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The White Matter Microintegrity Alterations of Neocortical and Limbic Association Fibers in Major Depressive Disorder and Panic Disorder

The Comparison

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Abstract: The studies regarding to the comparisons between major depressive disorder (MDD) and panic disorder (PD) in the microintegrity of white matter (WM) are uncommon. Therefore, we tried to a way to classify the MDD and PD.

Fifty-three patients with 1st-episode medication-naive PD, 54 healthy controls, and 53 patients with 1st-episode medication-naive MDD were enrolled in this study. The controls and patients were matched for age, gender, education, and handedness. The diffusion tensor imaging scanning was also performed. The WM microintegrity was analyzed and compared between 3 groups of participants (ANOVA analysis) with age and gender as covariates.

The MDD group had lower WM microintegrity than the PD group in the left anterior thalamic radiation, left uncinate fasciculus, left inferior fronto-occipital fasciculus, and bilateral corpus callosum. The MDD group had reductions in the microintegrity when compared to controls in the bilateral superior longitudinal fasciculi, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, and corpus callosum. The PD group had lower microintegrity in bilateral superior longitudinal fasciculi and left inferior fronto-occipital fasciculus when compared to controls.

The widespread pattern of microintegrity alterations in fronto-limbic WM circuit for MDD was different from restrictive pattern of alterations for PD.

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INTRODUCTION

The microintegrity of white matter (WM) is an important biomarker to elucidate the pathophysiology for different disorders in psychiatry field. Among the parameters, the fractional anisotropy (FA) can reveal the fluency of signal transmission within the fasciculus, which provides some clues of WM microintegrity. Among the disorders, the differentiation of WM microintegrity between the major depressive disorder (MDD) and panic disorder (PD) is a new field to investigate.

For the MDD, the pathophysiology of WM tracts might be associated with the ''limbic-cortico-striato-pallido-thalamic circuit'' model for depression.[1] The superior longitudinal fasciculus (SLF) connects the precentral gyrus with the Broca regions to form a circuit for higher cortical functions.[2] The microintegrity alteration in the left SLF is a core structure for MDD origin.[3] The higher density in the WM lesions of the left SLF and corpus callosum (CC) would disturb cognitive and affective functions.[4] The alterations in the SLF also corresponded to the neocortical association tracts for Sheline model of depression. The high-risk vulnerable marker for MDD also includes the FA values in the SLF and CC.[5] The disturbances in interhemispheric connections of CC are also the possible reason for MDD.[6] Our previous report also found significant WM microintegrity alterations in the SLF and anterior thalamic radiation of MDD, which also connect the fronto-limbic regions in the Sheline model.[7] The alterations of inferior fronto-occipital fasciculus (IFOF), which also suggested the dysfunction of parieto-occipital regions with the dorsolateral premotor and prefrontal areas in the Sheline model for MDD.[8] From the above literature, there are widespread alterations in the microintegrity of WM tracts for MDD.

In the ''fear network model'' for PD, the SLF and CC also play a significant role in the pathophysiology.[9] The SLF is a part of fronto-parietal network and the related spatial working memory.[10] The IFOF also influences the frontal-sensory system in fearful network model.[9] The early-life stress also causes anxious behaviors and structural changes in the CC.[11] Our previous study of PD also replicated the WM alterations in the SLF, IFOF, and CC.[12]

The clinical overlap of MDD and PD is an important aspect for clinical practice. The genetic–environmental interaction would influence the pathophysiology.[13] Due to the clinical overlap, the differentiation between the ''limbic-cortico-striato-pallidal-thalamic'' circuit model for MDD and ''fear network model'' for PD is an interesting issue. The ''limbic-cortico-striato-pallidal-thalamic'' model seemed more extensive than the ''fear network model.'' The enhanced fear acquisition and elevated synaptic plasticity in the ventral emotional network are also a part of pathogenesis for depression.[14] In addition, the enhanced fear perception and emotional disturbance seems to be exaggerated in MDD.[15] Based on the involved regions of 2 hypothetical models and more enhanced fear acquisition in MDD, we hypothesized that the MDD patients would have more severe alterations than PD patients in the following WM tracts, such as CC, IFOF, and SLF. In addition, a comparison pattern of WM microintegrity could be revealed after comparisons of MDD and PD.

