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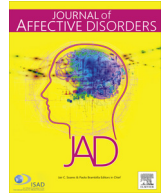
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## Research paper

## Neural connectivity of alexithymia: Specific association with major depressive disorder

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## ABSTRACT

**Background:** Alexithymia has been frequently associated with major depression disorders (MDD). Yet little is known about the exact relationship of alexithymia and MDD. In order to explore this subject matter, the neural connectivity associated with alexithymia in people with MDD and matched nonclinical controls were compared.

**Methods:** Twenty-two females diagnosed with first-episode MDD and twenty-one matched nonclinical controls were MRI brain-scanned with diffusion-tensor-imaging and resting-state-functional-imaging methods, and self-reported the Chinese 20-item Toronto Alexithymia Scale.

**Results:** Voxel-wise multiple regression analysis showed a group interaction effect regarding the correlation between white-matter-connectivity and alexithymia. Significant correlations were observed at the corpus-callosum in MDDs and at the right superior-longitudinal-fasciculus in the controls. These findings were then used to derive seeds for analyzing resting-state-functional-connectivity in each group separately. The results further revealed that alexithymia in MDDs were associated with reduced functional-connectivity in the right precentral-gyrus and several regions of the brain on the right which are associated with cognitive regulation in the default-mode-network. In contrast, among the control subjects, alexithymia was correlated with increased functional-connectivity between the right inferior-frontal-gyrus-triangularis and the right superior-occipital-lobe, which is associated with emotional response to external stimuli.

**Limitations:** Better participant selection, especially recruitment of medication-free samples, and the engagement of additional alexithymia assessments, should be considered in future investigations.

**Conclusions:** These findings supported our a priori hypothesis that MDDs and controls have distinct white-matter correlates of alexithymia, and these corresponded to the existing proposed neural correlates for the cognitive and affective characteristics of alexithymia respectively. Extended impacts of these microstructural changes on remote functional networks might help explain the distinct behavioral characteristics of alexithymia for these groups, as well as implications for therapeutic intervention of MDD.

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## 1. Introduction

Alexithymia (literally meaning “no words for feelings”) was first introduced by Sifneos (1973) to describe psychosomatic patients characterized by difficulties in identifying and communicating personal feelings, constriction of emotional expressions and fantasies, and a thinking style preoccupied by external events and limited introspections (Bankier et al., 2001; Nemiah et al.,

1976; Sifneos, 1973). Contemporary studies have identified alexithymia as a personality trait (Salminen et al., 2006), with prevalence estimated at ~10% amongst the general population (Franz et al., 2008; Mattila et al., 2006), and a predisposing factor for psychopathologies (Bankier et al., 2001; Taylor and Bagby, 2004).

### 1.1. Relationship between alexithymia and Major Depressive Disorder (MDD)

In particular, alexithymia and MDD are strongly related. Not only is there a much higher prevalence of alexithymia reported amongst the MDD population (~23–46%) (Honkalampi et al.,

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2000; Saarijärvi et al., 2001), but also people with alexithymia were found to have aggravated depressive symptoms, especially the somatic/affective symptoms of MDD (Guidi et al., 2011; Honkalampi et al., 1999). Such correlations allow alexithymia to be proposed as a potential candidate for subtyping MDD (Vanheule et al., 2007). Nevertheless, inconsistent findings have also been reported. A recent prospective study had found that alexithymia cannot be used to predict MDD, as based on the general population in Finland (Honkalampi et al., 2010). Factor analyses had also found that although alexithymia and depression were separate constructs (Marchesi et al., 2000; Parker et al., 1991), there were frequent overlaps during the measures conducted for both conditions (Hintikka et al., 2001). Hence, the relationship between alexithymia and MDD is relatively unclear.

### 1.2. Behavioral characteristics of alexithymia in MDD and nonclinical samples

Furthermore, alexithymia is a multi-dimensional construct with both cognitive and affective characteristics (Bermond et al., 2007; Taylor and Bagby, 2004). In fact, by reviewing past behavioral studies of alexithymia, distinct characteristics of alexithymia had been reported, depending on whether MDD or nonclinical samples were recruited. Studies taken from nonclinical samples had found that people with alexithymia have reduced sensitivity regarding response to emotional stimuli (Lane et al., 1996; Parker et al., 1993), attenuated interoceptive awareness and physiological reactivity that reflect diminished emotional experience (Herbert et al., 2011). This group has also had tendencies to focus on somatic sensations rather than symbolic representations of words and images upon emotional arousal (Karlsson et al., 2008). In contrast, studies of MDD patients had reported that alexithymia was associated with heightened emotional and physiological arousals, which were interpreted as displacement behaviors for compensating their difficulties in cognitive regulation of emotional experiences (Troisi et al., 2000). Another postulation also suggested that symptoms of helplessness and hopelessness among MDD patients with alexithymia were associated with their attribution of emotional experiences to situational, dispositional or psychological causes due to difficulties in identifying and expressing bodily sensations and feelings (Duddu et al., 2003). As explained by a recent review-study: when capacities regarding both the experiencing and cognitive processing of emotional information are reduced (affective characteristics of alexithymia), the need for emotional regulation was relatively low (drawn from non-clinical samples); whereas for the case where the capacities regarding experiencing emotional information were high but capacities regarding cognitive processing of the information were low (cognitive characteristics of alexithymia), reduced cognitive regulation would lead to experiences of emotions being intensified (especially negative ones, as in MDD patients) (van der Velde et al., 2013). Nevertheless, empirical evidence is required to corroborate such postulations.

### 1.3. Major hypotheses on the neural correlates for the cognitive characteristics of alexithymia

There is not yet a universally accepted theory on the neural correlates of alexithymia and various brain regions have been hypothesized for their roles in shaping the cognitive and affective characteristics of alexithymia.

One prominent view holds that damages at the corpus-callosum (CC) would lead to the cognitive characteristics of alexithymia due to the compromised interhemispheric transferral of information, which would interfere the coordinations of the two cerebral hemispheres in due course of cognitive processing of emotional

information (Larsen et al., 2003). The CC hypothesis was originally proposed in study of split-brain patients (Hoppe and Bogen, 1977) and more recent studies also found supporting evidence (Lumley and Sielky, 2000; Parker et al., 1999; Romei et al., 2008). Nevertheless, direct neuroimaging evidence is lacking, while questions have been raised on the nature and directionality of the proposed impairments during cognitive transferral of information (Tabibnia and Zaidel, 2005).

