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Research paper

Connectivity between the anterior insula and dorsolateral prefrontal cortex links early symptom improvement to treatment response

Hsinsung Yuan[a,b], Xiao Zhu[a], Weijun Tang[c], Yiyun Cai[a], Shenxun Shi[a,1,**], Qiang Luo[d,e,1,*]

[a] Psychiatry Department of Huashan Hospital, Fudan University, Shanghai, China
[b] Psychiatry Department of Nanjing Meishan Hospital, Nanjing, China
[c] Radiological Department of Huashan Hospital, Fudan University, Shanghai, China
[d] Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China
[e] Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Ministry of Education), Fudan University, Shanghai, China

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ABSTRACT

Background: Early improvement (EI) following treatment with antidepressants is a widely reported predictor to the treatment response. This study aimed to identify the resting-state functional connectivity (rs-FC) and its related clinical features that link the treatment response at the time of EI.

Methods: This study included 23 first-episode treatment-naive patients with MDD. After 2 weeks of antidepressant treatment, these patients received 3.0 Tesla resting-state functional magnetic resonance imaging scanning and were subgrouped into an EI group ($N = 13$) and a non-EI group ($N = 10$). Using the anterior insula (rAI) as a seed region, this study identified the rs-FC that were associated with both EI and the treatment response at week 12, and further tested the associations of the identified rs-FC with either the clinical features or the early symptom improvement.

Results: Rs-FC between rAI and the left dorsolateral prefrontal cortex (dlPFC) was associated with EI ($t_{21} = -6.091$, $p = 0.022$ after FDR correction for multiple comparisons). This rs-FC was also associated with an interaction between EI and the treatment response at the week 12 ($t_{21} = -5.361$, $p = 6.37\text{e-}5$). Moreover, among the clinical features, this rs-FC was associated with the early symptom improvement in the insomnia, somatic symptoms, and anxiety symptoms, and these early symptom improvements were associated with the treatment response.

Conclusion: Rs-FC between the rAI and the left dlPFC played a crucial role in the early antidepressant effect, which linked the treatment response. The early treatment effect relating to rAI may represent an early symptom improvement in self-perceptual anxiety, somatic symptoms and insomnia.

1. Introduction

Most of the available treatment guidelines for major depressive disorder (MDD) recommend waiting 4–6 weeks to determine the antidepressant treatment response (Bauer et al., 2013; Kennedy et al., 2016; Lam et al., 2009). However, only approximately half of MDD patients respond to first-line antidepressant treatment (Trivedi et al., 2006). This unsatisfactory treatment effect in the first two months may cause patients to remain at a higher risk of suicide and have a higher probability of relapse (Nakajima et al., 2010; Pintor et al., 2003; Beasley et al., 2000; Machado et al., 2006; Dardennes et al., 2017). As a result, improving the early efficacy of MDD treatment is of crucial importance.

Early improvement (EI) helps recognize antidepressant treatment effects to facilitate treatment modification. Several researchers have found that an improvement of 20% in the HAMD-17 in patients in the second week of antidepressant treatment serves as a predictor of eventual response and remission (Gorwood et al., 2013; Henkel et al., 2009; Katz et al., 2004; Stassen et al., 2007; Szegedi et al., 2009; Tadić et al., 2010; Wagner et al., 2017; Vermeiden et al., 2015). The early onset of improvement as a predictive variable is of clinical importance because it can help practitioners decide whether to continue or modify treatment at an early stage, which can, in turn, increase overall patient

* Corresponding author: Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China.
** Co-corresponding author: Psychiatry Department of Huashan Hospital, Fudan University, No. 12 Urumqi Middle Road, Jingan District, Shanghai, Shanghai, China.
E-mail addresses: shishenxun@163.com (S. Shi), qluo@fudan.edu.cn (Q. Luo).
[1] These author contributed equally to this work.

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well-being, improve treatment compliance, and reduce morbidity. However, EI has not been clinically applied, since the underlying neural basis of the relationship between EI and the treatment response is largely unknown, and no strategy is able to guide clinical practice in terms of whether to switch medications (Kudlow et al., 2014; Lam, 2012).

