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Neuroanatomical substrates of depression in the elderly

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Summary. The etiology of depression in the elderly is poorly understood. In this study, magnetic resonance imaging was used to evaluate the role of subcortical structures in the pathophysiology of depression in the elderly. Elderly depressed patients were found to have smaller caudate nuclei, smaller putaminal complexes and in increased frequency of subcortical hyperintensities compared with normal, healthy controls. These findings were more pronounced in patients with late-onset depression. Based on these findings, the authors discuss the role of the basal ganglia in the pathophysiology of depression in the elderly.

Key words: Magnetic resonance imaging – Basal ganglia – Depression – Subcortical hyperintensities

Introduction

Between 1% and 2% of elderly adults who live in the community have major depression. In addition, a significant number of elderly subjects (> 10%) have depressive symptoms, albeit not sufficient in severity and persistence to meet criteria for an affective disorder (Blazer et al. 1987).

The causes of depression in the elderly are poorly understood. The concept that psychological and social factors are the primary contributors to the occurrence of depression in later life, although intuitively appealing, is not supported by available evidence (Blazer 1990). In addition, although a number of family, twin and molecular genetic studies have provided strong evidence for a hereditary predisposition in the etiology of affective disorder, genetic factors appear to be less significant in patients presenting with depression for the first time in later life (Hopkinson 1964; Slater and Cowie 1971).

There has been considerable speculation that structural changes in the brain are of primary importance in the etiology of late-life depression and may explain why genetic and psychosocial risk factors are less important. Gaupp [as quoted by F. Post (1962)] described 45 elderly patients with depression whom he cited as having depression secondary to arteriosclerosis. Gilarowsky also noted that affective symptoms in the elderly were due to arteriosclerotic changes (Post 1962). Post (1962) reported that 12 of 100 elderly depressed patients showed evidence on admission of focal brain damage either by history or by neurological signs. He noted that the cerebrovascular brain damage was more prevalent in elderly depressed patients than that reported in surveys of the elderly population. In most of the patients in Post's study, a close temporal association between the cerebrovascular accident and the onset of the affective disorder was noted. This led Post to suggest that the affective disorder was etiologically linked to the cerebrovascular pathology and that the latter probably played a significant role in precipitating the illness.

As leukoencephalopathy on magnetic resonance imaging (MRI) might reflect early and subtle alterations in the cerebrovascular system and is also an index of aging, we assessed the occurrence of patchy white matter lesions (leukoencephalopathy) in 35 patients with depression (Krishnan et al. 1988). The major finding of this study was a high prevalence (72%) of patchy white matter lesions in patients with late-onset depression (those whose first episode of depression started after the age of 45). The lack of controls limited the conclusions drawn from this study.

Coffey et al. (1988) replicated these findings with 67 elderly depressed patients referred for ECT. Of the 31 patients with computed tomography (CT) scans, 69% had evidence of leukoencephalopathy. Only 3 of the 36 patients who had MRI were read as normal. The most common findings were abnormalities of the subcortical white and gray matter, lateral ventricle enlargement and cortical atrophy.

In a subsequent study, Coffey et al. (1990) expanded their sample and compared elderly depressives with 22 age- and sex-matched community controls and confirmed

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that deep white matter hyperintensities were more common in patients with major depression.

Figiel et al. (1991) studied 19 elderly patients and compared the MRI scans of those with a late onset of their depressive symptoms to the scans of patients with early-onset depression. They found that both basal ganglia lesions and large deep white matter lesions were significantly more common in the patients with a later onset to their mood disorder. In addition, preliminary reports of our group have noted that the caudate and putamen nuclei are smaller in elderly depressed patients compared with controls (Husain et al. 1991; Krishnan et al., submitted for publication). We have speculated that the basal ganglia circuit is of primary importance in the pathophysiology of affective disorder through connections with structures in both the limbic system and the prefrontal cortex (McDonald and Krishnan 1992).

In the present study, the role of the caudate nuclei, putaminal complex (lenticular nucleus), thalamic nuclei and leukoencephalopathy (subcortical hyperintensities) were examined in elderly patients with either an early or a late onset to their depressive symptoms, and comparisons were made with normal controls. We sought to confirm our original findings of an increase in structural brain changes in patients with a later onset to their mood disorder and to provide further support for the hypothesis that these changes are critical in the genesis of late-onset depression.

