J Neurol (2005) 252 : 1345–1352
DOI 10.1007/s00415-005-0864-2

ORIGINAL COMMUNICATION

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Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia

Received: 5 January 2005
Received in revised form: 23 February 2005
Accepted: 7 March 2005
Published online: 5 July 2005

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Abstract *Objective* To investigate the pattern of brain atrophy across time in a sample of Parkinson's disease (PD) patients with and without dementia using voxel-based morphometry (VBM) analysis. *Methods* The initial sample comprised thirteen non-demented PD patients and sixteen demented patients. Longitudinal cognitive assessment and structural MRI were performed. The mean follow-up period was 25 months (SD = 5.2). From this initial group, eight PD patients with dementia (5 men and 3 women) and eleven PD patients without dementia (7 men and 4 women) were reevaluated. MRI 3D structural images were acquired and analyzed by means of the optimized VBM procedure with Statistical Parametric Mapping (SPM2). *Results* VBM analysis showed a progressive grey matter volume decrease in patients with PD without dementia in limbic, paralimbic and neocortical associative temporo-occipital regions. In patients with dementia the loss mainly involved neocortical regions. *Conclusion* VBM revealed a significant loss of grey matter volume in PD patients with and without dementia with disease progression. The decrease in limbic and paralimbic regions is widespread in non-demented patients. Neocortical volume reduction is the most relevant finding in patients with dementia. This suggests that the neocortex is a substrate for dementia in Parkinson disease.

Key words Parkinson's disease · dementia · MRI · voxel-based morphometry · longitudinal study

Introduction

In the last few years cognitive impairment of variable degrees has been increasingly recognized in patients with Parkinson's disease (PD) [16, 22]. There have been several cross-sectional studies in which prevalence of dementia in PD was reported to range from 18–41 % [1, 35, 38], although a recent longitudinal study in a community-based population has suggested a cumulative incidence of about 80 % [2].

The pathological findings observed in post mortem studies of PD with dementia (PDD) are Lewy body-type degeneration in limbic and cerebral cortical areas and Alzheimer-type changes of variable degree. Studies using alpha-synuclein antibodies to identify Lewy pathology support the view that dementia is closely correlated with the presence and density of neocortical and limbic Lewy bodies and neurites [4, 10, 27, 37]. Other studies have also suggested that the coincident Alzheimer-type pathology is an important contributor to dementia in PD [8, 14].

Structural imaging studies using the technique of voxel-based morphometry (VBM) have shown differences in gray-matter volume between demented PD patients and controls in cortical and subcortical cerebral regions. Specifically, Burton et al. [9] reported reduced gray matter volume in PDD patients compared with controls in the temporal lobe bilaterally, including hippocampus and parahippocampal gyrus, in the occipital lobe, the frontal and parietal lobes, and some subcortical regions. We have previously reported gray matter loss in the basal ganglia, hippocampus bilaterally, and left parahippocampal region in PDD [43].

The technique of VBM has been shown to be useful in characterizing regional brain decreases across time in degenerative diseases such as Alzheimer's disease [36] and in patients with cognitive impairment without dementia [46]. To our knowledge, there are no published studies on the progression of regional volume loss in PD using VBM. One longitudinal study, in which a technique for the quantification of absolute brain changes was used showed that non-demented PD patients had significant reductions in whole brain volume compared with controls over a two-year follow-up period [26].The present study aimed to determine the pattern of brain atrophy across time in PD patients with and without dementia using the VBM technique.

Methods

Patients

Patients were recruited from an outpatient movement disorders clinic (Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona). All of them fulfilled the UK Brain Bank criteria for PD [12]. The patients were part of a previously-studied initial sample of 29 patients: 13 PD and 16 PD with dementia. They were invited by telephone for a follow-up assessment. The average follow-up period was 25 months (SD = 5.2), similar to that reported in the only previous longitudinal study in PD [26]. Written informed consent was obtained for all subjects. The ethics committee of our hospital approved the study.

From the original PD sample without dementia, one subject declined to participate and another was demented at follow-up. Concerning the original PD sample with dementia, four subjects died, while in another four patients it was impossible to perform magnetic resonance imaging owing to severe motor impairment. Thus, eleven patients with PD and eight patients with PD with dementia were included in the follow-up evaluation.

