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ORIGINAL RESEARCH

Spontaneous thought-related network connectivity predicts sertraline effect on major depressive disorder

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Abstract

Sertraline is one of the most commonly prescribed antidepressants. Major depressive disorder (MDD) is characterized by spontaneous thoughts that are laden with negative affect—a "malignant sadness". Prior neuroimaging studies have identified abnormal resting-state functional connectivity (rsFC) in the spontaneous brain networks of MDD patients. But how antidepressant medication acts to relieve the experience of depression as well as adjust its associated spontaneous networks and mood-regulation circuits remains an open question. In this study, we recruited 22 drug-naïve MDD patients along with 35 normal controls and investigated whether the functional integrity of cortical networks associated with spontaneous thoughts is modulated by sertraline treatment. We attempted to predict post-treatment effects based upon what we observed in the pre-treatment rsFC of drug-naïve MDD patients. In the result, we demonstrated that (1) after the sertraline treatment, the medial temporal lobe of default network (DN_{MTL}) and mood regulation pathway—the fronto-parietal control network (FPCN), the thalamus, and the salience network (SN)—were restored to normal connectivity, relative to the pre-treatment condition; however, the altered connections of FPCN-core DN (DN_{CORE}), FPCN-SN, and intra-FPCN among MDD patients remained impaired; (2) thalamo-prefrontal connectivity provides moderate predictive power ($r^2 = 0.63$) for the effectiveness of sertraline treatment. In summary, our findings contribute to a body of evidence that suggests salubrious effects of sertraline treatment primarily involve the FPCN-thalamus-SN pathway. The pre-treatment rsFC in this pathway could serve as a predictor of sertraline treatment outcome.

Keywords Antidepressants · Depression · fMRI · Functional connectivity · Neuroimaging · Sertraline · Treatment

Li-Ming Hsu and Timothy Joseph Lane made equal contributions as co-first authors.

Hung-Wen Kao and Chi-Bin Yeh have equal contributions to the manuscript.

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Introduction

According to the World Health Organization (WHO), an estimated 350 million people suffer from depression (Smith 2014). About half of the patients taking antidepressant medication either fail to respond or suffer adverse effects; therefore, the search for personalized, precise means of predicting how patients will respond to a given medication has taken on a special urgency (Bousman et al. 2017). In current practice, selective serotonin reuptake inhibitors (SSRIs), such as sertraline, are commonly prescribed to alleviate depressive symptoms (Muijsers et al. 2002). Sertraline elevates post-synaptic serotonin levels by blocking the serotonin transporter (SERT), thereby reducing serotonin reuptake; hence more serotonin remains available in the spaces between neurons (Kranz et al. 2010). Although the relevant biochemistry is not well understood, use of sertraline in MDD can help to improve mood and reduce symptoms (Sheehan and Kamijima 2009). But 65%–80% of patients treated with an SSRI do not achieve full symptomatic remission. It is, therefore, crucial to understand how sertraline alleviates the symptoms of MDD.

Previous neuroimaging studies that target sertraline's therapeutic effects have evinced underlying neurophysiological abnormalities involving cerebral metabolism and cerebral blood flow, CBF (Mayberg et al. 1999; Neumeister et al. 2004; Savitz and Drevets 2009), as well as functional recovery of affected brain areas when treatment was successful (Davidson et al. 2003; Mayberg 2003). Significant reductions of regional CBF (rCBF) in the frontal, limbic, parietal, and temporal regions also have been found in MDD patients (Drevets et al. 2002; Ho et al. 2013; Smith and Cavanagh 2005). After antidepressant treatment with multiple psychotropic medications, improvement of rCBF in the left-dorsolateral prefrontal cortex (dlPFC) has been identified, although bilateral medial, dorsolateral, and parietal areas remain abnormally perfused in late-life depression (Duhameau et al. 2010). It remains unclear, however, whether the neurophysiological abnormality can be corrected by the sertraline treatment in MDD patients.

An alternative strategy for investigating MDD—the one adopted here—focuses on the relationship between spontaneous thoughts and corresponding resting-state functional MRI (rs-fMRI). The measured synchronized fluctuations across distant brain areas represent long-range resting state functional connectivity, rsFC (Fox and Greicius 2010). Investigations that employ rsFC have also identified localized aberrant hyper-connectivity in the subgenual anterior cingulate cortex (ACC) (Greicius et al. 2007), as well as elevated rsFC of amygdala, thalamus, and striatum, following sertraline treatments that reduce depressive symptoms (Anand et al. 2005a). These findings, however, seem insufficient to explain depressive, spontaneous thoughts. The approach of Christoff et al., on the other hand, demonstrating the large-scale network interactions that correlate with these spontaneous thoughts, holds promise of leading to a more adequate explanation (Christoff et al. 2016; Conio et al. 2019). In our study, we focused on the connectivity strength of the cortical networks, taking them to be neural correlates of spontaneous thoughts; that is, we have sought to identify inter-network interactions that can help identify the subset of MDD patients whose symptoms are most likely to be mitigated by sertraline.

