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White matter microstructural abnormalities in late-life depression

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ABSTRACT

Objective: To evaluate the location and the degree of white matter damage in late-life depression using diffusion tensor imaging (DTI).

Methods: Thirty-one patients with late-life depression and 15 healthy volunteers matched for age, gender and years of education received conventional MRI (magnetic resonance imaging) and MR-diffusion tensor scanning. The fractional anisotropy (FA) values of white matter were measured respectively in frontal and temporal regions and the corpus callosum.

Results: FA values were significantly decreased in the frontal (superior and middle frontal gyrus), and temporal (right parahippocampal gyrus) regions of elderly patients with depression compared with healthy controls.

Conclusion: Microstructural changes in the frontal (superior and middle frontal gyrus) and temporal (right parahippocampal gyrus) areas are associated with late-life depression.

Key words: late-life depression, MR-diffusion tensor imaging, fractional anisotropy

Introduction

Late-life depression refers to depressive syndromes defined in the International Classification of Diseases (ICD-10) (World Health Organization, 1992) which arise in adults aged over 65 years. In old age, depressive syndromes often occur in people with chronic medical illnesses, cognitive impairment, or physical disability. In addition to personal suffering and family disruption, depression worsens the outcomes of many medical disorders and promotes further disability. The pathogenesis is very complex with multiple and heterogeneous factors that may result in pathological changes in the brain contributing to characteristic

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emotional, cognitive and motor activity disorder (Cummings, 1993; Lockwood *et al.*, 2002). It is recognized that the limbic-cortical-striatal-pallidal-thalamic (LCSPT) tract modulates mood regulation and cognitive ability, which may contribute to the pathogenesis of late-life depression. A limbic-thalamic-cortical branch composed of the amygdala and hippocampus, the mediodorsal nucleus of the thalamus, and the medial and ventrolateral prefrontal cortex has been proposed as one arm of the LCSPT circuit (Swerdlow and Koob, 1987; Drevets *et al.*, 1992).

We used diffusion tensor imaging to examine the microstructure of white matter in the dorsolateral prefrontal cortex, parahippocampal gyrus and the genu and body of the corpus callosum. We proposed the hypothesis that patients with late-life depression might exhibit greater microstructural abnormalities (measured as lower fractional anisotropy (FA) values) than elderly healthy controls who were not depressed.

Methods

Thirty-one subjects aged 60 years or older attending the Sixth Hospital (Institute of Mental Health) of Peking University (11 males and 20 females) with a clinical diagnosis of late-onset depression (i.e. age at onset $\geq$55 years old) met the criteria of F31.X of the ICD-10, and scored $\geq$7 on the Hamilton depression scale (HAMD) (Hamilton, 1960) (Table 1). Seven of the 31 patients were drug free; the rest had taken antidepressants for less than six weeks. None of them had received electroconvulsive therapy (ECT).

Exclusion criteria included other major psychiatric disorders, substance abuse, primary neurological disorders (such as dementia or stroke), medical conditions which could impair cognitive function, and indwelling metal precluding magnetic resonance imaging (MRI).

Healthy controls were recruited from community-dwelling elderly individuals willing to participate in this research. Fifteen healthy controls were matched by age, gender and years of education (Table 1). Eligible healthy controls had no neurological disorders or medical conditions, and no previous history of depression.

All subjects were screened for contra-indications to MRI. Axial images were acquired with a Signa 1.5-T MR system (Signa CV/i, GE Medical Systems) using the standard head radiofrequency coil. After localization of slices to be imaged, an echo-planar imaging sequence was used for diffusion tensor analysis. The diffusion images were acquired with an image in each of 25 diffusion weighting directions, b value 0–1000 sec/mm^2, TR = 8000msec, TE = 80.8msec, 256 $\times$ 256 matrix, FOV = 26 $\times$ 20 cm, 3 mm slice thickness, and slice gap = 0 mm.

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Table 1. Demographic characteristics of the depression group and the control group

	DEPRESSION GROUP (N = 31) MEAN ± SD	COMPARISON GROUP (N = 15) MEAN ± SD	X^2/T/Z	P
Age	64.6 ± 5.21	64.3 ± 4.22	−.09 (t)	0.93
Gender				
Male (%)	11 (35.5%)	7 (46.7%)	0.53 (X^2)	0.47
Female (%)	20 (64.5%)	8 (53.3%)		
Education in years	9 (5–13)	9 (5–13)	−0.26 (Z)	0.80

A single echo scan providing T1-weighted images was acquired in the sagittal plane (slice thickness = 5 mm, slice gap = 1 mm). The anterior and posterior commissure plane was localized in midsagittal plane, and diffusion tensor imaging (DTI) was aligned with the anterior and posterior commissure plane. Each image took less than 5 minutes to acquire.

