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Pattern of brain atrophy in elderly patients with depression revealed by voxel-based morphometry

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Abstract

In this study, we explored to what extent brain abnormalities can be identified in specific brain structures of patients suffering from late onset depression. We examined the structural difference in regional gray and white matter volume between 14 community-dwelling patients suffering from geriatric depression and 20 age-matched non-depressed normal subjects by voxel-based morphometry (VBM) based on magnetic resonance imaging. All subjects also underwent an extensive neuropsychological assessment. Compared with control subjects, patients with depression were impaired in measures of verbal and visual memory, construction, executive ability, and information-processing speed. VBM of gray matter revealed a significant decrease of volume in the right rostral hippocampus, in the right amygdala and in the medial orbito-frontal cortex (gyrus rectus) bilaterally. In the correlation analysis of gray matter volume with the score of the geriatric depression scale, we observed a negative correlation with the medial orbito-frontal cortex (gyrus rectus) bilaterally. There were no differences in white matter volumes between patients with depression and healthy control subjects. The most important limitation of this study was sample size. A larger sample size may have improved detection of changes not reaching significance. Furthermore, our results may not be generalizable across depression severity or to hospitalized patients. The findings are consistent with our hypothesis that depression in the elderly is associated with local gray matter dysfunction.

Keywords: Voxel-based morphometry; Depression; Brain atrophy; Hippocampus; Gyrus rectus; Amygdala

1. Introduction

Depression in older adults can be disabling, contribute to problems with activities of daily living, and raise their dependence on others and the health care system (Oslin et al., 2000). Depression in the elderly has been shaped up as a complex problem, particularly difficult to diagnose due to medical illness, dementia syndromes, and heterogeneity of patient populations (Small, 1998). Furthermore, elderly patients show a slower response to antidepressant therapy than younger patients (Mandelli et al., 2007). In fact, there is evidence

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that depression in the elderly is strongly associated with poor cognitive function and decline (Yaffe et al., 1999). Abnormalities in specific brain structures and their interconnections may confer vulnerability to the development of late-life depression (Hoptman et al., 2006). A meta-analysis of studies that used magnetic resonance imaging (MRI) to assess the volume of the hippocampus revealed that patients with major depressive disorder have lower hippocampal volume relative to comparison subjects (Campbell et al., 2004). In addition to the traditional volumetric methods, recent advances in image analysis have produced new methods to map the entire brain instead of being restricted to single regions. One such technique is voxel-based morphometry (VBM), which objectively localizes focal gray and white matter volume changes throughout the entire brain (Ashburner and Friston, 2000; Brenneis et al., 2004; Taki et al., 2005; Jatzko et al., 2006; Mechtcheriakov et al., 2007; Egger et al., 2007). To our knowledge, it has not been applied to geriatric depression with the exception of one study that reported structural brain abnormalities in geriatric depression, particularly in patients with a longer course of illness (Bell-McGinty et al., 2002).

The main aim of the present study was to investigate altered density of gray and white matter in the whole brain of patients suffering from geriatric depression, and to reveal the atrophy pattern and alteration of different brain regions in order to provide evidence for a preferential vulnerability of some brain regions. Based on findings from previous neuroimaging studies in depression, we hypothesized that patients with geriatric depression would demonstrate volume reduction in medial temporal regions including the hippocampus, amygdala and medial prefrontal cortices. We further hypothesized that depressed patients are also suffering from cognitive impairment, and examined to what extent impaired cognitive parameters may contribute to the atrophy pattern.

2. Methods

2.1. Subjects

Patients were recruited from an outpatient clinic located at the Department of Psychiatry in Innsbruck, Austria. Healthy volunteers were recruited by advertising within the community. No financial remuneration was provided for study participation. As part of the diagnostic process, healthy control subjects and patients with a major depressive disorder were assessed by the same diagnostic procedure. Psychiatrists clinically examined all subjects, performed a standardized neurological examination, reviewed medical records, and conferred with referring physicians for all patients. All subjects underwent a neuropsychological assessment.