### 1.4. Major hypotheses on the neural correlates for the affective characteristics of alexithymia

Hypotheses on the neural correlates for the affective characteristics of alexithymia are more diverse. A longstanding view proposed deficits at the right hemisphere (or preference of the left hemisphere) (Bermond et al., 2005; Paradiso et al., 2011) would lead to dysfunctional perception and regulation of emotional behaviors (Borod et al., 1998). More recent evidence have focused on the role of the anterior cingulate cortex (ACC), although findings were mixed. Some studies found activities at ACC correlated negatively with alexithymia and suggested reductions in attention and response selection (Chester et al., 2015; Kano et al., 2003; Lane et al., 1998). Other studies claimed that alexithymia was correlated with increased activity at the dorsal ACC and implied this as the defense for increasing emotional inhibition (Pouga et al., 2010). Mixed findings were similarly reported regarding correlations between alexithymia and gray-matter measures of ACC in structural studies, with positive (Gündel et al., 2004), negative (Borsci et al., 2009; Ihme et al., 2013) and non-significant (Heinzel et al., 2012) results all being reported. To explain these controversial findings, an inverted U-shaped activation pattern has been proposed for the dorsal ACC, meaning that when tasks are low in cognitive load, ACC activities would increase with alexithymia, while when cognitive load in the tasks becomes strenuous, ACC activities associated with alexithymia would decrease (McRae et al., 2008; van der Velde et al., 2013). Another possible explanation for the differences in these findings might be the still debating functions of the dorsal ACC (which may be related with cognitive regulation, or appraisal and expression of emotions) (Etkin et al., 2011). Nevertheless, neuroimaging studies consistently found that dorsal ACC is coupled with activities in the right anterior insular (Paulus et al., 2003; Paulus and Stein, 2006), a brain region proposed for somatotopic representation of integrated sympathetic (versus left for parasympathetic) information from posterior-to-anterior progression (Craig, 2009). Hence, we speculate that the ACC and right hemisphere hypotheses for the affective characteristics of alexithymia may be linked with this strong coupling between ACC and the right-lateralized insular for processing of afferent information. Corroborating evidence can be found in the observation that reduced ability in labeling and identifying emotional faces in healthy subjects with alexithymia, particularly when they were under perceptual or temporal constraints, was accompanied by the reduced activations of the limbic and paralimbic brain regions (including the insular) (Ihme et al., 2014; Reker et al., 2010). In sum, a large body of research has suggested that dorsal ACC and right-lateralized deficits are related to alexithymia, particularly the affective characteristics associated with perception and experience of emotions, yet the exact underpinning mechanisms are still largely unknown.

A possible limitation in the existing body of literature is that most of the studies are based on gray-matters, while the role of white-matter fibers for providing connections of ACC with insular and other related brain regions might have been overlooked. To fill this gap, it would be important to identify the white-matter correlates for the affective characteristics of alexithymia. We hypothesized that disruptions at the right superior longitudinal

fasciculus (SLF), a longitudinal tract proposed for posterior-to-anterior (parietal-frontal) connection, may affect emotional attention for controlling perception and experience of emotions (Pourtois et al., 2013), as right-lateralization of this tract has also been found to be associated with the control of visual spatial attention (De Schotten et al., 2011). This proposal is supported by a recent voxel-based morphometry (VBM) study examining alexithymia in nonclinical subjects, which reported that affective characteristics of alexithymia were associated with both lower white-matter volumes of the right SLF and lower gray-matter volumes of the medial-orbitofrontal-cortex (while cognitive characteristics was associated with lower gray-matter volume of the ACC) (van der Velde et al., 2014).

### 1.5. The current study

White-matter connectivity has been demonstrated as a significant index for diagnosing and tracking brain dysfunctions in people with psychiatric disorders (Lim and Helpert, 2002). However, direct relationship between white-matter connectivity and alexithymia are rarely examined. Only a recent study on schizophrenia reported that alexithymia was negatively correlated with white-matter integrity at the CC, the left SLF, the inferior longitudinal fasciculus (ILF) and several other tracts (Kubota et al., 2012). Therefore, in the current study, we examined the white-matter connectivity of alexithymia with diffusion tensor imaging (DTI) data (Basser and Pierpaoli, 1996). Specifically, we explored the relationship of alexithymia and depression by studying the white-matter connectivity (indexed by fractional anisotropy, FA) in a group of patients diagnosed with first-episode MDD and a matched group of nonclinical controls. Based on the above discussions about the existing evidence of the neural correlates of cognitive and affective characteristics of alexithymia (see Sections 1.3 and 1.4), we hypothesized CC and right SLF as the white-matter correlates for cognitive and affective characteristics of alexithymia respectively. Moreover, following the above discussions on the behavioral characteristics of alexithymia (see Section 1.2) and the speculations by van der Velde et al. (2013), we proposed that MDD and nonclinical groups would be associated with cognitive and affective characteristics of alexithymia respectively. Combining both, we predicted that there would be significant group interaction effect for the white-matter correlates of alexithymia, with MDD group at CC (hypothesized white-matter correlates of cognitive characteristics) and nonclinical group at right SLF (hypothesized white-matter correlates of affective characteristics).

Analysis would be based on tract-based spatial statistics (TBSS), a technique recommended for reducing risks of local misalignments in VBM (Smith et al., 2006, 2007) and has been adopted in various previous studies of MDDs (Guo et al., 2012a, 2012b).

Moreover, since white-matter tracts were responsible for providing integral routes of communication for anatomically separated brain areas, connectivity disturbance of these tracts might induce extended impacts on the functional connectivity (temporal correlations of signal fluctuations) of spatially separated neural networks (Greicius et al., 2009). Therefore, seed-based resting-state functional connectivity magnetic resonance imaging (RfMRI) analyses (Fox and Raichle, 2007) were conducted to locate the remote brain regions with disturbances in functional coordination associated with alexithymia. As networks identified by both resting-state and task-related techniques were highly corresponded (Smith et al., 2009), resting-state method was adopted to avoid biases from the difference in individual task performance (Fox and Raichle, 2007).

## 2. Methods

### 2.1. Subjects and behavioral measures

The current study involved only females as test subjects, to avoid the influence of gender effect on the results (Levant et al., 2009). One group of the participants included 22 outpatients (MDD group, ages ranged from 25 to 55 years) receiving treatment at the David Trench Rehabilitation Center upon diagnosis of their first episode of MDD but not any other affective disorder according to the criteria in DSM-IV (American Psychiatric Association, 1994). Although we attempted to minimize the effect of medication by recruiting only newly diagnosed patients, these patients were taking anti-depressants at the time of the experiment (ranged from 3 to 16 weeks). They also fulfilled the following inclusion criteria: Chinese, right-handed, healthy individuals physically without histories of organic brain disorders, traumatic brain injuries, substance abuse/dependence disorders, psychotic disorders, and any other formal diagnosis of anxiety disorders. The other group was 21 nonclinical controls (NC group, ages ranged from 25 to 64 years) recruited from the local community. They had no history of psychological disorders and were matched with the MDD group by age, education level and estimated intelligence as assessed by the Raven's Progressive Matrices (Raven, 2000). All participants were assessed on the degree of alexithymia by the Chinese version of the 20-item Toronto Alexithymia Scale (TAS-20-C, Bagby et al., 1994; Zhu et al., 2007) and the level of depression was assessed by the Chinese version of the Beck Depressive Inventory (BDI-II-C, Byrne et al., 2004). They had all given their written and informed consent, as approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. Table 1 shows the demographic variables and affective profiles for the two groups.

Consistent with existing data, significant correlations between the rate of alexithymia (TAS-20-C) and degree of depression (BDI-II-C) were found, both across groups ( $r = .69, p < .001$ ) and for each group separately (MDD group:  $r = .546, p < .05$ ; NC group:  $r = .701, p < .001$ ).

### 2.2. Data acquisition and preprocessing

DTI data were acquired from a 3.0 T Philips scanner equipped with a standard 8-channel head coil, using 32 isotropically

**Table 1**

Demographic characteristics and affective profiles of MDD patients and nonclinical controls, including the group means, SDs, values of independent samples *t*-tests, and associated *p*-values.

