ORIGINAL CONTRIBUTION

White Matter Changes in Corticobasal Degeneration Syndrome and Correlation With Limb Apraxia

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Background: Data on white matter changes in corticobasal degeneration syndrome (CBDS) are not yet available, whereas cortical gray matter loss is a feature of this condition. The structural abnormalities related to a key feature of CBDS (limb apraxia) are unknown.

Objectives: To measure selective structural changes in early CBDS using diffusion tensor imaging and voxel-based morphometry and to evaluate the structural correlates of limb apraxia.

Design: Patient and control group comparison.

Setting: Referral center for dementia and movement disorders.

Participants: Twenty patients with CBDS and 21 matched control subjects.

Interventions: Clinical and standardized neuropsychological evaluations, including assessment of limb apraxia.

Main Outcome Measures: Gray and white matter changes in early CBDS.

Results: Diffusion tensor imaging revealed decreases in fractional anisotropy in the long frontoparietal connecting tracts, the intraparietal associative fibers, and the corpus callosum. Fractional anisotropy was also reduced in the sensorimotor projections of the cortical hand areas. Voxel-based morphometry showed a prevalent gray matter reduction in the left hemisphere (in the inferior frontal and premotor cortices, parietal operculum, superotemporal gyrus, and hippocampus). The pulvinar, bilaterally, and the right cerebellar cortex also showed atrophy. Limb apraxia correlated with parietal atrophy and with fractional anisotropy reductions in the parietofrontal associative fibers ($P < .01$). The limb-kinetic component of apraxia correlated with reduction of hand sensorimotor connecting fibers.

Conclusions: The present integrative approach to in vivo structural anatomy combines hodologic imaging, describing patterns of white matter connections between cortical areas, with neuropsychological data. This provides new evidence of gray matter and fiber tract abnormalities in early-phase disease and contributes to clarifying the neural basis of apraxia in CBDS.

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CORTICOBASAL DEGENERATION syndrome (CBDS) is characterized by higher cortical dysfunctions associated with progressive asymmetrical akinetic-rigid syndrome and limb dystonia or focal myoclonus. One of the most typical clinical features of CBDS is limb apraxia, which is present in up to 70% of patients.[1] Neuroimaging studies[2-4] help highlight the structural and functional abnormalities during the disease course. In the past few years, diffusion tensor imaging (DTI) has provided more subtle information about white matter (WM) tissue composition and has allowed the demonstration of fiber tracts in vivo.[5-7] To our knowledge, no DTI study in patients with CBDS is available.

In the present study, we applied 2 unbiased techniques for structural neuroimaging (DTI and voxel-based morphometry [VBM]) to patients with early-phase CBDS in an attempt to describe the initial gray matter (GM) and WM changes of the disease. Furthermore, to shed light on the structural abnormalities that lead to limb apraxia in CBDS, we specifically explored the neuroanatomical correlates.

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METHODS

PARTICIPANTS

Twenty patients with CBDS (13 men and 7 women; mean [SD] age, 62.7 [8.0] years), recruited from the Centre for Neurodegenerative Diseases and the Centre for Movement Disorders, University of Brescia, enrolled in the study. All the patients underwent a somatic and neurologic examination, routine laboratory examination, and brain structural magnetic resonance imaging (MRI). The diagnostic criteria for CBDS were used for patient inclusion.[1]

Twenty-one healthy individuals (8 men and 13 women; mean [SD] age, 65.6 [4.1] years) were recruited among patients' spouses and relatives to serve as control subjects. They were interviewed, assessed for neurologic or cognitive dysfunction, examined for diseases that were exclusion criteria for the patient group, and underwent structural brain MRI.

All the participants were right-handed and were made fully aware of the aims of the research. Written informed consent was obtained from all the participants. This study was conducted in accordance with the Brescia University Hospital, Brescia, ethics committee regulations and conformed to the Declaration of Helsinki. Anamnestic and clinical data were compared between patients with CBDS and controls using the unpaired *t* test or the χ^2 test. The significance level was set at $P<.05$. Analyses were conducted using a commercially available statistical software program (SPSS Inc, Chicago, Illinois).