Functional neuroimaging may increase our understanding of the neural basis of early improvement. In a previous study, the default mode network (DMN) (Shen et al., 2015; McGrath et al., 2013) and the subcortical network (Hou et al., 2018) were found to be different between the EI group and the group with no early improvement at the pretreatment scanning. However, these studies did not explain how EI could be related to the treatment response, and they failed to provide a strategy for switching medications in the early stages. Therefore, we hypothesized that scanning during the early stage of treatment, rather than during pretreatment, could reveal the neural correlates of EI that are also associated with the treatment response, which may be informative regarding whether a modification of the treatment at the early stage of treatment could increase the probability of treatment response.

EI in somatic symptoms has been consistently reported to be a predictor of treatment efficacy (Tokuoka et al., 2017; Farabaugh et al., 2010; Funaki et al., 2016; Sakurai et al., 2013; Katz et al., 2009, 2004; Yuan et al., 2019). Several studies have reported that abnormal anterior insula function plays an important role in the occurrence and development of somatic discomfort. (Craig, 2009; Zu et al., 2019; Xiao and Zhang, 2018; Dun et al., 2017; Eisenberger, 2015; Cristofori et al., 2015; Lu et al., 2016). However, few functional neuroimaging studies have reported that neuroimaging correlates with changes in somatic symptoms during early antidepressant treatment. A 2014 neuroimaging study associated resting-state functional connectivity between the insula and the prefrontal cortex with somatic symptom severity (Avery et al., 2014). Additionally, functional connectivity between the insular cortex and the subgenual anterior cingulate cortex (sgACC), which has been associated with various treatments of MDD (Dichter et al., 2015; Frodl, 2017; Pizzagalli et al., 2018; Fonseka et al., 2018; Keedwell et al., 2010; Mayberg et al., 2000; Straub et al., 2017; Liu et al., 2015a, b). In line with these findings, we hypothesized that the functional connectivity of the insular cortex may play an important role in the relationship between early treatment effects and the treatment response.

The main aim of the current study was to identify the neural correlates of EI after antidepressant treatment that were also associated with following treatment response. We first conducted a seed-based rsFC analysis of the insular cortex, given its implications in somatic symptoms, and then, we further explored the rsFC of the sgACC, given its general association with MDD treatments. We recruited 23 first-episode treatment-naive patients with MDD from Huashan Hospital, Shanghai, PR China. Two weeks after medical treatment began, we assessed symptom improvement and performed functional magnetic resonance imaging (fMRI) during the resting state. We followed these patients up until week 12 to assess the treatment response. The findings of the current study might provide new insights into the relationship between EI and treatment response in MDD.

2. Materials and methods

2.1. Participants

A total of 23 patients who were diagnosed with their first episode of MDD were recruited from the outpatient department of Huashan Hospital, Fudan University, Shanghai, China, as subjects for our current study. The patients were screened for an observational, real-world study with ongoing follow-up that aimed to investigate EI. Two trained psychiatry postgraduate students conducted a structured interview using the Chinese version of the Mini-International Neuropsychiatric Interview (MINI) for all participants. A diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Patients aged 18 to 43 years who were right handed, had first-episode depression, were treatment naive, and had a baseline 17-item Hamilton Depression Scale (HAMD-17) score >20 were included. Patients with any comorbid axis I disorder, severe head injury, substance abuse/dependence, or a prior medical history of the central nervous system disease were excluded. Particular exclusion criteria included (1) a history of psychoactive substance abuse, (2) current pregnancy or lactation, (3) any physical diseases assessed by personal history, or (4) a history of neurological disorders, other existing psychiatric disorders, or cardiovascular diseases. This study was approved by the Ethics Boards of Huashan Hospital, Fudan University. All participants provided their written informed consent.

2.2. Medical treatment

All patients received sertraline treatment (≤ 100 mg daily) after MDD diagnosis. The treatment dose started with half of the lowest dose and reached the effective dose (50 mg daily) on the third day of treatment. Dose adjustments were allowed during the first week. Patients underwent resting-state functional MRI scanning during the second week of treatment. After MRI scanning, patients who failed to reach the criteria of EI were changed to another first-line SSRI medication, paroxetine (≤ 40 mg daily) or escitalopram (≤ 15 mg daily), according to the preference of the patient.