The DTI were processed on GE Advantage Windows workstations with Functiontool2. A radiologist blind to the subjects' depression status placed oval regions of interest (ROI) in the white matter in the dorsolateral prefrontal cortex (superior and middle frontal gyrus), parahippocampal gyrus and the genu and the body of corpus callosum (Figure 1). Each area of ROI was 40 mm^2 and avoided gray structure and white matter hyperintensities. The frontal gyri ROIs were placed on the white matter of superior and middle frontal gyrus (Brodmann's areas 9, 10 and 46) in the third, fourth and fifth slices above the genu of the corpus callosum. The parahippocampal gyrus ROIs were placed on the white matter of the parahippocampal gyrus in the slices where both cerebral peduncles were seen clearly. The genu and the body of the corpus callosum regions of interest were placed on the white matter of slices where the genu and the body of corpus callosum were fully visible. The FA values on these slices of each side were averaged. The mean FA value of each brain region was derived from the average of more than one.

FA values were analyzed using independent t-tests to test the differences between the patients and controls. Correlations between the significant changes in FA values of depression and their clinical data (age, sex, vascular risk factors and medical illness) were calculated using partial correlations.

Results

A significant white matter FA reduction was found in frontal (superior and middle frontal gyrus), and temporal (right parahippocampal gyrus) regions in

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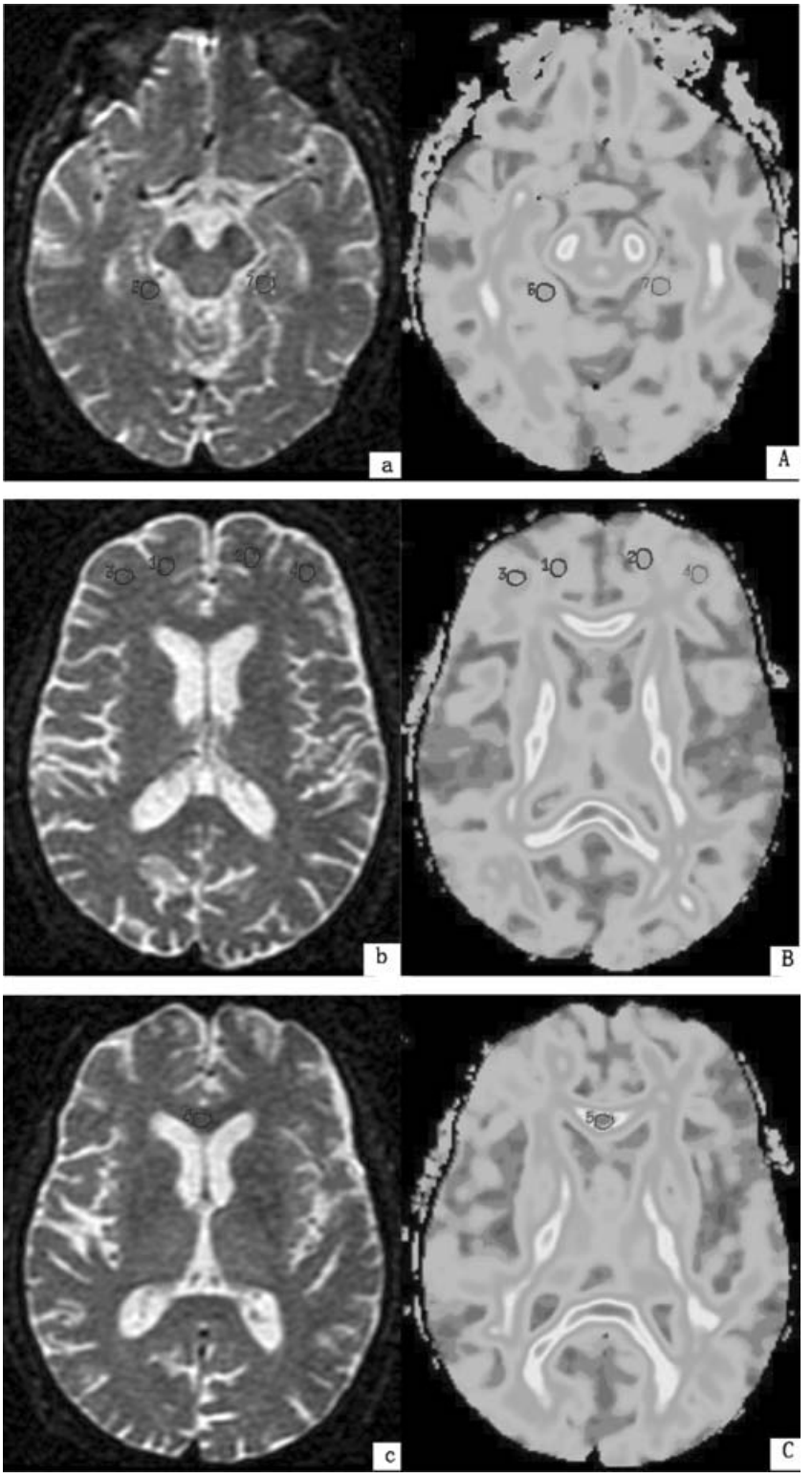


