Effective Connectivity Based EEG Revealing the Inhibitory Deficits for Distracting Stimuli in Major Depression Disorders

Jianxiu Li, Yanrong Hao, Wei Zhang, Xiaowei Li, and Bin Hu

Abstract—Emotional conflict control is impaired in major depression disorders (MDDs) and affects decision-making with further consequent social interactions dysfunction. However, neural correlates of conflict monitoring processes being modulated by different affective distractor stimuli are not clear in MDDs. In this article, we investigated abnormal neural basis of conflict monitoring processes in MDD patients by applying dynamic causal modeling (DCM) technique on electroencephalography (EEG). The results indicated that MDD patients showed lower N2 amplitudes regardless of stimulus conditions, and reduced activation within ACC region for incongruent stimuli, relative to healthy controls. Especially, MDDs had more negative N2 amplitudes to happy incongruent trials than happy congruent trials. Source localization analyses revealed that MDD patients had significantly enhanced left inferior temporal gyrus (ITG) activation, which is involved in written words processing. Further DCM analysis provided abnormal neural correlates through greater backward connections (fusiform→ITG, amygdala→ITG) on happy incongruent trials than happy congruent trials in MDD group. These findings indicate that only sad words induce significantly greater interference effects to positive target faces in MDD patients, which may be associated with ITG activity dysfunction. The findings may share new insights into the neural mechanisms of emotional conflict processing in MDDs.

Index Terms—Dynamic causal modeling, EEG, effective connectivity, emotional conflict, major depression disorders

1 Introduction

The capacity of the individuals to process emotional conflict is central for emotional self-regulation [1], [2]. Major depression disorder (MDD) as a serious and mostly incapacitating disorder is characterized by multiple abnormalities, including persistent depressed mood, diminished ability to think or concentrate, or indecisiveness [3]. Investigators have reported that depressed individuals selectively attend to negative information and are difficult to disengage attention from them, manifesting attentional bias toward negative stimuli [4], [5]. This negative attentional bias makes it easier for depression to misinterpret emotional conflict conditions [6], leading to a dysfunction in conscious perception and social interactions [7]. Therefore, in order to better elucidate the pathophysiology of MDD, it is important to understand the neural mechanisms emotional conflict processing.

The face-word Stroop task where task-irrelevant stimulus directly conflicts with the task-relevant stimulus is a potent way of gauging the emotional conflict [8], [9]. The task comprises a series of positive or negative facial expressions with emotional distractor word that are either emotionally congruent or incongruent with the presented face. The processing of task-irrelevant emotional words will interfere with the participant's cognitive processing for emotional faces. Slower reaction time and lower accuracy for incongruent stimuli relative to congruent stimuli have been reported in both healthy controls (HCs) [2], [9] and MDD patients [9], [10]. Recently studies have explored the brain mechanisms of emotional conflict processing in MDD patients [9], [11], [12], and found that patients exhibit the abnormalities of emotional conflict processing. However, the characteristics of cognitive processes being modulated by different affective distracting stimuli in emotional conflict monitoring are still indeterminate. A deeper understanding of which cognitive sub-processes are affected by conflict types is essential.

Electroencephalography (EEG) with high temporal resolution is suited to examine detailed time course of the neural processing [13], [14]. Several studies have reported N2 is associated with conflict monitoring [15], [16], [17]. N2 component is a negative-direction waveform detected at frontocentral electrodes that peaks between 250–350ms poststimulus. As an index of conflict processing, the N2

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component has been shown to be more negative on incongruent trials relative to congruent trials [18], [19], which is interpreted as increased interference [20]. Source location studies found that the generation of the N2 is implicated in the activation of anterior cingulate cortex (ACC) [16], [21]. Based on the conflict monitoring theory [22], [23], the ACC detects conflict or errors in performance and subsequently prompts prefrontal cortex areas to enhance control. Furthermore, we examined the face-sensitive N170 and vertex positive potential (VPP) components, which are significantly affected by emotion in the early phase of perception and attention processing [13], [24]. Haxby, *et al*. [25] reported that fusiform gyrus, occipital face area, and superior temporal gyrus comprise the core neural network for face perception. In particular, the magnitude of emotional conflict is likely to dependent on the degree of involuntary processing of emotionally distracting words. Existing researches recognize the critical role of left-hemisphere networks in the processing of written words, including the left anterior fusiform gyrus and left middle temporal gyrus [26], [27]. However, investigations of the interaction among brain regions involved in emotional face and word processing are relatively few.

Effective connectivity reveals the information flow from one brain region to another. Dynamic causal modeling (DCM) is a novel and effective connectivity approach that can infer hidden neuronal states behind brain responses by modeling EEG data as a dynamic input-state-output system, based on a Bayesian framework [28]. The theoretical background can be found in previous studies [28], [29]. DCM has been employed to model paradigms and attempts to explain event-related potentials (ERPs) using differences in terms of coupling changes among sources, especially for the both auditory and visual tasks where a clear driving sensory input can be defined [16], [30], [31]. However, to our knowledge, no studies focused on the DCM analysis in the face-word Stroop task in MDDs to investigate cognitive processes of emotional conflict monitoring. By combining ERPs with DCM technique, we were interested in exploring the neural evidence to facilitate our understanding of the emotional conflict processing.

The first aim of the current study was to understand the time series of conflict monitoring processes in MDDs. Based on prior literatures, we hypothesized that, MDD patients would demonstrate reduced emotional conflict monitoring abilities relative to HC subjects, manifesting as smaller N2 amplitude and reduced ACC activation. Moreover, MDD patients have difficulty suppressing attention to negative stimuli [4], [5]. Therefore, we expected that sad distractor words induced larger conflicts to the positive target faces in MDD patients, reflecting larger N2 amplitudes for happy incongruent trials than happy congruent trials. Because N170 and VPP components are indices of face-sensitive brain processes [13], [24], MDD group was expected to show larger N170 and VPP amplitudes on happy incongruent trials. In addition, for MDD patients, we also hoped to observe greater activities in left anterior fusiform gyrus and left middle temporal gyrus, which is important for the processing of written words.