Participants

All the MDD subjects were 1st-episode, medication-naive patients with a pure MDD diagnosis (DSM-IV criteria) at least moderate severity (Clinician Global Impression of Severity > 4, Hamilton rating scales for depression [HDRS] score > 20, Hamilton rating scales for anxiety [HARS] score < 5). The PD subjects were 1st-episode, medicine-naive patients with a pure PD diagnosis (DSM-IV criteria) at least moderate severity (Clinician Global Impression of Severity > 4, HDRS score < 7, HARS score > 22, Panic Disorder Symptom Severity Scale [PDSS] score > 15). Neither significant comorbidities nor previous psychotherapies were allowed for the eligible participants. The healthy controls had no significant psychiatric illnesses or significant medical illnesses. All of the patients and healthy subjects signed the informed consent that was approved by the 3 Institutional Review Boards at Taipei Tzu Chi Hospital, Cheng Hsin General Hospital, and National Yang-Ming University according to the institute where they were recruited. The patients were enrolled at Taipei Tzu Chi Hospital and Cheng Hsin General Hospital. The controls were enrolled at Taipei Tzu Chi Hospital, Cheng Hsin General Hospital, and National Yang-Ming University. At the time of the magnetic resonance (MR) scanning, none of the participants in the control group received psychotropic treatment. Handedness was also determined.[16] The sample of participants has some overlaps of our previous reports.[7,12]

MR Data Acquisition

The diffusion tensor imaging (DTI) data were obtained with a 3T scanner (Siemens Medical Solutions, Erlangen, Germany) housed at MR Center, National Yang Ming University. The detailed information of scanning parameters please refer to our previous report.[7]

DTI Analysis

The DTI analysis was performed by the FDT (FMRIB's Diffusion Toolbox v2.0) function that was implemented in the FSL (FMRIB Software Library),[17,18] which was developed by the Oxford Center for Functional MRI of the Brain (FMRIB), London, UK. The merged DTI images were preprocessed by reducing the stretches and shears in diffusion weighted images.[19] We also used a brain extraction tool[20] to remove the nonbrain tissue to obtain the mask to fit a diffusion tensor model. FA maps were computed by the above procedure.

FA images were visually inspected for the orientation and image quality. All the FA volumes were warped to the template by nonlinear registration.[21] The mean FA volume of all individuals was thinned to create a mean FA skeleton that represented the centers of all WM tracts for the presentations of the Tract-Based Spatial Statistics results. Individual FA values were warped onto the above mean FA skeleton (threshold: 0.2).

Statistical Analysis

Demographic and clinical data of MDD, PD patients, and controls such as age, HDRS scores, HARS scores, PDSS scores, genders, and handedness would be compared each other by Kruskal–Wallis nonparametric multiple sample test as $P < 0.05$. The duration of illness in MDD and PD groups was compared by Mann–Whitney U-test with statistical threshold as $P < 0.05$ (SPSS version 16.0, Chicago, IL).

The randomized function of FSL (version 2.1)[22] was performed the voxel-wise analyses for the FA skeletons to compare 2 groups' FA, respectively (MDD vs PD, MDD vs controls, and PD vs controls). For the main purpose of group comparisons, an ANOVA 1×3 factor analysis with group as the main random factor over all subjects. We also included global brain volume, age, gender, and duration of illness as covariates in the above analyses. We used familywise error (FWE) after multiple comparisons to find regions of FA deficits (threshold: FWE P value < 0.05 and cluster threshold > 50 voxels).

The FSL correlation analysis using general lineal model between the scores of clinical rating scales (HDRS, PDSS) and FA (with age and gender as covariates) was also performed (threshold: corrected $P < 0.05$, multiple comparisons) to delineate individual pathophysiology for MDD and PD.

RESULTS

Demographic and Clinical Data

We enrolled 53 patients with MDD, 53 patients with PD, and 54 controls. There were no significant differences in the age, gender, education years, and handedness between the 3 groups. A main group effect for MDD was observed in the HDRS scores while the patients with MDD were compared to the PD group or controls. In addition, a main group effect for PD was observed in PDSS and HARS scores when the PD patients were compared to the MDD group or controls (Table 1).

