**Brain volume patterns in corticobasal syndrome vs. idiopathic Parkinson’s disease**

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**Running title**

Different brain volume patterns in CBS vs IPD

**Keywords**

Corticobasal syndrome; idiopathic Parkinson syndrome; brain atrophy; voxel-based morphometry; multi-voxel pattern analysis.

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**Abstract**

Background and Purpose: Patients with a corticobasal syndrome (CBS) present a rare form of atypical parkinsonism characterized by asymmetric clinical symptoms and progressive motor and non-motor impairment, such as apraxia, alien limb phenomenon, aphasia, myoclonus, dystonia, and cognitive impairment. At early stages, clinical differentiation between CBS and idiopathic Parkinson’s disease (IPD) can be challenging. Methods: Using high-resolution T1-weighted images and voxel-based morphometry (VBM) we sought to identify disease-specific patterns of brain atrophy in a small sample of CBS and IPD patients at early stages of disease. We acquired MR images of 17 patients diagnosed with CBS and compared them with MR images of 17 subjects affected by IPD. Images were pre-processed and analyzed using VBM. Results: When compared to each other, the CBS and IPD patients of our cohort showed differences in regional white matter volume depending on the diagnosis, specifically in the contra- and ipsilateral superior longitudinal fascicle. Conclusions: In our small patients’ group, VBM was able to detect changes in regional white and gray matter volume between patients affected by CBS and patients with IPD as early as 1.5–2 years after the onset of the first motor symptoms.

**Introduction**

Corticobasal syndrome (CBS) is a rare form of atypical parkinsonism1 characterized by asymmetric clinical presentation of cortical dysfunction associated with clinical symptoms such as apraxia, alien-limb phenomenon, cortical sensory loss, myoclonus, non-fluent aphasia, and cognitive decline, but also extrapyramidal symptoms such as rigor and dystonia.2,3 At an early stage, clinical symptoms of CBS do not differ reliably from those of idiopathic Parkinson disease (IPD). However, an early differential diagnosis is desirable for an appropriate counselling of the patients, who are likely to experience substantially different courses of symptom progression depending on whether they are affected by CBS or IPD. Difficulties in the differentiation between CBS and IPD are caused by the similarity of symptoms at early stages of clinical manifestation. The asymmetric presentation in both diseases, the difficulty to distinguish a slight rigor from a beginning dystonia, as well as the potential absence of CBS pathognomonic symptoms can make the differential diagnosis challenging. The initial scarcity of motor impairment also relativizes the role of drug-response tests with levodopa and/or apomorphine. Quantitative determination of neurofilament light chain (NF-L) in cerebrospinal fluid has been proposed as a serological biomarker for a better distinction between CBS and IPD, but this technique is, for now, only available at highly specialized centers.4-7 The role of brain imaging is principally confined to the exclusion of vascular, inflammatory, traumatic, and metabolic pathologies that might cause symptomatic parkinsonism. As such, the diagnoses of CBS and IPD are based, at the current stage, on clinical assessment.

In the present study, we used high resolution T1-weighted imaging and VBM to delineate patterns of gray matter (GM) and white matter (WM) atrophy potentially helpful to differentiate CBS from IPD at an early stage of disease, i.e. 19-24 months after first clinical manifestation.

**Methods**

*Patients, diagnostics, and ethics.*

All patients were prospectively recruited at the Centre for Movement Disorders and Neuromodulation of the Heinrich-Heine-University Dusseldorf (Germany). Overall, 91 patients with atypical parkinsonism and 31 subjects with the clinical diagnosis of IPD were investigated. Written informed consent was obtained from all patients prior to enrolment. The study had been approved by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf, study-no. 2849) and was conducted in accordance with the Declaration of Helsinki.