Several thought-associated spontaneous connectivity networks were identified: default network (DN), salience network (SN), frontoparietal control network (FPCN), and mood regulation circuit (MRC) (Anand et al. 2005a; Mayberg et al. 1999; Stange et al. 2017). Briefly, in the theoretical neural model of spontaneous thoughts (Christoff et al. 2016), the DN can act as sources of variability in thought content over time (Seeley et al. 2007), whereas the SN exerts automatic constraints on the output of the DN (Menon 2015), and the FPCN constrains thought by flexibly coupling with the DN or SN (Christoff et al. 2009; Dixon et al. 2018). MRC can stabilize the mood and prevent extreme change in mood (Alexander and Crutcher 1990; Anand et al. 2005a; Cummings 1995; Schultz 1997). Furthermore, these networks can be anatomically defined into core brain regions. The DN includes anterior medial prefrontal cortex, (amPFC), posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), hippocampus (HC), parahippocampus (PHC), and retrosplenial cortex (RSC). The SN includes anterior insular (AI) and dorsal anterior cingulate cortex (dACC). The FPCN includes dlPFC and inferior parietal lobule (IPL). The thalamus and amygdala are hubs in MRC. Among those, the DN tends to be associated with self-referential/internally oriented processes (Buckner et al. 2008; Lane et al. 2016; Qin et al. 2016). Aberrant FCs in MDD patients have been observed within the DN, both during rest (Greicius et al. 2007) and during scanning sessions that include goal-directed tasks (Sheline et al. 2009). Moreover, antidepressant medication has been shown to be associated with altered FC of the DN (Hamilton et al. 2015; Posner et al. 2013). As for the SN, comprising the dACC and the AI, it tends to respond to both external and internal salient stimuli, generating appropriate responses and guiding behavior (Seeley et al. 2007). The FPCN is closely linked to executive control and is involved in both internally and externally oriented goal-directed thought (Dixon et al. 2014; Spreng et al. 2010). As this relates to MDD patients, reduced FC within the FPCN has been reported (Kaiser et al. 2015b). As for the MRC, FC abnormalities in thalamus and amygdala have been widely reported when depressed patients respond to negative mood stimuli (Anand et al. 2005a, b), where the thalamus is involved in emotional perception and regulation (Phillips et al. 2003), and the amygdala has been shown to be central to the brain's response to noxious stimuli (LeDoux 2000).

We conjecture that measuring thought-related networks and the neurophysiological fluctuations will help us to identify reliable predictors of treatment response. In pursuit of this goal, the present study examines inter-network interactions of MDD patients treated with sertraline. Specifically, we recruited drug-naïve patients, who were assessed by the Hamilton Depression Rating Scale (HAM-D), both prior to and subsequent to the treatment.

Methods

Subjects

We included 22 drug-naïve MDD patients and 35 normal controls (NC). The patients and normal controls were gender-, age-, education- and handedness-matched (see Table 1). Patients ranged in age from 20 to 65 years old; each satisfied the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of signs and symptoms for MDD. They were recruited from the outpatient clinic at Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. The experimental protocol was approved by the Institutional Review Board at Tri-Service General Hospital and informed consent was obtained from all subjects.

For MDD patients, the severity of depression was quantified using the 17-item HAM-D rating score (Williams 1988). Inclusion criteria for MDD subjects were as follows: for the 17-item HAM-D score, 18 or higher, and a minimum score of 2 on item 1, depressed mood; no use of medication for a period of at least 5 times the biological elimination half-life. Exclusion criteria for the MDD patient group were: those, evaluated with the mini-international neuropsychiatric interview, who met DSM-IV criteria for other comorbid neuropsychiatric diseases as primary diagnoses, albeit not including anxiety symptoms; those with a history of antidepressant medication; those with a history of alcohol or substance dependence or abuse, albeit not including caffeine or nicotine; those with a history of allergic reaction to sertraline; those with severe cardiovascular or cerebrovascular diseases; those with malignancies within the previous 5 years; female subjects who were pregnant, nursing or lactating; female subjects with childbearing potential who were not using a medically acceptable form of birth control; those who were acutely suicidal or homicidal, or who required inpatient treatment; those who exhibited positive urinary toxicology screening at baseline; those who had used alcohol during the previous week; those who suffered from serious medical or neurological illness; and, those who had metallic implants or other contraindications for MRI scanning.

For **NC** subjects, the inclusion criteria were as follows: no history of psychiatric illness, substance abuse or dependence, as based on a clinical interview, including the mini-international neuropsychiatric interview and a physical examination; no significant family history of psychiatric or neurological illness; no taking of any prescription known to affect the brain serotonin system within a one-year period prior to being admitted to the study; no use of alcohol for at least one week; and, no serious medical or neurological illness.

Sertraline treatment protocol

MDD patients started on sertraline within one week after they completed the baseline MRI imaging. They took 25 mg orally, per day, for 1 week; after one week they continued with a maintenance dose of 50 mg per day for the next 5 weeks. A neuropsychologist rated the patients based on the 17-item HAM-D scoring system at baseline and after six weeks of the sertraline treatment.