The Comparison Alterations in the WM Microintegrity of MDD and PD

The patients with MDD had lower FA values in the bilateral CC (Table 2, Figure 1A) and IFOF (Table 2, Figure 1B) than PD patients. In addition, reductions in the FA values were found in the bilateral IFOF (Table 2, Figure 1C), bilateral SLF (Table 2, Figure 1D), CC (Table 2, Figure 1E), and right inferior longitudinal fasciculus (ILF) (Table 2, Figure 1F) of MDD patients when compared to healthy controls. The patients with PD had lower FA values than the controls in the bilateral SLF and right IFOF (Table 2, Figure 1G). In addition, the scores of HDRS were negatively correlated with the FA values in the left SLF of the patients with MDD. There was also a negative correlation between the PDSS scores and the FA values in the right IFOF of PD patients. No significant correlations between the clinical variables and FA values were observed in the control group or across both groups. All the

TABLE 1. Demographic Data of Participating Patients and Controls

	MDD Patients (N = 53)	PD Patients (N = 53)	Controls (N = 54)	Sig *P* (2-Tailed), H df = 2
Age, mean (SD), years old	40.07 (8.99)	43.283 (10.11)	40.38 (10.51)	0.086, 4.907
Gender (number)	F (28), M (25)	F (28), M (25)	F (29), M (25)	0.995, 0.011
Duration of illness, mean (SD), months	5.03 (1.62)	5.35 (2.37)	0 (0)	MDD vs PD Mann–Whitney *U*-test *P* = 0.6
Educational years, mean (SD)	15.83 (0.84)	15.94 (1.08)	16.14 (0.76)	0.220, 3.031
Handedness	R (52), L (1)	R (52), L (1)	R (52), L (2)	0.786, 0.481
HDRS, mean (SD)	22.43 (2.34)	1.13 (0.89)	0.92 (0.70)	<0.001, 112.42
HARS, mean (SD)	2.20 (1.02)	23.35 (2.74)	1.25 (1.01)	<0.001, 117.88
PDSS, mean (SD)	N/A	21.43 (1.91)	N/A	N/A

Sig *P* (significance of *P*-value) was from Kruskal–Wallis nonparametric multiple sample test (H values) except duration of illness (Mann–Whitney *U*-test for nonparametric independent 2-sample *t*-test for MDD vs PD). df = degree of freedom, F = female, HARS = Hamilton rating scales for anxiety, HDRS = Hamilton rating scales for depression, M = male, MDD = major depressive disorder, N = number, N/A = not applicable, PD = panic disorder, PDSS = Panic Disorder Symptom Severity Scale, SD = standard deviation.

above results were FWE-corrected *P* value < 0.05 and cluster voxels more than 50.

DISCUSSION

In this study, we found a possible way to delineate the MDD and PD. The MDD patients seemed to have more severe WM microintegrity alterations than PD in the bilateral CC and left IFOF. In addition, a more widespread pattern of alterations was discovered in the bilateral IFOF, bilateral SLF, right ILF, and CC of patients with MDD. A relatively limited alteration of the bilateral SLF and right IFOF occurred in PD. According to our knowledge, this should be the 1st study to address the differentiation between MDD and PD in the field of WM microintegrity. Our study showed a possible category model with severity dimension to describe the fundamental differences between the 2 disorders in the WM microintegrity. The category model means the MDD had more widespread alterations than PD, especially in the CC and ILF. The severity dimension means MDD had more severe alterations than PD in the bilateral CC and left IFOF. Our study had a comprehensive comparison

between MDD, PD, and controls, which could help confirm the above category and dimension model for the MDD and PD in the WM etiology.

Apart from the comparison, the significance of current study revealed a possible clue for common pathway of "limbic-cortico-striato-pallido-thalamic circuit" model for depression[1] and "fear network model" for PD.[9] The common WM alteration pathways seemed to include the SLF and IFOF for MDD and PD in current study. It was compatible with the importance of frontal lobe in the pathophysiology of MDD and PD.[23–31] The frontal-related WM connections to other lobes, such as parietal, temporal, and occipital lobes, might have great influences in executive function, memory, and visual information processing.[32–38] Our results suggested that MDD and PD might have common disturbances in frontal-related WM tracts. The clinical significance in this field can be further evaluated in future study.