At inclusion, all patients underwent a clinical interview, thorough neurological examination with additional assessment of the Unified Parkinson’s Disease Rating Scale part III (UPDRS-III)8 and the Mini-Mental State Examination (MMSE),9 dopamine-response test, and diagnostic MRI including a T1-weighted- (0.75 and 1.0 mm) sequence. Duration of disease (DOD) was determined with respect to the onset of motor symptoms as reported by the patients. The initial working diagnosis of either atypical parkinsonism or IPD was based on the anamnesis, the clinical findings at the first neurological examination, and the results of the dopamine-response test. Follow-up clinical interviews, neurological re-examinations, and MRI follow-ups were scheduled every six months starting with inclusion in the study. Of the 91 patients with an atypical Parkinson syndrome initially recruited, 33 developed symptoms typical of CBS according to the criteria of Boeve et al,10 making this diagnosis the most likely one. Sixteen of them could not be enrolled in the final data analysis because of incomplete data or uncertain diagnosis. The remaining 17 subjects were group-matched for DOD with 17 patients with diagnosis of IPD according to the criteria of the United Kingdom Parkinson’s Disease Society Brain Bank.11,12

DOD at inclusion in the study differed between patients, ranging in both groups from 9 to 36 months. To achieve a better data comparability, all follow-ups were expressed in terms of DOD. For data analyses, we considered follow-ups “DOD=19-24 months” (DOD19-24) and “DOD=31-36 months” (DOD31-36), respectively corresponding to a DOD of about 2 and 3 years. Table 1 (CBS) and 2 (IPD) give an overview about available MRIs with respect to DOD.

In the first set of analyses, all patients were included (DODtotal=DOD19-24+DOD31-36; nCBS=17; nIPD=17) to look for disease-specific atrophy patterns in both GM and WM. In a second step, we then investigated whether comparable patterns of GM and WM difference between CBS and IPD were already present at the first follow-up (DOD19-24), potentially contributing to an early differential diagnosis 2 years after clinical onset (nCBS=11; nIPD=12).

*Brain Imaging.*

Brain imaging was performed using a 3-Tesla MR-tomograph (Magnetom Trio Tim System, Siemens Medical Solutions; Erlangen, Germany) with a standard CP head coil. Pulse sequences were as follows: sagittal 3D gradient echo sequence (repetition time TR 2300 ms, echo time TE 2.98 ms, 1 mm slice thickness, with one signal acquired), field of view (FOV): 256 mm and 256x256 matrix. All scans (inclusive follow-ups) were acquired by using the same scanner.

*Statistics.*

To investigate changes in brain morphology independently of the side of primary onset of motor symptoms, the data of patients with left-sided onset of motor symptoms were flipped (right-left flipping). This laterality correction takes into account that in both diseases changes in local brain morphology are more pronounced in one hemisphere and associated with the side of primary clinical manifestation (in the contralateral body side). We hypothesized that differences in GM and WM volume between groups might be more apparent when looking at laterality adjusted images. Of note, after flipping these should not more be referred to in terms of “right” and “left”, but need to be interpreted in terms of “ipsi-“ and “contralateral” to the body side of primary disease manifestation.

Pre-processing of T1-weighted images was performed using the Computational Anatomy Toolbox (CAT12, version 1904)13 for SPM12 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, University College, London, UK) running under Matlab R2021b. The preprocessing steps involved spatial normalization to the same stereotactic space (using the DARTEL algorithm implemented in SPM12), segmentation, and spatial smoothing (Gaussian kernel of 8 mm full-width at half maximum for GM images and 12 mm for WM images).

Voxel-wise brain analyses comparing CBS and IPD were performed separately using the normalized and smoothed GM and WM images. Modulated images were used for statistical analyses; correspondingly, GM and WM values are referred to as regional GM and WM volume.14 To avoid possible edge effects around the border between GM and WM and to include only relatively homogenous voxel, we excluded all voxels with an absolute intensity value of <0.1 (of a maximum value of 1).15,16 Due to the small sample size, non-parametric statistical tests were applied, as these are both robust to outliers and do not assume a normality of the data. Voxel-wise statistics were performed in the framework of the general linear model (GLM) implemented in the SPM12 toolbox SnPM13 (Statistical nonparametric Mapping, Department of Statistics and Warwick Manufacturing Group, University of Warwick, UK). Non-parametric statistical significance was tested with 10,000 permutations. The results from the GLM (with age, sex, and total intracranial volume as a nuisance variables) were corrected for multiple comparisons at the cluster level (family-wise error, FWE) based on an initial significance level of p<0.001.