MRI acquisition

All patients and normal controls underwent MRI in a 3T MR scanner (Discovery MR 750, GE Healthcare, Waukesha, WI, USA) using a body coil as transmission and a head-neck-spine array coil as signal reception. MRI protocol was performed

Table 1 Demographic and clinical characteristics

	Normal control ($n = 35$)	MDD Patient ($n = 22$)	p value
Mean age (SD)	40.1 (10.6)	40.7 (11.6)	0.6[a]
Right-handedness (%)	33 (94.2)	21 (95.5)	0.8[b]
Male (%)	12 (34.3)	5 (22.7)	0.4[b]
Mean education (SD)	15.3 (1.8)	13.0 (3.8)	0.4[c]
Mean HAM-D score (SD)	0 (0.0)	Pre: 24.5 (2.9) Post: 7.9 (5.3)	<0.001[d]
Anxiety (%)	0 (0.0)	6 (27.3)	NA

[a] Mann-Whitney U test

[b] Chi-square test

[c] Median test

[d] Paired t-test between pre- and post-treatment MDD patients

within one week before the start of sertraline treatment for the first time (Pre); it was repeated within one week after completion of the 6-week sertraline treatment (Post). To avoid motion artifact generated during the scan, the head position was immobilized with cushions, inside the coil, after the alignment. High resolution T_1-weighted anatomic images were acquired using a 3D BRAVO sequence (inversion-prepared fast spoiled gradient-echo) with a repetition time (TR) of 10.2 ms, an echo time (TE) of 4.2 ms, an inversion time of 450 ms, a flip angle (FA) of 12 degrees, number of excitation (NEX) of 1, a field-of-view (FOV) of 256 mm, a slice thickness of 1 mm, and a matrix size of 256 × 192 (interpolated to 256 × 256). In addition to the high-resolution 3D anatomic sequences, all subjects underwent a rs-fMRI scan in which they were given no specific instructions other than to keep their eyes closed and remain still. The rs-fMRI scans used T_2^*-weighted echo-planar imaging with the following parameters: TR/TE, 2500/30 ms; FA, 90°; FOV, 220 × 220 mm^2; matrix size, 64 × 64; slice thickness, 3.5 mm; 40 slices; intersection gap, 1 mm; 200 brain volumes. Noncontrast perfusion imaging was performed using pseudo-continuous arterial spin labeling (pCASL) technique, with a 3D background suppressed fast spin-echo stack-of spiral readout module (8 arms with 512 points in each spiral arm, TR/TE = 4737 ms/10.5 ms, labeling duration = 1500 ms, post-labeling delay = 1525 ms, in-plane matrix = 128 × 128, NEX = 3, slice thickness = 4 mm). The data that support the findings of this study are openly available in Figshare at https://figshare.com/s/df6798c1813a543a7eb7.

Data preprocessing

The quantitative CBF maps were analyzed from pCASL perfusion data on an Advantage Windows workstation using Functool software (version 9.4, GE Medical Systems) and were calculated with the equation:

$$\mathrm{CBF} = 6000 \cdot \lambda \frac{\left(1-e^{\frac{ST}{T_{1t}}}\right)e^{\frac{PLD}{T_{1b}}}}{2\varepsilon T_{1b}\left(1-e^{-\frac{LT}{T_{1b}}}\right)NEX_{PW}}\left(\frac{PW}{SF_{PW}PD}\right)$$

where T1 of blood (T_{1b}) was assumed to be 1.6 s, T1 of tissue (T_{1t}) was 1.2 s, partition coefficient (λ) was 0.9, labeling efficiency (ε) was 0.6, saturation time (*ST*) was 2 s, labeling duration (*LT*) was 1.5 s, and post-labeling delay (*PLD*) was 1525 ms, *PD* is the partial saturation of the reference image. *PW* was the perfusion weighted or raw difference image. SF_{PW} was the scaling factor of *PW*. NEX_{PW} was the number of excitation for *PW* images. Voxel-wise CBF maps were transformed into Montreal Neurological Institute (MNI; www2.bic.mni.mcgill.ca/) space using information from their T1 coregistration. The rs-fMRI data preprocessing was conducted in AFNI (Cox 1996), including slice timing and head motion correction, after discarding the first 10 functional volumes. The spike was removed from the time series using 3dDespike in AFNI. Data were then spatially normalized to a template in SPM and resampled resolution of 2 × 2 × 2 mm^3 and smoothed with a 6-mm full-width half-maximum (FWHM) Gaussian kernel to increase the spatial signal to noise ratio. Next, time courses of the six head motion correction parameters, white matter (WM), and cerebrospinal fluid (CSF) also served as uninteresting covariates. Here the WM and CSF masks were generated by segmenting the T1 high-resolution structural images in SPM segmentation and thresholded by 0.95. The data were band-pass filtered (0.01–0.1 Hz) using 3dBandpass in AFNI. Finally, data were censored for motion with a threshold of 0.5 mm for a frame-to-frame change in Euclidean norm of the six motion parameters (Power et al. 2014, 2015). And, all subject keeps >95% fMRI imaging volumes.