Figure 1. For legend see facing page.

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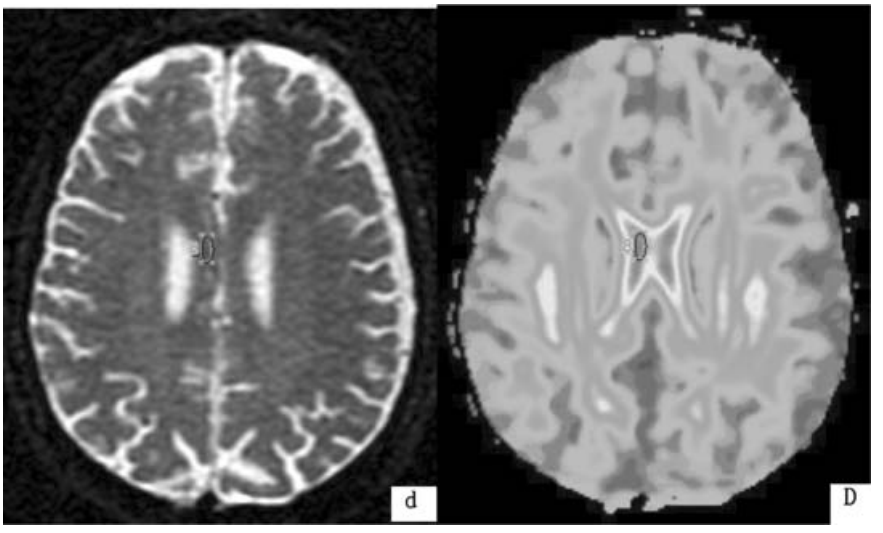


Figure 1. Axial T2-weighted images(a, b, c, d) and corresponding FA maps (A, B, C, D) showing location of ROIs in parahippocampal gyrus (ROI 6, 7), superior and middle frontal gyrus (ROI 1, 2, 3, 4), the genu (ROI 5) and the body of corpus callosum (ROI 8). Note: a color version of these images is available by emailing the corresponding author, Xin Yu, directly.

Table 2. Difference in regional fractional anisotropy values between 31 depressed and 15 normal control elderly subjects

BRAIN REGIONS	DEPRESSED GROUP FA (N = 31) MEAN ± SD	COMPARISON GROUP FA (N = 15) MEAN ± SD	T	P
Right parahippocampal gyrus	0.164 ± 0.022	0.183 ± 0.022	−2.805	0.007**
Left parahippocampal gyrus	0.161 ± 0.022	0.175 ± 0.019	−1.991	0.053
Right superior frontal gyrus	0.176 ± 0.032	0.215 ± 0.029	−3.990	0.000**
Right middle frontal gyrus	0.201 ± 0.029	0.225 ± 0.026	−2.614	0.012*
Left superior frontal gyrus	0.196 ± 0.314	0.220 ± 0.358	−2.353	0.023*
Left middle frontal gyrus	0.193 ± 0.022	0.223 ± 0.305	−3.658	0.002**
Body of corpus callosum	0.538 ± 0.059	0.570 ± 0.043	−1.872	0.068
Genu of corpus callosum	0.481 ± 0.079	0.508 ± 0.069	−1.151	0.256

FA = fractional anistrophy.
*p < 0.05; **p < 0.01.