The follow-up assessment included a history provided by the patient and the caregiver, a neurological (Unified Parkinson's Disease Rating Scale (UPDRS) [18] and Hoehn and Yahr Rating Scale [28]) and neuropsychological examination, and MRI.

The diagnosis of dementia at follow-up was made by the neurologist based on an interview with the patient and a caregiver using the Diagnostic and Statistical Manual of Mental Disorders, Revised Fourth Edition (DSM IV-TR) [3] as a guide, along with administration of the Mini Mental State Examination (MMSE) [20]. Subjects needed a MMSE score of 23 or lower and DSM-IV-TR items to fulfill dementia criteria. Presence of hallucinations was assessed by a structured interview developed in our hospital. The scale comprised items covering the type (visual, auditory, tactile and olfactory) and temporal aspects of the hallucinations (time of day, frequency and duration). Depression was rated using the Hamilton scale [24].

Neuropsychological assessment

Subjects were tested individually in a well-lit, quiet room by a neuropsychologist experienced in testing neurologically impaired individuals. The neuropsychological assessment included test of memory, and of visuoconstructive and frontal lobe functions. The Rey Auditory Verbal Learning Test (RAVLT) assesses immediate memory span, new learning and delayed recall [34]. It consists of 15 words read aloud for five consecutive trials, each trial being followed by a free recall test. After a 20-min. delay period, each subject is again required to recall the words in the list. The Digit Span forward and backward subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) was used to assess attention and working memory. Here, subjects have to recall a series of digits in the same order and in reverse order. The modified version of the WAIS Block Design subtest was used to examine visuospatial and visuoconstructive abilities. We used the reduced version (four blocks) without registering the execution time. Letter fluency was used to test prefrontal functioning [34]. Individuals were given 1 minute to generate words starting with F, A, and S, excluding proper nouns and numbers.

Statistical analysis

Statistical analysis was carried out using SPSS 11.0. For clinical and demographic variables, we used the Mann-Whitney U-test for independent samples. The neuropsychological measures at both sessions were analyzed using the non-parametric Wilcoxon test for related samples.

MRI and Voxel-Based Morphometry

MRI acquisitions were performed using a 1.5 Tesla Signa Nvi/Cvi 8.4 General Electric (Milwaukee, USA). The imaging protocol included axial 3D IR Prep SPGR (Inversion Recovery Prepared Spoiled Gradient-echo) sequence of the entire brain and the following parameters: TR (Repetition time) = 17; TE (Echo time) = 5; TI (Inversion time) = 300; 1.5 mm thickness; FOV (Field of view) = 24x24; 256x256; 1 NEX (Number of excitations).

Images were analyzed with MATLAB 6.5 (MathWorks, Natick, MA) and SPM2 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK). Original MR Images registered in DICOM format (one two-dimensional file per slice) were organized into three-dimensional files (volumes) by means of MRIcro software (University of Nottingham, UK) and saved in ANALYZE 7.5 format compatible with SPM2. Images were aligned along the anterior-posterior commissure (AC-PC) line.

Application of the optimized voxel-based morphometry (VBM) procedure [23], as well as details of our acquisition protocol and analyses are described elsewhere [43]. Paired *t*-tests using SPM2 were undertaken to compare base-line vs. follow-up gray matter volumes within each group. VBM analysis was thresholded at voxel level p uncorrected < 0.001. Only the significant clusters of more than 20 contiguous voxels were considered in the analysis. We only interpreted clusters with a p corrected < 0.05.

Results

Both groups were comparable in terms of age, sex and years of education. There were no differences in disease duration or stage of the illness, although the PDD group

did show a higher score on Part III of the Unified Parkinson's Disease Rating Scale. Both PD groups differed in the degree of mental impairment assessed by Mini Mental State Examination in both evaluations: baseline and follow-up (see Table 1).

Table 2 shows the clinical progression and the proportion of PD patients with hallucinations. We did not find any statistical significance regarding the progression of clinical severity evaluated by Hoehn and Yahr or by the UPDRS scale. None of the PD patients without dementia showed hallucinations, but this symptom occurred in all demented patients studied. Complex visual hallucinations (VH) were the most common type of hallucinatory phenomena. These were persistent in 6 of 8 cases. The presence of VH did not correlate with gray matter volume in the temporo-occipital region neither at baseline nor at the follow-up evaluation.