	MDD group ( <i>n</i> =22) mean (SD)	NC group ( <i>n</i> =21) mean (SD)	<i>t</i> -value	<i>p</i> -value
<b>Demographics</b>				
Age	37.6 (8.32)	41.9 (11.04)	-1.4201	.163
Years of education	12.9 (2.83)	13.4 (4.55)	-.4102	.684
RPM	247.5 (10.51)	252.2 (12.80)	-1.3101	.198
Length of medication (weeks)	6.81 (3.26)	NA	NA	NA
<b>Affective profiles</b>				
BDI-II-C	25.9 (13.35)	7.3 (7.17)	5.7332	< .001***
TAS-20-C	59.1 (11.65)	49.8 (10.28)	2.7646	.009**

**Note:** MDD=major depressive disorder, NC=nonclinical control, RPM=raw scores of the Raven's Standard Progressive Matrices Test, BDI-II-C=Chinese Beck Depression Inventory-II, TAS-20-C=20-Item Toronto Alexithymia Scale (Chinese version).

\*\*  $p < .01$ .

\*\*\*  $p < .001$ .

distributed orientations for diffusion-sensitizing gradients at a *b*-value of 1000 s/mm<sup>2</sup>, with the scanning parameters as follows: time of echo (TE)=65 ms, repetition time (TR)=11,375 ms, flip angle=90°, field of view (FOV)=225 mm, acquisition matrix=112 × 112, slice thickness=2 mm, slice gap=0 mm, 74 slices in axial plane, voxel size=2 × 2 × 2 mm<sup>3</sup>, and total acquisition time=830 s.

The collected DTI data were then processed using the FMRIB Software Library version 5.0.2 (FSL, Smith et al., 2004). All source data were corrected for head motion and eddy currents by affine registration referencing the first *b*=0 image, using the FMRIB Diffusion Toolbox (FDT, part of FSL). FA images were subsequently generated from the corrected data by fitting diffusion tensors with the DTIFIT (part of FSL) and by extractions made from the brain using the mask generated by the Brain Extraction Tool (BET, part of FSL, Smith, 2002). Tract-Based-Spatial Statistics version 1.2 (TBSS, part of FSL) was engaged to create a mean FA skeleton for representing the centers of all tracts that are common to all participants, by thinning and applying a threshold of .2 on the FA value on the mean FA image after it was normalized (nonlinear registration to the 1 × 1 × 1 mm<sup>3</sup> Montreal Neurological Institute 152 space). The mean FA skeleton would then be applied to individual FA images to restrict the evaluation of diffusion parameters prior to projection to individual skeletonized FA images. These skeletonized FA images were then applied and used for analysis by voxel-wise permutation-based nonparametric inference using the FSL Randomize version 2.5 (Nichols and Holmes, 2002) using 5000 permutations with the threshold-free cluster enhancement option (TFCE).

R-fcMRI data were acquired with a T2\*-weighted echo-planar imaging sequence for 6 min (during which the participants were awake but had their eyes closed) inside the same MRI machine as the DTI data, with the scanning parameters as follows: time of echo (TE)=30 ms, repetition time (TR)=2000ms, flip angle=90°, field of view (FOV)=230 mm, acquisition matrix=64 × 64, slices thickness=3.5 mm, slice gap=0 mm, 40 slices in axial plane, voxel size=3.5 × 3.5 × 3.5 mm<sup>3</sup>. Preprocessing of the acquired functional images and single-subject level calculation of functional connectivity were performed using DPARSF (Yan and Zang, 2010) and REST (Song et al., 2011), while group-level analysis was conducted by Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK), all running on a commercial software package (MATLAB, v7.14, The MathWorks Inc., Natick, MA, 2000).

The first 10 slices of all source R-fcMRI data were discarded before the preserved data were spatially realigned to the middle slice in order to adjust for the differences in the time of acquisition of multiple slices within an image and corrected for head-motion. The resulting images were then co-registered to their individual high-resolution T1 image equivalents, and then normalized to the 3 × 3 × 3 mm<sup>3</sup> MNI template by unified segmentation and then spatially smoothed with a 6 mm, full-width, half-maximum (FWHM) Gaussian kernel. Nuisance variables were regressed out, including the six head motion parameters, mean signals of the whole brain (the global trend), white-matter and cerebrospinal fluid. These images, after removal of linear trends and after being band-pass filtered (at .01–.08 Hz) to remove the cardiac and respiratory signals, were ready for statistical analysis.

2.3. Data analysis

Age was controlled in all of the following analyses to remove any discrepancies or impacts on the results due to age-related factors, as their effects had been observed continually in studies of depression (Mirowsky and Ross, 1992) and alexithymia (Mattila et al., 2006). Thus, it would be undesirable for this effect to be restated in the present study.

For DTI data, firstly, in order to test the hypothesis that alexithymia would be associated with white-matter integrity at different locations for the two groups, voxel-wise multiple regression in separate analyses, using CC and right SFL as region of interest (ROI) based on a priori hypotheses, were conducted on the skeletonized FA images across all participants, with group and alexithymia (measured by TAS-20-C scores, demeaned before entered into the model) as regressors. Any significant group interaction effect would be further examined by extracting the mean FA values from the result clusters and entered into linear regression models for analyses.

Secondly, to test that CC and right SLF are white-matter correlates of alexithymia for MDD and NC group respectively, voxel-wise multiple regression analyses, using these tracts as ROI, were conducted on each group separately, with any potential effect of depression removed by entering the BDI-II-C scores as covariate of no interest. Mean values of FA and other apparent diffusion coefficients (ADCs), including mean diffusivity (MD, volumetric measure for the degree of diffusion), radial diffusivity (RD, diffusivity perpendicular to the principal axons) and axial diffusivity (AD, diffusivity parallel to the principal axons), would also be extracted

