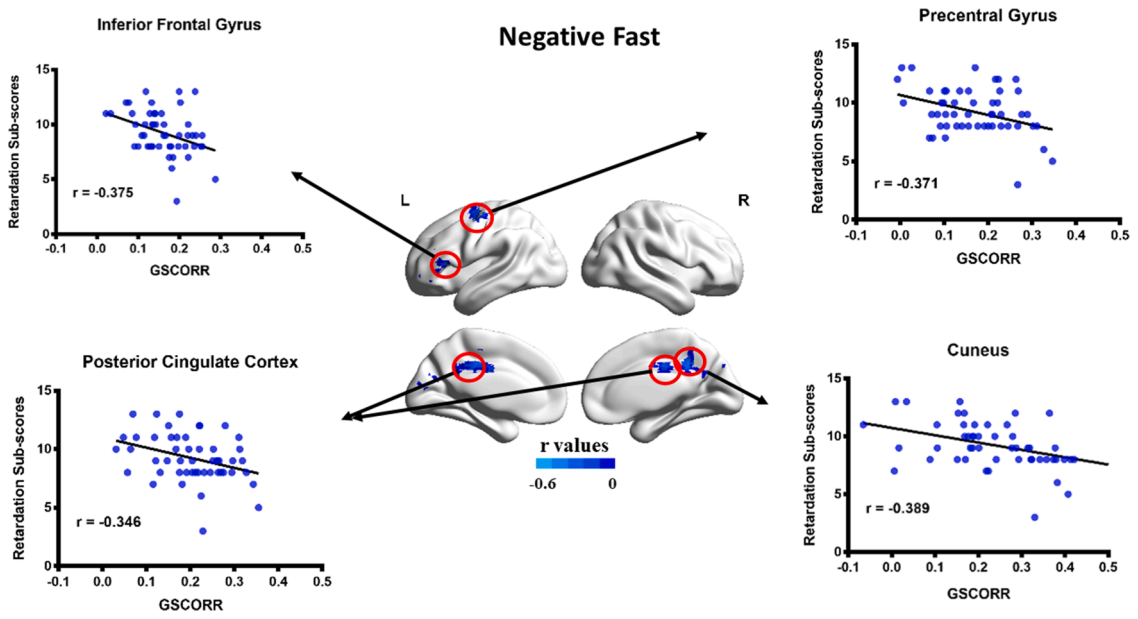

Fig. 4. Voxel-wise correlation of GSCORR in the condition of Negative Fast with the retardation factor score of HDRS-24 in MDD group ($p < 0.05$, Alphasim correction). HDRS-24: 24-item Hamilton Depression Rating Scale.

4. Discussion

In the present study, we observed a significant interaction between time speed and emotion of GSCCORR in various DMN regions in healthy subjects, confirming their core functional role for both types of processing. Secondly, we show that MDD exhibits reduced task-related GS topography (GSCORR) in these DMN regions during specifically fast processing of negative emotions, suggesting a weaker capacity of adapting to more demanding task load in MDD. Importantly, we observed that these task-related GS topographical changes in DMN were related to psychomotor retardation. Together, we here for the first time demonstrate the task-sensitive nature of changes in global brain topography in DMN relative to the whole brain in acute unmedicated MDD. More generally, we demonstrate how the brain's global spatial-topographic changes in MDD are related to temporal features, i.e., fast speed, on both levels, that is, the brain's task-related activity and the subjects' psychopathological symptoms.

As to our knowledge this is the first time GS is investigated during task states in MDD and, more generally, psychiatric disorders. Our findings complement recent observation of global DMN abnormalities in resting-state in MDD by showing their task-sensitive nature and their association with symptoms of psychomotor retardation. Hence even seemingly regional task-specific changes in DMN are related to global activity changes in the brain's overall topography. That further supports the assumption of MDD being primarily a global or systemic rather than local-regional or network disorder of the brain.

