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# Disruption of the structural and functional connectivity of the frontoparietal network underlies symptomatic anxiety in late-life depression

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ABSTRACT

The present study investigated functional connectivity and white matter integrity of the fronto-parietal network (FPN) to reveal the neural mechanisms that underlie late-life depression (LLD). Fifty patients with LLD and 40 non-depressed controls were included in the study. A multi-parametric approach was used by applying independent component analysis (ICA) to estimate functional connectivity of the FPN and by applying tractbased spatial statistics to examine white-matter integrity in tracts to the FPN. Patients with LLD exhibited functional abnormalities in the right inferior frontal gyrus, middle frontal gyrus, and inferior parietal gyrus and lower white matter fractional anisotropy in the right inferior fronto-occipital fasciculus, anterior thalamic radiation, and uncinate fasciculus. Alterations of functional connectivity and white matter fractional anisotropy in these regions were negatively correlated with the severity of symptomatic anxiety in LLD patients. The right inferior frontal gyrus might be a crucial hub in transferring information between these abnormal regions. Significant correlations were found between anxiety symptoms and brain alterations, suggesting that impairments in the FPN network might be involved in symptomatic anxiety in elderly individuals with depression.

## 1. Introduction

Depression that occurs after 60–65 years of age is typically referred to as late-life depression (LLD), which affects 4–10% of elderly adults [1–3]. Late-life depression is a heterogeneous illness that is characterized by depressed mood, anhedonia, and cognitive problems, especially high rates of psychic and somatic anxiety [4,5]. In contrast to depression in the younger population, LLD is frequently associated with aging-related neurodegeneration, cognitive impairment, and somatic complaints. Changes in brain network connectivity are a neurobiological biomarker of LLD, but the specific brain regions that are involved in these changes remain poorly understood. Exploring changes in the structural and functional connectivity of brain networks that are related to symptoms could provide a better understanding of the neural mechanisms that underlie LLD.

Evidence from structural and functional brain imaging studies on LLD has shown that cognitive control network dysfunction in LLD involves brain regions including the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC) [6,7]. These cognitive control-related regions can be divided into two cognitive control networks. The frontoparietal network (FPN), including the dlPFC, inferior parietal lobule, intraparietal sulcus, precuneus, and middle cingulate cortex, may serve to initiate and adjust control, whereas the cingulo-opercular network, including the ACC, anterior insula/frontal operculum, and thalamus, may provide stable set maintenance [8]. Considering the FPN has high degree of connectivity and is involved in various executive functions [9], the role of the FPN in mental disorders has gained increasing research attention [10,11]. Changes in the FPN may play a common role in multiple mental disorders, including depression, by disrupting a domain-general cognitive control feedback mechanism [12]. A recent study showed that the severity of depressive symptoms negatively correlated with the between-network global connectivity of the FPN in the general population [13]. However, the correlation between functional abnormalities of the FPN and clinical symptoms of LLD is not clearly understood.

The integrity of white matter fiber tracts that connect the FPN with

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other regions might be important in the neuropathology of LLD. Fractional anisotropy (FA) is a diffusion tensor imaging (DTI)-derived metric that describes the directionality of water diffusion, which reflects membrane integrity and myelin thickness [14]. Sheline et al. demonstrated that there is pathological disruption of the white matter integrity in the superior longitudinal fasciculus in LLD, and this structure connects the frontal, parietal, occipital, and temporal lobes and serves as a key connective structure in the FPN [15]. Microstructural abnormalities in other regions that are connected with the FPN have also been reported in individuals with LLD, including lower FA in the ACC and uncinate fasciculus, compared with healthy individuals [6,16,17]. Some studies have used tractbased spatial statistics (TBSS) to estimate structural connectivity in LLD [18,19], which is an automated approach that permits the voxelwise analysis of white matter in the whole brain. This approach confers superior objectivity and interpretability in DTI analyses compared with methods that use a priori-defined regions [20]. Several studies that employed TBSS reported widespread white matter abnormalities in LLD, and the regional differences were most prominent in the frontal lobe and association and projection fibers. However, a few studies did not find a significant difference in FA between LLD patients and elderly individuals without depression [21,22]. Moreover, changes in white matter in the superior frontal gyrus and superior longitudinal fasciculus have been shown to predict future depressive symptoms [19], but other studies reported there were no such correlations [15,18]. The functions of brain networks are based on their structures. Evidence shows that there are both functional and structural abnormalities in the FPN in LLD. Abnormalities in the white matter that connects the FPN may be closely related to functional deficits in the FPN. However, the links between structural changes and brain network dysfunction in LLD remain poorly understood.