Another aim was to evaluate the effective connectivity within the cortical areas implicated in emotional faces and distracting words processing. In particular, we focused DCM analysis on the effects of congruence on happy faces, which investigated the neural correlates of inhibitory deficits for negative distractor materials on conflict monitoring processes in MDD patients. We speculated that the observed differences in ERP amplitudes between happy congruent stimuli and happy incongruent stimuli could be explained by changes involving forward connections, backward connections, or bidirectional connections among brain regions. The study of the effective connectivity in MDDs may inform us the mechanisms of affective computing in the brain.

TABLE 1
Demographic Characteristic for the MDDs and HCs

	MDDs	HCs	Test
Age (year)	37.30±11.27	31.90±9.44	$t(138) = 1.64$ $p = 0.11$
Female/male	9/11	11/9	$\chi^2(1) = 0.40$ $p = 0.53$
Education			
Primary school	3(15%)	0(0%)	$\chi^2(2) = 3.82$
Secondary education	13(65%)	13(65%)	$p = 0.15$
University education	4(20%)	7(35%)	

Abbreviations: MDDs, major depression disorders; HCs, healthy controls.

2 Material and Methods

2.1 Subjects

The study was approved by the Ethics Committee of the Tianshui Third People's Hospital. All subjects provided written informed consent and were compensated for their participation.

A total of 22 MDD patients were enrolled in this study. The diagnosis of patients was determined by a psychiatrist using the Mini International Neuropsychiatric Interview [32]. Meanwhile, the Patient Health Questionnaire-9 (PHQ-9) was applied to assess the severity of depressive symptoms. Supplementary material, which can be found on the Computer Society Digital Library at http://doi.ieeecomputersociety.org/10.1109/TAFFC.2021.3054953 displays a detailed inclusion and exclusion criteria. Twenty healthy controls (HCs) were recruited from the local community, and had no history (including personal and family) of psychiatric illness, psychoactive substance abuse, and depression.

All enrolled subjects were right-handed and had a normal or corrected-to-normal vision. Two MDD patients were excluded due to huge muscle artifacts. As a result, 20 MDDs and 20 HCs were included in the final analysis. Table 1 shows the demographic characteristics of subjects. MDDs and HCs were matched for age, gender, and education ($ps > 0.05$). As expected, patients exhibited significant greater PHQ-9 scores relative to HC individuals.

2.2 Study Procedure

We employed a face-word Stroop task (Fig. 1) [33]. For ease of comparison with literature studies, happy and sad faces were drawn from the well-known international affective pictures systems (IAPS) [34] and were converted into grey scale. All non-facial features such as hair or clothing were removed, and a red Chinese character "高兴" (which means "happy") or "悲伤" (which means "sad") was roughly projected on the

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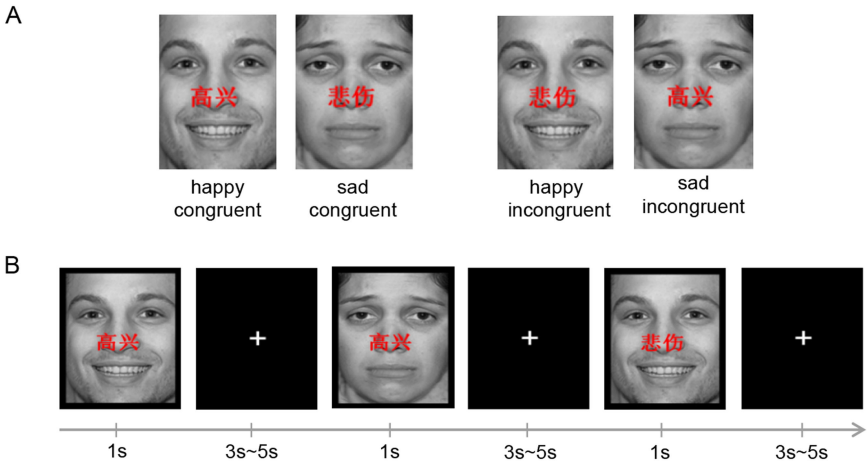

Fig. 1. Face-word Stroop task. (A) An example of stimuli materials for four experimental conditions. (B) Example timelines used in the face-word Stroop task. In each trial, subjects needed to recognize the facial affect with happy or sad expressions that had either "高兴" (which means "happy") or "悲伤" (which means "sad") word written across them. Words were written in red.

nose of face (Fig. 1A). The crossing of distractor word types with target face types was divided into four sets of 40 items each, comprising happy congruent trials (the word "高兴" overlapped happy face), happy incongruent trials (the word "悲伤" overlapped happy face), sad congruent trials (the word "悲伤" overlapped sad face), and sad incongruent trials (the word "高兴" overlapped sad face).

Fig. 1B describes the sequence of events. In each trial, stimulus showing happy or sad facial expression with an emotional word overlapped was presented for 1s in the center of screen. The inter-trial interval varied randomly between 3s to 5s, during which subjects were presented with a fixation cross. Subjects were instructed to ignore the word and to made emotional valence (happy or sad) judgments of faces as quickly as possible. The experiment consisted of 160 trials in total with 40 trials assigned into each condition, and was run on E-Prime software (version 2.0, Psychology Software Tools Inc., Pittsburgh PA, USA). Reaction times (RTs) were analyzed for both MDD and HC groups (see Supplementary material for details, available online).

2.3 EEG Data Acquisition and Preprocessing

EEG activity was recorded by Net Station software (version 4.5.4) using the 128 Ag/AgCl electrodes embedded in a flexible cap (Electrical Geodesics; Koninklijke Philips, Amsterdam, The Netherlands) in a quiet room. The impedance of each electrode was less than 60 Kohm throughout the recording [11]. The Supplementary material, available online presents the preprocessing step of EEG data.

The pre-processed EEG data were segmented into 800 ms intervals that ranged from -200 ms before stimulus onset until 600 ms thereafter, and the activity from -200 ms to -100 ms pre-stimulus serving as the baseline. The pre-stimulus baseline period ended at -100 ms to avoid including any stimulus-related activity that smeared into the baseline [35]. Approximately 2 percent of trials (signal amplitude exceeding $\pm 100\ \mu V$) were excluded for each trial type.