Subjects and methods

Twenty-five elderly (aged over 60 years) patients (17 female, 8 male) who met DSM-III criteria for major depression were studied. Mean age (± SD) of the patients was 74.1 (± 6.6) years. The diagnosis of major depression was made on the basis of clinical interviews and all available information from the medical record. A comprehensive inventory of vascular risk factors (VRFs) was also collected (e.g., hypertension, diabetes mellitus, coronary artery disease, etc.). Fourteen patients were classified as having late-onset depression and 11 patients as early-onset depression based upon whether the first episode was before or after the age of 60. The mean age of the late-onset patients (76.9 ± 6.5) was significantly higher than that of the early-onset patients (70.6 ± 4.9) ($t = 2.63$, $df = 23$, $P < 0.05$).

Twenty elderly (> 60 years) control subjects (11 female, 9 male) were recruited from the community, and detailed demographic data were collected for each subject (e.g., age, sex, race, handedness). Each subject received a comprehensive neuropsychiatric evaluation including physical, neurological and mental-status examinations. None of the subjects had evidence of previous or present neurological or psychiatric illness. The mean age (± SD) of the control subjects was 72.5 (± 3.6) years and was not significantly different from the patient group ($t = 1.05$, $df = 38.5$, $P = 0.30$). Control subjects were likewise not significantly different in age from early-onset depressed patients ($t = 1.22$, $df = 24$, $P = 0.23$) but were significantly younger than the late-onset depressed group ($t = 2.26$, $df = 18.5$, $P < 0.05$).

MRI methods

Brain MRI scans were obtained using a General Electric 1.5 T Signa System. The subject's head was positioned with the canthomeatal line at 0° from the vertical axis and the imager's laser grid centered at the nasion. All axial T1- and T2-weighted image acquisitions were parallel to the canthomeatal line. Axial images were 5 mm thick with a 2.5-mm interslice gap (except for one patient who had 7-mm-thick contiguous slices with no interslice gap) and covered the entire brain.

Basal ganglia and thalamus measurements

Intermediate and T2-weighted (TR 2500/2800, TE 30/40 for most) axial images were used for caudate nuclei, putaminal complex (lenticular nucleus, which included both the putamen and globus pallidus), thalamic nuclei and cerebral hemisphere measurements, because these acquisitions allowed for maximal gray and white matter distinction. The volumes of the caudate nuclei, lenticular nuclei, thalamic nuclei and cerebral hemispheres were measured by K.R.R.K. and calculated with methods based on the Cavalieri theorem of systematic sampling (Cavalieri 1966) and point counting method (Chalkley 1943; Weibel 1979). Volumes reported represent the sum of the right and left nuclei for each individual subject. The coefficient of error was calculated for each individual as described by Gunderson and Jensen (1987). The application of these methods to assess caudate, putamen and cerebral volume has been previously described (Krishnan et al. 1990; Husain et al. 1991).

White-matter hyperintensity grading

The number and size of subcortical white matter hyperintensities (SCHs) larger than 5 mm in "actual" size were noted in both patient and control subjects. Then assessments were made on T2-weighted scans. This was conducted using a standard neuroanatomic atlas and blind to diagnosis but not age or sex of the subjects. The subjects were then assigned a grade for frequency of SCH (grade 0 = absent; grade 1 = only one SCH; grade 2 = 2–5 SCHs; grade 3 more than 5 SCHs) as well as size of the largest SCH (grade 0 = less than 5 mm; grade 1 = 5–8 mm; grade 2 = larger than 8 mm). This grading system was utilized since it is simple, reproducible and provides an adequate quantification for group comparisons. Further, assignment of a 0 to all SCHs under 5 mm ensured exclusion of other neuropathological entities, such as perivascular spaces and sulci, which can also appear bright on T2 and intermediate images. Periventricular bands or frontal caps were not included as SCH. For purposes of analysis, subjects with grade 0 or grade 1 lesions were combined into a single grouping and compared with those manifesting more severe SCH.

Statistical analysis

Data were analyzed using PC SAS. Group comparisons were made using a two-tailed *t*-test procedure or Fisher's exact test. Analyses of covariance (ANCOVAs) according to the general linear models procedure (proc GLM, type III sum of squares) were used to assess the main effects of diagnosis and onset of illness while covarying for age, sex and cortical volume. Correlations between continuous variables were examined using Pearson product-moment coefficients, while relationships involving ordinal variables were assessed using Spearman rank-order correlations. Seven patients and 15 control subjects were included in preliminary studies of caudate and putamen nucleic size (Husain et al. 1991, Krishnan et al., submitted for publication). They were remeasured for this investigation by the first author.

Results

MRI findings as a function of diagnosis

Elderly depressed patients exhibited significantly smaller caudate nuclei ($P < 0.0001$) and putaminal complex ($P < 0.01$) volumes than controls of similar age (Table 1).