Results of the neuropsychological assessment are presented in Table 3. Across time the PD group showed a decreased performance on several tests, but only the scores in digit forward reached statistical significance. The raw scores of the group with dementia decreased on all tests, and the RAVLT learning score reached significance.

VBM results are described in Table 4 and illustrated in Figs. 1 and 2. When compared with baseline, the group without dementia showed significant clusters of reduced gray matter volume in the right anterior and posterior cingulate gyrus, bilateral temporo-occipital region, bilateral insula, right hypothalamus and nucleus accumbens, and left hippocampus. The PDD group showed a decrement in gray matter volume in the right fusiform gyrus, right parahippocampal gyrus and hippocampus, right temporo-occipital region, and right medial anterior temporal gyrus.

To investigate the relationship between cognitive decline and brain volume loss, we performed an analysis of covariance (ANCOVA) using the neuropsychological scores that achieved statistical significance or a trend towards it in the base-line vs. follow-up conditions. Specifically, for the PDD patients we included the RAVLT learning scores and for the PD patients the RAVLT learning and digit forward scores. When entered into the analyses the above mentioned covariates, the grey matter differences between pre and post MRI acquisitions lost significance. This suggested that cognitive decline is related to grey matter volume loss.

Table 1 Demographic and clinical characteristics of the sample at the follow-up

	PD	PDD	Test statistics	p-value
Age (years)	74.45 ± 4.6	70.25 ± 10.1	37.00[a]	0.559
Gender (men/women)	7/4	5/3	0.003[b]	0.960
Years of education	7.73 ± 4.03	7.63 ± 5.8	39.00[a]	0.671
Disease duration (years)	12.36 ± 6.6	13.50 ± 5.7	38.00[a]	0.619
Hoehn and Yahr stage	3.2 ± 0.9	3.9 ± 1.0	27.00[a]	0.145
UPDRS III	21.09 ± 6.3	42.38 ± 18.6	20.00[a]	0.047*
Hamilton score	4.27 ± 5.4	3.13 ± 2.6	43.50[a]	0.968
MMSE baseline	28.64 ± 1.03	20 ± 2.39	0.001[a]	< 0.0005*
MMSE follow-up	27.55 ± 1.4	15.50 ± 5.7	1.00[a]	< 0.0005*

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *UPDRS* Unified Parkinson's Disease Rating Scale; *MMSE* Mini Mental State Examination
[a] Indicates calculated using Mann-Whitney U-test
[b] Indicates calculated using the χ^2 test
* denotes significant ($p < 0.05$) differences between PD and PDD patients

Table 2 Clinical results at baseline (Time 1) and follow-up (Time 2) in PD samples

	Group	Time 1	Time 2	z-value Wilcoxon test (Time 1 vs. Time 2)	p-value
Hoehn and Yahr stage	PD	2.9 ± 0.8	3.2 ± 0.9	–1.32	0.187
	PDD	3.2 ± 0.9	3.9 ± 1.0	–1.76	0.078
UPDRS III	PD	22.27 ± 11.7	21.09 ± 6.3	–0.31	0.759
	PDD	32.0 ± 6.3	42.38 ± 18.6	–1.12	0.262
Presence of hallucinations	PD	–	–	–	–
	PDD	8/8	6/8		

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *UPDRS* Unified Parkinson's Disease Rating Scale

Table 3 Neuropsychological test scores

Task	Group	Time 1	Time 2	z-value Wilcoxon test (Time 1 vs. Time 2)	p-value
RAVLT Learning	PD	35.00±6.1	30.64±5.9	−1.94	0.052
	PDD	20.57±6.1	13.86±5.2	−2.37	0.018*
RAVLT Forgetting	PD	3.36±1.9	2.09±4.4	−1.24	0.215
	PDD	2.29±2.7	1.75±1.5	−0.43	0.670
Digit forward	PD	7.36±2.01	6.18±1.2	−2.01	0.045*
	PDD	5.57±1.0	5.38±1.4	−0.37	0.713
Digit backward	PD	3.91±1.8	3.73±1.0	−0.49	0.623
	PDD	2.29±1.4	1.63±1.3	−1.09	0.276
Block design	PD	16.73±5.6	14.64±5.5	−1.27	0.205
	PDD	5.14±7.2	3.43±4.8	−0.74	0.461
Letter fluency (FAS)	PD	8.48±4.0	7.50±3.6	−1.38	0.168
	PDD	4.29±3.9	3.19±2.5	−1.33	0.183