Analyses (1-2) were performed separately for 2 datasets (A-B). In the first analysis, data were used including all patients available (DODtotal). In the second analysis, only the data at DOD19-24 were used. For both datasets, the following analyses were performed:

1. Comparison of GM maps to identify regions with differences in GM volume between CBS and IPD. As outlined above, this set comprised 2 analyses: A1=DODtotal, GM; B1= DOD19-24, GM.
2. Comparison of WM maps to identify regions with differences in WM volume between CBS and IPD. As outlined above, this set comprised 2 analyses: A2=DODtotal, WM; B2= DOD19-24, WM.

In addition, we extracted mean volume scores from the clusters identified and performed correlation analyses between volume scores and clinical scores (UPDRS-III and MMSE) to identify a potential relevance for the behavioral level.

**Results**

*Demographic data*

Concerning the demographic data, onset of motor symptoms occurred in CBS at a more advanced age than in IPD (meanCBS=65.9, SDCBS=7.3, meanIPD=52.0, SDIPD=11.3 years; pU-Test<0.001). The male/female ratio was notably different in CBS (2/15) compared to IPD (13/4, chi<0.001). With regard to the clinical scores, the CBS cohort showed a more severe motor impairment (UPDRS-IIICBS: mean=25.5, SD=10; UPDRS-IIIIPD: mean=12.0, SD=8.8; pU-Test=0.001), but no statistical differences in cognitive impairment (MMSECBS: mean=27.5, SD=3.1; MMSEIPD: mean=29.4, SD=1.3; pU-Test=0.053). No differences in the onset of motor symptoms regarding body sides were found between CBS and IPD (left/right ratio in CBS=9/8 and in IPD=12/5, chi=0.29). CBS patients showed reduced brain volume as compared to IPD patients in GM (meanCBS=565, SDCBS=47.5, meanIPD=631, SDIPD=54.1; pU-Test=0.001) and WM (meanCBS=462, SDCBS=47.4, meanIPD=542, SDIPD=66.5; pU-Test=0.003). For further demographic and clinical details, see Tables 1 (CBS) and 2 (IPD).

*Statistics*

*Analysis A: DODtotal*

As compared to IPD, patients suffering from CBS showed reduced volume in fronto-parietal WM contralateral (10,230 voxels, pFWE=0.003) and ipsilateral (3,871 voxels, pFWE=0.015) to the clinical onset side (A1; see Figure 1). In addition, contralateral parietal GM volume was reduced in CBS compared to IPD patients (690 voxels, puncorrected=0.012), surviving the first step criteria for correction of multiple comparisons (A2). However, this cluster did not survive FWE correction for multiple comparison (pFWE=0.062), which is considered to be a conservative threshold. The reduction in contralateral brain volume correlated across GM and WM (r=0.771; p<0.001). Furthermore, UPDRS-III scores were correlated with contralateral (r=-0.553, pSpearman=0.001) and ipsilateral (r=-0.548, pSpearman=0.001) WM volume scores, as well as with contralateral GM volume scores (r=-0.439, p=0.013). In addition, clinical MMSE scores correlated with WM volume scores on the contralateral (r=0.461, pSpearman=0.007) and ipsilateral (r=0.403, pSpearman=0.02) side of motor symptoms onset, but not with GM volume scores (p=0.099). For further information, see Table 3.

*Analysis B: DOD19-24*

At DOD19-24, patients suffering from CBS presented, as compared to the IPD group, reduced volume in fronto-parietal WM contralateral (6,953 voxels, pFWE=0.003) as well as ipsilateral (2,641 voxels, pFWE=0.015) to the onset side of motor symptoms (B1; see Figure 2). As compared to IPD, CBS patients showed reduced parietal GM volume contralateral to the side of motor symptoms onset (601 voxels, puncorrected=0.011), which did not survived correction for multiple comparisons (pFWE=0.068; B2). The contralateral volume reduction was correlated across GM and WM (r=0.817; p<0.001). In addition, UPDRS-III scores were correlated with contralateral (r=-0.594, pSpearman=0.004) and ipsilateral (r=-0.611, pSpearman=0.003) WM volume scores, as well as with contralateral GM volume scores (r=-0.441, pSpearman=0.040). Furthermore, clinical MMSE scores correlated with contralateral (r=0.511, pSpearman=0.013) and ipsilateral (r=0.450, pSpearman=0.031) WM volume scores, but not with GM volume scores (pSpearman=0.112). For further information, see Table 3.