ERP analyses mainly focused on VPP, N170 components (170-230 ms) associated with face processing, and N2 component (260-320 ms) associated with conflict monitoring. The choice of time windows was guided by previous studies [13], [17], [36]. We extracted ERP amplitudes at the electrode sites (VPP and N2: FC1, FC2, C1 and C2; N170: P7 and P8) by measuring peak values in the time windows for each participant. Then an average activity measured at these electrode sites was calculated. For ERP amplitudes, we performed a $2 \times 2 \times 2$ repeated-measures ANOVA with emotional face (happy vs. sad) and congruency (congruent vs. incongruent) as within-subjects factors, and group (MDDs vs. HCs) as a between-subjects factor using the SPSS statistical software. A Greenhouse-Geisser method was used to correct for non-sphericity.

2.4 Correlation Analysis

To examine the relationship between behavior and electrophysiological signature, we used Pearson's correlation test to correlate the RTs and ERP amplitudes on congruent and incongruent trials separately. In addition, the correlations between the ERP magnitudes were evaluated to investigate the effect of early face processing on conflict detection. Then, the group difference was compared by applying Fisher's z transformed correlation coefficients. Z-critical value is 1.96 for $p<0.05$ significance level.

2.5 Source Reconstruction of ERP Components

We removed the electrode located on the neck/face area, and finally used 104 scalp electrodes for source reconstruction. 3D source reconstruction routine implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm/), was used to identify ERP cortical sources activity. First, we created individual head meshes consisting of 8196 vertices using a template structural image "single_subj_T1.nii" (as provided by SPM12). The coordinate system of EEG electrodes was coregistered into MRI space (MNI coordinates). Second, we calculated the EEG forward solution based on a 3-layered boundary element method (BEM), including scalp, skull and brain compartment [37]. The final step is to invert the resulting forward model using the multiple sparse priors (MSP) algorithm within a Parametric Empirical Bayesian framework to obtain brain activity in source space [38]. MSP algorithm utilizes both hierarchical bayesian and empirical bayesian to reconstruct the distributed dipole sources, which allows inferring the changes of effective connectivity in task

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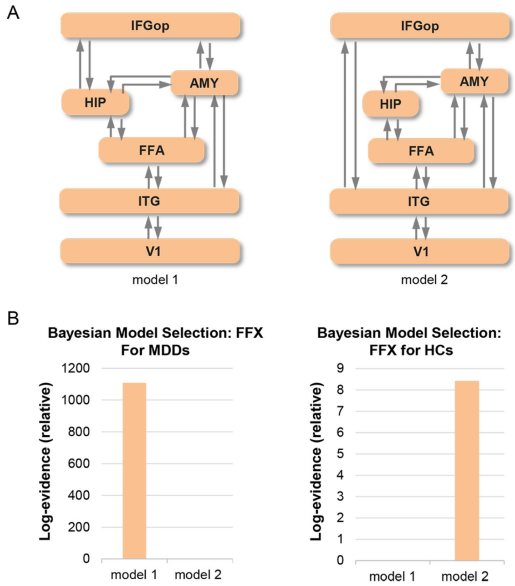

Fig. 2. DCM model space. (A) Two model structures are consist of a combination of forward, backward, and bilateral connections among six brain regions. Model 2 differs from model 1 in the presentation of bilateral connections between ITG and IFGop. V1 = primary visual cortex; ITG = inferior temporal gyrus; FFA = fusiform gyrus; HIP = hippocampus, AMY = amygdala; IFGop = inferior frontal gyrus pars opercularis. (B) BMS results at the group level under FFX confirmed that model 1 is the most likely model hierarchy for MDDs. Model 2 is the most likely model hierarchy for HCs.

execution. The Greedy Search fitting algorithm was used for optimizing the MSP approach [39].

We performed source analysis on VPP (170-230 ms) and N2 (260-320 ms) components. The reconstructed images were obtained for each participant on happy congruent trials, happy incongruent trials, sad congruent trials, and sad incongruent trials. The statistical analysis of source imaging maps was performed using a full factorial ANOVA of second-level random-effects analysis based on SPM12, with emotional face, congruency and group as the three factors. The statistical threshold was set at $p<0.05$ with family-wise error (FWE) correction.

2.6 Dynamic Causal Modeling

The DCM aims to interpret ERPs using a coupled cortical source network through a biologically plausible model (neural mass model). Its key is to form assumptions and construct a plausible model. Details on this standard procedure of the DCM analysis can be found in several publications [29], [31]. Because MDD patients selectively attend to negative information, we were primarily interested in the effects of negative distractive words on MDDs in emotional conflict processing.

We modeled ERP differences between happy congruent trials and happy incongruent trials using the time interval of 0-400ms, because these signals can capture the cortical responses of N170, VPP, and N2 components. The following two-step strategy was used to reduce the number of potential model combinations [31]. First, we specified two plausible model pairs (Fig. 2A) to identify whether emotional conflict monitoring was mediated by the processing of task-irrelevant emotional information. The model was restricted to the left hemisphere where the main findings with regard to the distractor words processing were evident in previous studies [26], [27]. The two models share common structures, including primary visual area (V1), inferior temporal gyrus (ITG), fusiform (FFA), hippocampus (HIP), amygdala (AMY) and inferior frontal gyrus pars opercularis (IFGop), yet they differed in some connections. The selection of nodes in the DCM model was guided by the source localization results in current study and some literatures [33], [40], [41], and the MNI coordinates of six selected regions were specified as: V1{-36;93;-8}, ITG{-14;-16;-48}, FFA{-46;-24;-24}, HIP{-28;-78;16}, AMY{-24;0;-22}, and IFGop{-46; 16;28}. We constructed the following model 1: ITG close to V1 receives subcortical visual inputs. From ITG onwards, the pathway was considered to hierarchically connect FFA and AMY. In addition, the FFA was connected with AMY and HIP for mediating the face perception [40]. An indirect pathway was specified from the HIP to AMY. At the highest level in the hierarchy, the HIP and AMY were connected with IFGop, respectively. All these connections were reciprocal. Model 2 added the connection between ITG and IFGop, which may be involved in interactions between stimulus visibility and task [27].

Second, once the optimal model was established, we further examine where the task-specific modulation occurred. We constructed two additional models by altering the modulation as forward (F) and backward (B), in contrast to the optimal model (bidirectional connection (FB)) that resulted from the first step. Subsequently, Bayesian model selection (BMS) was applied to identify the most likely connectivity pattern tested at the group level under the fixed effects assumption (FFX) [42].