2.3. Behavioural assessments

During the study, the *Eysenck Personality Questionnaire* (*EPQ*) (Eysenck and Eysenck, 1975), *Yale-Brown Obsessive Compulsive Scale* (*Y-BOCS*) (Goodman et al., 1989), *Childhood Trauma Questionnaire (CTQ-SF)* (Bernstein et al., 2003), *Patient Health Questionnaire-9 (PHQ-9)* (Kroenke et al., 2001), *Generalized Anxiety Disorder Scale-7 (GAD-7)* (*Spitzer et al., 2006*), and *Liebowitz Social Anxiety Scale* (*LSAS*) were completed by all patients in the outpatient clinic on Monday morning and Thursday afternoon; two trained psychiatry postgraduate students assessed the patients via the *17-item Hamilton Depression Scale (HAMD-17)* and the *Hamilton Anxiety Rating Scale (HAM-A)* (Maier et al., 1988). Patients were asked to provide marital status, educational level, occupation, family history, presence of somatic diseases, whether depression fluctuated with the menstrual cycle, mental disease family history, tobacco and alcohol history, etc. Meanwhile, patients' medical history was collected during the visit, which included how long the symptoms had been apparent, information about previous mental diseases, etc. In this study, at the initial visit and at weeks 2, 4, 8 and 12 of treatment, the *PHQ-9* and *GAD-7* were used to assess patients' self-rated depression and anxiety symptoms, and *Asberg's Antidepressant Side-Effect Rating Scale* (*SERS*) was used to assess drug side effects since the last visit. The notion of EI was defined as a 20% reduction in the HAMD-17 total score from the time point before treatment to the second week of treatment. Treatment response was defined as a 50% reduction in the HAMD-17 total score from the time point before treatment to the 12th week of treatment. We used positive predictive value (PPV) and negative predictive value (NPV) to measure the degree to which early symptomatic improvement can predict who becomes stable responders by the end point. (Kudlow et al., 2012) The PPV of EI was defined as the number of patients with EI and response divided by the number of patients with EI and response + the number of patients with EI but no response. The NPV of EI was defined as the number of patients without EI and response divided by the number of patients without EI and response + the number of patients without EI but with response.

2.4. Neuroimaging scans

MRI data were acquired at baseline using a 3.0 T MR scanner (Siemens 3.0T) equipped with an eight-channel head coil array. During

Table 1
Pre-treatment demographic and clinical characteristics of the early improvement group and the group without early improvement.

	Early improvement (n = 13)	No early improvement (n = 10)	$t/\chi 2$	p
age ($\bar{x} \pm s$, years)	31.27 ± 7.9	28.50 ± 6.4	0.876	0.392
gender (F/M)	9/4	9/1	0.372	0.603
course of depression ($\bar{x} \pm s$, months)	15.23 ± 24.2	9.50 ± 19.1	0.591	0.561
HAMD-17	26.61 ± 5.4	26.22 ± 2.38	0.203	0.841
HAMA	25.46 ± 6.3	24.88 ± 5.32	0.221	0.828
GCI	5.07 ± 1.3	4.66 ± 1.4	0.716	0.482
Y-BOCS	11.08 ± 8.4	10.77 ± 9.1	0.079	0.938
LSAS anxiety	25.95 ± 17.4	23.72 ± 17.2	0.501	0.614
avoidance	26.17 ± 18.8	24.84 ± 16.7	0.291	0.772
CTQ-SF emotional abuse	9.30 ± 5.43	12.00 ± 4.0	−1.268	0.221
physical abuse#	7.90 ± 3.9	8.80 ± 5.6	NA	0.605
sexual abuse	7.50 ± 2.1	7.40 ± 2.5	0.950	0.925
emotional neglect	17.70 ± 1.6	16.70 ± 1.6	1.396	0.180
physical neglect	10.70 ± 5.9	12.00 ± 5.0	−0.534	0.600
treatment response (yes/no)	11/2	5/5	3.192	0.074
mean FD	0.0739 ± 0.036	0.0702 ± 0.024	0.274	0.787

Abbreviations: $\bar{x} \pm s$, the mean ± SD; HAMD-17, 17-item Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Scale; CGI, Clinical Global Impressions Scale; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; LSAS, Liebowitz Social Anxiety Scale; SDSS, Social Disability Screening Schedule; EPQ, Eysenck Personality Questionnaire; CTQ-SF, Childhood Trauma Questionnaire. Response indicates a decrease in HAMD-17 of more than 50%, remission indicates a HAMD score less than 7, and the mean FD indicates the mean framewise movement during MRI. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; #: This was rejected by the hypothesis of normal distribution, and underwent a Mann-Whitney U test.