Image analysis

Functional connectivity analysis

All rs-fMRI data were used to generate brain network components, using a group-level independent component analysis (gICA) (MELODIC; FSL). The number of components was set to 20. The spatial distribution of individual components were identified using dual regression (Zuo et al. 2010), and a one-sample t-test was performed to generate the group component maps. The spontaneous networks for DN, SN, and FPCN, from 20 ICA group component maps, were then identified (Fig. S1). The thalamus and amygdala were also included as key regions for MRC (Peng et al. 2012). Furthermore, according to a previous study (Christoff et al. 2016), the DN could be classified into core DN (DN_{CORE}) subsystem and medial temporal lobe (DN_{MTL}) subsystem. Therefore, to evaluate the FC alternation related to spontaneous networks, we manually defined cortical and sub-cortical anatomical regions from the Brodmann area (BA) and automated anatomical labeling (AAL) template, respectively, within DN_{CORE}, DN_{MTL}, SN, and FPCN networks. The overlapping regions from the anatomical regions and gICA-based networks were chosen as seeds for further analysis (Fig. S1). The seed of thalamus was chosen from the AAL template. In sum, twelve ROIs (Table S1) were selected as seed for further whole brain seed-based connectivity analysis, includes AI, dACC, amPFC, PCC, vmPFC, HC, PHC, RSC, dlPFC, IPL, thalamus, and amygdala.

A whole brain seed-based connectivity analysis was estimated in normal controls, pre- and post-treatment depressed patients. Voxel-wise correlation analyses were performed between each seed region and the rest of the brain. To investigate the significant difference between pre-treatment patients and normal controls, the two-sample t-test was performed. The correlation coefficients in each voxel were transformed to Z-

scores, using the Fisher r-to-z transformation for group-level comparisons. The significant threshold was set to $p_{corrected} < 0.05$ (corrected by 3dClustSim, details in *Statistics*). Then, the significant cluster was selected for further analyses. The averaged z-value in each cluster was used in the statistical comparisons and the correlation analysis among functional connectivity and treatment changes.

The amplitude of low-frequency fluctuations analysis

Since the connection changes may arise from local fluctuation alternation (Di et al. 2013), we analyzed the amplitude of low-frequency fluctuations (ALFF), using the AFNI (3dRSFC) to evaluate the local fluctuation in rs-fMRI. We computed the ALFF value of each voxel as the average square root of a given frequency (0.01–0.1 Hz) in the power spectrum.

Statistics

For group-level comparisons between NC and Pre-treatment MDD patients, two-sample t-tests were used to compare FC, ALFF, and CBF. Brain regions with significant FC differences between HC and Pre groups were selected as ROIs for comparing the Post group to both NC and Pre groups. For functional connectivity and ALFF, the significance threshold was set at $p_{corrected} < 0.05$, within a predefined brain mask created by defined Brodmann and AAL templates. For CBF analysis, one patient without CBF data was excluded, and the significance threshold was set as $p_{corrected} < 0.05$. All the *p*-values were corrected, using 3dClustSim with spatial autocorrelation function (ACF) in AFNI. The ACF was estimated (3dFWHMx in AFNI) for computing the spatial autocorrelation of the fMRI data as a function of radius. A smoothing parameter which consisted of the averaged ACF across subjects was used with the 3dClustSim function in AFNI to estimate the probability of false positive cluster. The significance threshold was set to $p_{corrected} < 0.05$ ($p_{uncorrected} < 0.001$, cluster size >104 mm^3) for FC and ALFF, and $p_{corrected} < 0.05$ ($p_{uncorrected} < 0.001$, cluster size >1264 mm^3) for CBF. In the ROI comparison, the two-sample t-test was used in the comparison between Post and NC and the paired t-test was used for Pre-Post comparisons ($p_{corrected} < 0.05$). All the p values were corrected by false discovery rate (FDR) correction. To demonstrate the relationships among the identified connections before treatment and the changes of HAM-D score after treatment, Spearman correlation and permutation testing were conducted, where the data was randomly resampled 100,000 times, enabling estimation of the Spearman correlation for each permutation. The *r*-value distribution was obtained, and the significance level was set at $p < 0.05$ against the randomized distribution. Furthermore, we conducted the nonparametric regression by rank regression method (Snell et al. 1996) to investigate the association between the index within HAM-D score and the selected significant connection. The *p* value was estimated by permutation testing, which we performed 100,000 times to estimate the regression for each permutation. The distribution of the estimated coefficient was obtained, and the significance level was set as $p < 0.05$ against the randomized distribution.

Results

Clinical characteristics

Clinical characteristics are listed in Table 1. There was no significant difference between NC and MDD patients in age, sex, handedness, and education while Pre-depression severity (HAM-D score) was significantly higher than Post ($p < 0.001$, Fig. S2).

Functional connectivity

Table 2 shows the significant FC changes between NC, and Pre groups ($p_{corrected} < 0.05$) and the post-hoc analysis comparing Post to NC and Post groups. According to the post-hoc analysis of significant FC change in ROIs, group comparisons of Post group with NC and Pre groups showed that connections could be classified into non-treatment-related and treatment-related. Non-treatment-related connections evinced significant differences between patients (Pre and Post) and NC (Fig. 1, dot line). The FC of dACC (SN)-aIPL (FPCN), dACC (SN)-PCC (DN_{CORE}), and PCC (DN_{CORE})-dlPFC (FPCN) were significantly higher in patients than in NC. In contrast, the FC within FPCN (dlPFC-aIPL) was significantly lower in patients than in NC (Fig. S3).