The present study investigated the structural and functional characteristics of the FPN in elderly individuals with LLD to elucidate the neuropathology of this disorder. We hypothesized that individuals with LLD have significantly lower functional connectivity and lower white matter FA in regions of the FPN than do nondepressed individuals. We also expected to find a correlation between symptom severity and abnormalities of the FPN. To test these hypotheses, we adopted a multiparametric approach by combining functional connectivity of the FPN, as estimated by independent component analysis (ICA), with white matter integrity of the FPN, as determined by TBSS. Overall, we explored the coordinated structural and functional mechanisms in brain circuits that are involved in LLD.

## 2. Materials and methods

### 2.1. Ethical statemen

The present study was approved by the Research Ethics Review Board of the Peking University Institute of Mental Health. All of the subjects provided informed written consent to participate in the study.

### 2.2. Subjects

Fifty patients with LLD (60–82 years old, mean age = 67.65 ± 5.64 years) and 40 nondepressed controls (NCs; 60–82 years old, mean age = 66.14 ± 6.57 years) were included in the study between May 2018 and June 2019. All of the subjects were assessed by two experienced psychiatrists using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), and the Structured Clinical Interview for the DSM (SCID). The severity of depression was assessed using the 24-item Hamilton depression rating scale (HAMD) [23]. The severity of anxiety was assessed using the Hamilton anxiety rating scale (HAMA). Overall cognitive function was rated using the mini-mental state examination (MMSE) [24] and Montreal cognitive assessment (MoCA) [25]. The LLD group consisted of consecutively recruited subjects who met the DSM-IV [26] criteria for unipolar major depression without psychotic features. All of the LLD patients were currently experiencing an episode of depression. Among the 50 LLD patients, 42 were receiving antidepressant monotherapy (23 were taking a selective serotonin reuptake inhibitor [SSRI], 16 were taking a serotonin-norepinephrine reuptake inhibitor [SNRI], and three were taking a noradrenergic and specific serotonergic antidepressant [NaSSA]). Eight of the LLD patients were antidepressant-naive. Four participants had a HAMA score of less than 7, 16 participants had a HAMA score of 7–13, 16 participants had a HAMA score of 14–21, and 14 participants had a HAMA score of greater than 21. None of the LLD participants met the DSM-IV criteria for anxiety. None of the LLD patients had received psychotherapy. For all the subjects, the exclusion criteria included the following: (1) current or previous diagnosis of schizophrenia, bipolar disorder, substance abuse, substance-induced depression, or dementia, (2) an MMSE score of < 26, (3) severe somatic disease (e.g., brain tumors, metastatic cancer, or unstable cardiac, hepatic, or renal disease), (4) treatment with drugs that are associated with depression (e.g., antipsychotics, steroids, α-methyl-DOPA, clonidine, reserpine, tamoxifen, and cimetidine), and (5) any contraindication to functional magnetic resonance imaging (fMRI; e.g., having a pacemaker or implanted metal). The participants in the NC group were recruited through advertisements and were excluded if they were experiencing or had a history of any psychiatric disorder or had a family history of a psychiatric disorder. The two groups were matched for age, sex, and educational level. The demographic and clinical measures are presented in Table 1.

### 2.3. Neuroimaging acquisition

All of the subjects underwent scans using a research-dedicated 3.0 T GE EXCITE HD scanner (GE Medical Systems, Milwaukee, WI, USA). High-resolution T1-weighted images were first acquired with an SPGR EDR sequence (field of view [FOV] = 25.6 $cm^3$, flip angle = 12°). We then performed 8-min resting-state fMRI (rs-fMRI) scans with a gradient-echo echo-planar imaging (EPI) sequence (FOV = 22.0 $cm^3$, TR = 2000 ms, TE = 30 ms, flip angle = 90°, number of slices = 43, total scans = 240). Diffusion tensor imaging was performed using a single-shot spin-echo EPI sequence (FOV = 24 $cm^3$; TR = 8980 ms, TE = 92 ms; flip angle = 90°, number of directions = 64 and 8 b0 images). During data acquisition, the subjects were instructed to stay awake, keep, and keep their head still.

### 2.4. Resting-state functional magnetic resonance imaging data

#### 2.4.1. Preprocessing

All of the images were checked for artifacts, structural abnormalities, and pathologies by a qualified neuroradiologist. We excluded the data of subjects whose head motions were > 2.0 mm or 2.0° during rs-fMRI scanning. The FSL analysis package was then used (Functional MR Imaging of the Brain [FMRIB] software library; www.fmrib.ox.ac.uk/