Table 1. Demographic and MRI data

	Depressed patients	Healthy controls	χ^2/t	*df*	*P*
Sample size (*n*)	25	20			
Females/males	17/8	11/9	$\chi^2 = 0.80$	1	0.37
Age range (year)	62–88	68–82			
Mean age ± SD (year)	74.1 ± 6.6	72.5 ± 3.6	$t = 1.05$	38.5	0.30
Caudate volume (ml) (R + L)	3.46 ± 1.17	4.83 ± 0.95	$t = 4.22$	43	0.0001
Putamen complex (ml) (R + L)	3.68 ± 1.33	4.81 ± 1.33	$t = 2.83$	43	0.007
Thalamus (cc) (R + L)	5.74 ± 1.88	6.39 ± 1.42	$t = 1.28$	43	0.21
Cortical volume (ml) (R + L)	1042.8 ± 147.1	1028.0 ± 173.4	$t = 0.31$	43	0.76
SCH frequency					
Grades 0, 1	12	16	$\chi^2 = 4.84$	1	0.03
Grades 2, 3	13	4			
SCH size					
Grades 0,1	15	17	$\chi^2 = 3.38$	1	0.07
Grade 2	10	3			

Table 2. Comparison of early-onset and late-onset depression

	Early onset	Late onset	χ^2/t	*df*	*P*
Sample size (*n*)	11	14			
Females/males	8/3	9/ 5			1.00*
Age range (year)	62–78	62–88			
Mean age ± SD (year)	70.6 ± 4.9	76.9 ± 6.5	$t = 2.63$	23	0.015
Caudate volume (ml) (R + L)	4.22 ± 1.11	2.87 ± 0.84	$t = 3.48$	23	0.002
Putamen complex (ml) (R + L)	4.31 ± 0.86	3.19 ± 1.45	$t = 2.27$	23	0.03
Thalamus (cc) (R + L)	6.23 ± 2.09	5.36 ± 1.67	$t = 1.16$	23	0.26
Cortical volume (ml) (R + L)	1054.5 ± 172.4	1033.7 ± 129.9	$t = 0.34$	23	0.73
SCH frequency					
grades 0, 1	5	7			1.00*
grades 2, 1	6	7			
SCH size					
grades 0, 1	7	8			1.00*
grade 2	4	6			

*Fisher's exact test

No differences between depressed patients and controls were observed for measurements of the thalamus or cortical volume ($P > 0.10$).

Following covariance adjustment for age, sex and cortical volume, depressed patients remained characterized by smaller caudate ($F_{(1, 41)} = 20.44$, $P < 0.0001$) and putaminal volumes ($F_{(1, 41)} = 8.19$, $P < 0.01$), with thalamic volumes continuing to be not significantly different between groups ($F_{1, 41)} = 0.54$, $P = 0.47$). Caudate volume was correlated with both lenticular ($r = 0.55$, $P < 0.004$) and thalamic nuclei volume ($r = 0.57$, $P < 0.003$) in patients. In controls, caudate volume was likewise related to lenticular volume ($r = 0.58$, $P = 0.007$) but did not correlate significantly with thalamic volume ($r = 0.22$, $P = 0.36$). Lenticular volume did not relate to thalamic volume in patients ($r = 0.28$, $P = 0.18$) but did correlate significantly in controls ($r = 0.58$, $P = 0.007$).

Depressed patients exhibited a greater frequency of large SCHs compared with controls ($P < 0.05$). Although grade 2 SCH size also tended to be more preva-