3 Results

3.1 Behavioral Data

The results of the statistical test for RTs showed a significant main effect of group ($F_{1,38} = 6.66$, $p = 0.014$), with MDD participants (667.16±57.13 ms) responding more slowly than HCs (619.44±70.56 ms). Furthermore, main effects of emotional face ($F_{1,38} = 23.88$, $p < 0.0005$), congruency ($F_{1,38} = 29.07$, $p < 0.0005$), and a marginal interaction effect of emotional face×congruency×group ($F_{1,38} = 3.24$, $p = 0.079$) were also observed. The significant main effect of congruency demonstrated that the current paradigm elicits the intended Stroop effects, and highlights RT slowing specific to incongruent trials in participants.

To avoid missing some results, as recommended by Boik [43], we conducted simple-simple effect analyses to understand the causes of the marginally significant 3-way interaction. Specifically, we explored the effect of congruency for each level of emotional face in MDD group and HC group, and the effect of group for each level of emotional face and congruency. Table S1-S2 and Fig. S1A present the results of simple-simple effect analyses. We found that, when identifying happy faces, RTs of incongruent trials were longer than those of congruent trials in both MDDs ($F_{1,38} = 27.91$, $p < 0.0005$) and HCs ($F_{1,38} = 5.22$, $p = 0.028$). In addition, HCs had larger RTs to sad incongruent trials relative to sad congruent trials ($F_{1,38} = 5.02$, $p = 0.031$). The results of between-group comparisons showed that MDD group had significant larger RTs on happy incongruent

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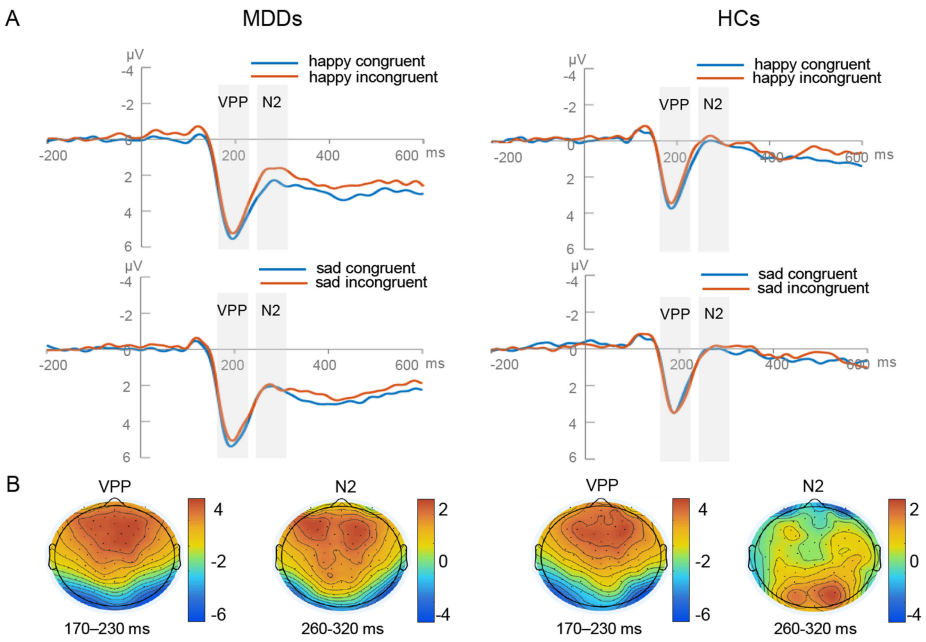

Fig. 3. ERP waveforms and scalp topographies. (A) ERP waveforms were averaged over FC1, FC2, C1, and C2 to reflect the ANOVA findings for the VPP and N2. (B) Scalp topographies of the VPP and N2 were obtained by averaging the topographies across all conditions.

trials ($F_{1,38} = 6.60$, $p = 0.014$), on sad congruent trials ($F_{1,38} = 7.20$, $p = 0.011$), and on sad incongruent trials ($F_{1,38} = 6.15$, $p = 0.018$) compared to HC group.

We further compared the magnitude of interference effects between MDD group and HC group. The RT differences ($\mathrm{RT}_{\text{incongruent trials}} - \mathrm{RT}_{\text{congruent trials}}$) for each emotional face were entered into a 2×2 ANOVA with two factors: group (MDDs vs. HCs) and $\mathrm{face}_{\mathrm{score}}$ ($\mathrm{happy}_{\mathrm{score}}$ vs. $\mathrm{sad}_{\mathrm{score}}$). Only a trend for an interaction between $\mathrm{face}_{\mathrm{score}}$ and group was observed ($F_{1,38} = 3.24$, $p = 0.079$). Further simple effect tests clarified that this interaction was due to significantly larger RT Stroop score for happy faces ($F_{1,38} = 4.50$, $p = 0.041$) in MDD group (26.63±20.24) compared with HC group (11.52±24.63), but not for sad faces (Fig. S1B).

3.2 ERP Data

Table S3 lists the detailed amplitudes of ERP components. For N170 amplitudes, there was no significant main or interaction effects.

VPP amplitudes showed a main effect of group ($F_{1,38} = 4.61$, $p = 0.038$), reflecting a larger VPP amplitude in MDD patients ($6.00 \pm 2.14\,\mu\mathrm{V}$) than HCs ($4.31 \pm 2.89\,\mu\mathrm{V}$), as shown in Fig. 3.

For N2 amplitudes, there was a significant main effect of group (Fig. 3, $F_{1,38} = 11.83$, $p = 0.001$), suggesting more negative N2 amplitude in HC individuals ($-0.65 \pm 2.36\,\mu\mathrm{V}$) than MDD patients ($1.40 \pm 1.61\,\mu\mathrm{V}$). In addition, there was a significant main effect of congruency ($F_{1,38} = 4.75$, $p = 0.036$) and a marginal interaction effect of emotional face × congruency × group ($F_{1,38} = 3.56$, $p = 0.067$). Consistent with behavioral data analysis, for the above three-way interaction, simple-simple effect analyses were performed, and the results revealed that MDD patients had more negative N2 amplitudes to happy incongruent trials relative to happy congruent trials (incongruent, $1.00 \pm 1.66\,\mu\mathrm{V}$; congruent, $1.73 \pm 1.35\,\mu\mathrm{V}$; $F_{1,38} = 11.44$, $p = 0.002$).