Table 2

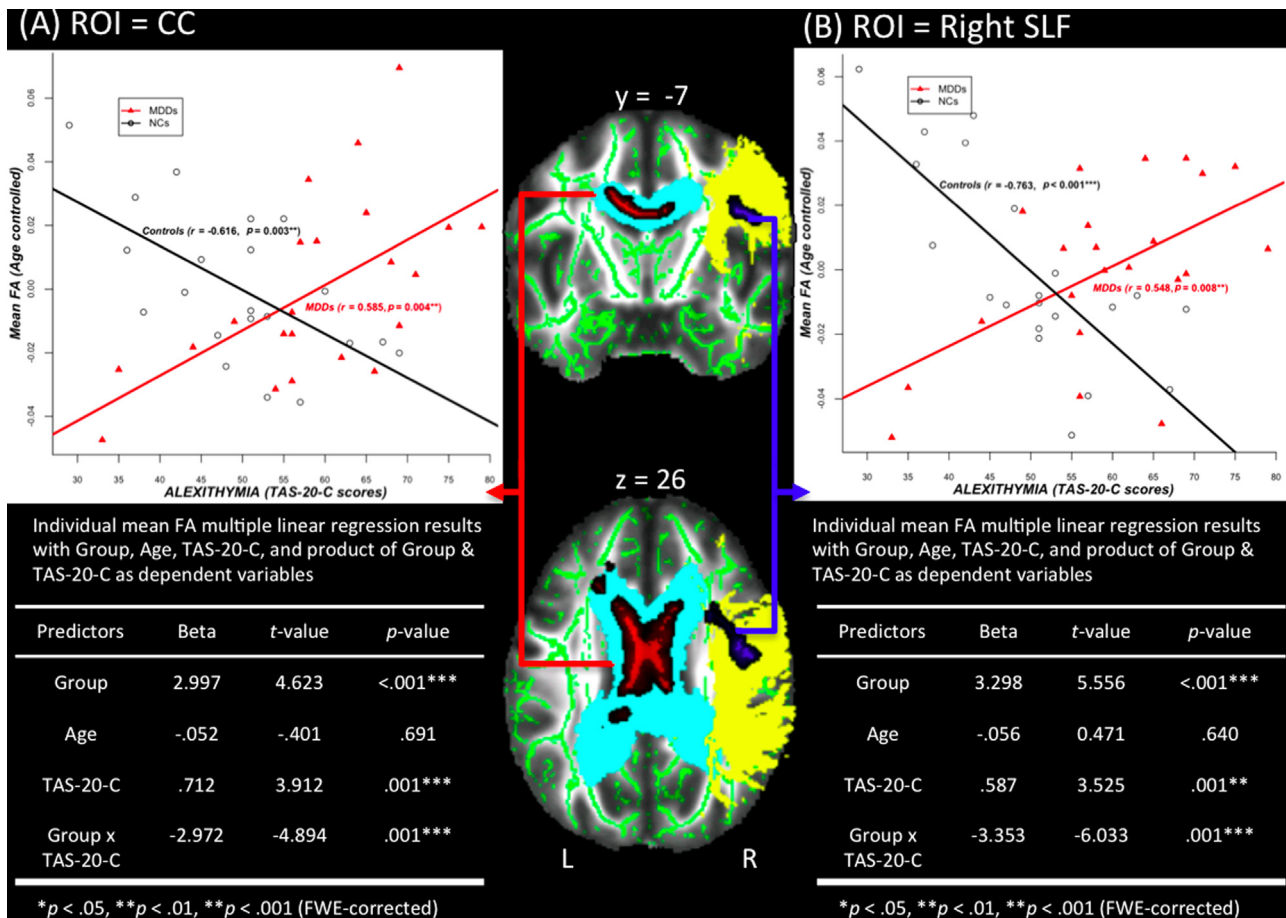
(A) Result clusters (by entering both groups' data) with significant group interaction effect on the correlations between FA and TAS-20-C scores (age controlled). (B) Result clusters (by entering data in each group separately) with significant correlations between FA and TAS-20-C scores (age, BDI-II-C scores controlled).

ROI	CC			Right SLF			No. of voxels	p-value	Peak voxel			
	Clusters	No. of voxels	p-value	Peak voxel	z	1 × 1 × 1 mm <sup>3</sup>			x	y	z	
		1 × 1 × 1 mm <sup>3</sup>		x	y	z	1 × 1 × 1 mm <sup>3</sup>		x	y	z	
<b>(A) Clusters with significant group interaction effect (age controlled)</b>												
1	2198		.005**	-8	0	28	221		.022*	45	-6	26
2	49		.046*	-7	29	1	77		.031*	31	4	30
3	40		.047*	-8	-35	23						
4	23		.047*	-10	-44	17						
5	13		.049*	-13	30	-8						
<b>(B) Clusters with significant correlations with in any one group (age, BDI-II-C scores controlled)</b>												
	CC (positive correlation, MDD group)						Right SLF (negative correlation, NC group)					
1	199		.029*	5	-12	26	356		.012*	47	-6	25
2	33		.046*	-13	-18	31	16		.046*	31	2	30

Note: FA=fractional anisotropy, TAS-20-C=20-Item Toronto Alexithymia Scale (Chinese version), BDI-II-C=Chinese Beck Depression Inventory-II, MDD=major depressive disorder, NC=nonclinical control.

\* *p* < .05.

\*\* *p* < .01 (FWE-corrected).



**Fig. 1.** Voxel-wise multiple regression analysis, using both body of corpus callosum (CC) and superior longitudinal fasciculus (SLF) separately as region of interest (ROI), showed significant group interaction effects for the correlation between TAS-20-C scores and FA (MDD > NC), after regressing out age as a covariate of no interest ( $p < .05$ , FWE-corrected). To aid visualization, the results (red for ROI=CC, blue for ROI=right SLF) were thickened (using `tbss_fill`, as implemented in FSL) and overlaid on the mean FA maps (co-registered to the MNI152 template) and mean skeletonized FA (green) from the 22 MDD patients and 21 NC controls, the standard mask for CC (cyan) and right SLF (yellow). The coronal and axial slices shown were  $y = -7$ ,  $z = 26$  (MNI coordinate). Individual mean FA extracted from the result clusters with (A) ROI=CC (B) ROI=right SLF for both groups were plotted against TAS-20-C scores in the upper scatterplots, and results for the parameters of linear regression model for mean FA, using Group, Age, TAS-20-C and Group  $\times$  TAS-20-C scores as regressors, were shown in the tables underneath. **Note:** MDD=major depressive disorder, NC=nonclinical control, TAS-20-C=Toronto Alexithymia Scale (Chinese version), FA=fractional anisotropy. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

from any significant result cluster for further inference of the FA results.

Statistical threshold for DTI analysis was set at  $p < .05$ , controlled for family-wise error rate (FWE-corrected). White-matter tracts obtained in the result clusters were identified with reference to the two white-matter atlases—the ICBM-DTI-81 white-matter labels atlas and the JHU white-matter tractography atlas—provided by Johns Hopkins University (<http://cmrm.med.jhmi.edu>) (Mori et al., 2005).

For r-fcMRI data, separate analyses were conducted for each group, based on the result clusters identified in the DTI analysis within the ROIs of the a priori hypotheses (that could be fortunately be confirmed) for the respective group. Specifically, by adopting the method for geometrical segmentation of the mid-sagittal CC (Hofer and Frahm, 2006) and SFL (Makris et al., 2005), we identified the specific segments within CC and right SLF where the white-matter correlates were located. Termination points were determined as the brain regions (ROIs) that are connected by these specific tract segments. We then engage these ROIs as seeds for functional connectivity calculation, by having the mean neural activities of all voxels within the corresponding seed ROIs for each participant extracted and correlated (using Pearson's correlation,  $r$ ) with all other brain voxels for every time point within the time course of the preprocessed r-fcMRI data. These were then