**Table 1**
Demographic and clinical characteristics in late-life depression and non-depressed control groups.

| | LLD group $n$ = 50 | NC group $n$ = 40 | $F/t/\chi^2$ | $p$ |
|---|---|---|---|---|
| Sex (% male) | 13 (26%) | 15 (37.5%) | 2.599 | 0.107 |
| Age (years) | 67.65 ± 5.64 | 66.14 ± 6.57 | 1.176 | 0.243 |
| Education (years) | 13.02 ± 3.18 | 12.25 ± 3.71 | 1.093 | 0.277 |
| HAMD score | 19.32 ± 4.35 | 2.35 ± 2.07 | 26.086 | < 0.001 |
| HAMA score | 17.46 ± 7.57 | 2.78 ± 2.04 | 11.913 | < 0.001 |
| MMSE score | 28.10 ± 1.40 | 28.40 ± 1.32 | −1.036 | 0.303 |
| MoCA score | 25.18 ± 2.65 | 24.65 ± 2.84 | 0.913 | 0.364 |
| Comorbidities | | | | |
| Hypertension | 16 (32%) | 10 (25%) | 0.53 | 0.467 |
| Diabetes | 5 (10%) | 5 (12.5%) | 0.141 | 0.708 |
| Medication load index | 0.84 ± 0.37 | — | — | — |

fsl) to preprocess the data. We discarded the first 10 volumes of raw EPI data to ensure that the signal reached equilibrium. The remaining 230 volumes were corrected by slice-timing alignment, motion correction (using the MCFLIRT method), registration (using the FLIRT method), normalization, spatial smoothing with a 6 mm Gaussian kernel, and high-pass temporal filtering with a 150 s cutoff frequency (0.007 Hz). We then used individual structural volumes to transform each subject's resting-state data into the Montreal Neurological Institute (MNI) space using the FLIRT program in FSL. In the present study, to remove the influence of the global signal on the results, we performed two preprocessing steps, but the final results were not significantly different [27,28].

#### 2.4.2. Independent component analysis

Group ICA was conducted using the MELODIC and dual regression program (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/DualRegression). We first concatenated all of the subjects' data and applied 23 components to identify the network patterns of functional connectivity in the LLD and NC groups (20–30 independent components were processed separately). According to the clinicians' evaluations, the brain network with 23 components encompassed the most brain regions (Appendix Fig. S1). The model order was estimated using the Laplace approximation to Bayesian evidence for a probabilistic principal component model. The FPN was chosen using spatial correlation with a set of predefined templates [29]. Next, we used dual regression to perform between-subject analysis using FSL tools [30]. In stage 1, the group spatial maps were regressed to each subject's 4D dataset to generate a set of time courses. In stage 2, those time courses were regressed to the same 4D dataset to obtain a subject-specific set of spatial maps. The IC maps were then compared between groups on a voxelwise basis for statistical analysis using nonparametric permutation testing (5000 permutations), revealing group differences in network connectivity. To compare fMRI measures between two groups, a contrast matrix of network connectivity was constructed using general linear models (GLMs), with head motion parameters, age, sex, educational level, medication load, and the presence or absence of global signals as covariates ($p < 0.05$, with false discovery rate [FDR] correction) [31,32]. We further analyzed functional connectivity in patients who took antidepressants and drug-naive patients separately (Appendix Fig. S2).

### 2.5. Diffusion tensor imaging data

#### 2.5.1. Preprocessing

The DTI data were preprocessed and analyzed using tools that are included in FSL software. To create individual FA images, FDT was used to fit a tensor model to the raw diffusion data, and then, the BET tool was used to extract the brain. Head movements and eddy current distortions in the DTI data were corrected, and a diffusion tensor model was fit at each voxel using DTIFIT. The FNIRT nonlinear registration tool was used to align all of the subjects' FA images, and 0.2 was chosen as the mean FA skeleton image threshold for a common space.

#### 2.5.2. Tractbased spatial statistics

Tractbased spatial statistics were used to examine the differences in FA in the whole brain between the LLD group and NC group. Each subject's FA images were nonlinearly aligned with the standard space template, and a mean FA image for the whole sample was calculated and thinned to create a mean FA "skeleton". Skeleton images of each subject's FA image were then produced and projected onto the mean skeleton using GLMs to identify the location at which the FA value differed significantly among these skeletons. The GLM design matrix incorporated head movement parameters, age, sex, educational level, and antidepressant use as covariates, with 5000 permutations. The statistical threshold was set to be $p < 0.05$ (fully corrected for multiple comparisons using familywise error [FWE] across all white matter tracts in the wholebrain analysis).

### 2.6. Statistical analysis

Demographic and clinical characteristics were analyzed for between-group differences using two-sample *t*-tests for continuous variables and the $\chi^2$ test for categorical variables. Comparisons of white matter FA in the FPN between groups were performed using analysis of variance (ANOVA), with age, sex, and antidepressant use as covariates. Pearson correlation analyses were performed to assess correlations between significant functional and structural findings and the clinical variables, including HAMD scores, HAMA scores, MMSE scores, and MoCA scores in each group separately. The tests were two-tailed, and $p < 0.05$ indicated statistical significance; the level of significance was corrected for multiple comparisons in the correlation analysis. To prevent false positives, Bonferroni correction was used across the four clinical measures for correlations with functional connectivity and FA measures, and these correlations were only considered significant when $p < 0.0125$ ($0.05/4 = 0.0125$).