EXCLUSION AND INCLUSION CRITERIA

Stringent exclusion criteria were applied, as follows: (1) cerebrovascular disorders, hydrocephalus, and intracranial mass as documented by MRI; (2) a history of traumatic brain injury or another neurologic disease; and (3) significant medical problems. The inclusion criteria were as follows: (1) fulfillment of the criteria for probable CBDS and follow-up for at least 2 years after enrolling in the study, with the diagnosis of CBDS confirmed at the follow-up examination; (2) mild functional decline (basic activities of daily living [ADLs] score <1); and (3) onset of the first symptoms within 4 years.

CLINICAL AND NEUROPSYCHOLOGICAL ASSESSMENT

Motor impairment was evaluated by means of the motor section of the Unified Parkinson Disease Rating Scale (UPDRS-III). Instrumental and basic ADLs were assessed as well. Behavioral and psychiatric disturbances were evaluated by means of the Neuropsychiatry Inventory and the Frontal Behavioral Inventory. Assessment of global cognitive function was performed according to a standardized battery (**Table 1**).

Apraxia was assessed using the test of De Renzi et al.[8] We chose this ideomotor apraxia test because (1) it has been normalized on the Italian population; (2) it examines only intransitive gestures, which have been proposed to be best suited to tap ideomotor apraxia without ideational apraxia involvement; and (3) it is performed only on imitation, which makes it possible to test nonmeaningful and meaningful actions. The test of De Renzi et al examines equal proportions of movements executed with the whole arm and hand (complex gesture) and with the hand and fingers (simple gesture), the latter allowing limb-kinetic apraxia to be evaluated. As specified in the original normative data, scores of less than 53 (of a possible 72) indicate apraxia, scores greater than 62 are normal, and scores in between are borderline.

In patients with CBDS, both arms were examined separately because motor impairment is asymmetrical, and either the left or the right arm may be involved at the beginning of the disease. Furthermore, the development of clumsiness, a stiff hand, the inability to use utensils or appliances, and the inability to use both hands as before disease onset were evaluated by means of an interview with the primary caregiver in daily contact with the patient (Frontal Behavioral Inventory, apraxia or alien hand, on a scale from 0 [none] to 3 [severe]).

MRI DATA ACQUISITION

The MRI was performed using a 1.5-T system (Symphony; Siemens, Erlangen, Germany). For VBM analysis, 3-dimensional magnetization–prepared rapid gradient-echo T1-weighted images were acquired using the following settings: echo time, 3.93 milliseconds; repetition time, 2010 milliseconds; flip angle, 15°; and field of view, 250 mm. This yielded 176 contiguous 1-mm-thick sections. The DTI was performed by means of echo-planar imaging at 1.5 T with a standard head coil for signal reception. The DTI axial sections were obtained using the following settings: matrix, 128×128; echo time, 122 milliseconds; repetition time, 6600 milliseconds; flip angle, 15°; field of view, 220 mm; no gap (5-mm thickness); and voxel size, $1.7\times1.7\times5.0$ mm. Three acquisitions were averaged. Diffusion weighting was performed along 6 independent directions with a b value of 1000 s/mm^2. A T2-weighted image with no diffusion weighting was also obtained (b=0 s/mm^2).

Table 1. Neuropsychological Assessment in 20 Patients With CBDS

Test	Test Scores: Patients With CBDS, Mean (SD)	Test Scores: Cutoff Value[a]
Short story	9.3 (4.4)	>7.5
Raven progressive colored matrices	23.4 (7.9)	>17.5
Rey figure copy	24.0 (10.3)[b]	>27
Rey figure recall	10.3 (7.0)	>9
Phonemic fluency	26.5 (12.7)	>17.35
Semantic fluency	10.3 (3.7)	>7.25
Token test	29.7 (7.9)	>26
Digit span	5.5 (1.7)	>5
Trail Making Test A, s	163.0 (182.2)[b]	<70
Trail Making Test B, s	271.8 (177.1)[b]	<170

Abbreviation: CBDS, corticobasal degeneration syndrome.
[a] Cutoff values are in accordance with Italian normative data.
[b] Pathologic scores.