the scan, participants were asked to lie quietly in the scanner with their eyes open and were instructed to refrain from thinking about anything in particular. Functional images were obtained axially using a single-shot, gradient-recalled echo-planar imaging sequence parallel to the line of the anterior–posterior commissure. The acquisition parameters were as follows: repetition time (TR) 2000 ms; echo time (TE) 30 ms; flip angle (FA) 90°; field of view (FOV) 256 mm; matrix 64 × 64; slice thickness 3.4 mm; and gap: 0 mm. A total of 210 volumes were acquired for each subject. High-resolution T1-weighted images were also acquired for spatial normalization with a three-dimensional spoiled gradient recalled sequence: 176 sagittal slices; TR 2300 ms; TE 2.98 ms; FOV 256 mm; matrix 256 × 256; slice thickness 1 mm; and no gap.

Resting-state fMRI data was preprocessed using a pipeline (https://github.com/weikanggong/Resting-state-fMRI-preprocessing) built on FSL (https://fsl.fmrib.ox.ac.uk/fsl), AFNI (https://afni.nimh.nih.gov/) and the BrainWavelet toolbox (http://www.brainwavelet.org/), which was designed to remove motion artefacts, mainly including brain extraction, slice timing, motion correction, smoothing (with a spatial Gaussian kernel full-width at half maximum of 6 mm), wavelet despiking, regressing out WM/CSF/Motion (Friston-12) parameters and temporal filtering (0.01–0.1 Hz)). The functional images were first registered to the T1 image and then normalized to 3 mm standard space (BBR, flirt and fnirt in FSL); the framewise displacement was estimated, and no participant had an FD exceeding 0.2 mm.

2.5. Statistical analysis

We applied the Power 264-atlas, which has equally sized 10 mm-diameter spheres centred at 264 coordinates and has been widely used in functional brain network analyses (Power et al., 2011), to the resting-state fMRI scans to extract the time series data for each of the 264 brain areas. The total number of resting-state functional connections (FC) was 34,584. On the Power 264 atlas, the MNI space that responded to either the left or right anterior insula (AI; −35, 20, 0 and 36, 22, 3, respectively) were selected as the seed regions of interest (ROI). By considering head motion, sex and age as covariates, the association between EI and each FC was assessed by a linear model with the presence of EI as an independent variable and each FC as a dependent variable. As our primary hypothesis was about the FC of AI, we first applied an FDR correction for multiple comparisons among the 2 × 263 functional connections of the bilateral AI seed-ROIs. Furthermore, we used the bilateral subgenual anterior cingulate cortex (sgACC) (8, 42, −5 and −3, 44, −9 in the Power 264-atlas) as two additional seed-ROIs and followed the same approach described above that was used for the seed ROI of AI.

Next, we calculated the correlations between the identified significant functional connections and the outcome measures. The reduction rate of the HAMD-17 score at week 12 was used as the first indicator for the assessment of the outcome. We first tested the main effects of both the EI at week 2 and the treatment response at week 12 on the FC by using a linear model with the same covariates described above. In cases where there was no significant main effect on the identified FC, we tested the interaction effect between EI and the treatment response. In other words, the FC was compared among four groups of patients defined by the value of two variables: the presence of EI and the presence of a treatment response. The interaction effect was also tested with a continuous variable, namely, the reduction rate of the symptom score, interacting with the binary variable EI.

Finally, we tested the correlation between the scale scores, including the PHQ-9 total score, GAD-7 total score, and various subscales of the HAMD-17 and HAMA, and the identified significant functional connections. HAMD-17 was factorized as (1) depression, (2) anxiety, and (3) insomnia (Fleck et al., 2010). HAMA was factorized as (1) anxious mood and (2) somatic symptoms. Additionally, to assess differences between depression and anxiety self-rated scores and the other rating scores, depression and anxiety self-rated total scores were divided by the other ratings' total scores. For categorical data, we used the chi-squared test for group comparisons. For continuous data, if the hypothesis of normal distribution was not rejected by the Kolmogorov-Smirnov test, an independent two-sample t-test with unequal variances was used; otherwise, the Mann-Whitney U test was used. Among these variables, this study used a general linear model to examine relationships among previously discovered functional connections. The receiver operating characteristic curve (ROC) was used to test the predictive value.