## 3. Results

### 3.1. Demographic and clinical characteristics

No significant differences in age, sex ratio, or educational level were found between the LLD and NC groups. For clinical characteristics, the LLD group had significantly higher depression and anxiety symptom scores than did the NC group. No significant differences in the MMSE or MoCA scores were found between groups (Table 1).

HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

### 3.2. Functional magnetic resonance imaging measures

After ICA decomposition, the left FPN and right FPN were identified (Fig. 1). The left FPN ($r = 0.59$) and right FPN ($r = 0.54$) were correlated with predefined templates of resting-state networks [29]. Dual-regression analysis of the right FPN showed significant differences between the LLD and NC groups (Fig. 2A). We assessed intrinsic functional connectivity in the FPN and functional connectivity between the left FPN and right FPN. Compared with the NC group, the LLD group exhibited significantly lower intrinsic functional connectivity in the right inferior frontal gyrus (IFG), right middle frontal gyrus (MFG), and right inferior parietal gyrus (IPG) with other regions within the FPN ($p < 0.05$, FDRcorrected; Table 2). No significant difference in functional connectivity was found between the left FPN and right FPN. Anxiety symptoms in LLD patients, as measured by the HAMA scores, were negatively correlated with intrinsic functional connectivity of the IFG, MFG, and IPG with other regions within the right FPN ($r = -0.43$, $p = 0.002$; after controlling for depression scores: $r = -0.38$, $p = 0.006$), whereas no significant correlations were found in the NC group ($r = -0.08$, $p = 0.65$; after controlling for depression scores: $r = -0.06$, $p = 0.72$; Fig. 2B). No significant correlations of intrinsic functional connectivity were found with the HAMD scores ($r = -0.23$, $p = 0.11$), MMSE scores ($r = -0.31$, $p = 0.026$; after controlling for depression scores: $r = 0.29$, $p = 0.04$), or MoCA scores ($r = -0.20$, $p = 0.16$; after controlling for depression scores: $r = -0.22$, $p = 0.13$). The results of the subgroup analysis showed that both the antidepressant patients and drug-naive patients exhibited a decrease in functional connectivity in the right FPN compared with the NC group ($p < 0.05$, FDR-corrected), and no significant difference was found between the antidepressant group and drug-naive group (Appendix Fig. S2).

All of the clusters were statistically significant ($p < 0.05$, FDR-corrected, controlling for sex, age, and antidepressant use). FPN, frontoparietal network; LLD, late-life depression; NC, non-depressed control.

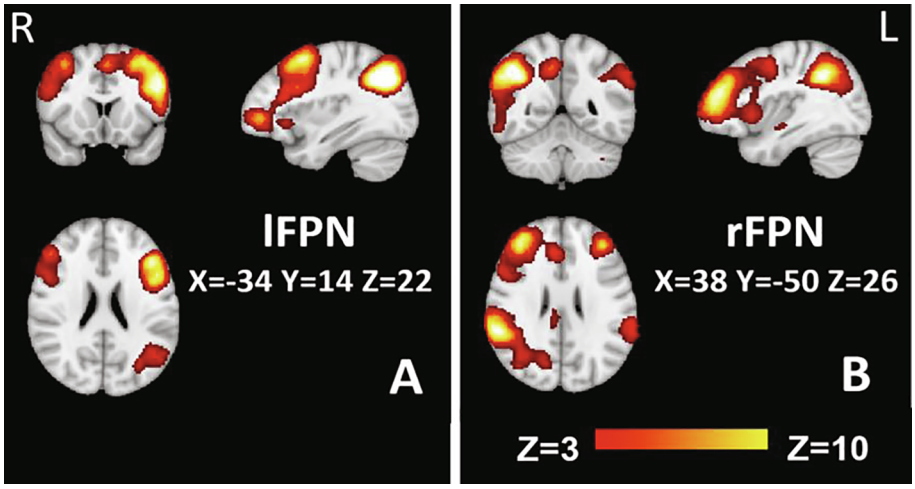


**Fig. 1.** Resting-state networks in late-life depression patients and non-depressed controls generated by ICA. (A, B) Group means of left fronto-parietal network (lFPN) (A) and right fronto-parietal network (rFPN) (B). ICA, independent component analysis.