Within a more general framework, our study can be seen as another step in providing empirical support for the spatiotemporal approach postulated in the 'Resting-state hypothesis of depression' (RSHD) (Northoff et al., 2011; Scalabrini et al., 2020). In a nutshell, the RSHD postulates the resting and task state's spatial and temporal changes to be key in mediating depressive symptoms. Depressive symptoms are then traced to most fundamental and therefore global temporal and spatial changes (rather than more regional primarily affective or cognitive changes) in neural activity as postulated in "Spatiotemporal Psychopathology" (Fingelkurts and Fingelkurts, 2019; Northoff, 2016, 2018; Northoff et al., 2020). Our approach converging the neural measurement of global spatial-topographic changes, i.e., GSCORR, with the slow-fast stimulation of emotional pictures allows probing for such spatiotemporal approach to both brain and psychopathological symptoms. In sum, our findings support the RSHD by showing (i) the global nature of task-specific changes in DMN as measured by GSCORR; (ii) the relation of these global topographic activity changes to a temporal dimension in the task, i.e., fast-negative stimuli; and (iii) the relation of these global-local task-specific changes during fast-negative stimuli to a more or less analogous temporal dimension in the psychopathological symptoms, i.e., psychomotor retardation.

4.1. Task-sensitive changes in GS topography in DMN of HC subjects

Investigation of global signal and its topography focused mainly on the resting-state in healthy subjects (Li et al., 2019a, 2019b; Liu et al., 2017; Power et al., 2017). In addition to a succinct GS topography, some studies demonstrated the relationship of resting-state GS topography to personality traits (Li et al., 2019a) and circadian changes (Orban et al., 2020). Together, these observations suggest that GS topography is related to cognition and behavior including their respectively underlying task states. That raises the question of task-related modulation of GS topography. This was tested recently in our study on healthy subjects (Zhang et al., 2020). They demonstrate that different tasks modulate the frequency in the occurrence of different networks and their co-activation pattern (CAPs) in a somewhat task-sensitive manner. For instance, employing mostly visual tasks, the visual network exhibited high frequency in its CAP's during task states relative to rest (Zhang et al., 2020).We show a clear differentiation of GS topography in DMN in the different tasks. Especially the factor of time speed and its interaction with negative emotion yielded significant GSCORR change in DMN functional connectivity (pACC/VMPFC, PCC, and angular gyrus, etc.) as well as in some non-DMN regions. This finding suggests that global signal topography in especially DMN (as calculated relative to the whole brain in GSCORR) is task-sensitive in healthy subjects.

4.2. Task-specific reduction of GS topography in DMN of MDD

Previous studies on resting-state global signal topography of MDD observe significant increases in the degree of GSCORR in various DMN regions including pACC and PCC (Han et al., 2019; Scalabrini et al., 2020; Scheinost et al., 2018). Specifically, Scalabrini and colleagues (Scalabrini et al., 2020) demonstrated that these increases in within-DMN resting-state functional connectivity (rsFC) are related to

abnormal increases in inter-network rsFC between DMN and non-DMN. We here extend these findings from the resting state level to task states; this opens the opportunity to associate psychological significance and ultimately psychopathological symptoms with altered GS topography within and beyond DMN. Our findings show that MDD exhibits reduced GSCORR in mostly DMN regions during specifically fast processing of negative emotions. Unlike healthy subjects, reduced GSCORR means that MDD subjects remain unable to increase their functional connectivity between DMN regions (pACC/VMPFC, PCC, angular gyrus, etc.) to the whole brain when fast processing of negative emotions is required. Since we measure the functional connectivity of these DMN regions relative to the rest of the brain, i.e., non-DMN, lack of task-specific GSCORR increase must be considered a truly global (rather than local) phenomenon. Given that DMN-non-DMN relation in resting-state is abnormally tilted towards the DMN (Scalabrini et al., 2020), we assume that this affects task-related activity: as already increased in rest, GSCORR in DMN can no longer increase in MDD during high cognitive load in task states as required during fast processing of negative emotions. One may consequently assume decreased reactivity of DMN GSCORR changes to especially high task load resulting in reduced rest-task modulation (Northoff, 2011). As postulated in the RSHD (Northoff et al., 2011), reduced rest-task modulation leads to the lack of GSCORR differentiation between the different task conditions which is exactly what we observe in our MDD subjects.

4.3. Global signal topography and psychopathological symptoms

We demonstrate so far task-specific reductions in global brain activity and its topography in MDD. Given that even the GSCORR changes in DMN are global in their source, one may assume that different psychological domains including their respective symptoms are related to such global neural changes. We, therefore, probed in our unmedicated MDD sample whether the various symptom dimensions of MDD are all related to the task-specific GSCORR reductions in DMN and non-DMN. Our findings confirm our hypothesis. Firstly, this interaction between time speed and emotion in various DMN regions in HC, confirming their core functional role in both types of processing. Next we observed that GSCORR during specifically the condition of negative-fast is related to the retardation factor score of HDRS in MDD. Psychomotor retardation correlated negatively with GSCORR in DMN and non-DMN regions: higher scores in the degree of psychomotor retardation were related to lower values of GSCORR values. This suggests that the lack of task-related GSCORR increase in DMN (and non-DMN) during specifically fast-negative impairs the coupling of emotional and motor function resulting in psychomotor retardation. More generally, task-specific global changes in topography may potentially account for the coupling of different symptoms including affective, cognitive, vegetative, and motor as it is typical for MDD.