Inclusion criteria required a Mini-Mental State Examination (MMSE) score higher than 26 for healthy subjects and depressed patients. Major depressive disorder was diagnosed according to the DSM-IV criteria (American Psychiatric Association, 1994). Patients had to have a score in the Geriatric Depression Scale (GDS); (Yesavage et al., 1982) higher than 15. DSM-IV diagnoses were assigned to all subjects in a consensus diagnostic conference using procedures conforming to the longitudinal, expert, and available data standard (Spitzer et al., 1992). Only patients who had experienced their first depressive episode at the age of 60 or older were included. Informed consent was obtained from all participants for the study, which was approved by the local ethics committee of the Medical University Hospital Innsbruck, Austria.

Exclusion criteria for healthy subjects and depressed patients included 1) another major psychiatric illness, such as bipolar disorder, schizophrenia, and schizoaffective disorder; 2) current or long-term alcohol or drug dependence; 3) primary neurological illness, such as dementia, stroke, Parkinson's disease, seizure disorder, and multiple sclerosis; 4) metal in the body that precluded MRI.

Apolipoprotein E (Apo E) phenotyping was performed by isoelectric focusing using control 2/2, 3/3, and 4/4 plasma samples on the same gels. Patients were informed about possible consequences of ApoE phenotyping. Assessment of somatic burden was based on the annual medical examination performed by an internist as part of each subject's routine care. The treating physician compiled a medical problem list on the basis of the patient's history, physical examination, and available laboratory data. The resulting total number of medical problems served as an index of medical burden at the time of the study assessment (Miller et al., 1992).

2.2. Neuropsychological assessment

All subjects were evaluated with the MMSE (Folstein et al., 1975). They were tested on verbal memory, learning, free recall and recognition subtests of the CERAD battery (Rosen et al., 1984), figural memory (free recall, CERAD), object naming (Boston Naming Test — short version, CERAD), categorical verbal fluency (animals/min, CERAD), planning (CLOX Test part 1, Sunderland et al., 1989), constructive abilities (copy geometrical shapes, CERAD; CLOX Test part 2), divided attention and cognitive flexibility (Trail Making Test-B, Reitan, 1958).

2.3. Voxel-based morphometry (VBM)

2.3.1. Data acquisition, pre-processing and analysis

All participants were scanned on the same 1.5 Tesla Siemens Symphony MRI scanner using a T_1-weighted FLASH (fast low angle shot) 3D sequence with a repetition time (TR) of 9.7 ms, an echo time (TE) of 4 ms, a matrix size of 256 × 256 and a field of view of 230 mm, yielding sagittal slices with a thickness of 1.5 mm and an in-plane resolution of 0.98 × 0.98 mm. Structural MRI was conducted within 1 to 2 weeks of the baseline evaluation.

Statistical parametric mapping software (SPM2 — The Wellcome Department of Cognitive Neurology, London, UK) was used for image processing and statistical analysis. We applied the optimized VBM protocol to the image data as reported by Good et al. (2001). This protocol includes a study-specific template, extraction of mis-segmented areas and the modulation of the data with the Jacobian determinants.

2.3.1.1. Custom template creation. The creation of the study-group-specific template was performed to minimize the scanner-specific bias by averaging all images from the study-specific subject group, after normalization using linear 12-parameter affine-only transformation. Custom tissue probability maps were obtained by segmenting the individual normalized images into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), averaging and smoothing with an isotropic Gaussian kernel of 8-mm full-width at half-maximum (FWHM).

2.3.1.2. Segmentation. The optimized VBM protocol includes two segmentation steps. (1) Segmentation was performed in native space, and non-brain tissue was removed automatically by modulation with an individually derived brain-tissue mask. (2) Segmentation was performed after applying the normalization parameters to the original whole brain images (as described below), including removal, once again, of non-brain tissue, followed by reslicing onto a voxel size of 1 × 1 × 1 mm.

2.3.1.3. Normalization. The spatial normalization parameters were estimated by matching the native space individual GM image with the study-specific GM template using combined 12-parameter linear and non-linear (7 × 9 × 7 basis functions) transformation. The parameters resulting from this spatial normalization step were then reapplied to the original structural images.

2.3.1.4. Modulation. Multiplying voxel values of the segmented images with the Jacobian determinants was implemented to convert the gray matter segments into measures of absolute gray matter volume, as opposed to relative gray matter volume, following spatial normalisation.