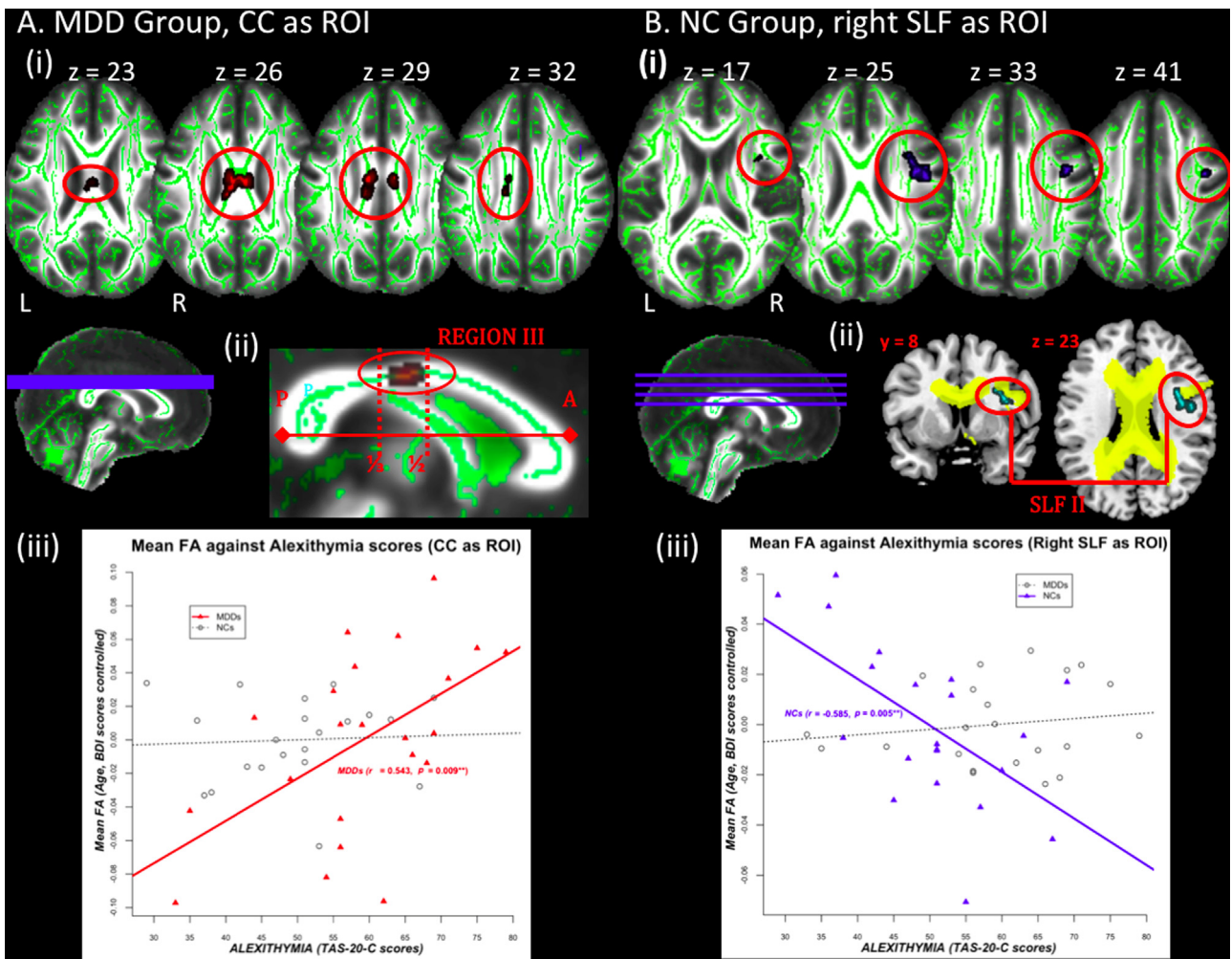
transformed to Fisher's Z scores to produce the standardized functional connectivity ( $z$ -fc) maps. The  $z$ -fc maps for participants in each group were entered into second-level, voxel-wise, multiple regression models for identifying the locations where significant correlations between  $z$ -fc and TAS-20-C scores would be found, after controlling BDI-II-C scores. Results were voxel-level height thresholded at  $p < .001$  and peak- or cluster-level  $p < .05$  (FWE-corrected). Brain anatomical regions were identified with reference to Anatomical Automatic Labeling (AAL, Tzourio-Mazoyer et al., 2002).

### 3. Results

#### 3.1. Structural connectivity analysis

##### 3.1.1. Comparison on the correlations of FA and alexithymia across MDD and NC groups using CC and right SLF as ROI

Multiple clusters were observed with significant group interaction effect on the correlations between TAS-20-C scores and FA (only MDD > NC, not MDD < NC), by adopting the body of CC and the right SLF separately as ROIs (see Table 2A). No cluster was found to have significant correlation of FA, either by group or TAS-20-C scores alone.



**Fig. 2.** (A) (i) Voxel-wise multiple regression analysis using CC as ROI showed significant positive correlations between TAS-20-C scores and FA in the MDD group after regressing out both age and BDI-II-C as covariates of no interest ( $p < .05$ , FWE-corrected). To aid visualization, the results (red) were thickened (using `tbss_fill`, as implemented in FSL) and overlaid on the mean FA maps (co-registered to the MNI152 template) and mean skeletonized FA (green). The axial slices shown were from  $z = 23$  to  $32$  (MNI coordinate). (ii) The result clusters overlaid on the mid-sagittal view of the mean FA map showed that it mainly lied on region III of the corpus callosum (posterior half minus posterior third) based on the mid-sagittal corpus callosum topology (Hofer and Frahm, 2006). (iii) Scatterplots of mean FA extracted from the result cluster (from 2(A) (i)) showed that only mean FA from the MDD group was significantly correlated with TAS-20-C scores, after controlling for age and BDI-II-C scores (red solid line indicating positive correlation), but not those from the NC group. (B) (i) Voxel-wise multiple regression analysis using right SLF as ROI showed significant negative correlations between TAS-20-C scores and FA in the NC group after regressing out both age and BDI-II-C as covariates of no interest ( $p < .05$ , FWE-corrected). To aid visualization, the results (blue) were thickened (using `tbss_fill`, as implemented in FSL) and overlaid on the mean FA maps (co-registered to the MNI152 template) and mean skeletonized FA (green). The axial slices shown were from  $z = 17$  to  $41$  (MNI coordinate). (ii) The result clusters overlaid on the coronal and axial view of a standard T1-weighted brain template, with the nearby brain regions (yellow) to indicate that it mainly lied on subcomponent II SLF (Makris et al., 2005). (iii) Scatterplots of mean FA extracted from the result cluster (from (B) (i)) showed that only mean FA from the NC group was significantly correlated with TAS-20-C scores, after controlling for age and BDI-II-C scores (blue solid line indicating negative correlation), but not those from the MDD group. **Note:** MDD= major depressive disorder, NC=nonclinical control, CC=Corpus Callosum, SLF=superior longitudinal fasciculus, ROI=region of interest, TAS-20-C=Toronto Alexithymia Scale (Chinese version), BDI-II-C=Chinese Beck Depression Inventory-II, FA=fractional anisotropy. For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.

To further examine this interaction effect of group, mean FAs for individual participants were extracted from the result clusters and plotted against TAS-20-C score, as well as entered into linear regression model. The results showed that all three regressors, including group, TAS-20-C score and their cross product, were significant predictors of mean FA (see Fig. 1).