The post-hoc comparisons among the NC, Pre, and Post groups showed significant treatment-related functional connectivity (Fig. S4) in the AI (SN)-thalamus: higher FC in Pre and in the thalamus-dlPFC (FPCN) and PHC (DN_{MTL})-dlPFC (FPCN), whereas lower FC in Pre (Fig. 1, solid lines).

Correlation between functional connectivity and HAM-D

We estimated the Spearman correlation among antidepressant treatment changes (HAM-D difference, Pre-Post) and the significant connections. Among the treatment-related connections for the Pre-treatment group, only the connection between the thalamus and left superior frontal gyrus evinced a significant correlation between antidepressant treatment effect and FC (Fig. 2 left, $p_{corrected} < 0.05$).

Furthermore, for the Pre-treatment group, to investigate the index within the HAM-D score and to identify components associated with the connection between the thalamus and left superior frontal gyrus, we conducted nonparametric

Table 2 T-test of functional connectivity changes among health control (NC), pre- (Pre) and post-(Post) treatment patients

Brain region	T-test[a] between NC and Pre					Post-hoc t-test	
	Cluster size	x, y, z, MNI coordinates			t-test	NC-Post[a]	Pre-Post[b]
SN seed: dACC							
Right Precuneus	51	40	−76	38	−6.0	−3.3**	2.04
Right inferior parietal lobule	18	66	−24	28	−4.0	−3.1**	1.3
SN seed: AI							
Right thalamus	39	14	−16	10	−4.9	−1.2	3.0*
DN_{CORE} seed: PCC							
Left middle frontal gyrus	13	−34	38	38	−4.7	−4.6*	0.7
DN_{MTL} seed: PHC							
Right inferior frontal gyrus	20	54	20	18	4.3	1.2	−2.8*
FPCN seed: aIPL							
Right middle frontal gyrus	17	46	22	42	4.1	2.5*	−1.4
Seed: thalamus							
Left middle frontal gyrus	13	−8	46	48	4.8	1.2	−6.6**

MNI Montreal Neurological Institute, *BA* Brodmann's area, *SN* salience network, DN_{core} core default network subsystem, DN_{MTL} default network subsystem centered around the medial temporal lobe, *FPCN* frontoparietal control network, *dACC* dorsal anterior cingular cortex, *AI* anterior insula, *PCC* posterior cingular cortex, *RSC* retrosplenial cortex, *aIPL* anterior inferior parietal lobule

[a] Two sample t-test

[b] Paired t-test

$p < 0.05$ for t-test between NC and Pre, **3dClustSim**-corrected. * $p < 0.05$, ** $p < 0.01$, corrected for post-hoc test

regression between the connection and 17 items in HAM-D score. Nonparametric regression calculated over the HAM-D scores for 'Somatic symptoms (general)', 'insight', 'Work and interests', and 'Suicide' revealed a significant major positive association, correlating with the connection between the thalamus and the left superior frontal gyrus (Fig. 3, $p < 0.05$). Furthermore, the scores for 'Anxiety somatic' revealed a non-significant trend with that connection ($0.1 > p > 0.05$).

Cerebral blood flow and amplitude of low-frequency fluctuations

To evaluate the local physiological indices in rs-fMRI, we estimated the CBF and ALFF. Results indicated that neither was there a significant difference for the CBF or ALFF analysis in the whole brain nor was there a significant local activation change in the significantly FC changed regions among NC, Pre, and Post groups (Fig. S5).

Discussion

We investigated sertraline modulation of MDD's doleful, spontaneous thoughts, focusing on inter-network neuronal connections and on the MRC. For MDD patients, disturbed functional connectivity was evinced by alterations in the connections of FPCN-DN, FPCN-SN, FPCN-thalamus, thalamus-SN, and intra-FPCN. It is especially important to note that, after the sertraline treatment, the FPCN-thalamus-SN pathway and DN_{MTL}-FPCN connection returned to the same connectivity level as that found in the NC group. Notably, the thalamus-dlPFC connection evinced a significant association with the treatment. In contrast to these positive effects, among MDD patients, the altered connections of FPCN-DN_{CORE}, FPCN-SN, and intra-FPCN remained impaired, even after sertraline treatment. These findings suggest that the 6-week sertraline treatment partially modulates a select set of dysfunctional brain circuits in those MDD patients whose depression abates. Thus far, this is the first in-vivo MRI study to evince a correlation between sertraline treatment response and the thalamus-FPCN connection in pre-treatment drug-naïve MDD patients.