3.3 Correlation Analysis

On happy incongruent trials, a significant correlation between VPP amplitudes and N2 amplitudes was observed in MDDs patients ($r = 0.452$, $p = 0.046$). Fig. S2A (left panel, blue line) shows details of the results that as the VPP amplitude increased, the N2 amplitude became more positive (i.e., smaller N2 amplitude). This pattern also was observed on sad congruent trials ($r = 0.557$, $p = 0.011$), but not in HC group (Fig. S2B).

Moreover, negative correlations of N2 amplitudes with RTs on happy incongruent trials ($r = -0.58$, $p < 0.01$, $Z = 2.10$), sad congruent trials ($r = -0.48$, $p < 0.04$, $Z = 2.44$) and sad incongruent trials ($r = -0.51$, $p < 0.03$, $Z = 2.42$) were observed in HC group, but not in MDD group (Fig. S3). The direct statistical tests revealed $Z > 1.963$, $p < 0.05$, which provided firm evidence for both groups being different with regard to the correlations between RTs and ERP amplitudes.

3.4 Source Reconstruction Results

We compared the activation of brain sources from two aspects: 1) the comparison between congruent trials and incongruent trials within a single group (between-condition comparison); 2) the comparison between the groups in the incongruent trials (between-group comparison). Fig. 4 illustrates the results of source analyses (p<0.05 with FWE correction).

3.4.1 *Between-Condition Comparison*

The differences between incongruent trials and congruent trials only were found in the time interval of the VPP, but not in time interval of the N2. For VPP component, current densities exhibited significant differences in MDD group, with activations being higher during happy incongruent trials than happy congruent trials (Fig. 4A). As demonstrated in Table 2, in MDD group, these activations were observed

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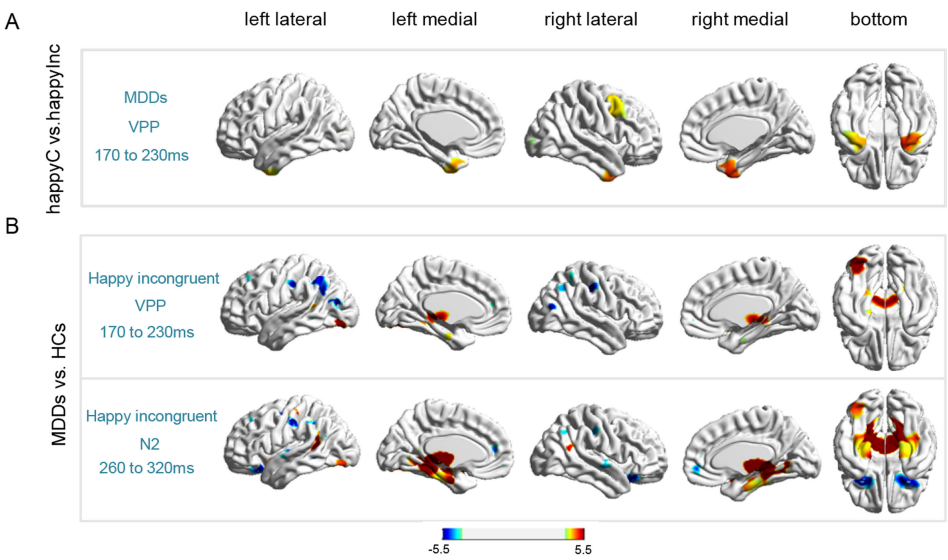

Fig. 4. ERP Source analysis. (A) The statistical differences between happy congruent trials (happyC) and happy incongruent trials (happyInc) are shown for VPP component in MDDs. The brain regions labeled with yellow/red indicate happyInc>happyC. (B) The statistical differences between MDDs and HCs on happy incongruent trials in time windows of VPP and N2 components, respectively. The brain regions labeled with yellow/red indicate MDDs>HCs, while green/blue indicates MDDs<HCs. Significance level is 0.05 with FWE corrected.

TABLE 2
Comparison of Congruent and Incongruent Tasks for MDD Patients in Time Ranges of VPP

Structure	Left/Right	MNI coordinates			P^*	Z
		x	y	z		
Happy incongruent > happy congruent						
Middle frontal gyrus	R	36	6	62	$p = 0.013$	4.49
Inferior frontal gyrus pars opercularis	R	22	6	32	$p = 0.014$	4.47
Fusiform gyrus	L	-46	-24	-24	$p = 0.008$	4.61
	R	14	-16	-48	$p<0.0005$	5.26
Inferior temporal gyrus	L	-16	-14	-48	$p = 0.004$	4.79
Superior occipital gyrus	L	-18	-86	2	$p = 0.034$	4.25
Cuneus	R	2	-92	20	$p = 0.048$	4.15

*Significant at $p<0.05$.

in right middle frontal gyrus (MFG), right inferior frontal gyrus pars opercularis (IFGop), fusiform gyrus (FFA), left inferior temporal gyrus (ITG), left superior occipital gyrus (SOG), and right cuneus. In addition, the results of congruency on sad faces did not show significant differences in both groups.

3.4.2 Between-Group Comparison

Incongruent stimuli with simultaneous emotion and conflict processing are considered to have higher network involvement. Thus, we examined the differences between MDDs and HCs in the cortical areas on incongruent trials.

Fig. 4B presents the significant results between two groups on happy incongruent trials. As showed in Table 3, for the VPP, compared with HC group, MDD group had higher activity in left inferior occipital gyrus (IOG), left middle temporal gyrus (MTG), left lingual and left precentral, and lower activity in left superior frontal gyrus (SFG) and inferior parietal gyrus (IPG). For the N2, MDD patients showed decreased current densities in anterior cingulate gyrus (ACC), left SFG, superior temporal gyrus (STG), and insula on happy incongruent trials. Additionally, MDDs had higher activity in postcentral, left FFA, MTG and left IPG regions relative to HC group (Table 3).

For sad incongruent trials, we observed significantly decreased activations in ACC, SFG and STG regions in MDDs than HCs. The detailed results of group differences are summarized in Table S4.

3.5 Dynamical Causal Modeling

3.5.1 Inference on the Model Space

The neural mechanism underlying conflict monitoring processing that are modulated by the negative distractor stimuli is the interest point of current research. As illustrated in Fig. 2B, BMS results at the group level under FFX revealed that the model 1 was far superior to the model 2 for MDD patients. On the contrary, HC individuals had consistent evidence in favor of the model 2.