Values are mean ± SD
PD Parkinson's disease; *PDD* Parkinson's disease with dementia; *RAVLT* Rey Auditory-Verbal Learning Test; *RAVLT Learning* Sum of words correctly recalled of Trial 1 to 5; *RAVLT Forgetting* Number of words lost after the 20-minute delay; *FAS* Sum of all admissible words for the three letters divided by three
* denotes significant score decrease in the follow-up

Table 4 Results from the analysis of decreases in grey matter volume in PD groups*

Cerebral Region	Cluster		Voxel			
	Number of voxels	Corrected p	Z value	Talairach's coordinates		
				x	y	z
Decreases in gray matter volume in PD group in the follow-up						
Right anterior cingulate gyrus	8482	< 0.0005	4.72	1	31	19
Right temporo occipital region	6179	< 0.0005	4.41	44	−65	0
Left insula	3241	< 0.0005	4.29	−32	2	9
Right insula	1612	0.002	4.18	37	−6	0
Right posterior cingulate gyrus	1614	0.002	4.11	11	−49	30
Left temporo occipital region	982	0.021	1.01	−37	−62	12
Right hypothalamus/Nucleus accumbens	1314	0.006	3.98	1	−9	−5
Left hippocampus	921	0.026	3.44	−22	−19	−11
Decreases in gray matter volume in PD group with dementia in the follow-up						
Right fusiform gyrus/Right Hippocampus and parahippocampal gyrus	4773	< 0.0005	4.58	26	−56	−8
Right temporo occipital region	1059	0.018	4.04	40	−56	6
Right medial anterior temporal gyrus	781	0.050	3.93	42	−18	−6

* Each reported anatomical location exceeds a voxelwise statistical threshold of $p < 0.001$ uncorrected level. The cerebral regions are referred to the location of the cluster. The Tailarach coordinate refers to the location of the most statistically significant voxel in the cluster

Discussion

The present research provides the first *in vivo* documentation using VBM of progressive gray matter loss in PD with disease progression. Both patients with and without dementia showed volume reductions in neocortical and limbic structures. In PD patients without dementia the brain loss broadly involved the paralimbic regions (anterior and posterior cingulate and insular cortex) along with other limbic structure such as the hippocampus. Grey matter loss in the associative temporo-occipital neocortex also occurred. In demented patients limbic volume loss was only observed in the hippocampus and the neocortical decrement tissue involved regions in temporal and occipital lobes.

In the non demented PD group we observed a clear paralimbic and limbic involvement. This is consistent with post-mortem data showing neuronal loss and Lewy body pathology in insular cortex and cingulate gyrus in PD [5, 7]. Moreover, hypoperfusion of insular region in a group of non-demented advanced PD has been re-