### 3.3. Diffusion tensor imaging measures

Whole-brain TBSS revealed that the LLD group exhibited significantly lower FA in right frontal regions (inferior fronto-occipital fasciculus [IFoF], anterior thalamic radiation, and uncinate fasciculus; $p = 0.012$, FWE-corrected) and lower FA in left-hemisphere regions (anterior thalamic radiation, cingulum, inferior longitudinal fasciculus, superior longitudinal fasciculus, IFoF, and forceps major; $p < 0.05$, FWE-corrected) compared with the NC group (Table 3, Fig. 3A). The mean FA values in the right FPN were extracted for comparisons between the LLD and NC groups using ANOVA while controlling for sex, age, and antidepressant use. The LLD group exhibited significantly lower FA than did the NC group ($F_{1,89} = 5.362$, $p = 0.023$; Fig. 3B). The HAMA scores were negatively correlated with the white matter FA values in the right frontal clusters, and TBSS showed group differences ($r = -0.37$, $p = 0.017$; after controlling for depression scores: $r = -0.37$, $p = 0.008$), whereas no significant correlations were found in the NC group ($r = 0.08$, $p = 0.64$; after controlling for depression scores: $r = 0.13$, $p = 0.43$; Fig. 3C). No significant correlations of FA were found with the HAMD scores ($r = -0.59$, $p = 0.68$), MMSE scores ($r = 0.29$, $p = 0.04$; after controlling for depression scores: $r = 0.28$, $p = 0.05$), or MoCA scores ($r = 0.21$, $p = 0.15$; after controlling for depression scores: $r = 0.20$, $p = 0.16$). We further analyzed the correlations between functional disturbances and structural abnormalities. A positive correlation was found between functional connectivity in the right FPN and white matter FA values in the right frontal clusters

**Table 2**
Clusters showing significant differences in functional connectivity in the right FPN between LLD and NC groups.

| Cluster index | Anatomic region | Side | Cluster Size | MNI coordinates | | |
|---|---|---|---|---|---|---|
| | | | | x | y | z |
| 1 | Inferior frontal gyrus | R | 139 | 40 | 11 | 30 |
| 2 | Middle frontal gyrus | R | 32 | 48 | 14 | 41 |
| 3 | Inferior parietal gyrus | R | 35 | 35 | −44 | 49 |
| 4 | Supramarginal gyrus | R | 27 | 35 | −36 | 41 |
| 5 | Middle cingulum | R | 23 | 17 | −33 | 43 |

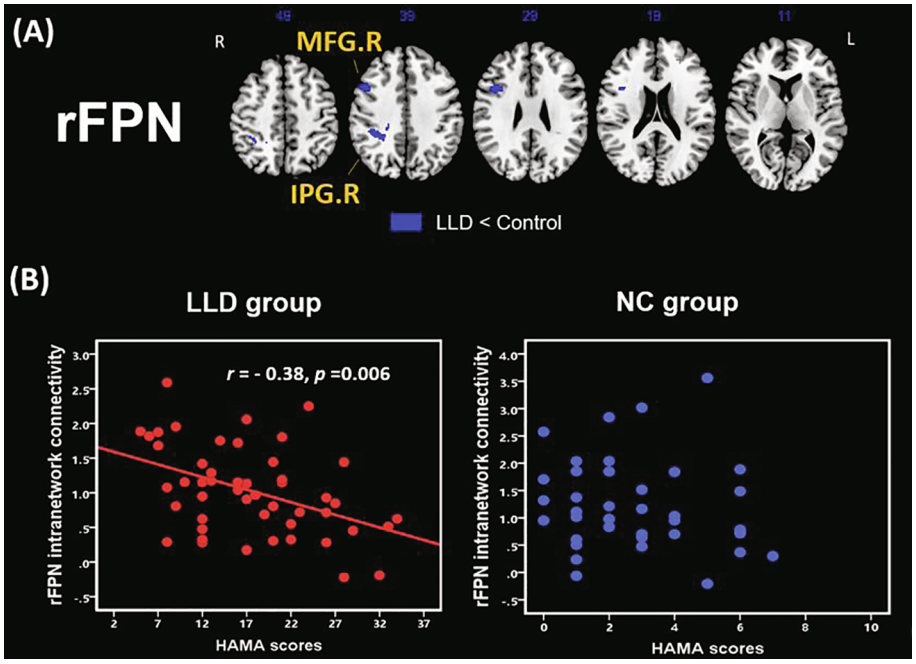


**Fig. 2.** Decrease in functional connectivity in patients with late-life depression (LLD) compared with non-depressed controls. (A) Dual-regression analysis of the right FPN showed significant differences between the LLD and NC groups. The decrease in intrinsic functional connectivity in LLD is shown in blue and overlaid on a template with coordinate planes in white. (B) Functional connectivity of the right FPN in the LLD group showed a negative correlation with anxiety symptoms, measured by HAMA scores, whereas no such correlation was found in the NC group. rFPN, right fronto-parietal network; IFG.R, right inferior frontal gyrus; IPG.R, right inferior parietal gyrus.