We then investigated the task-related modulation mechanism by comparing the optimal model with two derivative models (Fig. 5; MDD group: model 1-F, model 1-B and model 1-FB; HC group: model 2-F, model 2-B and model 2-FB). In MDDs, BMS results at the group level under FFX

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TABLE 3
Comparison of MDD Patients and HC Group for Happy Incongruent in Time Ranges of VPP and N2

Structure	Left/Right	MNI coordinates			p^*	Z
		x	y	z		
VPP component						
Happy incongruent: MDDs > HCs						
Inferior occipital gyrus	L	-40	-84	-12	$p<0.0005$	5.62
Lingual	L	-8	-26	-6	$p<0.0005$	5.33
Middle temporal gyrus	L	-50	-48	12	$p = 0.003$	4.82
Precentral	L	-38	-12	52	$p = 0.041$	4.20
Happy incongruent: HCs > MDDs						
Superior frontal gyrus	L	-20	34	48	$p = 0.022$	4.36
Superior temporal gyrus	L	-46	-40	16	$p<0.0005$	5.35
Inferior parietal gyrus	L	-48	-26	36	$p<0.0005$	5.73
	R	38	-50	52	$p<0.0005$	4.72
N2 component						
Happy incongruent: MDDs > HCs						
Postcentral	L	-34	-22	50	$p<0.0005$	7.04
	R	30	-38	38	$p<0.0005$	5.42
Fusiform gyrus	L	-34	-80	-14	$p = 0.004$	4.84
Middle temporal gyrus	L	-52	-50	12	$p<0.0005$	6.01
	R	58	-54	18	$p = 0.001$	5.45
Inferior parietal gyrus	L	-32	-42	42	$p<0.0005$	5.74
Happy incongruent: HCs > MDDs						
Superior frontal gyrus	L	-22	-6	44	$p = 0.001$	5.18
Superior temporal gyrus	L	-56	-16	4	$p = 0.001$	5.25
Insula	R	30	22	-18	$p = 0.0001$	5.23
Anterior cingulate gyrus	L	-12	46	12	$p = 0.003$	4.91
	R	8	44	12	$P = 0.038$	4.29

*Significant at $p<0.05$.

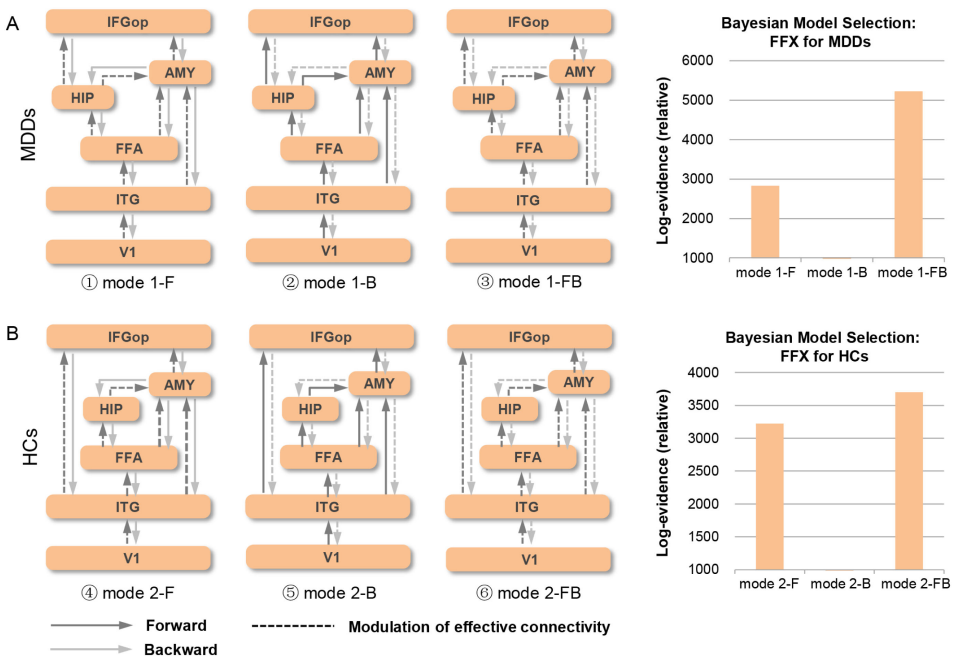

Fig. 5. The models for testing task-related modulation. BMS results at the group level under FFX confirmed that model 1-FB and model 2-FB are the most likely model hierarchy for MDDs (A) and HCs (B), respectively. The modulation is the effect of congruency on the happy trials.

indicated clear evidences for a prominent modulation of the model 1-FB (Fig. 5A, the largest log-evidence). In HCs, we observed that the model 2-FB (Fig. 5B) in log-evidence was far superior to the model 2-F modulation and model 2-B modulation under FFX at the group level, respectively. Collectively, bidirectional modulation appears to be more vital for happy incongruent network compared to happy congruent network.

3.5.2 *Inference on the Modulatory Effect*

Fig. 6A shows significant connections for the best model within MDDs (blue) and HCs (wathet blue), respectively.

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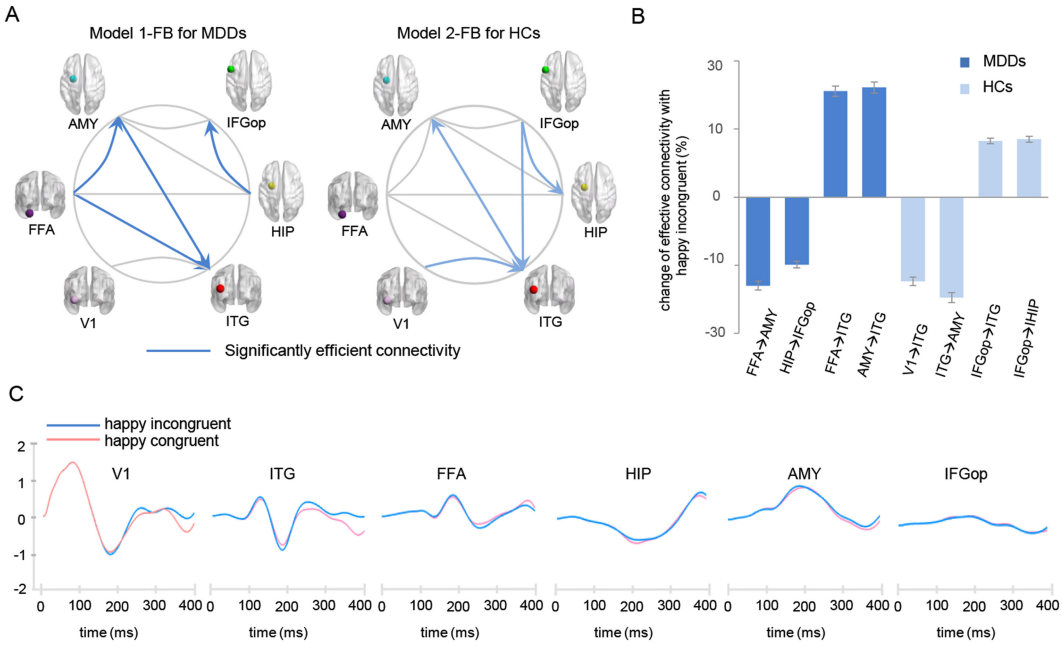

