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Blood pressure and white matter integrity in geriatric depression

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Abstract

Background—Cerebrovascular disease may increase vulnerability to geriatric depression, a syndrome often accompanied by frontal-subcortical lesions. High blood pressure is a risk factor for cerebrovascular disease and white matter changes. This study examined whether and in which brain regions blood pressure is associated with compromised white matter integrity in elderly depressed patients.

Methods—We studied the association between blood pressure and white matter integrity assessed by diffusion tensor imaging (fractional anisotropy, FA) in 41 older patients with major depression. Correlations between FA and blood pressure, after controlling for age, were examined with a voxelwise analysis.

Limitations—This study did not employ a healthy control group. Moreover, the relatively small sample size precluded a comparison of patients with and without hypertension.

Results—Significant associations between FA and blood pressure were detected throughout the anterior cingulate and in multiple frontostriatal and frontotemporal regions.

Conclusions—Compromised frontal-striatal white matter integrity may be the anatomical background through which blood pressure confers vulnerability to depression.

Keywords

geriatric depression; Cardiovascular risk; diffusion tensor imaging

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CONTRIBUTORS Authors GSA, KOL, and CFM designed the study and wrote the protocol. Authors GSA, GRE, and DO managed the literature searches and analyses. Authors MJH, BAA, and FG-D undertook the statistical analysis, and author MJH wrote the first draft of the manuscript. Author JH wrote the DTI sequence used herein. All authors contributed to and have approved the final manuscript

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Introduction

We previously proposed that cerebrovascular disease predisposes to some geriatric depressive syndromes (Alexopoulos et al., 1997; Krishnan et al., 1997). This view was based on the high prevalence of depression in patients with vascular risk factors or diseases and the presence of cerebrovascular lesions in many individuals with geriatric depression. The mechanisms by which cerebrovascular risk factors predispose to geriatric depression are unclear. However, clinical, neuroimaging, and neuropathology findings suggest that depressed elders have abnormalities in frontal-subcortical circuitry (Alexopoulos et al., 2002a; O'Brien et al., 1998; Steffens et al., 2001). Moreover, recent findings suggest that microstructural white matter abnormalities in frontal-subcortical areas predict poor or slow response of geriatric depression to an antidepressant (Alexopoulos, Kiosses, Choi, Murphy, and Lim, 2002a).

Abnormal blood pressure is a risk factor for stroke and white matter hyperintensities (WMH) (Dufouil et al., 2001; Fjorbank et al., 2007; van Dijk et al., 2004). Although there is some evidence that high blood pressure may increase vulnerability to geriatric depression (Niu et al., 2008), it has been unclear whether elevated blood pressure preferentially impairs the brain structures implicated in geriatric depression. For this reason, the current study focuses on the relationship of blood pressure and white matter integrity in depressed patients to explore whether high blood pressure is associated with microstructural abnormalities in frontal-subcortical white matter regions. To this end, we performed a voxelwise analysis of diffusion tensor imaging (DTI), which provides a measure of white matter integrity.

Method

Participants

Patients were 41 adults aged 60–86 (mean: 70.1, SD: 6.3) recruited at a University-based Geriatric Psychiatry clinic who were enrolled in an escitalopram treatment trial. The female to male ratio was 1.56. They had received education for 7–22 years (mean: 16.1, SD: 3.0). Their depression was of moderate severity (HDRS mean: 23.8 SD: 4.0) and their MiniMental State Examination scores ranged from 24–30 (mean: 28.3, SD: 1.6).

Scans were performed during a 2-week single blind drug washout/placebo lead-in phase. All participants met DSM-IV criteria for major depression after a Structured Clinical Interview for DSM-IV (SCID-R), had a 24-item Hamilton Depression Rating Scale (Hamilton, 1960) (HDRS) of 18 or greater and were not demented (by DSM-IV criteria). Exclusion criteria included history of psychiatric disorders other than depression (except personality disorders) prior to the onset of their depression, severe or acute medical illness within 3 months preceding the study, neurological disorders (i.e., dementia or delirium, history of head trauma, Parkinson's disease), use of drugs known to cause symptoms of depression (e.g., steroids), and MMSE < 24. All participants signed informed consents approved by Institutional Review Boards.

Blood Pressure

Seated blood pressure was measured with a sphygmomanometer after the participant sat resting for 5 minutes. Three measurements were taken at one-week intervals. The average diastolic blood pressure (DBP) and systolic blood pressure (SBP) across measurements were the independent variables.