**Table 3**
Clusters of lower white matter FA in the LLD group compared with the NC group.

| Cluster index | White matter tracts[a] | Side | Cluster Size | MNI coordinates | | |
|---|---|---|---|---|---|---|
| | | | | x | y | z |
| 1 | Inferior fronto-occipital fasciculus | R | 5441 | 32 | 45 | 6 |
| | Anterior thalamic radiation | R | | | | |
| | Uncinate fasciculus | R | | | | |
| 2 | Anterior thalamic radiation | L | 536 | −17 | −61 | 46 |
| 3 | Inferior longitudinal fasciculus | L | 2131 | −49 | −27 | −15 |
| | Superior longitudinal fasciculus (temporal part) | L | | | | |
| | Superior longitudinal fasciculus | L | | | | |
| 4 | Inferior fronto-occipital fasciculus | L | 80 | −28 | −62 | 21 |
| | Forceps major | | | | | |
| 5 | Inferior fronto-occipital fasciculus | L | 34 | −23 | −86 | −2 |
| | Inferior longitudinal fasciculus | L | | | | |
| | Forceps major | | | | | |

[a] White matter tracts as defined by the Johns Hopkins University White-Matter Tractography Atlas. All of the clusters were statistically significant ($p < 0.05$, FWE-corrected, controlling for sex, age, and antidepressant use). FA, fractional anisotropy; LLD, late-life depression; NC, non-depressed control.

($r = 0.38$, $p = 0.008$; after controlling for depression scores: $r = 0.33$, $p = 0.012$). To generate a combined structural and functional map, fMRI and TBSS data were plotted in the same space (Fig. 4). Lower functional connectivity was mainly observed in the right IFG, which is a crucial region of the FPN. Lower structural FA was mainly observed in the right IFoF, which connects the IFG and occipital and posterior temporal regions.

## 4. Discussion

In the present study, we observed lower functional connectivity in the right FPN and lower FA in tracts related to the right FPN in the LLD group than in the NC group. The functional or structural changes in these abnormal regions were negatively correlated with the severity of anxiety symptoms in the LLD group. These findings suggest that the neural underpinnings of anxiety in LLD involve disturbances in functional and structural connectivity in the right FPN, especially in the right IFG.

Supporting our hypothesis, lower connectivity in the right FPN was observed in the LLD group. Dysfunction of the FPN is characterized by the ineffective transmission of information between prefrontal and parietal regions during cognitive processing [33]. A meta-analysis of rs-fMRI studies revealed lower functional connectivity in the FPN in individuals with depression than in those without depression [34] changes in connectivity between cognitive control systems and emotion processing systems in depression patients may be related to deficiencies