The connection of DN_{MTL}-FPCN and pathway of FPCN-thalamus-SN pathway were significantly changed in MDD subjects, and both circuits returned to normal after sertraline treatment. Specifically, after sertraline treatment, the enhanced dlPFC-PHC (DN_{MTL}) connectivity might be associated with less time sinking into memory or mental simulations (Christoff et al. 2016). The DN_{MTL} is also closely connected to the DN_{CORE}; this connection serves as a key component for information flow through the DN system (Andrews-Hanna et al. 2010). The post-treatment attenuated insula-thalamus connection might imply a reduction of disgust perception (Phillips et al. 1997). The aberrant communication in FPCN-thalamus-SN pathway might,

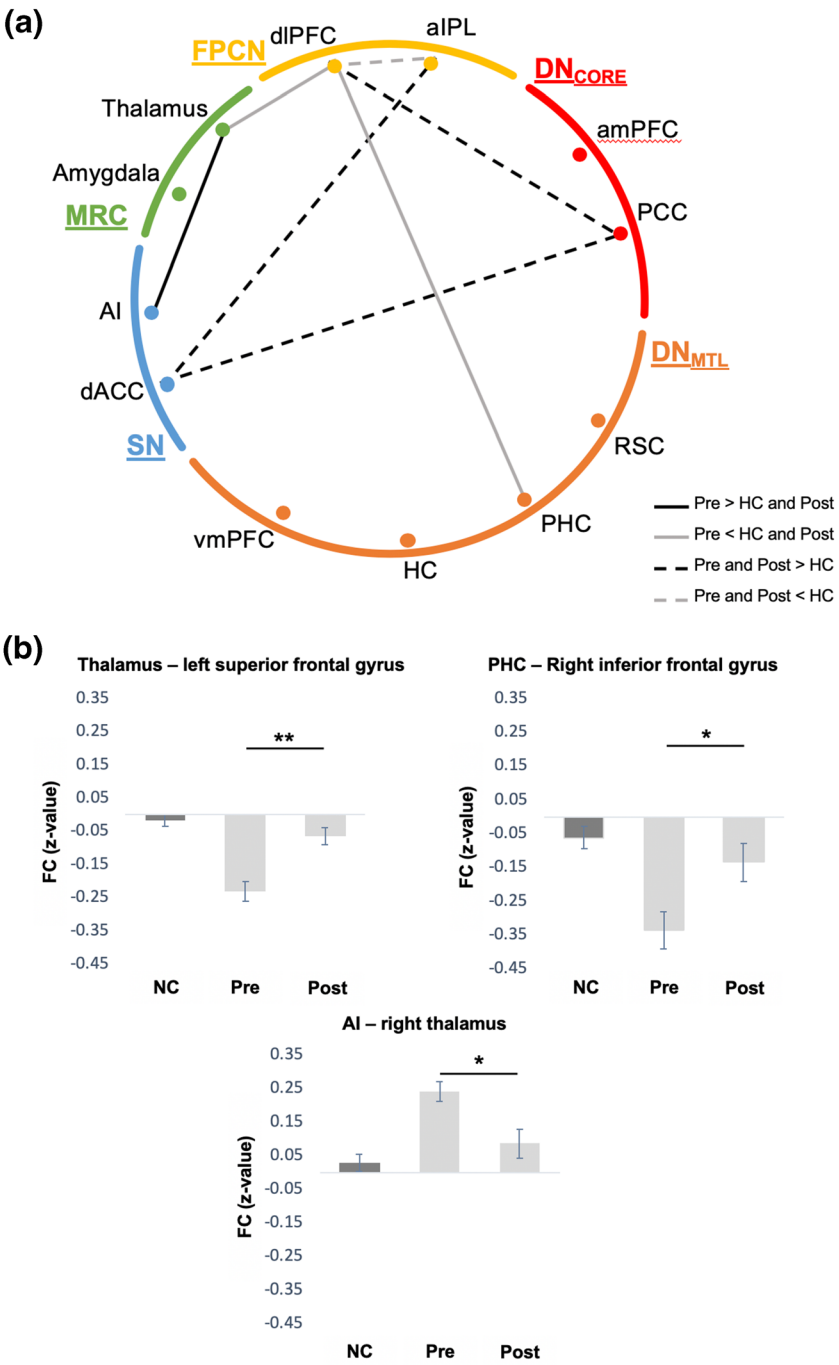

Fig. 1 **a** Graphic summary of functional connectivity changes among NC, pre- (Pre) and post- (Post) treatment groups. Color coding indicates different brain networks. The solid line represents the treatment effect on higher (black) and lower (gray) connectivity in Pre group compared with the other two groups. The dotted line represents the non-treatment effect on higher (black) and lower (gray) connectivity in NC group compared with MDD patient groups. **b** The post-hoc connectivity comparison on the treatment-related connections (FDR corrected $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$)

in part, mediate some prominent depressive symptoms including mood, anxiety, and lethargy. The thalamus receives most sensory information and relays it to appropriate parts of the cerebral cortex, which directs high-level functions such as speech, action, thought, and learning (Halassa and Kastner 2017; Nakajima and Halassa 2017). The midline thalamus is strongly modulated by

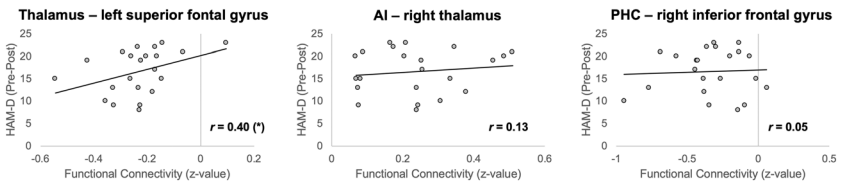

Fig. 2 The correlations between HAM-D score changes (Pre-Post) and the treatment-related functional connectivity before sertraline treatment. The correlation is significant between the thalamus and left superior frontal gyrus ($r = 0.48$, $p_{corrected} < 0.05$). The p value was corrected by FDR correction