3. Results

3.1. Demographics

Twenty-three patients were eligible for analysis and underwent fMRI scanning (Table 1). Demographic and clinical data of patients and controls are provided in Table 1. Fifty-six percent of these patients reached EI in the second week of treatment. The PPV of EI for the

Table 2
Statistical correlations between the connectivity between the right anterior insula and left dorsolateral prefrontal cortex and the outcomes, including early improvement and treatment response at week 12, and the interaction of these variables.

	Model		Bootstrap							
	R	*p*	*B*	SE	LLCI	ULCI	*p*	*t*	*p*	FDR *p*
EI	0.852	0.000	−2.320	−0.010	−3.005	−1.883	0.001	−6.091	1.56E-5	0.022
Response	0.543	0.043	−0.642	0.019	−1.442	0.053	0.095	−1.807	0.090	–
EI × Response	0.812	0.001	−0.138	−0.005	−0.208	−0.083	0.003	−5.361	6.37E-5	–

Abbreviation: EI: early improvement. SE: standard error; LLCL: lower control limit of the 95% confidence interval after bootstrapping; and ULCL: upper control limit of the 95% confidence interval after bootstrapping.

treatment response was 84%, and the NPV was 50%. The response rates at week 12 were significantly different in the groups that showed EI and no EI. However, it is difficult to differentiate these groups based solely on pretreatment information (all $p > 0.05$). The data showed that the subjects in both groups had similar degrees of depression, anxiety, social anxiety, compulsive symptoms and social disability severity at baseline.

3.2. Functional connectivity associated with the interaction between EI and treatment response

There was only one functional connection associated with EI that survived FDR correction. Compared with the non-EI group, the EI group had stronger functional connectivity between the right anterior insula (rAI) and the left dorsolateral prefrontal cortex (dlPFC, on the power 264 template, MNI space= [−20,45,39]) ($p = 0.022$, FDR corrected). However, we found that rAI-dlPFC functional connectivity was not significantly related to the treatment response at week 12 ($t_{21} = -1.807$; bootstrap $p = 0.095$), but the functional connection was significantly associated with an (EI) × (treatment response at week 12) interaction ($b = -0.138$; $t_{21} = -5.361$; bootstrap $p = 0.003$) (Table 2; Fig. 1). ROC analyses revealed two effects of rAI-dlPFC functional connectivity: first, in differentiating response and non-response from the EI group (AUC = 0.825; $P = 0.032$; 95% CI, 0.612 to 1.000) and, second, in differentiating the non-response group from the response group (AUC = 0.745; $p = 0.073$; 95% CI, 0.529 to 0.961). With the subgenual ACC as the seed-ROI, no functional connectivity survived the FDR correction for multiple comparisons, with $p > 0.07$ in the correlations with EI and $p > 0.06$ in the correlations with the treatment response.

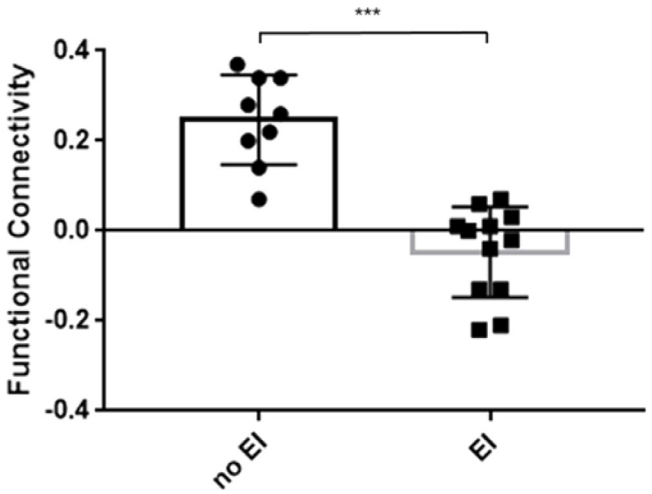

Fig. 1. This figure shows the difference in the connectivity of the right anterior insula and left dorsolateral prefrontal cortex between the early improvement group and the non-improvement group. EI: early improvement. ***$p < 0.001$.