The IFOF radiates backward from the frontal lobe via the lateral border of caudate nucleus to the occipital and posterior temporal lobes.[39] The SLF is a bidirectional WM tract connecting the anterior and posterior part of brain, including the

TABLE 2. The WM Tract Microintegrity Patterns and Differences in MDD Group, PD Group, and Controls

Group Comparisons	Cluster	MNI Coordinates	Cluster Voxels	T Value (Peak Voxels)
PD > MDD	Bilateral CC	(−5, 9, 23) and (5, 9, 23)	652	5.01
	Left IFOF	(−19, 31, 30)	219	4.94
MDD > PD	Negative finding			
NC > MDD	Bilateral IFOF	(24, −57, 29) and (−24, −57, 29)	128	4.46
	Bilateral SLF	(32, −50, 34) and (−32, −50, 34)	116	4.34
	Right ILF	(31, −51, 29)	103	4.29
	CC	(0, −10, 25)	77	4.16
MDD > NC	Negative finding			
NC > PD	Bilateral SLF	(−31, −42, 36) and (31, −42, 36)	98	4.38
	Right IFOF	(19, −56, −36)	57	4.27
PD > NC	Negative finding			

CC = corpus callosum, IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, MDD = major depressive disorder, NC = normal controls, PD = panic disorder, SLF = superior longitudinal fasciculus.
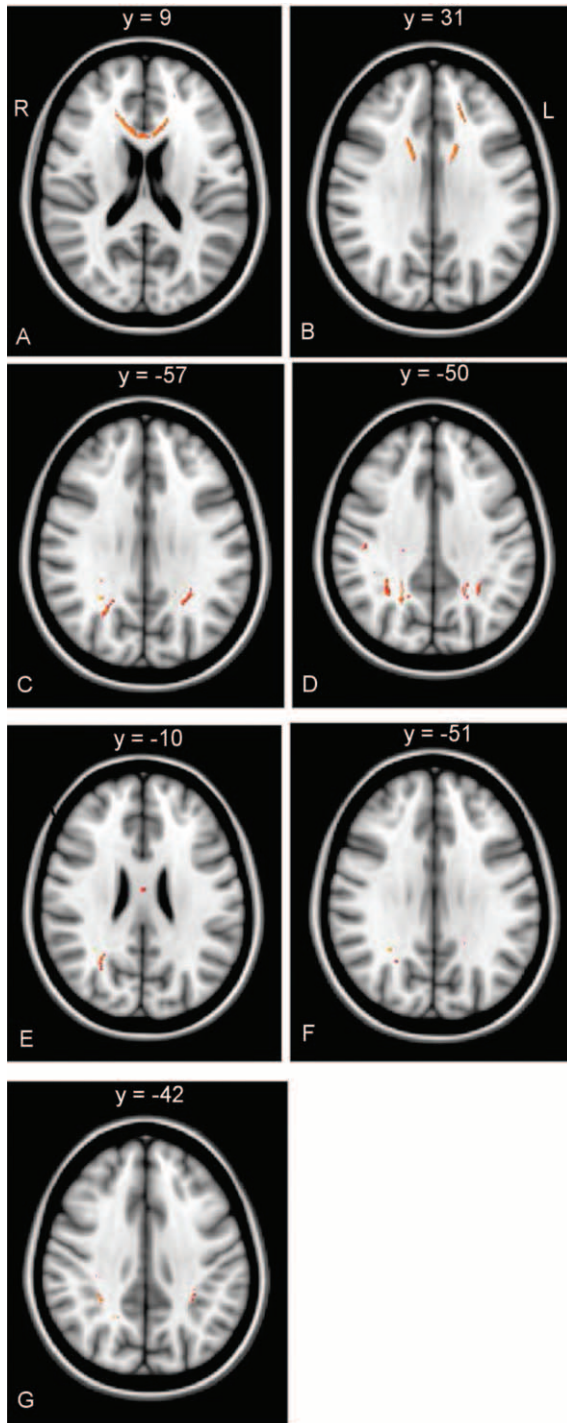
FIGURE 1. The comparison pattern of WM microintegrity alterations in MDD and PD. The patients with MDD had lower FA values in the bilateral CC (A) and IFOF (B) than PD patients. In addition, reductions in the FA values were found in the bilateral IFOF (C), bilateral SLF (D), CC (E), and right ILF (F) of MDD patients when compared to healthy controls. The patients with PD had lower FA values than the controls in the bilateral SLF and right IFOF (G). CC = corpus callosum, FA = fractional anisotropy, IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, MDD = major depressive disorder, PD = panic disorder, SLF = superior longitudinal fasciculus, WM = white matter.