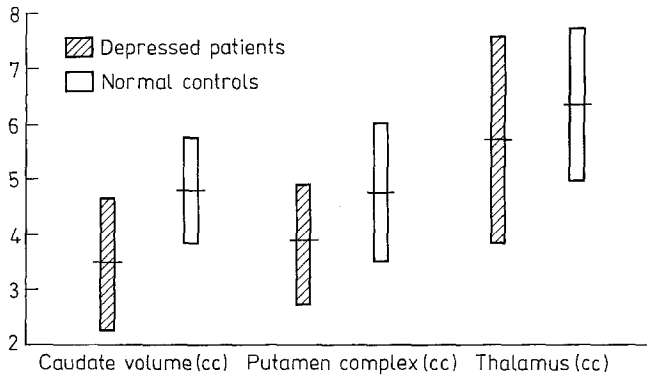

Fig. 1. Caudate, putamen and thalamus volumes in depressed patients and controls

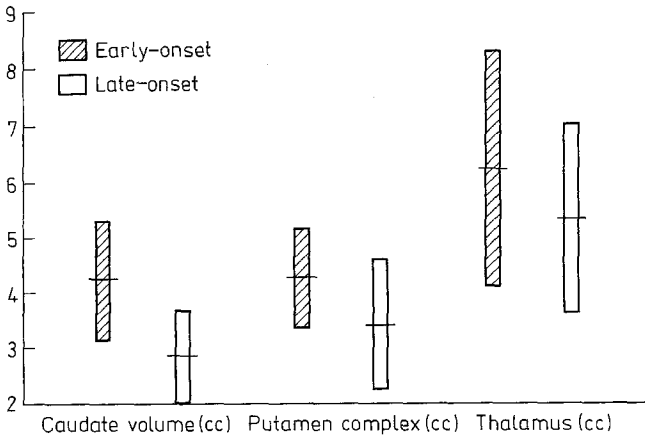

Fig. 2. Caudate, putamen and thalamus volumes in late-onset and early-onset patients

lent among depressed patients, results fell marginally short of significance ($P = 0.07$). SCH was more pronounced in the frontal regions.

In the patient group, age was significantly correlated with volumes of the caudate ($r = 0.61$, $P = 0.001$), putamen ($r = -0.57$, $P = 0.003$) and thalamus ($r = -0.48$, $P = 0.02$) but did not relate to cortical volume ($P = 0.54$), or to SCH frequency ($r = 0.14$) or size ($r = 0.08$, $P > 0.10$). Similarly, for normal controls, significant correlations were obtained between age and both putaminal ($r = 0.0005$) and thalamic volume ($r = 0.52$, $P = 0.02$); however, the correlation between age and caudate volume fell short of conventional significance ($r = 0.39$, $P = 0.09$). As with the patient sample, correlations between age and cortical volume ($r = 0.06$) and both SCH frequency ($r = 0.03$) and size ($r = 0.03$) failed to achieve significance ($P > 0.10$).

MRI findings as a function of early versus late onset

Early-onset depressed patients demonstrated significantly larger caudate ($P < 0.002$) and putaminal complex ($P < 0.05$) volumes than late-onset patients (Table 2). Thalamic volumes, however, did not differ significantly between the two patient groups ($P = 0.26$). Examination of the two depressed groups relative to controls revealed

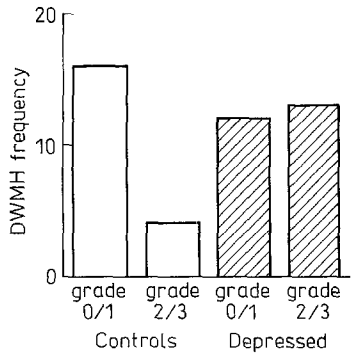

Fig. 3. Frequency of deep white matter hyperintensity in depressed patients and controls

significant differences for the caudate ($F_{(2, 39)} = 13.15$, $P < 0.0001$) and putamen ($F_{(2, 39)} = 4.18$, $P < 0.02$) but not the thalamus ($F_{(2, 39)} = 0.26$, $P = 0.77$). Tukey pairwise comparisons for the caudate revealed significant differences between late-onset depressed and both early-onset depressed and controls. No differences were noted between early-onset depressed patients and controls. Likewise, for the putamen, significant differences were noted between late-onset depressed patients and both early-onset patients and controls. Again, no differences were noted between early-onset patients and controls.

SCH frequency tended to be greater in late-onset patients compared with controls ($\chi^2 = 3.39$, $df = 1$, $P < 0.07$), and SCHs tended to be larger in late-onset depressives ($\chi^2 = 3.28$, $df = 1$, $P = 0.07$), although these differences fell just short of statistical significance. Similarly, SCH frequency was more prevalent in early-onset patients compared with controls ($\chi^2 = 3.88$, $df = 1$, $P < 0.05$), but size was not significantly different ($\chi^2 = 1.85$, $df = 1$, $P = 0.17$). There were no significant differences in SCH frequency between early- and late-onset depressives ($\chi^2 = 0.05$, $df = 1$, $P = 0.82$), nor were there differences in SCH size ($\chi^2 = 0.11$, $df = 1$, $P = 0.74$). There were not significant sex or right-left differences within groups (see Figs. 1–3).