The two overall models were also significant (CC as ROI:  $F(4,38) = 6.612, p < .001, R^2 = .410$ ; right SLF as ROI:  $F(4,38) = 9.726, p < .001, R^2 = .506$ ). Mean FAs extracted by adopting CC as ROI could be predicted by the following formulas:

$$\text{MDD group: FA} = .6246 - .0001392 * \text{Age} + .001583 * \text{TAS}$$

$$\text{NC group: FA} = .7806 - .0001392 * \text{Age} - .001407 * \text{TAS}$$

Mean FAs extracted by adopting right SLF as ROI could be predicted by

$$\text{MDD group: FA} = .4077 + .0001669 * \text{Age} + .001454 * \text{TAS}$$

$$\text{NC group: FA} = .5988 + .0001669 * \text{Age} - .002302 * \text{TAS}$$

### 3.1.2. Separate group analyses using CC and right SLF as ROI

As shown in Table 2B, two clusters were found to have significant correlations between FA and TAS-20-C, positively (not negatively) for MDD group with CC as ROI, and negatively (not positively) for NC group with right SLF as ROI, both controlled for BDI-II-C scores.

Fig. 2A shows the clusters within CC where significant positive correlations between FA and TAS-20-C scores were observed.

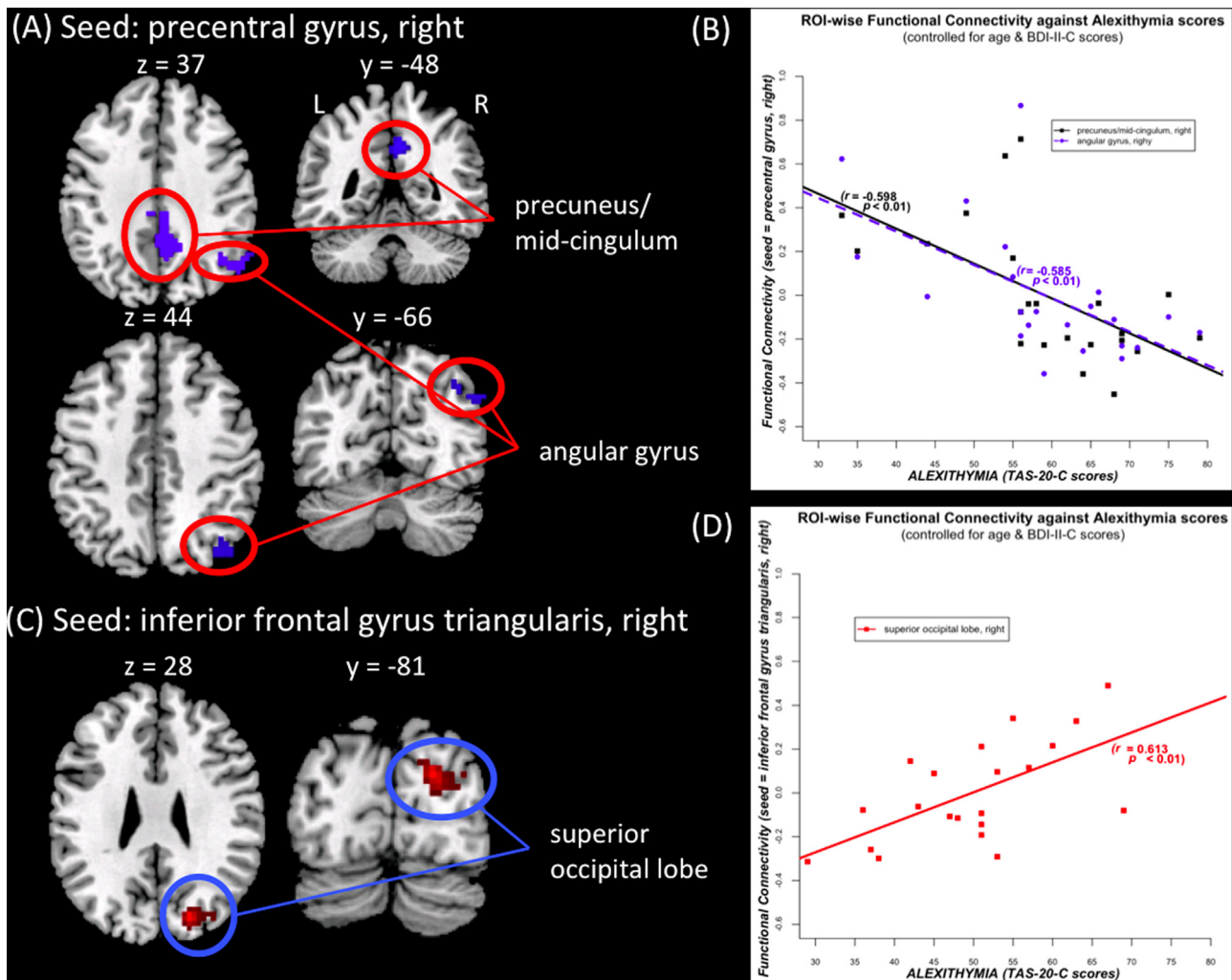
By method of geometrical segmentation of mid-sagittal CC (Hofer and Frahm, 2006), the result clusters were found to be lying at Region III of CC, that is, the posterior half-minus-posterior third of CC (see Fig. 2A(ii)). As proposed by these authors, this region is comprised of callosal motor fibers (CMFs), which project into the primary motor cortices.

Furthermore, by plotting mean FA extracted from the result clusters against the TAS-20-C scores for each participant,

**Table 3**  
r-fcMRI results (voxel-height threshold  $< .001$ , cluster-level  $p < .05$ , FWE-corrected) with age and BDI-II-C scores controlled: (A) clusters with significant negative correlations between functional connectivity with right PreCG (seed) and TAS-20-C scores in MDD group. (B) clusters with significant positive correlations between functional connectivity with right IFG\_triangularis (seed) and TAS-20-C scores and in NC group.

Brain Region (BA)	Cluster-level			Peak-level			MNI coordinates		
	$p$ (fwe-corr)	$p$ (uncorr)	$k$	$p$ (fwe-corr)	$p$ (uncorr)	$t$ -Value	$x$	$y$	$z$
<b>(A) MDD group (negative correlation)</b>									
PCUN/mid-cingulum (BA 23)	.000	.000	102	.883	.000	4.99	6	-48	36
				.941	.000	4.82	6	-33	36
ANG (BA 19/39)	.010	.005	61	.986	.000	4.56	60	-60	36
				.999	.000	4.28	42	-72	42
				1.000	.000	4.11	51	-66	36
<b>(B) NC group (positive correlation)</b>									
SOL (BA 19)	.003	.000	71	.000	.000	10.18	21	-81	27
MOL (BA 19)				1.000	.001	3.85	36	-81	27

**Note:** r-fcMRI=resting-state functional connectivity, BDI-II-C=Chinese Beck Depression Inventory-II, TAS-20-C=20-Item Toronto Alexithymia Scale (Chinese version), PreCG=precentral gyrus, IFG\_triangularis=inferior frontal gyrus, triangularis, MDD=major depressive disorder, PCUN=precuneus, ANG=angular gyrus, NC=nonclinical control, SOL=superior occipital lobe, MOL=mid-occipital lobe.