frontal, parietal, temporal, and occipital lobes. The ILF connects the anterior part of temporal and occipital lobes. It is also an indirect pathway anteriorly joining the uncinate fasciculus to relay the information to frontal lobe.[39] The IFOF and ILF are strongly correlated in function[40] and the impairments would be associated with thought disorders, visual emotion, and cognitive impairments.[41] The IFOF, SLF, and ILF belong to the neocortical association pairs. There is also a moderate correlation between these tracts due to the phylogenetic similarities.[40] The more severe alterations in the IFOF and right ILF in MDD might represent the more involvements in the related emotional and cognitive functions.[41] The impairments in the SLF occurred in both MDD and PD suggested that the additional visuospatial attention[42] would also be altered in MDD and PD. In addition to the neocortical association fibers, the CC plays a major role in the WM pathophysiology of MDD, especially when compared to the PD. The CC connects both hemispheres to control cognition and emotion,[4] which would be impaired in depression due to the disturbance of interhemispheric connection.[6] The more severe alterations in the WM microintegrity of CC and IFOF in MDD than PD were probably associated with the influences of emotion, cognition, and other limbic-related functions in the CC and IFOF.[8,43] In addition, the IFOF connects the frontal lobe with occipital and temporal lobes through the caudate nucleus. The CC also connects the bihemispheric limbic regions. The more involvement of IFOF and CC microintegrity in MDD also corresponded to the ''limbic-cortico-striato-pallidal-thalamic'' model of depression. It also supported our hypothesis of more widespread alterations of WM tracts in depression due to the clinical severity and function impairments. In the whole view of our results, the neocortical association fibers, such as IFOF, ILF, and SLF, are significantly impaired in MDD and PD. However, the involvement of limbic-related interhemispheric fibers, such as CC, would contribute the differentiation point between MDD and PD.

The findings in current study also replicated the several WM tracts in our previous reports in MDD and PD, respectively.[12,44] For the MDD, the CC results replicated the results of several previous reports in MDD[8,43,45] and some of the reports also involved the ILF,[45] IFOF,[8] and SLF,[45] which also correspond to our study results. Most results showed widespread alterations in WM microintegrity of MDD patients. However, some studies argued against the association of WM microintegrity disruption and depression,[46] or with increased anatomic connectivity of cortico-limbic circuit.[47] Our results found no alterations in the WM microintegrity of the cingulum, which has been found with significant alterations in several MDD studies.[45] However, our study had less impact from aging, medication, and chronicity, which makes the strengths totally different from previous studies with patients in late-onset depression.[48] In summary, the findings in MDD group corresponded to our original hypothesis of ''limbic-cortico-striato-pallidal-thalamic'' circuit with more widespread involvement of WM tracts.

For the PD, the findings of IFOF and SLF also corresponded to several previous reports.[12] However, several studies found increased WM microintegrity in PD.[49] Therefore, several review articles criticized the applications of DTI analysis in the study of pathophysiology for PD and the significance of findings.[50] However, the IFOF might be important for integration of frontal lobe-related inhibitory control and occipital lobe-related sensory inputs in the ''fear network model'' for PD.[9,12] The fear circuitry theory of PD also included the SLF.[51] The overgeneralization of conditioned fear also provoked panic attacks.[52] The SLF-related fear modulation also would be associated with anxiety-related

microintegrity alterations.[53] In summary, the less widespread involvement of WM tracts also corresponded to ''fear network model'' for PD, which corresponded to our original hypothesis.

LIMITATIONS

Our study had several limitations.

(1) The cross-sectional design and lack of further tractography might limit the interpretations.

(2) DTI is still a nonspecific measure that does not provide information about the underlying causes for the reported microstructural pathology.

(3) The detailed histopathologic validation of FA in healthy humans is still missing, even with some animal evidences.[54]

(4) The lack of power and limited directional resolution of the suboptimal DTI protocol (30 directions) in this study would be associated with the limited number of structures involved.

(5) The current DTI method does not make it possible to disentangle the white matter tract of the crossing fibers to a high certainty in the brain, and our study results were not confirmed by tractography.

(6) The findings may not be diagnostically specific to MDD as the same white matter tract abnormalities are observed in other disorders, as for example, schizophrenia.

CONCLUSION

The degree of alterations in the neocortical association and interhemispheric fibers might help differentiate MDD and PD. The more widespread pattern of microintegrity alterations in the fronto-limbic WM circuit represents the comparison pattern for MDD, which was different from the restrictive pattern of alterations for PD in the frontal and sensory-related WM circuit.

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