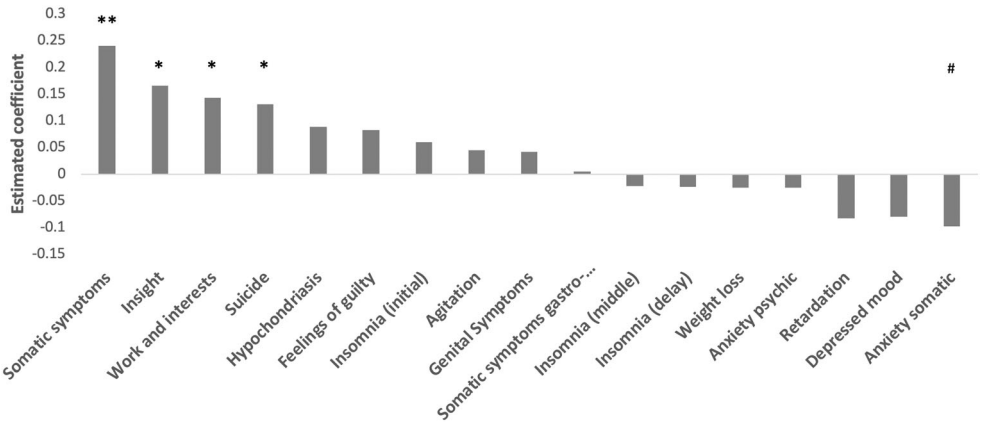

Fig. 3 The estimated coefficient of 17 items in HAM-D score in nonparametric regression analysis with the functional connectivity of thalamus and left superior frontal gyrus ($^{*}p < 0.05$, $0.05 < {}^{\#}p < 0.1$)

the ascending reticular activating system and plays a crucial "alerting" role in salience detection (Cho et al. 2013; Matsumoto et al. 2001). Loss of functional communication between the medio-dorsal nucleus and the mPFC has been shown to reduce behavioral flexibility (Parnaudeau et al. 2013), inhibit learning, and disrupt decision-making in both humans and animals (Mitchell 2015). In MDD patients, reduced volume (Dupont et al. 1995; Kong et al. 2014) and abnormal PET activation (Greicius et al. 2007) in the thalamus appear to be associated with mood disorders. Yang et al. found that sertraline treatment results in altered FC between frontal and limbic brain regions, resulting in greater inhibitory control over brain regions that mediate emotion processing (Yang et al. 2014). Our findings were consistent with these studies and further confirm that sertraline treatment could yield its therapeutic effect by regularizing functional connectivity in the FPCN-thalamus-SN pathway.

It is difficult to predict how effective sertraline treatment will be for any individual patient. Several brain regions associated with treatment response in MDD have been suggested: these include frontal (Alexopoulos et al. 2012), limbic (Andrew Kozel et al. 2011; Buckner et al. 2008; Fu et al. 2013), and temporal regions (Langenecker et al. 2007). As for treatment-resistant depression patients, many were found to have impaired functional connectivity of the prefrontal-thalamic circuit (Li et al. 2013; Lui et al. 2011; Yamamura et al. 2016); these findings suggest the critical role that this circuit might play in treatment response.

The relationship between the treatment effect and brain connectivity are probably the result of brain mechanisms that are acted upon by the administered medication. Previous studies of neurotransmitters indicated that there is an association between the pretreatment levels of SERT in the thalamus and treatment response to SSRIs (Kugaya et al. 2004; Yeh et al. 2015). We further demonstrated that pre-treatment functional connectivity between the thalamus and the fronto-parietal control network could serve as a potential predictor of sertraline treatment outcome, as reflected by an explicit association with emotion-related indices in HAM-D.

Depression is, among other things, characterized by excessively negative thoughts that are not specifically related to life events; thus, for purposes of this study, we devoted special attention to functional networks related to spontaneous thoughts. Studies of depressive rumination suggest that the content of these thoughts could, in large part, reflect a dysfunction of executive control (Lane & Northoff 2017; Nolen-Hoeksema et al. 2008). Abnormal communication within the FPCN may underlie some deficits in cognitive control that are commonly observed in patients with depression, and also contribute to symptoms such as difficulty in concentration or emotional self-regulation (Snyder 2013). Previous studies of MDD patients also demonstrated functional and structural changes in regions related to the FPCN network (Goodwin 1997; Webb et al. 2014). Christoff et al. hypothesized that the FPCN shapes or constrains thoughts through its mediation of interaction with other networks (Christoff et al. 2016). For example, the FPCN can couple with the DN, to mediate internally focused, deliberate autobiographical planning (Spreng et al. 2010). An important part of the FPCN, the dlPFC, plays a significant role in working memory and other aspects of executive function: directly relevant to our investigations, hyper-connectivity between the DN and the left dlPFC could be critical for goal-directed regulation of attention and emotion (Fales et al. 2008; Veltman et al. 2003; Vincent et al. 2008). Also, in response to negative emotional distractors, depression was associated with hyper-connectivity between regions responsive to salience (viz., the SN) and regions that mediate internal mentation (Kaiser et al. 2015a). Overall, enhanced communication among the FPCN, DN, and SN coupled with reduced communication within the FPCN, might underlie a predisposition for or ongoing rumination, while also serving as a mechanism that biases control systems to allocate resources toward spontaneous thoughts, rather than toward engaging the external world (Christoff et al. 2016; Kaiser et al. 2015a).