2.3.1.5. Smoothing. Finally, all modulated images were smoothed with a 10-mm FWHM Gaussian kernel to reduce confounding by individual variation in gyral anatomy. It also has the effect of rendering the data more normally distributed (by the central limit theorem). (Ashburner and Friston, 2000).

Smoothed and segmented gray matter partitions were subjected to analysis of covariance (ANCOVA). Total intracranial volume (TIV) and mean voxel value were included as covariates to increase statistical power. In addition, we performed separate correlation analyses using the "multiple regression (with constant)" function of SPM2. Neuropsychological tests revealing significant group differences after Bonferroni correction for multiple testing (Table 2) were treated as covariate-of-interest, with age, sex, and TIV as confounding covariates. Two linear contrasts (1, −1) were made for positive and negative correlations, respectively. The statistical parametric maps were thresholded at P uncorrected <0.001 with an extent threshold of 25 contiguous voxels.

Further, we applied a small volume correction (SVC) including all hypothesized regions with a threshold of $P<0.05$ false discovery rate (FDR) corrected on voxel level. Volumes of interest (VOI) covering the entire hypothesized region were defined using the WFU PickAtlas Tool (http://www.fmri.wfubmc.edu) (Maldjian et al., 2003).

3. Results

As shown in Table 1, sex, age and education were not significantly different between patients suffering from depression and healthy control subjects. Apolipoprotein E alleles were equally distributed between patients and

Table 1
Characteristics of the study participants

	Healthy subjects ($n=20$)	Depressive patients ($n=14$)	P-score
Age	72.3±7.77 [60–84]	71.4±7.49 [61–86]	0.78
Education (years)	10.8±2.69 [8–17]	9.4±2.24 [8–15]	0.10
Sex	m=7; f=13	m=4; f=10	0.77
ApoE 3/4; 4/4	2	2	0.68
GDS	7.38±3.43 [2–14]	21.14±4.22 [15–27]	$P<0.001$

Data represent mean±S.D.
m = male; f = female; ApoE — Apolipoprotein E; GDS — geriatric depression scale.

control subjects. Somatic disease burden was also equally distributed between the two groups. Ten patients were taking antidepressants at the time of enrollment. Seven out of ten patients were treated with sertraline with a mean dosage of 69±19.4 mg (mean±S.D.). Three patients were treated with mirtazapine with a mean dosage of 25±6.4 mg (mean±S.D.). Four patients had a history of psychotic depression which was treated with risperidone or olanzapine. None of the patients had ever been treated with typical antipsychotics.

Patients with geriatric depression showed significantly poorer performance on neuropsychological tests (Table 2). After correction for multiple comparisons (Bonferroni, significance level set at $P<0.0031$), several cognitive domains were significantly different from cognitive performance in control subjects.

3.1. VBM results: group comparison

When all patients with depression ($n=14$) were compared with healthy controls (n=20), a significant decrease of gray matter volume (GMV) was revealed in the right amygdala (MNI coordinates: $x=22$, $y=-9$, $z=-18$, $k=918$, $T=4.22$, $Z=3.71$, $P=0.006$ corrected),

Table 2
Cognitive profile of study participants

	Healthy subjects	Depressive patients	*P*-score
MMSE	28.57±0.81	27.21±0.97	$P<0.001$*
CERAD verbal learning	20.81±2.96	14.79±3.89	$P<0.001$*
CERAD verbal delayed recall	7.29±1.49	4.71±2.58	0.002*
CERAD verbal recognition	10.00±0.00	9.86±0.53	0.727
CERAD constructional praxis (copy)	10.81±0.40	9.93±1.07	0.011
CERAD constructional praxis recall	10.09±1.14	6.43±2.93	$P<0.001$*
CERAD Boston naming task	14.67±0.58	13.21±1.72	0.007
NAI-figure test	9.57±2.25	8.09±1.76	0.004
Clox1	13.29±1.15	10.00±3.16	0.004
Clox2	14.29±0.72	13.00±1.53	0.009
Trailmaking A (seconds)	46.04±18.25	90.31±73.95	0.04
Trailmaking B (seconds)	112.69±35.51	131.50±45.15	0.279
Verbal fluency animals 1st minute	22.05±5.74	15.93±6.65	0.012
Verbal fluency animals 2nd minute	13.71±4.52	7.43±4.29	$P<0.001$*
Verbal fluency "s"-words 1st minute	14.90±3.25	8.50±4.74	$P<0.001$*
Verbal fluency "s"-words 2nd minute	10.62±3.63	4.29±2.43	$P<0.001$*