**Fig. 3.** r-fcMRI results (voxel-height threshold  $< .001$ , cluster-level  $p < .05$ , FWE-corrected) with age and BDI-II-C scores controlled: (A) functional connectivity between PreCG (seed) and PCUN/mid-cingulum and ANG, all on right hemisphere, were found to have significant negative correlations with TAS-20-C scores in MDD group. (B) Scatterplots of ROI-wise functional connectivity between the right PreCG and the two clusters were plotted against TAS-20-C scores for each participant in the MDD group, after controlling for age and BDI-II-C scores. (C) Functional connectivity with right IFG\_triangularis (seed) and right SOL were found to have significant positive correlations and TAS-20-C scores and in NC group. (D) Scatterplots of ROI-wise functional connectivity between the right IFG\_Triangularis and right SOL was plotted against TAS-20-C scores for each participant in the NC group, after controlling for age and BDI-II-C scores. **Note:** PreCG=precentral gyrus, MDD=major depressive disorder, ROI=region of interest, TAS-20-C=Toronto Alexithymia Scale (Chinese version), BDI-II-C=Chinese Beck Depression Inventory-II, PCUN=precuneus, ANG=angular gyrus, IFG\_Triangularis=inferior frontal gyrus, triangularis, SOL=superior occipital lobe.



significant positive correlation was only observed in the MDD group ( $r=.543, p=.009$ ) but not in the NC group ( $r=.053, p=.821$ ) (see Fig. 2A(iii)). Finally, to investigate the contribution of diffusivity indexes that underpin FA, mean MD, RD, AD were also extracted from the result clusters for individual participants in the MDD group. FA was found to have significant negative correlations with RD ( $r=-.991, p<.001$ ) and MD ( $r=-.908, p<.001$ ), but not with AD ( $r=.230, p=.395$ ). These findings suggested that increasing FA within CC in MDD group was not related to increased diffusivity at the principle axons, but reduced diffusivity as reflected by the reduced volumetric measure (MD) and diffusivity perpendicular to the principal axons (RD). One possible explanation was the reduced diameters of the relatively large and less densely packed CMF axons (Aboitiz et al., 1992; Beaulieu, 2010; Hofer and Frahm, 2006; Paul, 2011).

Fig. 2B presents the clusters within right SLF where significant negative correlations between FA and TAS-20-C scores were found. Similar to the preceding findings, based on the geometrical segmentation of SFL (Makris et al., 2005), the result clusters were found to be located at the subcomponent II of SFL (lateral to the CC but medial to the middle-frontal-gyrus and the pars-opercularis of the inferior-frontal-gyrus) (see Fig. 2B(ii)), which is a major association pathway between the PFC and the posterior parietal region that has been found to be primarily responsible for regulating visual spatial attention for perception (De Schotten et al., 2011).

Again, by plotting mean FA extracted from the result clusters with regard to each participant against the TAS-20-C scores, significant negative correlations were observed in the NC group ( $r=-.585, p=.005$ ) but not in the MDD group ( $r=.150, p=.504$ ) (see Fig. 2B(iii)). Examination of correlations between mean FA and mean MD, RD, AD extracted from the result clusters for individual participant found significant positive correlation for AD ( $r=.665, p=.003$ ) and significant negative correlation for RD ( $r=-.843, p<.001$ ), but only marginal significant correlation for MD ( $r=-.458, p=.073$ ). These further affirmed that the decreasing FA in association with TAS-20-C scores at the right SLF for the NC group was related to decreasing white-matter diffusivity.

### 3.2. Resting-state functional connectivity analysis

#### 3.2.1. Seed-based analysis for MDD group

Functional connectivity was computed based on seeds at bilateral-precentral-gyri (PreCG, AAL label of primary motor cortex), the termination points connected by CMFs (neural correlate of alexithymia in MDD group revealed in structural connectivity analysis). Significant negative correlations with TAS-20-C scores were found for the functional connectivity between the right PreCG and clusters at the right precuneus (PCUN)/mid-cingulum (BA 23) and right angular gyrus (ANG, BA 19/39) (see Table 3A and Fig. 3A). Scatterplot showing the correlations between TAS-20-C scores and the ROI-wise functional connectivity (between right PreCG and the results clusters) with regard to each participant in the group is presented in Fig. 3B. No significant positive correlation between TAS-20-C and functional connectivity with the right PreCG and no significant positive or negative correlation between TAS-20-C and functional connectivity with the left PreCG were found.

#### 3.2.2. Seed-based analysis for NC group

PFC was the frontal termination point connected by SLF II (neural correlate of alexithymia in NC group revealed in structural connectivity analysis), particularly the right IFG, which is connected to the anterior insular for representing the afferent bodily feelings from the sensory network (Craig, 2009). Thus, functional connectivity was computed using the right IFG (including labels in AAL: IFG-opercular, BA44/48; IFG-triangularis, BA45; IFG-orbital,

BA47) as seeds. Significant positive correlation with TAS-20-C scores was found for the functional connectivity between right IFG-triangularis (IFG\_triangularis, BA45) and the right superior-occipital-lobe (SOL, BA 19) (see Table 3B and Fig. 3C). Scatterplot showing the correlation between TAS-20-C scores and the ROI-wise functional connectivity (between right IFG-triangularis and right SOL) extracted for each participant in the group is presented in Fig. 3D.

## 4. Discussion

This study explored the relationship between alexithymia and MDD based on white-matter connectivity and seed-based resting-state functional connectivity. The results confirmed our a priori hypothesis that the alexithymia-correlated white-matter can be located at distinct locations in the CC for the MDD group and in the right SLF in the NC group. Further study of r-fcMRI analyses, using the seeds derived from white-matter connectivity results, revealed that there are extended impacts of the microstructural changes associated with alexithymia on remote functional networks. These findings will be discussed in more details in the following section in light of the distinct behavioral characteristics displayed by people with alexithymia among the two groups (discussed in Section 1.2). To the best knowledge of the authors, this is the first combined structural (DTI) and functional (r-fcMRI) connectivity study for examining the relationship between alexithymia and MDD.

### 4.1. Structural connectivity of alexithymia in MDD and NC groups

DTI analysis showed that alexithymia was associated with reduced connectivity at the CC in the MDD group, particularly at the CMFs that specialized in the transfer of sensorimotor information. Our findings provided supporting neural evidence for the hypothesis regarding the CC (Larsen et al., 2003) and the association of MDD with cognitive characteristics of alexithymia (van der Velde et al., 2013). They were also consistent with previous findings that decreasing white-matter connectivity in the CC was associated with increasing degree of alexithymia in people diagnosed with schizophrenia (Kubota et al., 2012), and also increasing severity of depression (positively correlated with alexithymia) in MDD patients (Cole et al., 2012).

In contrast, DTI results in the NC group indicated that alexithymia was associated with reduced diffusivity at the right SLF, particularly at the subcomponent responsible for connecting the PFC with posterior region responsible for regulating of spatial attention during visual perception. The results corroborated previous findings regarding the right SLF as the neural correlate of affective characteristics of alexithymia in healthy subjects (van der Velde et al., 2014).