MRI

Scanning took place on the 1.5 T Siemens Vision Scanner (Erlangen, Germany) at Nathan Kline Institute's Center for Advanced Brain Imaging. Patients received an magnetization

prepared rapidly acquired gradient echo (MPRAGE) T1-weighted scan (TR = 11.6 ms, TE = 4.9 ms, TI = 1017.6 ms, matrix = 256×256 , FOV = 320 mm, NEX = 1, slice thickness = 1.25 mm, 172 slices, no gap), as well as a turbo dual spin echo scan (TR = 5000 ms, TE = 22/90 ms, matrix = 256×256 , FOV = 240 mm, slice thickness = 5, 26 slices, no gap), and a DTI scan (TR = 6000 ms, TE = 100 ms, matrix = 128×128 , FOV = 320, NEX = 7, slice thickness = 5 mm, 19 slices, no gap) acquired in an oblique axial plane parallel to the anterior commissure – posterior commissure line. The *b*-value for the DTI scan was 1000 s/mm². Eight diffusion sensitization directions were used (Jones et al., 1999).

Postprocessing

Fractional anisotropy (FA) was calculated using AFNI's (Cox, 1996) nonlinear computation algorithm 3dDWItoDT, which assures positive definite matrices. The FA images were transformed into Talairach space using methods described elsewhere (Ardekani et al., 2003).

A T1-weighted template was created from a scan of a subject whose intracranial volume was the closest to the mean for the first 11 patients and then put into Talairach space using AFNI (Cox, 1996). The skulls for these scans were stripped using FSL's BET (<http://www.fmrib.ox.ac.uk/fsl/bet/index.html>). The volumes of skull-stripped brains were computed in MEDx (Sensor Systems, Sterling, VA). To increase the representativeness of this template to the study population, we iteratively registered the T1-weighted images from 101 subjects ranging in age from 60 to 86 years. Images were masked for white matter to reduce the number of comparisons.

Data Analysis—Because FA is negatively correlated with age (Pfefferbaum et al., 2000; Salat et al., 2005), we computed partial correlations between both diastolic and systolic BP and FA on a voxelwise basis, controlling for age. Partial correlations were tested for significance using *t*-tests. To reduce Type I error, we used the thresholding method described by Baudewig and colleagues (Baudewig et al., 2003). This approach finds clusters of voxels (100 mm³) each with significant group differences ($p < 0.05$) and then applies the constraint that one of the voxels in the cluster must be significant at $p < 0.001$. The thresholded correlation maps were superimposed onto the T1-weighted template using AFNI software (Cox, 1996).

Results

The mean diastolic blood pressure ranged from 61.3 to 91.3 mm Hg (mean: 73.6, SD: 6.8 Hg). Mean systolic blood pressure ranged from 107.3 to 160.7 mm Hg (mean: 129.1; SD: 13.4)

High diastolic blood pressure was significantly associated with low FA (negative correlations) bilaterally in the dorsal anterior cingulate, left dorsal cingulate and inferior frontal gyri, and right dorsomedial prefrontal white matter (Figure 1). Negative correlations were observed in the white matter adjacent to the lentiform nucleus and putamen, left insula, left thalamic white matter, bilateral middle temporal gyrus, right superior temporal gyrus, and the right inferior parietal lobule. Diastolic blood pressure was positively correlated with FA in left precentral gyrus, inferior parietal lobule, and precuneus white matter. Similar results, although somewhat more variable, were found for systolic blood pressure.

Discussion

The principal finding of this study is that high blood pressure is associated with microstructural white matter abnormalities (lower FA) in the dorsal anterior cingulate and multiple frontostriatal and frontotemporal white matter regions. To our knowledge, this is the first study demonstrating a relationship between blood pressure and microstructural white matter impairment in these areas in depressed elderly patients. Our findings are consistent with the

observation that WMH of depressed patients are primarily located in frontal subcortical areas; most of these abnormalities are due to ischemic changes (Thomas et al., 2002).