Data represent mean±S.D. Data were analyzed with Mann–Whitney *U*-test.
*Indicates cognitive domains that were significantly different after Bonferroni correction for multiple testing. The Bonferroni-corrected significance level was set at $P<0.0031$.

Table 3
Relative decrease of gray matter volume in elderly patients with depression relative to their corresponding group of healthy controls matched for age and gender

		Peak coordinates[a]			*k*	*T*-score	*Z*-score	*P*-value[b]
		x	*y*	*z*				
Amygdala								
	Right	22	−9	−18	918	4.22	3.71	0.006
Hippocampus								
	Right	25	−14	−20	540	4.15	3.66	0.013
Medial orbito-frontal cortex (gyrus rectus)								
	Right	6	13	−21	271	3.97	3.53	0.018
	Left	−21	14	−24	102	4.20	3.70	0.026

[a] Coordinates are given in MNI space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca).
[b] *P*-values are given after false discovery rate (FDR) correction for multiple comparisons with a small volume correction using binary masks covering the whole structure of interest.

Table 4
Regions of gray matter showing volume alterations correlating to clinical parameters (GDS and CERAD constructional praxis)

Region		MNI coordinates[a]			*k*	*T*	*Z*	*P*-value[b]
		x	*y*	*z*				
Negative correlation of GMV with GDS								
Medial orbito-frontal cortex								
(Gyrus rectus)	Right	2	15	−20	96	3.48	3.18	0.046
	Left	−9	12	−24	50	3.68	3.34	0.038
Positive correlation of GMV with CERAD constructional praxis								
Hippocampus								
	Right	22	−18	−17	1001	3.97	3.55	0.030
	Left	−22	−14	−17	3239	3.61	3.28	0.014
Putamen								
	Right	22	7	4	6490	5.38	4.51	<0.001
	Left	−24	6	3	4155	3.68	3.34	0.013
Nucleus caudatus								
	Right	9	11	0	1966	4.34	3.82	0.001
	Left	−2	5	−8	1377	3.92	3.51	0.005
Insula								
	Right	40	10	−2	9913	4.76	4.11	0.002
	Left	−43	14	−5	9833	4.73	4.09	0.004
Thalamus								
	Left	−10	−14	0	5019	3.91	3.51	0.007

[a] Coordinates are given in MNI space (Montreal Neurological Institute, http://www.bic.mni.mcgill.ca).
[b] *P*-values are given after false discovery rate (FDR) correction for multiple comparisons with a small volume correction using volumes of interest defined by WFU PickAtlas Tool (http://www.fmri.wfubmc.edu).

the rostral part of the right hippocampus (MNI coordinates: $x=25$, $y=-14$, $z=-20$, $k=540$,, $T=4.15$, $Z=3.66$, $P=0.013$ corrected), as well as the medial orbito-frontal cortex (gyrus rectus) bilaterally (MNI coordinates: $x=6$, $y=13$, $z=-21$, $k=271$, $T=3.97$, $Z=3.53$, P corr.$=0.018$ and $x=-21$, $y=14$, $z=-24$, $k=102$, $T=4.20$, $Z=3.70$, P corrected$=0.026$) (Fig. 1).

There were no regions showing significant increase in GMV, and there was no significant group difference in white matter volume in patients with depression relative to healthy controls. GMV changes are shown in Table 3.

3.2. VBM results: correlation analysis

In the correlation analysis of gray matter volume with the geriatric depression scale, we observed a significant negative correlation with the medial orbito-frontal cortex (gyrus rectus) bilaterally (MNI coordinates: $x=2$, $y=15$, $z=-20$, $k=96$, $T=3.48$, $Z=3.18$, P corrected$=0.046$ and $x=-9$, $y=12$, $z=-24$, $k=50$, $T=3.68$, $Z=3.34$, P corrected$=0.038$) (Table 4).