Is time speed with abnormal slowing a fundamental or basic neuronal disturbance in MDD? Being manifest in the time speed of the neuronal level itself, reduced slowing may shape psychological functions including motor, emotion, and cognition in a corresponding way in MDD. Accordingly, abnormal slowing may provide the link or "common currency" of neuronal and psychological levels (Kolvoort et al., 2020; Northoff et al., 2021, 2020). Motor, cognitive, and affective changes including their symptom coupling may then ultimately be traced to the temporal and spatial dynamics of the neuronal activity itself as postulated in "Spatiotemporal Psychopathology" (Fingelkurts and Fingelkurts, 2019; Northoff, 2016, 2018; Northoff et al., 2020).

4.4. Limitations

We did not include the measurement of interoceptive variables like respiration rate or heart rate in our fMRI acquisition. This made it impossible to investigate whether changes in specifically motor cortex (and adjacent sensory cortex) are related to changes in its entrainment of respiration-related input streams as it has been shown recently in HC subjects (Zhang et al., 2020). We can therefore not determine whether the breathing itself is abnormal in MDD leading to reduced motor cortex GS or whether reduced global synchronization in the motor cortex leads to reduced its reduced entrainment to the respiration-related input streams (Zhang et al., 2020). If the former were the case, one would expect the breathing rate change to hold across all four conditions of our task; this was not the case though as we observed motor cortex GS changes only during specifically negative emotion × fast time speed. Future studies combining both respiration measurement and GS topography are warranted to support our tentative assumption. Yet another feature of GS is its link to arousal as mediated by subcortical nuclei such as the nucleus basalis of Meynert (NBM) (Turchi et al., 2018; Zhang et al., 2020). A previous rest-task study on GS showed only the cortical regions' GS to be task-sensitive whereas subcortical regions did not show any task-related changes in GS (Zhang et al., 2020). We, therefore, refrained from investigating subcortical regions in our sample as we focused mainly on task-specific changes of GS.

5. Conclusion

Employing a unique acute unmedicated MDD subjects, we observed reduced GS topography in various DMN and some non-DMN regions during specifically the fast processing of negative emotions in MDD. Moreover, we showed how these changes in task-related GS topography are related to psychomotor retardation. Our findings demonstrate that, following recent resting-state findings, even task-specific seemingly local-regional changes in DMN in MDD are related to abnormalities in the brain's global topography. Additionally, these task-specific DMN changes mediate the temporal relationship of emotion (i.e., fast-negative stimuli) to psychomotor retardation. In sum, together with our previous study (Scalabrini et al., 2020), we provide further support for MDD being a truly global or systemic brain disorder where the DMN stands in abnormal relation to the whole brain during both rest and task states as suggested by the RSHD (Northoff et al., 2011). Moreover, these results suggest a key role for global changes in time speed with abnormal slowing on both neural and psychopathological levels of MDD as postulated in "Spatiotemporal Psychopathology" (Fingelkurts and Fingelkurts, 2019; Northoff, 2016, 2018; Northoff et al., 2020).

Ethical Statement

This work involving human subjects was ensured to be completed in accordance with the Declaration of Helsinki. The approval of this study was obtained from the Ethics Committee of the Second Affiliated Hospital of Xinxiang Medical University and Affiliated Zhongda Hospital of Southeast University. All participants provided written (signed) informed consent.

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CRediT authorship contribution statement

Xiang Lu: Formal analysis, Software, Writing – original draft,

Writing – review & editing, Visualization. **Jian-feng Zhang:** Formal analysis, Software, Methodology, Writing – original draft, Writing – review & editing. **Feng Gu:** Formal analysis, Software. **Hong-xing Zhang:** Investigation, Resources, Funding acquisition. **Meng Zhang:** Investigation, Resources. **Hai-san Zhang:** Investigation, Resources. **Rui-ze Song:** Investigation, Data curation. **Ya-chen Shi:** Data curation. **Kun Li:** Investigation, Resources, Data curation. **Bi Wang:** Investigation, Resources. **Zhi-jun Zhang:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Georg Northoff:** Conceptualization, Validation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.09.093.

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