**Discussion**

In the current study, we sought to identify brain imaging markers (in terms of biomarkers) able to distinguish CBS from IPD in a small sample of patients at an early stage of disease, when clinical symptoms might still be ambiguous. In summary, our data showed evidence for a WM atrophy in the bilateral fronto-parietal lobe of CBS vs. IPD patients.

Regional brain volume differences between CBS and IPD were more pronounced in the contralateral hemisphere. The laterality observed in our sample nicely mirrors that apraxia, a typical symptom of CBS present in 16 of 17 patients of our cohort, has been put in relationship with left-sided atrophy in CBS17,18 and left-sided ischemic lesions.19 Histopathological studies, however, have not explicitly described such laterality.20-24

GM analysis revealed an atrophy of the contralateral upper somatosensory cortex in CBS as compared to IPS. Of note, the cluster did not survive the conservative correction for multiple comparisons (DODtotal: p=0.062; DOD19-24: p=0.068), however since this finding matches well with our apriori hypotheses, we decided to report and briefly discuss it. A plausible phenotypical correlate of this finding may be represented by cortical sensory loss, a deficit often described in CBS and clinically manifesting with astereognosis. Very little is known about the origin of cortical astereognosis. An involvement of the left somatosensory cortex has been suggested by a study investigating stroke patients,17 and this would nicely fit with the current findings.

Investigation of the WM is usually performed by means of DTI and tractography, allowing the assessment of regional diffusion properties and orientation of fiber tracts. However, since the aim of the present study was not a fine-grained WM characterization but a rather crude estimation of cerebral volumetric differences between two diseases using a tool easily available in daily clinical praxis, we applied VBM. The most evident WM atrophy pattern found in the CBS cohort was located in the upper part of the frontal and the parietal lobe, in an oblong segment extending from the frontal lobe to the anterior part of the occipital lobe, “touching” the anterior parietal cortex. We identified this region as the dorsal component of the superior longitudinal fasciculus (SLF I). This fiber tract has been recently18 described as running within the cingulate or paracingulate gyrus, and connecting the anterior cingulate cortex, the medial aspect of the superior frontal gyrus, the pre-supplementary motor area (pre-SMA), the supplementary motor area (SMA) proper, the paracentral lobule, and the precuneus.19 The dorsal SLF I is supposed to play an important role in motor planning, since ideation of movements probably origins in the limbic system and is firstly relayed to the SMA and the premotor cortex before further integration via basal ganglia and cerebellum initiates and modulates the final activation of motor cortex. The affection of the dorsal SLF I supports the hypothesis that apraxia in CBS is probably due to an impaired connectivity in the neural pathway between “movement planning” and “movement execution”. Interestingly, pathological and imaging studies addressing apraxia in CBS outline rather GM than WM alterations, suggesting involvement of the parietal, premotor, and primary motor cortices (pathological studies)20-24 and atrophy of the inferior parietal cortex, left supplementary motor area, premotor cortex, and caudate nucleus (imaging studies).18,20,21

*Limitations*

The present study has some limitations that need to be pointed out.

First of all, it lacks a healthy control group, and the differences identified are specific to the comparison between CBS and IPD patients. Taking only the results of the brain imaging analysis into account, we would not be able to exactly state which group displays the pathological features, since both interpretations are conceivable: either the IPD group shows an increase in regional GM and WM volumes or the CBS group shows a decrease. IPD has been extensively studied using structural brain imaging, showing at early stages of disease (mean DOD=2 years) no GM or WM differences compared to healthy controls.22 This, as well as clinical findings such as apraxia in CBS, make the latter interpretation (i.e. WM decrease in CBS patients) much more likely. The current study is clinically driven and has a rather pragmatic approach to differentiate (or support differentiation of) patients with two different diseases at an early stage, when clinical symptoms might still be ambiguous and/or look very much alike. The comparison to a healthy group is surely interesting from a neurobiological perspective, but it is of less relevance to the clinician in a tertiary movement disorder center, dealing with pre-diagnosed patients in need of a differential diagnosis.

Second, the results presented in this work apply exclusively to the patients’ groups considered. For a general statement about brain volume differences in CBS vs. IPD, our cohorts were too small. Nevertheless, our results are robust and invite to repeat the analysis using greater populations.