Correlation with the clinical parameter "CERAD constructional praxis" revealed a significant positive correlation with the hippocampus (MNI coordinates: $x=22$, $y=-18$, $z=-17$, $k=1001$, $T=3.97$, $Z=3.55$, P corrected$=0.03$ and $x=-22$, $y=-14$, $z=-17$, $k=3239$, $T=3.61$, $Z=3.28$, P corrected$=0.014$), putamen (MNI coordinates: $x=22$, $y=7$, $z=4$, $k=6490$, $T=5.38$, $Z=4.51$, P corrected<0.001 and $x=-24$, $y=6$, $z=3$, $k=4155$, $T=3.68$, $Z=3.34$, P corrected$=0.013$), nucleus caudatus (MNI coordinates: $x=9$, $y=11$, $z=0$, $k=1966$, $T=4.34$, $Z=3.82$, P corrected$=0.001$ and $x=-2$, $y=5$, $z=-8$, $k=1377$, $T=3.92$, $Z=3.51$, P corrected$=0.005$), insula (MNI coordinates: $x=40$, $y=10$, $z=-2$, $k=9913$, $T=4.76$, $Z=4.11$, P corrected$=0.002$ and $x=-43$, $y=14$, $z=-5$, $k=9833$, $T=4.73$, $Z=4.09$, P corrected$=0.004$) bilaterally and the left thalamus (MNI coordinates: $x=-10$, $y=-14$, $z=0$, $k=5019$, $T=3.91$, $Z=3.51$, P corrected$=0.007$).

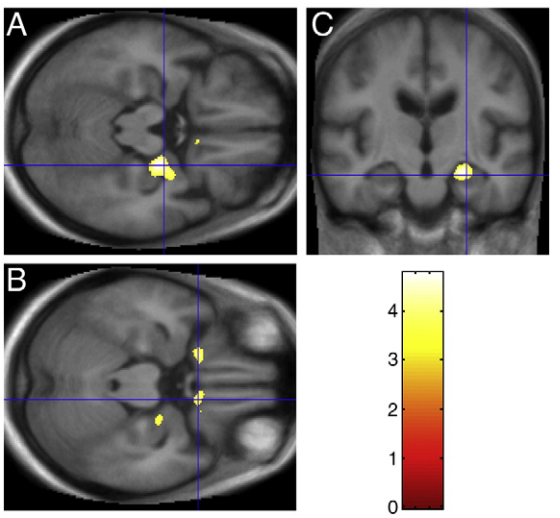

Fig. 1. Gray matter volume (GMV) decrease in patients with geriatric depression. GMV decrease in the right amygdala (A). GMV decrease bilaterally in the medial orbito-frontal cortex (gyrus rectus) and the rostral part of the right hippocampus (B). GMV decrease in the rostral part of the right hippocampus (C). All findings are superimposed in yellow on an averaged normalized image of all study participants. Threshold was set at $T>3.39$ (peak) according to $P<0.001$ uncorrected. The colour bar represents the range of t values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In this VBM study, we demonstrate smaller volumes of the right amygdala, right hippocampus and medial orbito-frontal cortex in patients with geriatric depression, compared with healthy subjects. The hippocampal volume loss in depression is well known, established by numerous volumetric MRI studies (Campbell et al., 2004). A recent MRI study found that the hippocampal volume loss depended on disease duration in two elderly patients groups with early and late disease onset (Janssen et al., 2007). However, we also detected a significant reduction in basal forebrain volumes in our sample of elderly patients with late disease onset as compared with age-matched control subjects, a finding that appears to be consistent with our a priori hypothesis that different brain regions are involved in geriatric depression.

As revealed by psychological tests, our patients suffered from distinct cognitive deficits, in addition to depression. The observed deficits comprised different cognitive domains with impairment mainly in memory and executive functions. Although no patient in the study fulfilled the criteria for early dementia, especially Alzheimer disease, the high number of cognitively impaired patients could indicate that we enrolled patients who were probably in a pre-dementia state. Indeed, it is known that depression is one of the first symptoms of Alzheimer disease in about 30% of Alzheimer patients (Meeks et al., 2006).