VRFs as a function of diagnosis

Fourteen of 25 patients (56%) and 10 of 20 controls (50%) were positive for VRFs. Among the group of patients with VRFs, 3 suffered from hypertension alone, while 5 suffered a combination of hypertension and at least one additional VRF (e.g., diabetes mellitus, coronary artery disease). Similarly, 5 control subjects suffered from hypertension alone, while one subject manifested a combination of hypertension and an additional risk factor. A breakdown of specific VRFs as a function of group status is presented in Table 3. Five of 11 (45%) early-onset patients exhibited VRFs, while 9 of 14 (64%) late-onset patients presented with VRFs. A Fisher's exact test revealed no significant differences in the prevalence of VRFs in patients versus controls ($P = 0.77$, two-tailed test), or between early- and late-onset groups ($P = 0.44$, two-tailed test). Likewise, there were not significant differences in age between those with (75.9 ± 5.9 years) and without VRFs (71.8 ± 6.9 years) in either patients ($t = 1.61$, $df = 23$, $P = 0.12$) or controls ($t = 18$, $P = 0.63$).

Table 3. Vascular risk factors as a function of diagnosis

Age	Sex (M/F)	Vascular risk factor
Early-onset depressives		
78	M	HTN, DM
67	F	HTN, DM
77	M	MI
67	F	CABG
74	F	DM
62	M	
68	F	
69	F	
70	F	
70	F	
75	F	
Late-onset depressives		
71	F	HTN
73	F	HTN
88	F	HTN
73	F	HTN, AF
80	F	HTN, CHF, AS
81	M	HTN, cardiomyopathy
79	M	MI
82	F	MI
73	M	CABG
62	M	
73	M	
77	F	
80	F	
84	F	
Controls		
68	F	HTN
70	M	HTN
72	F	HTN
73	M	HTN
73	F	HTN
79	M	HTN, MI
73	F	Cardiac arrhythmia
82	M	Cardiac arrhythmia
70	M	Cardiac angina
69	M	DM
69	F	
69	F	
70	F	
71	F	
71	M	
72	M	
72	M	
75	F	
76	F	
76	F	

HTN, Hypertension; DM, diabetes mellitus; CABG, coronary artery bypass graft; MI, myocardial infarction; AF, atrial fibrillation; CHF, congestive heart failure; AS, aortic stenosis

Discussion

The main findings of this study were that there were more neuropathological changes noted on the MRI scans of depressed elderly relative than in controls and that these changes were even more pronounced when the patient exhibited a later onset to her/his mood disorder. The caudate and lenticular nuclei (putaminal complex) volumes were significantly smaller in depressed patients compared with controls and in late-onset depressed patients compared with both early-onset patients and controls. These differences remained significant even after covarying for the effects of age, sex and cortical volume. Subcortical hyperintensities were also more frequent in elderly depressed patients compared with controls of equivalent age. The fact that caudate and lenticular nuclei volumes were smaller in both early- and late-onset elderly depressed patients suggests that the basal ganglia circuit is involved in the pathophysiology of affective disorders in general. Additional evidence comes from preliminary reports that these structures are small in young depressed patients (Husian et al. 1991; Krishnan et al. 1992). The higher frequency of SCHs in elderly depressed patients and a trend toward even greater frequency and size in late-onset patients compared with controls is consistent with previous studies (Krishnan et al. 1988; Coffey et al. 1988, 1990; Figiel et al. 1991).

The etiology of smaller basal ganglia in depressed patients is uncertain. It is possible that hereditary factors may play a central role. Another possibility is that the basal ganglia may become smaller secondary to depression itself (hypothetically due to damage from the excitatory amino acids, glutamate and aspartate, which are believed to be the primary afferents to the caudate and putamen nuclei from the cortex). Of interest is the possibility that such findings may be restricted to unipolar depression. Our data showing that changes in the basal ganglia circuit and SCH are more pronounced in late-onset depressed patients suggest that these organic factors may be particularly significant in the pathophysiology of affective disorder in these patients.

The SCHs and smaller basal ganglia observed in late-onset depressives may also have a common origin in atherosclerotic changes that occur with both aging and cardiovascular disease (e.g., hypertension, coronary artery disease, diabetes). Accumulating evidence supports an increase in SCH as patients age and have increased cardiovascular risk factors (reviewed by McDonald et al. 1991). The medullary arteries supplying the basal ganglia are particularly subject to ischemia, since they are long, thin branching vessels without collateral circulation. Ischemic events may lead to eventual atrophy. Our findings showing no differences in the prevalence of VRFs between early-onset depressed, late-onset depressed and controls suggest that it is the lesions per se and not VRFs which are of primary etiological significance.

The present research supports our hypothesis (McDonald and Krishnan, in press) that elderly depressives, particularly those with a late onset to their mood

disorder, may have an increased vulnerability to depression due to neuroanatomical factors. Although white-matter hyperintensities have been reported in bipolar patients, their etiological significance is likely to be different (Dupont et al. 1987; Swayze et al. 1990). Further research is needed to determine the origin of these changes and possible relationship to important public health issues, including the relationship to cardiovascular risk factors.

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