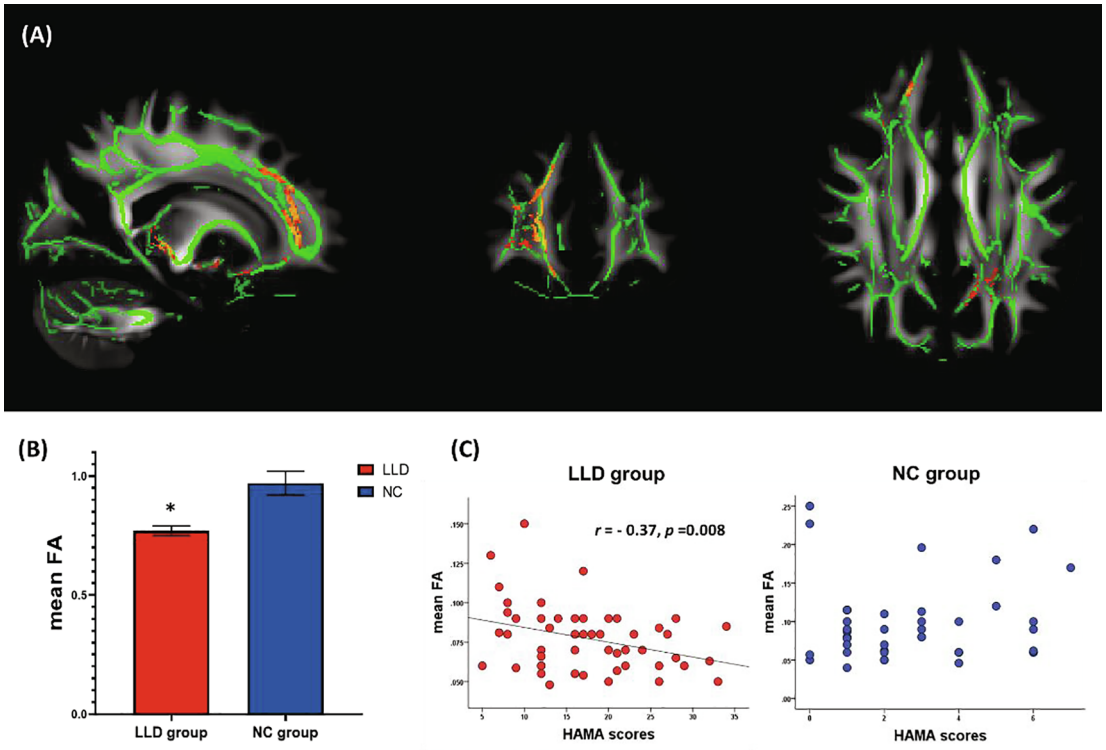


**Fig. 3.** Whole-brain TBSS analysis of differences in FA values between the late-life depression (LLD) group and non-depressed control (NC) group ($p < 0.05$, FWE-corrected). (A) Sagittal, coronal, and transversal axial sections of the white matter skeleton (green) superimposed on the mean FA brain template. Yellow and red indicate regions with significantly lower FA values in the LLD group compared with the NC group. (B) Mean FA values in the right frontal cluster were significantly lower in the LLD group compared with the NC group (*$p < 0.0125$). (C) The FA values were negatively correlated with HAMA scores in the LLD group, whereas the NC group showed no such correlation. FA, fractional anisotropy; HAMA, Hamilton Anxiety Rating Scale.

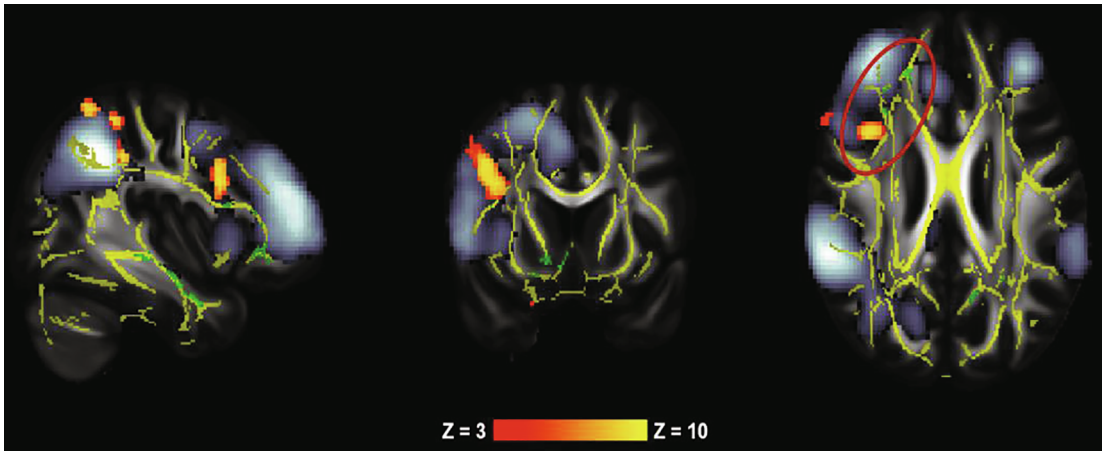


**Fig. 4.** Combined structural/functional map. Decreases in functional connectivity in the late-life depression (LLD) group are represented in yellow and red and overlaid on right FPN regions in blue and gray. Decreases in fractional anisotropy values in the LLD group are represented in green and overlaid on the white matter skeleton in yellow. The red circle indicates both abnormal functional connectivity and poorer white matter integrity in the right frontal lobe. rFPN, right fronto-parietal network.

in mood regulation. In the present study, we found that the function of the inferior frontal gyrus, middle frontal gyrus, and inferior parietal gyrus in LLD group was significantly different with that of the NC group, which is consistent with the findings in a previous study [7]. These regions may play an important role in the neuropathology of LLD.

In the present study, we found a negative correlation between connectivity within the right FPN and the severity of anxiety symptoms in LLD patients. Depressed elderly individuals frequently suffer from concurrent symptoms of anxiety [35]. Evidence suggests that comorbid anxiety in LLD predicts severe, persistent, and treatment-resistant depressive illness [36] and suicidal ideation [37]. A recent neuroimaging study showed that anxiety symptoms are associated with smaller insular and orbitofrontal cortex volumes in LLD patients [38]. Impairments in metabolic activity in the dorsomedial parts of the frontal cortex have been observed in nongeriatric depressed patients with comorbid anxiety, suggesting that dysfunctional emotional top-down processing results in state anxiety [39]. The present results suggest that abnormal top-down control might be involved in the mechanism of symptomatic anxiety in LLD patients.

The present TBSS results revealed frontal abnormalities in LLD patients at the structural level. The LLD group exhibited significantly lower FA in the right frontal region, which consisted of the IFoF, anterior thalamic radiation, and uncinate fasciculus, than did the NC group. The level of FA in these regions was significantly correlated with anxiety severity in the LLD group. White matter volume decreases in the frontal regions have been reported in elderly individuals with depression [16,40]. The IFoF plays an important role in integrating frontal lobe-related inhibitory control and occipital lobe-related sensory inputs [41]. The frontal lobes might be connected to the occipital lobes through the IFoF to modulate panic responses to external stimuli [42]. In the present study, the reduction in FA in the IFoF might interfere with sensory integration and cognitive inhibition in response to sensory stimuli and emotions [41], which might be associated with the pathophysiology of anxiety in LLD patients.