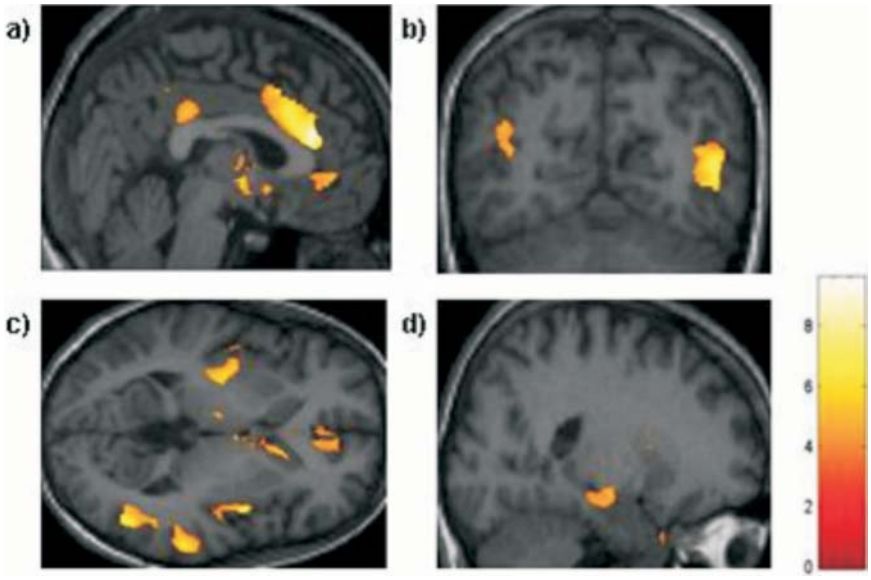

Fig. 1 Results of the comparison between initial and follow-up MRI in non-demented PD patients. Voxels reaching significance at the uncorrected $p < 0.001$ level are rendered on T1 image. Clusters of gray matter loss are seen in **a**) right anterior and posterior cingulate gyrus, right hypothalamus and nucleus accumbens (**b**) bilateral temporo occipital region (**c**) bilateral insula, right anterior cingulate, and right temporal region (**d**) left hippocampus

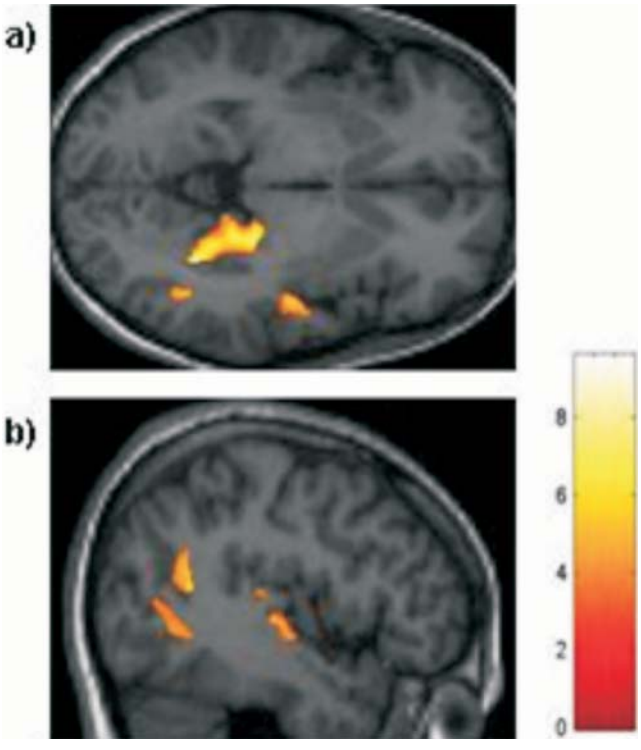

Fig. 2 Gray volume loss in demented PD patients. Voxels reaching significance at the uncorrected $p < 0.001$ level are rendered on T1 image. Clusters of volume difference are observed in (**a**) right fusiform gyrus, hippocampus and parahippocampal areas and (**b**) right temporo occipital region and right medial anterior temporal gyrus

ported previously [31]. We also observed a progressive volume loss of hippocampus. Using manual volumetric analysis comparing PD patients with and without dementia, Camicioli et al. [11] found a pattern in hippocampal reduction. Non demented patients showed hippocampal volume value between those of demented patients and controls suggesting progressive hippocampal loss in PD.

Old age, advanced stage of the disease, and impairment in verbal memory have been identified as risk factors to the development of dementia [32, 33]. Our PD sample is old, shows an advanced H & Y stage, a trend to memory decline, and a significant hippocampal reduction, but they have not developed dementia in two years of follow up. Longer longitudinal studies would be necessary to identify possible evolution to dementia. In this way, Aarsland et al. [2], found that more than three quarters of their PD cohort developed dementia in an 8-year study period.

In demented patients volume loss involved several neocortical areas. This is consistent with single-photon-emission CT studies in which marked perfusion deficits were described in posterior associative regions [30, 44] and with neuropathological studies which suggest a relationship between the presence of dementia and cortical pathology (LB-type degeneration or and Alzheimer-Type pathology) [4, 8, 10, 14, 27, 37]. Our results with VBM neuroimaging support the concept that the neocortex is a substrate for dementia in PD, in addition to limbic [6] and subcortical structures [13, 40, 47].