Furthermore, groups were not well age matched, with the CBS cohort being 14 years older in average. Similar age differences between CBS and IPD have also been described in the general population,23,24 with CBS patients tending to be older than IPD patients are. As such, we consider our study sample to be clinically representative, with young age at first motor symptom manifestation shifting the likelihood towards the diagnosis of IPD.

A further limitation is represented by the use of the same scanner for all follow-ups in both the cohorts. This enhances data comparability, but does not allow the assumption that the same accuracy can be achieved across scanner sites and MR machines.

The major strength of the current study is its simplicity with respect to brain imaging and statistical analyses, and, from an economic point of view, specifically with respect to costs and availability of the imaging procedure.

When plotting the correlation between GM and WM in the clusters identified by the group comparison (Figure 1 and 2), it appeared that both patient groups could well be separated based on the available imaging data. Against this background it would have been tempting to perform multivariate pattern analyses. However, considering the small sample size, implying a lack of statistical validity and generalizability, we abstained from doing so. In larger cohorts, this approach should be further investigate, since it has the potential to provide valuable information to the clinician encouraging one of the two diagnoses. If our results will be confirmed by studies with greater populations, clinicians being in doubt or even suspecting CBS could, in future, look specifically at left sided SLF I WM to encourage or discourage the one or the other diagnosis.

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**References**

[1] Irwin DJ. Tauopathies as clinicopathological entities. Parkinsonism Relat Disord 2016; Suppl 1:29-33.

[2] Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496-503.

[3] Höglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: The Movement Disorder Society criteria. Movement Disorders 2017.

[4] Svenningsson P. Corticobasal degeneration: advances in clinicopathology and biomarkers. Curr Opin Neurol 2019;32:597-603.

[5] Hall S, Öhrfelt A, Constantinescu R, et al. Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders. Arch Neurol 2012;69:1445-52.

[6] Holmberg B, Johnels B, Ingvarsson P, Eriksson B, Rosengren L. CSF-neurofilament and levodopa tests combined with discriminant analysis may contribute to the differential diagnosis of Parkinsonian syndromes. Parkinsonism Relat Disord 2001;8:23-31.

[7] Constantinescu R, Rosengren L, Johnels B, Zetterberg H, Holmberg B. Consecutive analyses of cerebrospinal fluid axonal and glial markers in Parkinson's disease and atypical Parkinsonian disorders. Parkinsonism Relat Disord 2010;16:142-5.

[8] Movement Disorder Society task force on rating scales for Parkinson’s disease. The Unified Parkinson’s Disease Rating Scale (UPDRS): status and recommendations. Mov Disord 2003;18:738–50.

[9] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.

[10] Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 2003;Suppl 5:15-9.

[11] Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992; 42:1142-6. Erratum in: Neurology 1992;42:1436.

[12] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.

[13] Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. Neuroimage 2013;65:336-48.

[14] Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21-36.

[15] Gerber P, Schlaffke L, Heba S, Greenlee MW, Schultz T, Schmidt-Wilcke T. Juggling revisited - a voxel-based morphometry study with expert jugglers. Neuroimage 2014;95:320-5.

[16] Luders E, Kurth F, Toga AW, Narr KL, Gaser C. Meditation effects within the hippocampal complex revealed by voxel-based morphometry and cytoarchitectonic probabilistic mapping. Front Psychol 2013;4:398.

[17] Moll J, de Oliveira-Souza R. Hemispheric dominance for stereognosis in a patient with an Infarct of the left postcentral sensory hand area. Cogn Behav Neurol 2017;30:102-15.

[18] Kamali A, Flanders AE, Brody J, Hunter JV, Hasan KM. Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. Brain Struct Funct 2014;219:269-81.

[19] Komaitis S, Skandalakis GP, Kalyvas AV, et al. Dorsal component of the superior longitudinal fasciculus revisited: novel insights from a focused fiber dissection study. J Neurosurg 2019;132:1265-78.

[20] Rohrer JD, Rossor MN, Warren JD. Apraxia in progressive nonfluent aphasia. J Neurol 2010;257:569-74.

[21] Zadikoff C, Lang AE. Apraxia in movement disorders. Brain 2005;128:1480-97.

[22] Agosta F, Canu E, Stojković T, et al. The topography of brain damage at different stages of Parkinson's disease. Hum Brain Mapp 2013;34:2798-807.

[23] Wenning GK, Litvan I, Jankovic J, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. J Neurol Neurosurg Psychiatry 1998;64:184-9.