Fig. 6. Effective connective. (A) Pathways with connectivity parameters significantly different from zero in MDDs (blue) and HCs (wathet blue). The connections are labeled as the relative change of effective connectivity on happy incongruent trials versus happy congruent trials ($p<0.05$, corrected). (B) Specific values of significant connections in MDDs and HCs. (C) Time series of each brain region averaged among MDD patients in the most probable model 1-FB. The time series for each patient was normalized by their mean and standard deviation.

The connections are labeled as the relative change of effective connectivity on happy incongruent trials than happy congruent trials. As can be seen in Fig. 6B, MDD patients had weaker forward connections (FFA→AMY, HIP→IFGop) and stronger backward connections (AMY→ITG, FFA→ITG). In HC individuals, the strengths of the forward connections (V1→ITG, ITG→AMY) were decreased, while the strengths of the backward connections (IFGop→ITG, IFGop→HIP) were increased. Further, the source time series, averaged among MDD patients in the most probable model 1-FB, suggested that the more negative N2 amplitudes on happy incongruent trials versus happy congruent trials primarily associated with enhanced activity in left ITG, as showed in Fig. 6C.

4 Discussion

The present study employed a face–word Stroop paradigm to investigate the impaired emotional conflict processing in MDD patients. First, ERP components were applied to explore the temporal characteristics of brain activity. Then we investigated the mechanism underlying the effect of emotional task-irrelevant stimuli on emotional monitoring processes.

4.1 Behavior

For behavioral data, a significant main effect of congruency (slower RTs for incongruent trials than congruent trials) was observed in participants performing the face-word Stroop task, supporting the validity of the paradigm. Specifically, MDDs and HCs showed robust emotional Stroop effect on happy incongruent trials than happy congruent trials, as previously reported [9], [10]. The difference in RTs between congruent trials and incongruent trials, named Stroop score, allows assessing the magnitude of interference effect [44]. We further compared the between-group differences on Stroop scores and results showed that MDDs had higher RT Stroop scores compared to HCs. Deeper processing of negatively distractive stimuli in MDDs may lead to stronger behavioral Stroop effects. The findings support the ideas that the magnitude of conflict can be evaluated by the deterioration of behavioral performance [45], [46]. In addition, compared to sad congruent trials, HC group exhibited longer RT for sad incongruent trials, but not in MDD group. When identifying the sad facial expressions, in MDD group, positive irrelevant words did not significantly interfere with the processing of negative target faces. The results of this study suggest that emotional conflict processing in MDDs may be characterized by an attentional bias for negative distractive stimuli. Notably, in HC group, although both positive and negative distractive stimuli interfere with the participant's cognitive processing for emotional faces, the overall RTs of HCs was lower than that of MDDs, which is consistent with the previous findings [11], [17].

4.2 ERPs Findings

Abnormal modulation of emotional expressions on early components is found to be variable in MDDs [36], [47]. Inconsistent results observed may be due to different stimulus types. In our study, we found that patients with MDD had larger VPP amplitudes over the fronto-central region relative to HCs, regardless of stimulus conditions. VPP component is affected by emotion expressions in the early phase of perception and attention processing, which has been confirmed in previous study [48]. The results exhibit that MDD patients allocate larger attention to emotional faces relative to HCs. In addition, MDD group had comparable VPP amplitudes for happy and sad faces. It may be explained by the study of Luo, *et al.* [24], who proposed that affective facial expressions (i.e., fearful and happy) have not been distinguished during the time period of the VPP. The present results support the

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observation that relative to HC individuals, stimulus processing is enhanced in MDD patients regardless of its emotional content. These findings might reflect an increased motivation or task engagement in MDD patients, as better performance on the task might be more important to patients. Furthermore, consistent with the previous study [13], we did not find amplitude differences for the N170.

Neuropsychological studies have highlighted the role of the N2 in conflict monitoring, demonstrating that larger N2 amplitudes may reflect greater resources being devoted to action monitoring [18], [21]. As expected, we found lower N2 amplitudes in MDD group compared to HC group. Previous studies examined the N2 in populations with impaired ability to suppress task-irrelevant stimuli, and found attenuated N2 amplitudes [44], [49]. Based on the literatures and the results of the N2 in current study, we thought that MDD patients have worse detection processing for emotional conflicts relative to HCs, who might be more susceptible to misinterpret conflict conditions during conflict detection processing. Notably, in MDD group, we observed enhanced N2 amplitude to happy incongruent than happy congruent trials. As mentioned in [50], N2 component is sensitive to the extent to which individuals attend to task-irrelevant information than to task-relevant information. The finding suggests that MDD patients recruit greater cognitive resources to sad distractor words during the processing of positive target faces, which can also be verified by worse performance on happy incongruent trials. In particular, only sad distractor words in MDD group evoked larger emotional conflict. Further, we performed correlation analyses of RTs and N2 amplitudes for each of four experimental conditions. Except for happy congruent stimuli, significant negative correlations between RTs and N2 amplitudes were found in HCs under other conditions, whereas no such effect was present in MDDs (Fig. S3). The results corroborate the ideas of Wiebke, *et al.* [45], suggesting that the degree of response conflict, as indexed by N2 amplitudes, correlates with subsequent behavioral performance in HC group. Combined with behavioral data, these results revealed that MDD patients have a dysregulation of conflict monitoring processing when dealing with emotional conflicts.