Clinical and neuroimaging findings suggest a relationship between fronto-striatal dysfunction and geriatric depression. Disorders compromising frontal pathways, including vascular dementia, Parkinson's disease, and Huntington's disease are more likely to result in depression than cortical dementias (Sobin et al., 1997). Executive dysfunction, a disturbance resulting from compromised integrity of frontal structures and their connections, is common in geriatric depression (Lockwood et al., 2002; Nebes et al., 2001) and persists after improvement of mood-related symptoms (Murphy et al., 2004; Nebes et al., 2003). Elderly depressed patients with executive dysfunction have pronounced psychomotor retardation, reduced interest in activities and pronounced disability (Alexopoulos, Meyers, Young, Campbell, Silbersweig, and Charlson, 1997; Alexopoulos et al., 2002b; Krishnan, Hays, and Blazer, 1997), a clinical presentation resembling medial frontal lobe syndromes. Structural neuroimaging studies have documented reduced volumes of the anterior cingulate, the orbitofrontal cortex and the gyrus rectus in geriatric depression (Ballmaier et al., 2004). Moreover, hyperintensities in frontal subcortical structures are prevalent in geriatric depression (Coffey et al., 1990; Krishnan, Hays, and Blazer, 1997; Steffens et al., 1999). Assuming that frontal circuitry compromise constitutes a vulnerability factor to geriatric depression (Alexopoulos et al., 2005), our findings suggest that depression in patients with high diastolic pressure is in part mediated by compromise in frontostriatal white matter.

Positive correlations between blood pressure and FA were also found, primarily in posterior regions. These results are difficult to interpret. Assuming that frontal compromise is one of the anatomical abnormalities predisposing to depression (Alexopoulos, 2001; Krishnan et al., 2004), one may speculate that high white matter integrity in posterior regions offers insufficient protection from depression. Another possibility is that these findings reflect high anisotropy due to loss of crossing fibers.

This study has several limitations. First, there was no normal control group. Second, the small sample size allowed only relationships with large effect sizes to be identified and prevented comparisons between subjects with and without hypertension. Third, the large number of comparisons, even after applying a white matter mask to the images, increased the risk of Type I error. Finally, the impact of crossing fibers on FA cannot be addressed in the current study.

If confirmed, these findings would suggest that frontal-subcortical dysfunction may be one of the mechanisms by which high blood pressure, a known vascular risk factor, confers vulnerability to geriatric depression. On a clinical level, the relationship of blood pressure to frontal-subcortical white matter compromise suggests that patients with diastolic hypertension should be examined for clinical syndromes contributed by frontal-subcortical dysfunction, including depression and executive function impairment.

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Figure 1.

Map of correlations between diastolic blood pressure and FA for patients with geriatric depression. Blue indicates negative correlations and yellow indicates positive correlations. Significant correlation clusters are superimposed on a high-resolution T1-weighted image in Talairach space. Every 4th slice is shown, slices are from left to right hemisphere.

Table 1

Location of significant correlations between fractional anisotropy and mean diastolic blood pressure (threshold: 100 contiguous voxels all significant at $p < .05$, with at least one voxel significant at $p < .001$).

Nearest GM Location ^{1,2}	Size	Talairach Coordinate ³	t-value ⁵
Negative Correlations			
Anterior cingulate (bilateral)	1573	-14, 22, 18	-2.57
L dorsal cingulate gyrus (BA32)	279	-11, 18, 38	-2.52
L dorsal cingulate gyrus (BA24)	161	-17, -8, 38	-2.52
R medial frontal gyrus	150	14, 41, 20	-2.66
L inferior frontal gyrus	383	-40, 15, 19	-2.66
L inferior frontal gyrus	110	-22, 23, -8	-2.51
L lentiform nucleus (PLIC)	517	-30, -20, -1	-2.63
R lentiform nucleus (ALIC)	916	15, 8, 1	-2.51
L BA13/insula	169	37, 16, 18	-2.50
L thalamus	210	-14, -4, 9	-2.40
L middle temporal gyrus	182	-40, -48, 6	-2.39
L middle temporal gyrus	126	-32, 41, 0	-2.49
R middle temporal gyrus	577	39, -50, 8	-2.53
R superior temporal gyrus (arcuate fasciculus)	122	36, -53, 23	-2.46
R inferior parietal lobule	292	44, -35, 36	-2.72
Positive Correlations			
L precentral gyrus	360	-35, -12, 37	2.51
L inferior parietal lobule	110	-52, -32, 30	2.59
L precuneus	105	-20, -61, 32	2.78

¹Notes: GM=Gray Matter

²L = Left, R = Right

³Talairach coordinate of maximum of correlation cluster

⁴BA=Brodmann Area, ALIC = anterior limb of the internal capsule, PLIC=posterior limb of the internal capsule

⁵mean of cluster.