Moreover, the left superior longitudinal fasciculus and inferior longitudinal fasciculus also showed lower FA in the LLD group. The superior longitudinal fasciculus connects the frontal, parietal, occipital, and temporal lobes, which play an important role in connecting the FPN. The inferior longitudinal fasciculus connects the anterior and medial temporal lobes to the occipital lobe, which is involved in emotions and language [43,44]. The widespread distribution of white matter abnormalities in the frontal, parietal, and cingulate areas has been suggested to explain the association between depression and cognitive dysfunction in elderly individuals [45]. In our study, the pathology in the superior longitudinal fasciculus and inferior longitudinal fasciculus might be expected to affect multiple cognitive domains and impair emotion regulation.

Based on our fMRI and DTI results, the IFG might be a crucial hub that transfers information among these abnormal regions in LLD patients. Lower functional connectivity was mainly observed in the right IFG, which is a crucial region of the FPN. Decreased structural FA was mainly observed in the right IFoF, which is a direct pathway that connects the occipital, posterior temporal, and frontal regions, including the IFG [46]. Abnormalities in the IFG have been reported in major depressive disorder patients [47]. The right IFG has been previously shown to be strongly activated in the stop-signal task, which is related to cognitive inhibition [48]. Damage to the right IFG impairs performance in executive control tasks by disrupting inhibition [49]. Ineffective information processing by the right IFG might be related to higher impulsivity and a lack of inhibitory control [50]. Atypical integrity in the IFoF in LLD patients may negatively affect information transfer from the IFG in the FPN, resulting in less inhibitory control and more impulsivity, which can manifest as anxiety symptoms (e.g., restlessness). Previous neuroimaging studies have reported that white matter abnormalities in LLD patients are most prominent in the frontal lobe. The fMRI studies also showed functional abnormalities in the frontal region in LLD patients. However, the correlation between FA and functional connectivity in the frontal region in LLD patients has not been previously reported. The patients who were included in the present study might have good homogeneity with patients with more severe symptoms, and the results demonstrate the importance of IFG.

The present study has limitations. The cross-sectional design might limit the generalizability of our results. No conclusions about causality regarding the observed relationships between anxiety symptoms and functional connectivity/white matter integrity can be drawn from our findings. Damage to white matter fibers may impair communication among anxiety-regulating brain regions and subsequently cause information transfer failure [51,52]. In the present study, we did not control for the duration of anxiety or depression symptoms, which might have affected the neuroimaging results. Larger studies and longitudinal studies on the relationship between anxiety and functional/structural changes in the FPN are necessary to clarify the direction of any possible causal relationships. Another limitation of the present study was that most of the patients had previously taken or were currently taking antidepressant medications. Evidence suggests that antidepressants can affect brain structure [53]. Although we attempted to control for antidepressant use, the inclusion of patients who used medication may have confounded our findings. An additional

limitation was that the sample sizes of the LLD and NC groups were relatively small. Moreover, researchers recommend that data recorded with head movements > 0.2 mm are removed [54,55]. However, some difficulties in data acquisition were encountered with the participants in the present study, who had LLD and an average age of 67 years old. Head motion parameters were regressed in the statistical analysis. Thus, we did not use the most stringent head motion removal parameters. Additional longitudinal studies with larger sample sizes need to be conducted to investigate the effects of different symptoms, medications, and comorbidities on structural and functional changes in the brain in LLD patients.

## 5. Conclusions

In conclusion, we found that anxiety symptoms in LLD patients are associated with dysfunction of the right FPN and white matter FA in tracts to the right FPN. Understanding the mechanisms that underlie the manifestation of anxiety symptoms in LLD patients is critical, especially considering that anxiety is strongly related to a high risk of adverse events, such as suicide. The elucidation of these mechanisms may allow anxiety symptoms to be identified and managed earlier, thereby improving brain health and disease remission in patients with LLD.

## CRediT authorship contribution statement

**Hui Li:** Conceptualization, Investigation, Formal analysis, Writing - original draft. **Xiao Lin:** Methodology, Visualization, Software, Writing - review & editing. **Lin Liu:** Methodology, Visualization, Software, Writing - review & editing. **Sizhen Su:** Investigation. **Ximei Zhu:** Investigation. **Yongbo Zheng:** Investigation. **Weizhen Huang:** Investigation. **Jianyu Que:** Investigation. **Le Shi:** Validation. **Yanping Bao:** Validation. **Lin Lu:** Supervision. **Jiahui Deng:** Supervision. **Xinyu Sun:** Supervision.

## Declaration of Competing Interest

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

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2020.102398.

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