### 4.2. Functional connectivity of alexithymia associated with the structural changes in MDD and NC groups

For the MDD group, only functional connectivity in the right, but not the left, hemisphere was affected, which may suggest the impairment of CC for the left-to-right direction. This concurred with the postulation that the right hemisphere is the dominant center for processing emotional information and regulation of emotional feelings incurred subjectively (Bermond et al., 2005; Paradiso et al., 2011). In particular, alexithymia in the MDD group was found to be associated with reduced connectivity among the right PreCG and two right brain regions in the DMN, namely the PCUN/mid-cingulum and ANG (Buckner et al., 2005; Uddin et al., 2009). These were essential regions involved in processing of self-

related attention and memories of emotional information (Grei-  
cius et al., 2009; Kober et al., 2008; Seghier, 2013), as well as  
processing of stimulus value (Lin et al., 2012) and regulation of  
emotions (Kohn et al., 2014). Similar findings with lower con-  
nectivity in the cognitive emotion processing subnetwork of the  
DMF has also been found in another resting-state study of alex-  
ithymia, and the authors interpreted this as associated with the  
less introspective thinking of alexithymia (Liemburg et al., 2012).  
For the current study, since reducing diffusivity in association with  
alexithymia has been observed at the tract connecting the left and  
right PreCG, particularly at CMF, we proposed to relate the reduc-  
ing functional coupling with the reducing interhemispheric  
transfer of information (the CC hypothesis), particularly sensor-  
motor information, for emotional processing in the right hemi-  
sphere. As DMN is associated with spontaneous, rather than goal-  
directed brain activities (Fox and Raichle, 2007), the reducing  
functional coupling between the PreCG and emotional processing  
network in the DMN might reflect reducing automatic evaluation  
and regulation of emotional information associated with alex-  
ithymia. Alternatively, since brain activities are suggested to be  
switching between the central executive network (CEN) and the  
DMN (Menon and Uddin, 2010; Sridharan et al., 2008), the reduc-  
ing functional coupling in DMN would also suggest increasing  
goal-directed effort (implying greater difficulties) for cognitive  
evaluation and regulation of emotional information. This increas-  
ing effort in cognitive emotional regulation might explain the in-  
creasing displacement behaviors, in terms of heightened emo-  
tional and physiological arousal (Troisi et al., 2000); as well as the  
increasing somatic/affective symptoms found in MDD patients  
with alexithymia (Guidi et al., 2011; Honkalampi et al., 1999).

In contrast, for the NC group, r-fcMRI results showed that  
alexithymia was associated with increasing connectivity between  
right IFG\_triangular and right SOL. This was consistent with the ob-  
servation in a previous r-fcMRI study that there was higher con-  
nectivity at the right IFG for the alexithymic group of a nonclinical  
sample (Liemburg et al., 2012) and was implied by these authors as  
reflecting that the alexithymic group engaged suppression tech-  
niques, rather than verbalizing strategies, for emotional regulation.

Nevertheless, IFG has been suggested for a role in the selection  
of context-appropriate attention (Kober et al., 2008), as well as  
analysis of emotional meaning and affect-labeling (Aron et al.,  
2004). Specifically, the right IFG\_triangular has been found to be in-  
volved in processing of emotional information and evaluation of  
affective salience (Rota et al., 2009). In light of the current findings  
that alexithymia in the NC group was associated with reduced  
diffusivity of SLF II, the tract proposed for connecting the IFG and  
SOL, we suggest that this increasing functional coupling might  
help to compensate the reducing perceptual information passed  
from the SOL to IFG\_triangular for evaluation of emotional salience  
for exogenous stimuli. This interpretation is consistent with our pro-  
posal that affective alexithymia may be associated with disrup-  
tions of the highly interconnected network for processing of af-  
ferent sensory information, including the ACC, IFG and right  
anterior insular (Craig, 2009), and also concurred with a previous  
study which found that joint activation of ACC (as well as the  
dorsolateral prefrontal-cortex DLPFC and parietal regions) and the  
anterior insular/IFG was associated with conscious access of visual  
perceptual information, based on the attention blink paradigm  
(Kranzloch et al., 2005). Similar evidence was observed in a pa-  
tient with lesion at the right SOL (BA19), who was found to have  
both relative lowered level of selective visual spatial attention and  
high level of affective alexithymia (Ho and Lee, 2013). Another  
coherent interpretation was offered by the authors of an EEG  
study, who also suggested that increase in brain reactivity at the  
anterior and/or posterior areas of the cortex in association with  
alexithymia (in nonclinical sample), particularly at the right

hemisphere and whilst the subjects were watching emotional  
clips, might reflect increase in their effort for emotional processing  
(Aftanas and Varlamov, 2007). Moreover, the relationship between  
capacity to experience emotions and the extent at which emo-  
tional significance of environmental stimuli could be identified has  
long been established in past studies (Lane et al., 1998; Phillips  
et al., 2003).

In summary, results of the r-fcMRI in NC group were consistent  
with the characteristic features of people with affective alex-  
ithymia, namely tendency to have difficulties in inducing emo-  
tional feelings ensuing external stimuli, preferences for diverting  
attention to external information (Vorst and Bermond, 2001) and  
mislabeling of somatic sensations (Taylor and Bagby, 2004).

#### 4.3. Limitations

Firstly, only the measure for alexithymia, TAS-20-C, was as-  
sessed. This mainly measures the cognitive characteristics of  
alexithymia. Although this enabled comparisons being made with  
most prior studies, engagement of other alexithymia measures,  
especially including the affective characteristics, would help vali-  
date the current findings. Secondly, only a limited number of fe-  
male patients were included in the sample due to the difficulties in  
recruiting patients, especially only patients diagnosed with first  
episode MDD was recruited to minimize the effect of medication.  
However, this would limit the generalizability of the current  
findings and also potentially inflate the effect size of the current  
findings (Yarkoni and Braver, 2010). Thirdly, due to ethical con-  
cerns, the effect of medication was not controlled, as well as the  
levels of alexithymia across the two groups. Future research would  
need to better select their samples to minimize these potential  
confounds.

For the imaging results, the exact microstructural changes re-  
presented by the diffusivity indexes had yet to be confirmed. Use  
of tractography techniques could be considered to obtain more  
precise locations of the tracts. For the r-fcMRI analysis, the current  
study was based on the seeds derived from DTI findings, future  
studies may engage a more exhaustive search to further identify  
other functional networks that might also be affected by alex-  
ithymia. Moreover, controversies on anticorrelations associated  
with removal of global brain signals should also be observed. Fi-  
nally, the present study was correlative in nature, therefore, causal  
inference would have to be established in the future by lesion and  
prospective studies.

## 5. Conclusions

The present study confirmed the hypothesis that white matter  
integrity of the CC and the right SLF was correlated with the de-  
gree of alexithymia in the MDD and NC group respectively. These  
are also neural correlates proposed for the cognitive and affective  
characteristics of alexithymia based on review of existing litera-  
ture. From the functional connectivity findings, we proposed that  
alexithymia in the MDD groups might be associated with reduced  
automatic emotional regulation and introspective thinking, with  
increased effort for cognitive regulation of emotional information;  
while alexithymia in NC group might be linked with reduced ca-  
pacity for evaluation of emotional salience of exogenous stimuli.  
These findings could shed some lights on the prevailing observa-  
tions that alexithymia in MDD patients is associated with the in-  
creased need for emotional regulation. They also provide addi-  
tional evidence for relating alexithymia with more blunted emo-  
tional experiences in NC samples. Finally, the present study has  
provided neurobiological evidence to support the importance in  
separating healthy and clinical samples for analyses in studies of

alexithymia in the future.

#### Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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