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Table 3. Correlations between the significant changes in FA values of depression and their clinical data: r (P)

	RIGHT PARAHIPPOCAMPAL GYRUS	LEFT PARAHIPPOCAMPAL GYRUS	RIGHT SUPERIOR FRONTAL GYRUS	RIGHT MIDDLE FRONTAL GYRUS	LEFT SUPERIOR FRONTAL GYRUS	LEFT MIDDLE FRONTAL GYRUS
HAMD	0.140(0.468)	0.076(0.695)	0.173(0.369)	0.096(0.619)	0.053(0.786)	0.433(0.109)
age	−0.281(0.125)	−0.186(0.315)	0.086(0.644)	0.228(0.218)	0.081(0.665)	−0.112(0.549)
sex	0.026(0.888)	0.079(0.672)	0.090(0.628)	0.038(0.840)	−0.313(0.086)	0.128(0.492)
medcom	0.150(0.439)	0.306(0.107)	0.206(0.285)	0.070(0.719)	0.470(0.106)	0.028(0.887)
vasc R/F	0.229(0.233)	0.391(0.036)	−0.033(0.867)	0.024(0.902)	−0.238(0.213)	0.054(0.781)

HAMD = Hamilton Depression rating scale; medcom = medical comorbidity; vasc R/F = vascular risk factors.

late-life depression compared to healthy controls. FA value differences between the two groups in the left parahippocampal gyrus did not reach the level of statistical significance ($p = 0.053$).

Depressed subjects exhibited lower FA values than healthy controls in all regions of interest (Table 2).This difference reached a level of statistical significance in the superior and middle frontal gyrus and right parahippocampal gyrus.

There was no correlation between FA changes and clinical data (Table 3).

Discussion

This study found significantly decreased FA values in frontal (superior and middle frontal gyrus), and temporal (right parahippocampal gyrus) regions in geriatric depressed patients compared to healthy controls. Differences in FA values between groups were statistically significant.

ROI location

Late-life depression is characterized by emotion disorder and cognitive disability. It is recognized that the limbic-cortical-striatal-pallidal-thalamic tract modulates mood regulation and cognitive ability, which may be related to the pathogenesis of late-life depression. There is a hypothesis that the prefrontal area coordinates the mood-cognitive complex. Impairment of the dorsolateral prefrontal cortex (Brodmann's areas 9, 10, 46**)** may result in a dorsolateral prefrontal syndrome characterized by executive dysfunction. Executive dysfunction has also been found in depressed elderly subjects. The limbic system is composed of limbic lobar areas (hippocampus, parahippocampal gyrus, cingulate gyrus**,** dentiform gyrus) which are closely connected to subcortical structures. Afferent nerve fibers of the hippocampus originate from the parahippocampal gyrus. Impairment of the fibers can result in mood and cognitive disorder. Recollection memory is critically dependent upon the integrity of the hippocampus and parahippocampal gyrus (Duffy and Campbell, 1994; Kiosses *et al.,* 2000; Tekin and Cummings, 2002). The corpus callosum has the most important nerve fibers which are responsible for connecting both cerebral hemispheres. Furthermore, the genu of the corpus callosum plays an important role in connecting the anterior cerebral hemispheres including the frontal and temporal gyri.

Method

DTI is a variation of MRI that measures the diffusion of water in tissues. This can help measure and quantify a tissue's orientation and structure, making it an ideal tool for examining cerebral white matter and neural fiber tracts. A diffusion

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tensor at each location on a regular lattice describes a volumetric average of the directional properties of diffusion within each voxel. The observation that diffusion is anisotropic in areas of white-matter fiber bundles allows tracking of fibers through the lattice. The fibrous nature of white matter is apparent in DT-MRI. White matter may exhibit remarkable differences in diffusion, dependent on which direction the diffusion sensitizing gradients are applied and also on the direction of the white-matter tracts imaged. Several different ways of calculating anisotropy have been proposed, but most authors have used FA due to its simple scaling between 0 and 1 (0 = isotropic diffusion; 1 = highly anisotropic or directional diffusion) and its use of eigenvalues. It can reflect the integrity of neural fiber tracts (Moseley *et al.*, 1991; Basser and Pierpaoli, 1996).