The cortical volume loss in the sample of patients with dementia included a marked decrease in volume in the fusiform gyrus with disease progression. The volume reduction of this cerebral region could be related with high densities of Lewy bodies in medial temporal regions in patients with dementia with Lewy bodies and demented PD patients with visual hallucinations [25]. The progressive tissue loss that we found might influence the persistence and progressive nature of halluci-

nations in PD [17, 21]. However, we found no correlation between grey matter volume and presence of visual hallucinations either in baseline or in the follow-up evaluation. So, although volume reduction of this cerebral region might be partially related with visual hallucinations, additional factors such as neurochemical deficits reported in these patients seem to be necessary for the presence of this symptom (see Diederich et al., for a review) [15].

Surprisingly, the progressive volume loss in PD patients without dementia was widespread and marked. These results could reflect the different regional involvement with disease progression in agreement with neuropathological staging reported by Braak et al. [7]. These authors described the topographic extent of PD-related brain lesion (Lewy neurites/bodies) in progressive stages. According to this study, limbic and paralimbic degeneration (Stage 4) precede neocortical degeneration (Stage 5 and 6). The demented patients are probably in a more advanced neuropathological stage in which degeneration of the limbic and paralimbic regions may be less active. Such interpretation could explain why patients without dementia showed a widespread gray matter loss. In fact neuropathological [19] and neuroradiological [29, 39, 42] studies suggest that a slower progression occurs in more advance stages of the disease.

The small sample size and the high number of decreased brain areas are points against carrying out a classical correlation analysis. However, when considering the cognitive scores of PD samples as covariates, the gray matter differences between pre and post MRI acquisitions lost significance. This suggests a relationship between cognitive status and gray matter loss across time.

One limitation of the study is the small sample tested in the follow-up. However, our sample is comparable in term of size to that reported by Hu et al. [26] and we studied well matched groups in terms of disease duration. Additionally, in the present report we used a quantitative and automatic approach which contributes a novel and complementary analysis not performed until now.

A methodological consideration to bear in mind is that we considered the statistic maps threshold at $p < 0.001$ uncorrected for multiple comparisons. A comparison without a priori hypothesis of the brain regions that may have been affected by the progression of the disease in both groups should have been addressed using a p corrected value for multiple comparisons (for instance at $p < 0.05$). However, owing to the preliminary nature of this investigation since no previous data using VBM in longitudinal studies are available, as well as the small size of our samples we decided to use a less stringent cut-off.

Another limitation is the absence of a control group. Previous evidence from MRI studies showed an age-related loss of brain tissue. Good et al. [23], using VBM found that normal ageing is associated with a linear decline in grey matter with an accelerated loss in parietal and frontal areas and with a relative preservation of medial temporal lobe structures. Prominent tissue loss in frontal and parietal areas as compared to temporal and occipital areas have also been found in a longitudinal study performed using semi-automated techniques for a quantitative analysis of MR volumes of normal cognitive older adults [41]. In this way the temporal and occipital loss found in PD samples could be more related to the neurodegenerative process than to the age effect, given that these structures have a relative sparing with ageing. However, in a recent study using VBM, Tisserand et al. [45] reported decreases in gray matter density in various frontal regions but also in the temporal lobes in elderly subjects without cognitive decline. Brain volume changes in our PD groups could partially be explained by the age effect but the time between the first and the second assessment was the same for both groups examined, therefore the pattern of cerebral changes due to ageing should be similar.

In summary, this is the first study using VBM which found that both demented and non demented PD patients showed progressive grey matter loss in several cerebral regions. The neocortical grey matter decrease in demented patients suggests that cortical involvement plays an important role in dementia in Parkinson's disease. In the future, it will be essential to perform prospective longitudinal studies involving longer follow-up with a larger number of subjects and including healthy elderly people.

Acknowledgements This study was supported by the following grants: Red CIEN IDIBAPS-ISCIII RTIC C03/06 (E. Tolosa and C. Junque), 2001SGR00139 and 2001SGR00387 (Generalitat de Catalunya to C. Junque and E. Tolosa) and Award "Distinció per a la Promoció de Recerca Universitària Generalitat de Catalunya" to E. Tolosa and C. Junqué. B. Ramírez-Ruiz was funded by a grant AP-2001–0823 from the Ministerio de Educación, Cultura y Deporte and D. Bartrés-Faz by a Ramón y Cajal fellowship from the Ministerio de Ciencia y Tecnología.

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