Previous studies demonstrated that CBF and ALFF were coupled to glucose metabolism and other types of hemodynamic

activity (Aiello et al. 2015; Akgören et al. 1994; Hoge and Pike 2001; Zang et al. 2007), while the functional connectivity in rs-fMRI reflects patterns of neuronal communication (Buckner et al. 2013). Both CBF and ALFF have been used previously to investigate brain function in MDD patients: significant reductions of regional CBF in the frontal, limbic, parietal, and temporal regions have been found in MDD patients (Drevets et al. 2002; Ho et al. 2013; Smith and Cavanagh 2005), while other studies have reported opposite results (Duhameau et al. 2010; Lui et al. 2009) or no significant changes (Colloby et al. 2012; Järnum et al. 2011). Alterations in ALFF values in depression have been found in the frontal cortex, parietal cortex, temporal cortex, limbic system, visual network and cerebellum (Guo et al. 2013; Liu et al. 2014; Wang et al. 2012). Clearly, the relevant findings evince much inconsistency, and are often even directly in conflict with one another. This very substantial disagreement among studies may well be due to the heterogeneity of the study cohorts. In our study, we assessed the CBF/ALFF changes to drug-naïve MDD patients and found no significant differences among the three groups—NC, Pre-treatment, and Post-treatment—neither in the whole brain analysis nor in the regions of significant FC change among groups. In short, the significant FC alterations revealed by our investigations were not accompanied by any disparity in ALFF and CBF: that is, the dysfunctions of inter-network communications revealed by our study were against a backdrop of unaltered hemodynamics.

Limitations

The main limitation of this study is the small sample size; this limitation is the result of difficulties in recruiting drug-naïve participants. Second, some scale items in HAM-D are not optimized for the contemporary definitions of depression and other scales, such as Hospital Anxiety and Depression-Anxiety Scale (Zigmond and Snaith 1983), Montgomery-Asberg Depression Rating Scale (Montgomery and Asberg 1979), Beck Depression Inventory-II (Beck et al. 1996), and Clinical Global Impression Scale (Hale et al. 2010). Nonetheless, we chose HAM-D because it is one of the most common rating scales in use for depression and it shows good overall reliability and validity (Carneiro et al. 2015). For future studies, real-time assessment of thought content while scanning MDD patients would provide more insight into their mental health. Third, there are more females than males in our patient groups; however, we found no statistically significant gender effect in the comparison and correlation analysis. Fourth, the change of functional connectivity reflects a mixed placebo and treatment effect because we did not enroll a placebo-controlled group in our study. Moreover, we assumed that NC data could serve as a stable reference for comparison; therefore, we did not collect fMRI data on NC six weeks after the first scan. This omission, however, might not confound our findings, because another study evinced higher inter- than intra-subject reliability in limbic, DN, FPCN, and visual networks, over a one-month rsFC observation among thirty healthy adults (Chen et al. 2015). Fifth, in this study, in 22 MDD patients, 4 out of 21 had a smoking history, while for one subject it was not possible to obtain the smoking history. All the NC were non-smokers. Nevertheless, no smoking effects were exhibited in our comparisons of MDD and NC, nor was there a correlation between functional connectivity and HAM-D ($p > 0.32$). Finally, our observations might be confounded by statistical regression-to-the-mean, since we do not here present longitudinal follow-up data. But the implication of our findings—specific indications of how sertraline could be administered in a more precise, personalized manner—suggest that future studies focusing on interactions among neurocognitive networks is warranted, especially studies that focus on the FPCN-thalamus-SN pathway.

Conclusion

Findings adduced from this study support the hypothesis that MDD is associated with dysfunction of FC in neurocognitive networks; moreover, we found that part of the dysfunctional FC returned to normal after sertraline treatment. Our findings contribute to the body of evidence that suggests effects of sertraline treatment primarily involve the mood regulation circuit. Sertraline has the potential to enhance the responsiveness to external stimuli and lessen the negative perception of disgust on spontaneous thoughts, which is reflected by the partial alterations of mood regulation circuit in MDD patients. Furthermore, thalamo-prefrontal connectivity might provide the predictive leverage that enables it to serve as a biomarker for identifying that subset of MDD patients who could benefit most from sertraline treatment.

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Compliance with ethical standards

Conflict of interest Li-Ming Hsu declares that he has no conflict of interest. Timothy J. Lane declares that he has no conflict of interest. Changwei W. Wu declares that he has no conflict of interest. Chien-Yuan Lin declares that he has no conflict of interest. Chi-Bin Yeh declares that he has no conflict of interest. Hung-Wen Kao declares that he has no conflict of interest. Ching-Po Lin declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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