[24] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-42.

[25] Goldenberg G (1995) Imitating gestures and manipulating a mannikin-the representation of the human body in ideomotor apraxia. Neuropsychologia 33(1): 63-72

[26] Goldenberg G (1996) Defective imitation of gestures in patients with damage in the left or right hemispheres. Journal of Neurology, Neurosurgery & Psychiatry 61(2): 176-80

**Table 1: clinical data of the corticobasal syndrome cohort**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient | DOD19-24 | DOD31-36 | Gender | Age | Side of onset | Dystonia | Myoclonus | Apraxia† | Alien limb | Stereoagnosia‡ | MMSE | UPDRS-III |
| 1 | x |  | f | 72 | right | + | + | + | + | + | 30/30 | 29 |
| 2 | x |  | f | 66 | right | + | + | + | - | + | 30/30 | 42 |
| 3 | x |  | f | 66 | left | + | + | + | + | + | 22/30 | 30 |
| 4 | x |  | f | 73 | left | - | - | + | + | + | 28/30 | 36 |
| 5 | x |  | f | 68 | left | + | + | + | - | + | 26/30 | - |
| 6 | x |  | f | 56 | left | - | + | + | - | + | 27/30 | 17 |
| 7 | x |  | m | 66 | right | + | + | + | + | + | 30/30 | 4 |
| 8 | x |  | f | 66 | right | + | - | + | - | + | 30/30 | 10 |
| 9 | x |  | m | 69 | left | - | + | + | - | + | 26/30 | 21 |
| 10 | x |  | f | 57 | left | + | + | + | + | - | 22/30 | 22 |
| 11 | x |  | f | 74 | left | - | - | + | + | - | 29/30 | 32 |
| 12 |  | x | f | 59 | right | + | + | - | - | - | 30/30 | 21 |
| 13 |  | x | f | 64 | right | - | + | + | - | + | 29/30 | 21 |
| 14 |  | x | f | 76 | right | - | + | + | - | + | 29/30 | 12 |
| 15 |  | x | f | 62 | right | + | + | + | + | + | 30/30 | 19 |
| 17 |  | x | f | 49 | left | + | + | + | + | + | 28/30 | 34 |
| 18 |  | x | f | 67 | left | + | - | + | - | + | - | 42 |
| Mean±SD |  |  | m/f=3/15 | 65.9±7.3 | l/r=10/8 |  |  |  |  | 27.5±3.1 | 25.4±11.3 |  |

† According to Goldenberg’s hand- and finger-position tests.25,26 x=available; m=male; f=female; SD=standard deviation; DOD19-24=Duration of Disease between 19 and 24 month; DOD31-36= Duration of Disease between 31 and 36 months.‡ According to a clinical test in which a coin, a key, and a paper clip were successively placed into the hands of the patient who was then requested to recognize the three objects. + indicates the presence of a symptom, - indicates its absence. MMSE=Mini-Mental State Examination. UPDRS-III=Unified Parkinson’s Disease Rating Scale, Part III.

**Table 2: Clinical data of the idiopathic Parkinson’s disease cohort.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Patient | DOD19-24 | DOD31-36 | Gender | Age | Side of onset | MMSE | UPDRS-III |
| 1 | x |  | f | 70 | left | 30/30 | 5 |
| 2 | x |  | f | 61 | left | 30/30 | 24 |
| 3 | x |  | m | 72 | left | 30/30 | 2 |
| 4 | x |  | m | 52 | left | 30/30 | 9 |
| 5 | x |  | m | 53 | left | 29/30 | 10 |
| 6 | x |  | m | 41 | right | 28/30 | 12 |
| 7 | x |  | m | 34 | right | 29/30 | 13 |
| 8 | x |  | m | 61 | right | 30/30 | 13 |
| 9 | x |  | m | 41 | left | 30/30 | 7 |
| 10 | x |  | m | 58 | left | 29/30 | 9 |
| 11 | x |  | m | 38 | left | 30/30 | 7 |
| 12 | x |  | f | 40 | right | 30/30 | 5 |
| 13 |  | x | f | 55 | right | 25/30 | 18 |
| 14 |  | x | m | 43 | left | 30/30 | 6 |
| 15 |  | x | m | 61 | left | 30/30 | 19 |
| 16 |  | x | m | 41 | left | 30/30 | 38 |
| 17 |  | x | m | 63 | left | 30/30 | 7 |
| Mean ± SD |  |  |  | 52,0±11.3 | l/r=12/5 | 29.4±1.3 | 12.0±8.8 |

MMSE=Mini-Mental State Examination; UPDRS-III=Unified Parkinson’s Disease Rating Scale, Part III; x=available; m=male; f=female; SD=standard deviation; DOD19-24=Duration of Disease between 19 and 24 month; DOD31-36= Duration of Disease between 31 and 36 month.