4.3 Cortical Activity Findings

For VPP component, MDD patients had significant hyperactivity in right middle frontal gyrus (MFG), right inferior frontal gyrus pars opercularis (IFGop), fusiform gyrus (FFA) and left inferior temporal gyrus (ITG) on happy incongruent trials relative to happy congruent trials. ITG activity has been identified as the node of core semantic network [51]. The region is activated when participants make judgment about semantic content of the written text. In other several studies, researchers have found that the MFG and IFGop are implicated in semantic processing of words [26], [27]. The emergence of Stroop effect is contingent on interference caused by the automaticity of reading. These findings suggest that patients with MDD might be unable to neglect the effect of negative task-irrelevant distraction, eventually leading to abnormal emotional conflict processing in patients. In addition, patients had lower activation in inferior parietal gyrus (IPG) on happy incongruent trials compared to HCs. The IPG has been proved to be important for orientation of attention to target stimulus [52]. Boros, *et al.* [53] noted that when more effort is required to actively extract semantic information from visual input, it is accompanied by IPG deactivation. The results suggest that MDDs have decreased processing to positive target faces. In conclusion, the high activation of important word reading areas and the low activation of important facial perception areas may be responsible for the strong N2 amplitude of the happy incongruent trials observed in MDDs.

For N2 component, source localization analyses indicated that MDDs had reduced activation within anterior cingulate (ACC) region in response to incongruent trials, relative to HCs. The conflict monitoring theory proposes that ACC contributes to cognitive control by detecting conflicts in information processing and subsequently prompts areas of the prefrontal cortex to increase control [22], [23]. Previous studies have shown that cognitive control is impaired in patients with MDD [9], [11], [12], and this dysfunction is accompanied by poor behavioral performance during the incongruent conditions [44], [54]. In our study, the deactivation in ACC provide evidence of impaired conflict processing in MDD patients, and may be associated with the larger Stroop interference effects. In addition, a previous study indicated that distractors can consciously trigger top-down control processes by modulating ACC activity to attenuate conflict [45]. Etkin, *et al.* [33] partially applied DCM to perform psychophysiological interaction analysis in a Stroop task and reported that HC group resolve emotional conflicts by rostral ACC to inhibit amygdala activity. Therefore, a disruption of ACC in its performance monitoring function may contribute to the impaired cognitive control in MDD patients. These findings have implications for our understanding of emotional conflict processes in MDD patients.

4.4 Emotional Conflict Monitor Networks

As mentioned above, MDD patients exhibited inhibitory deficits for negative semantic materials. Further DCM analysis provided abnormal neural correlates through greater backward connections (AMY→ITG, FFA→ITG) on happy incongruent trials than happy congruent trials. The activation of AMY has been associated with the processing of both negative and positive emotions [30], [55], [56], [57], and plays a vital role in enhancing emotional attention [58]. A major model for prioritizing processing and attention to emotional stimuli posits that the amygdala modulates sensory pathways through its projections to the visual cortex. Through this mechanism, the AMY facilitates perception and attention to emotionally salient stimuli on the basis of rapid stimulus assessment [59]. Furthermore, the results of source localization showed that happy incongruent stimuli evoked greater activations in ITG region relative to happy congruent stimuli in MDDs. The increased responses in ITG region may reflect amplified processing of sensory pathways mediated by the AMY. Specially, the ITG has been considered to be a key region for the processing of written text [51]. The stronger coupling may contribute to the greater interference effects observed in MDDs being induced by negative distractor words. Haxby, *et al.* [25] reported that FFA area is responsible for facial visual analysis and forward transport of their output to the anterior affective areas that include the AMY, insula,

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and inferior frontal gyrus. The increased backward connection from FFA to ITG may be due to the modulation of fusiform processing. We also observed significantly attenuated modulation from FFA to AMY in MDDs. It would associate positive facial processing deficits with attenuated connectivity between face-sensitive areas and anterior affective areas in MDDs.

Notably, in HC individuals, significantly increased modulations were IFGop→ITG and IFGop→HIP. Previous studies confirmed that the connection among frontal cortex areas and HIP facilitates the processing of positive emotional stimuli [41], [60]. Additionally, in a fMRI study, Chotiga, *et al.* [27] demonstrated that left IFGop has an important role in involving in interactions between stimulus visibility and task. These findings suggest that increased backward connections (IFGop→ITG, IFGop→HIP) enhance neural responses in areas that are directly relevant to the task. Moreover, a reduction of forward connectivity from the V1 to ITG was observed in HCs. The effect observed in temporal regions may be caused by projections from both forward and backward connections.

5 Limitations

This study provides new insights into the dysfunction of emotional conflict monitoring in MDDs, but there are some limitations need to be addressed by future work. First, an important limitation here arises from limiting the conclusions to models explicitly defined in DCM. Although we included additional structures of DCM as competing hypothesis to perfect our research, the introduction of other advanced tools [61], [62] is important for exploring emotional conflict control. Second, only emotional Stroop effect was investigated in MDDs, whereas the combination of emotional and non-emotional task led to robust interference conflict that need to be further explored. Moreover, because of potential impact of cultural difference [63], IAPS pictures as stimulus material may induce unexpected confounding effects. Finally, the relatively small sample size minimize the likelihood of findings of behavioral or biomarker parameters. Future work should strive for larger sample sizes and consider different stimulus materials (such as, IAPS and native Chinese Affective Picture System) to obtain more general findings.

6 Conclusions

In sum, we applied DCM technique on ERP data to investigate the neural mechanisms of the emotional conflict monitoring process in MDD patients. The present results demonstrated that patients have an attenuated ability to monitor emotional conflict. In particular, deficits in the inhibition of sad distractor stimuli made MDD patients more susceptible to dysregulated emotion monitoring. The results from DCM analysis showed that a forward connection (FFA→AMY) and feedback connections (AMY→ITG, FFA→ITG) were significant modulated by happy incongruent trials in MDDs. Although multiple variables have been proposed to improve predictive accuracy since early depression studies, finding robust biomarkers to identify depression remains an important challenge in this research area. Our results may serve as biomarkers for detecting cognitive impairment. Further researches are warranted to test the robustness of these results in order to provide aid for auxiliary diagnosis of depression.

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