3.3. Baseline clinical features and early symptom changes associated with rAI-dlPFC functional connectivity

The changes in symptoms and early symptoms that were associated with rAI-dlPFC functional connectivity included the pretreatment depression self-rated score ($B = 0.018$; bootstrap 95% CI, 0.008 to 0.030; $t_{21} = 2.704$; $p = 0.015$) and the anxiety self-rated score ($B = 0.022$; bootstrap 95% CI, 0.005 to 0.037; $t_{21} = 2.745$; $p = 0.014$). In addition, early symptom improvement in insomnia ($b = -0.257$; bootstrap 95% CI, −0.528 to −0.760; $t_{21} = 2.772$; $p = 0.013$), anxiety ($b = -0.327$; bootstrap 95% CI, −0.481 to 0.142; $t_{21} = 2.712$; $p = 0.015$) and somatic symptoms ($b = 1.183$; bootstrap 95% CI, −0.333 to 0.011; $t_{21} = 2.116$; $p = 0.049$) from pretreatment to week 2 had a trend-level correlation with rAI-dlPFC functional connectivity. Among these symptoms, improvements in anxiety ($t_{21} = 2.210$; $p = 0.007$) and somatic symptoms ($t_{21} = 2.832$; $p = 0.008$) from pretreatment to week 2 were significantly associated with treatment response (Table 3).

4. Discussion

This study found that young, first-episode, treatment-naive MDD patients at a general hospital showed EI in the second week of SSRI administration, which was associated with the treatment response at week 12. This study confirmed the hypothesis that the insula is associated with the medical treatment of MDD and identified, for the first time, that its resting-state functional connectivity with the left dlPFC is associated with both EI at week 2 and its interaction with the treatment response at week 12. These results may inform the mechanisms of EI after the administration of the antidepressants and further contribute to improving the early efficacy of the treatment for first-onset MDD.

As our evaluation of symptoms was based on interviews, for example, somatic symptoms were evaluated based on patients' complaints, the self-perceived sensation that clinical symptoms improved might be the main contribution to the observed EI (Wiech et al., 2010; Lutz et al., 2013; Schmid et al., 2013; Chen et al., 2014; Adolfi et al., 2017; Liu et al., 2018). This finding can be understood in the following ways: First, somatic symptoms in MDD have been associated with prolonged inflammatory responses in patients or with a long period of antidepressant treatment (Leuchter et al., 2010; Romera et al., 2012; Harada et al., 2016; Jaracz et al., 2016) and have also been identified as a factor indicating poor prognosis in MDD (Altin et al., 2014; Wardenaar et al., 2015). Second, somatic symptoms in MDD are mainly related to anxiety, leading to muscle tension pain, chest pain, palpations and related autonomic nerves symptoms (Hung et al., 2014; Demyttenaere et al., 2008; Paulus, 2013; Sgoifo et al., 2015). Third, in East Asian culture, both anxiety and depression symptoms are often inseparable from the somatization of depression (Kleinman, 1982). This may be especially true in the patient population sampled at the general hospital in the current study, as a large portion of the MDD patients in this study came to the hospital for insomnia or somatic discomfort (Zhao et al., 2018; Novick et al., 2013; Bair et al., 2003; Simon et al., 1999).

Notably, EI in the somatic symptoms was associated with a change in the functional connectivity between AI and dlPFC. Given that the

Table 3
Statistical correlations between clinical symptoms and connectivity, the response at week 12 and the interaction between early improvement and treatment response.

	rAI-dlPFC					Response					EI × Response				
	B	LLCI	ULCI	*T*	*P*	*B*	LLCI	ULCI	*T*	*P*	*B*	LLCI	ULCI	*T*	*P*
Insomnia% changes	−0.257	−0.528	−0.760	2.772	.013	.326	.055	.656	2.105	.044	1.484	.575	2.825	2.647	.018
HAMA% changes	−0.327	−0.481	.142	2.712	.015	.438	.129	.781	2.210	.007	1.957	.924	3.417	2.749	.014
Somatic symptom% changes	−1.183	−0.333	.011	2.116	.049	.355	.104	.541	2.832	.008	1.388	.369	2.150	2.850	.012
PHQ-9	.018	.008	.030	2.704	.015	−0.006	−0.032	.051	−0.458	.649	−0.051	−0.141	.018	−1.132	.274
GAD-7	.022	.005	.037	2.745	.014	−0.027	−0.057	0.00	−1.993	.092	−0.094	−0.213	−0.003	−1.821	.087
PHQ-9/HAMD	.573	.098	1.081	2.501	.023	−0.107	−1.138	.611	−0.257	.808	−2.083	−5.35	.446	−1.378	.187