Our VBM findings revealed a smaller volume for the anterior part of the right hippocampus, suggesting that the hippocampus comprises different subregions of specific vulnerability. Our results are in agreement with a previous VBM study in elderly subjects with depression that also revealed a smaller right hippocampal volume compared with that in healthy subjects (Bell-McGinty et al., 2002).

The bilateral hippocampal–entorhinal volume correlates inversely with years since onset of depression, suggesting that total lifetime duration of depression is significantly associated with hippocampal volume loss bilaterally (Sheline et al., 1999). Accordingly, a recent volumetric MRI study has demonstrated that hippocampal volume loss is more enhanced in elderly patients with early onset of depression compared with age-matched patients with late onset (Janssen et al., 2007). In addition, our study revealed a volume change in the right amygdala, whereby the anterior part of the hippocampus is difficult to delineate from the adjacent amygdala. Studies have been contradictory about the relative amygdala volume in patients suffering from depression compared with healthy subjects. A statistically significant deficit in amygdala volume (Sheline et al., 1998; Sheline et al., 1999; Tang et al., 2007) and no significant difference in amygdala volume (Mervaala et al., 2000) have both been reported. An even higher amygdala volume has been found in patients with a first episode of major depression relative to comparison subjects (Frodl et al., 2002). Functional neuroimaging studies of the anatomical correlates of familial major depressive disorder and bipolar disorder have identified abnormalities of resting blood flow and glucose metabolism in depression in the amygdala and the orbital and medial prefrontal cortical areas that are extensively connected with the amygdala (Mayberg et al., 1999; Mayberg et al., 2000; Drevets, 2003).

Our data support that the medial orbito-frontal cortex exhibits a significantly reduced volume in patients with late onset of depression, without any changes in gray and white matter volumes of the other frontal cortex. To our knowledge, this finding is novel for geriatric depression. Furthermore, the volume reduction in orbito-frontal cortex, as observed in our study, significantly correlated with scores on the geriatric depression scale. A statistically significant and isolated volume reduction in medial orbito-frontal (gyrus rectus) cortical volume was also reported in patients with major depression (Bremner et al., 2002). In an MR-based parcellation of the prefrontal cortex in elderly depressed patients, volume losses were more extensive including also the anterior cingulate, the gyrus rectus, and the orbito-frontal cortex (Ballmaier et al., 2004). In general, volume reductions in patients with depression are supposed to be caused by reduced densities of neurons and glia in the affected regions (Rajkowska, 2000). The orbito-frontal cortex is known to play a role in emotional and visceral regulation. The projections from the basolateral amygdala to the prefrontal cortex are required for learned associations to influence more complex behavioural responses (Cardinal et al., 2002). Damage to the orbito-frontal cortex results in deficits in emotion, mood, and social regulation (Damasio et al., 1994). In addition, alterations in the prefrontal cortices in depression have been shown to be relevant to pharmacotherapy (Lidstone and Stoessl, 2007).

Our findings on neuropsychological functioning are in general agreement with the existing literature (Boone et al., 1994; Butters et al., 2004). We detected that patients with depression show impairments in measures of verbal and visual memory, construction and information-processing speed compared with control subjects. Our patients with late-life depression also had significant limitations in executive functioning, as already reported in previous studies (Lockwood et al., 2002). Cognitive dysfunction may be an integral component of the disorder in elderly patients with depression. While some cases of depression and cognitive impairment in elderly patients develop against the background of subclinical dementing disorders, other cases do not progress into irreversible dementia (Alexopoulos et al., 1993). Whether our patient sample carries a specific risk for converting into dementia has to be explored in prospective longitudinal studies.

Our study has several limitations. The most important limitation of this study was sample size. A larger sample size may have improved detection of changes not reaching significance. Furthermore, our results may not be generalizable across depression severity or to hospitalized patients. All patients were ambulatory and living independently in the community. Furthermore, the depressed patients were not a homogenous group as far as their cognitive functions are concerned. Therefore, in further larger studies, patients should be stratified according to their cognitive abilities.

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