**Table 3: General Linear Model for Analyses A and B**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Analysis | |  | General linear model | | | | | |  | UPDRS-III | |  | MMSE | |
|  | Size | pFWE | x | y | z | t-value |  | r | p |  | r | p-value |
| A: DODtotal | 1: GM |  | 690 | 0.062 | -20 | -34 | 45 | 5.16 |  | -0.429 | 0.013 |  | 0.292 | 0.099 |
|  |  |  |  |  | -27 | -38 | 48 | 4.87 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 2:WM |  | 10,230 | 0.002 | -33 | -42 | 39 | 5.78 |  | -0.559 | 0.001 |  | 0.461 | 0.007 |
|  |  |  |  |  | -32 | -16 | 32 | 4.62 |  |  |  |  |  |  |
|  |  |  |  |  | -16 | 12 | 33 | 4.58 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | 3871 | 0.009 | 28 | -52 | 51 | 4.43 |  | -0.548 | 0.001 |  | 0.403 | 0.020 |
|  |  |  |  |  | 20 | 14 | 40 | 4.12 |  |  |  |  |  |  |
|  |  |  |  |  | 15 | -2 | 40 | 3.89 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| B: DOD19-24 | 1: GM |  | 601 | 0.068 | -26 | -39 | 48 | 5.03 |  | -0.441 | 0.040 |  | 0.340 | 0.112 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 2: WM |  | 6,953 | 0.003 | -28 | -14 | 33 | 5.30 |  | -0.594 | 0.004 |  | 0.511 | 0.013 |
|  |  |  |  |  | -16 | 0 | 42 | 4.68 |  |  |  |  |  |  |
|  |  |  |  |  | -32 | -39 | 36 | 4.59 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | 2,641 | 0.015 | 15 | -12 | 32 | 4.88 |  | -0.611 | 0.003 |  | 0.450 | 0.031 |
|  |  |  |  |  | 14 | 3 | 36 | 4.38 |  |  |  |  |  |  |
|  |  |  |  |  | 36 | -10 | 26 | 4.00 |  |  |  |  |  |  |

MNI-coordinates (x, y, z) of peak voxels with corresponding t-values for significant clusters (p<0.001; Family-wise-error-corrected on cluster-level) identified in analyses A (DODtotal) and B (DOD19-24). Negative x-values describe clusters contralateral to the onset side of motor symptoms. In addition, the correlations of the cluster volume scores with clinical UPDRS-III and MMSE scores are given. MMSE=Mini-Mental State Examination. UPDRS-III=Unified



**Figure 1: General Linear Model of Analysis A (DODtotal)**

Statistical non-parametric map of gray matter (red, A1) and white matter (blue, A2) volume changes in corticobasal syndrome patients as compared to those in idiopathic Parkinson’s disease patients at duration of disease between 19 and 36 month (DODtotal). Sagittal slices are shown of the hemisphere contralateral (x-35, x-25, and x-15) and ipsilateral (x28, x20, and x12) to the onset side. Volume scores were correlated across the gray matter (GM) and white matter (WM) clusters (r=0.771; p<0.001) contralateral to the onset side. For further details, see Table 3.



**Figure 2: General Linear Model of Analysis B (DOD19-24)**

Statistical non-parametric map of gray matter (red, B1) and white matter (blue, B2) volume changes in corticobasal syndrome patients as compared to those in idiopathic Parkinson’s disease patients at duration of disease between 19 and 24 month (DOD19-24). Sagittal slices are shown of the hemisphere contralateral (x-28, x-20, and x-12) and ipsilateral (x22, x17, and x12) to the onset side. Volume scores were correlated across the gray matter (GM) and white matter (WM) clusters (r=0.817; p<0.001) contralateral to the onset side. For further details, see Table 3.