Abbreviations:% change: the% change in the score from before treatment to the second week of treatment; rAI-dlPFC: connectivity between the right anterior insula and the left dlPFC; LLCL: lower control limit of the 95% confidence interval after bootstrapping; and ULCL: upper control limit of the 95% confidence interval after bootstrapping.

anterior insula has been implicated in both the regulation of the autonomic nerve system (Paulus, 2013; de Morree et al., 2016; Cechetto, 2014), the modulation of appraisal (Schafer et al., 2015; Davey et al., 2017) and dysfunction in introception (Craig, 2009; DeVille et al., 2018; Eggart et al., 2019; Harshaw, 2015), its strong connectivity with dlPFC might underlie persistent thoughts related to the self-perception of somatic symptoms in anxiety (Reinecke et al., 2014; Paulus and Stein, 2006). In our study, the decreased functional connectivity between these two brain regions was significantly associated with the early efficacy of SSRIs, and stronger functional connectivity was associated with both less early improvement at week 2 and a lower treatment response at week 12. While the AI is a key node in the salience network (SN), the dlPFC is an important node of the central-executive network (CEN). The salience network mediates 'switching' between the activation of the DMN and the activation of the CEN to guide appropriate responses to relevant salient stimuli (Menon and Uddin, 2010). When the salience network is impaired in MDD (Manoliu et al., 2013), increased AI-dlPFC connectivity may be a compensatory mechanism (Johnston et al., 2007; Menon and Uddin, 2010), and the disrupted interactions in this triple network system may contribute to the characteristic symptoms of MDD, such as spontaneously occurring affect, over-responding to emotional cues, and emotional disinhibition (Hamilton et al., 2013). Changes in brain activity have been observed in ACC and after taking antidepressants (Dichter et al., 2015; Pizzagalli et al., 2018; Korb et al., 2011). However, whether the change in ACC activation is an indicator of treatment response is still under investigation (Lueken and Hahn, 2016; Fonseka et al., 2018; Chau et al., 2017). In our study, the effects of antidepressants may occur in both the early improvement group and the group that saw no early improvement. The ACC activities of these groups changed simultaneously, but the effect was not closely related to improvement in depression symptoms.

For patients who did not show EI, the increased connectivity between rAI and the left dlPFC could be targeted by repetitive transcranial magnetic stimulation (rTMS) treatment. Previous studies have shown that the left dlPFC is one of the most effective sites for rTMS treatment of depression (Lefaucheur et al., 2014; Baeken et al., 2017; Mutz et al., 2018). Left dlPFC stimulation improves somatic symptoms both in affective disorder and in many somatic diseases (Fierro et al., 2010; Leung et al., 2018; Seminowicz et al., 2018; Phillips et al., 2018), and the mechanism of action seem to be this region's interaction with the insula (Knott et al., 1996; Tik et al., 2017). Meanwhile, increased activation of the insula by transcutaneous vagus nerve stimulation (tVNS) can also reduce the activation of the DMN (Treuer et al., 2013). Therefore, patients who have relatively obvious somatic symptoms tend to overestimate the severity of the disease, and treatments decoupling the dlPFC and the insula might help clinical improvement, especially when EI is not seen in antidepressant treatment.

This study has several limitations. First, the sample size is relatively small. We used an exploratory design to perform fMRI scanning during the second week of treatment rather during at pretreatment, and the next step is to verify the results on a large multi-centric sample. Second, the mean age of the patients in this study was relatively young. Many MDD studies set the inclusion criteria to be patients who are over 30 years old to exclude the possibility of including patients with bipolar disorder. In the current sample, after 12 weeks of follow-up, no patients were diagnosed with bipolar disorder.

5. Conclusions

This study found that EI in the second week after SSRI administration was associated with treatment response at week 12 in first-episode treatment-naive MDD patients at a general hospital, and decreased functional connectivity between rAI and dlPFC might mediate this association. In particular, decreased connectivity was associated with the self-perceptual sensation of improvement in both insomnia and somatic symptoms. These findings highlight the involvement of the insula in early improvement following treatment and present potential strategies to improve the early efficacy of the treatment.

Ethical statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

CRediT authorship contribution statement

Hsinsung Yuan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft. **Xiao Zhu:** Investigation. **Weijun Tang:** Investigation. **Yiyun Cai:** Supervision. **Shenxun Shi:** Conceptualization, Investigation, Methodology, Project administration, Resources, Validation. **Qiang Luo:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Software.

Declaration of Competing Interest

None.

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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.2019.09.041.

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