Results

Our findings, which showed a significant white matter FA reduction in frontal (superior and middle frontal gyrus) and temporal (right hippocampal gyrus) regions in late-life depression compared to healthy controls, suggest that the white matter integrity of these regions is impaired. This conclusion shows some similarity with other studies. Dorsolateral prefrontal cortex and hippocampal changes have been described in several studies, including reduced volume on MRI (Steffens *et al.*, 2002; Taylor *et al.*, 2003), magnetic resonance spectroscopy (biochemical abnormalities) (Kumar *et al.*, 2002), positron emission tomography (hypometabolism) (Kimbrell *et al.*, 2002), and DTI (lower FA) (Taylor *et al.*, 2003). Our conclusion is not in complete agreement with Taylor *et al.* (2004), who found a lower FA only for the right superior frontal gyrus. The difference may be because our number of subjects is larger and we imaged a greater number of slices in every ROI location.

Our findings support the theory that microstructural changes in white matter may result in disconnection of cortical and subcortical regions. If these changes affect the limbic-cortical-striatal-pallidal-thalamic tract involved in mood regulation, they may contribute to the pathogenesis of depression in elderly people.

Correlations with clinical features

This study did not find any correlation between changes in FA values in ROIs and recorded clinical features of depression, severity (as expressed in HAMD scores), age, sex, presence of medical co-morbidity or vascular risk factors. The lack of correlation with vascular risk factors differs from reports supporting the vascular depression hypothesis (Alexopoulos *et al.*, 1997).

Our observations, therefore, do not implicate any etiological role of age, sex, presence of medical comorbidity or vascular risk factors in late-life depression.

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Conflict of interest

None.

Description of authors' roles

Qiong Yang collected and analyzed the imaging data and wrote the paper. Nan Hong formulated research questions and supervised the imaging data analysis, and carried out the statistical analysis. Xuebing Huang performed the clinical assessment of the subjects and collected the clinical data. Xin Yu formulated the research questions, designed the study, supervised the data collection and analysis, and wrote the paper.

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References

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D. and Charlson, M. (1997). "Vascular depression" hypothesis. *Archives of General Psychiatry*, 54, 915–922.

Basser, P. J. and Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance*, 111, 209–219.

Cummings, J. L. (1993). The neuroanatomy of depression. *Journal of Clinical Psychiatry*, 54, 14–20.

Drevets, W. C., Videen, T. O., Price, J. L., Preskorn, S. H., Carmichael, S. T. and Raichle, M. E. (1992). A functional anatomical study of unipolar depression. *Journal of Neuroscience*, 12, 3628–3641.

Duffy, J. D. and Campbell, J. J. (1994). The regional prefrontal syndromes: a theoretical and clinical overview. *Journal of Neuropsychiatry and Clinical Neurosciences*, 6, 379–387.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56–61.

Kimbrell, T. A. *et al.* (2002). Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biological Psychiatry*, 51, 237–252.

Kiosses, D. N., Alexopoulos, G. S. and Murphy, C. (2000). Symptoms of striatofrontal dysfunction contribute to disability in geriatric depression. *International Journal of Geriatric Psychiatry*, 15, 992–999.

Kumar, A. *et al.* (2002). Frontal white matter biochemical abnormalities in late-life major depression detected with proton magnetic resonance spectroscopy. *American Journal of Psychiatry*, 159, 630–636.

Lockwood, K. A., Alexopoulos, G. S. and van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry*, 159, 1119–1126.

Moseley, M. E., Kucharczyk, J., Asgari, H. S. and Norman, J. D. (1991). Anisotropy in diffusion-weighted MRI. *Magnetic Resonance in Medicine*, 19, 321–326.

https://doi.org/10.1017/S1041610207004875 Published online by Cambridge University Press

Steffens, D. C., Payne, M. E., Greenberg, D. L., Byrum, C. E., Welsh-Bohmer, K. A. and Wagner, H. R. (2002). Hippocampal volume and incident dementia in geriatric depression. *American Journal of Geriatric Psychiatry*, 10, 62–71.

Swerdlow, N. R. and Koob, G. F. (1987). Dopamine, schizophrenia, mania and depression: toward a unified hypothesis of cortico-striato-pallido-thalamic function. *Behavioral and Brain Sciences*, 10, 197–245.

Taylor, W. D. *et al.* (2003). Smaller orbital frontal cortex volumes associated with functional disability in depressed elders. *Biological Psychiatry*, 53, 144–149.

Taylor, W. D. *et al.* (2004). Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. *American Journal of Psychiatry*, 161, 1293–1296.

Tekin, S. and Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *Journal of Psychosomatic Research*, 53, 647–654.

World Health Organization (1992). *International Classification of Diseases*. 10th revision. Geneva: World Health Organization.

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