MRI ANALYSIS

Preprocessing and statistical analyses were implemented using a statistical parametric mapping software package (SPM2; Wellcome Department of Imaging Neuroscience, London, England [http://www.fil.ion.ucl.ac.uk/spm]) running on MATLAB 6.5.1 (MathWorks, Natick, Massachusetts).[9]

Optimized VBM analysis was performed according to the method of Good and colleagues,[10] as previously published.[6,7] Optimally normalized magnetization-prepared rapid gradient-echo images were segmented into GM, WM, and cerebrospinal fluid segments. Modulated GM and WM images were smoothed with a 10-mm full-width half maximum kernel. To avoid potential bias from the normalization process, anatomical and gray and white matter templates—referred to a stereotactic space (Talairach)—were created, including all T1-weighted images of patients and controls. The normalized, segmented, and smoothed data were statistically tested using a general linear model based on gaussian field theory using analysis of covariance, with the total amount of GM and WM treated as a nuisance covariate to detect local areas of relative accelerated loss of GM and WM volume. The statistical threshold was set at $P<.05$, false discovery rate correction for multiple comparisons, with a minimum cluster size of 20 voxels.

For DTI, the fractional anisotropy (FA) (an index of directional selectivity of water diffusion) was determined for each voxel by using computer software (BrainVISA 1.6; SPSS Inc). A customized template was obtained by taking the average of all par-

Table 2. Locations of the Peaks of Regional Reduction in Gray Matter in Patients With CBDS Compared With Controls

Brain Region (Patients With CBDS vs Controls)	Peak Coordinates, mm[a]			*t* Statistic	*z* Value	Cluster Size
	x	y	z			
Left dorsolateral frontal cortex	−46	23	8	4.30	3.85	
	−50	17	36	4.01	3.63	
Left premotor cortex	−45	3	35	5.05	4.38	
Left parietal operculum	−52	−9	12	4.49	3.99	19 347
Left superotemporal gyrus	−57	−18	11	4.83	4.23	
Left insula	−48	−11	3	4.39	3.91	
Left uncus	−34	6	−20	4.13	3.72	
Left superoparietal cortex	−23	−47	60	3.47	3.20	1021
Right dorsolateral frontal cortex	46	30	9	4.41	3.93	
Right superotemporal gyrus	51	10	−4	5.00	4.34	2415
Right insula	46	10	−4	5.00	4.34	
Right/left thalamus–pulvinar	8	−31	2	5.78	4.85	
	0	−10	18	3.51	3.24	2893
Right cerebellar cortex	18	−83	−30	4.22	3.79	3370

Abbreviation: See Table 1.
[a] The x, y, and z values localize the areas of gray matter reduction according to the Talairach stereotactic coordinates.

ticipants' T2-weighted images (b=0 s/mm^2), previously normalized to the echo-planar imaging template in the Talairach standard stereotactic space. We calculated the normalization variables that best fit each T2-weighted image by using a customized echo-planar imaging template, and the variables were then applied to FA maps and to T2-weighted images. The T2-weighted normalized images were then segmented into GM, WM, and cerebrospinal fluid. A WM binary mask was created from the WM segments obtained in the previous step and was applied to each participant's normalized FA map to include only the voxels belonging to the WM regions in the statistical analysis. The masked normalized FA maps were smoothed with a 10-mm full-width half maximum kernel. The smoothed WM segments were then statistically tested by means of a general linear model based on gaussian field theory. The FA differences between groups were assessed using a *t* test statistical design (statistical threshold of $P<.05$, false discovery rate correction for multiple comparisons, minimum cluster size of 20 voxels).

CORRELATION ANALYSES

We conducted a linear regression analysis of VBM and FA data using SPM2, entering the following subscores from the test of De Renzi et al[8]: (1) sum of both limb scores, (2) sum of the right and left simple gesture scores, and (3) sum of the right and left complex gesture scores, all as independent variables. The dependent variable was FA. Age was entered into the model as a nuisance variable. We reported findings meeting the threshold of $P<.001$ and also $P<.01$ (uncorrected for multiple comparisons) based on an a priori hypothesis.

RESULTS

PARTICIPANTS

The mean (SD) value of the UPDRS-III was 20.8 (10.4) and of the Mini-Mental State Examination was 25.0 (3.6). The mean (SD) instrumental ADLs (lost) value was 1.1 (2.0), and the basic ADLs (lost) value was 0.70 (0.50). The mean (SD) disease duration was 2.0 (1.4) years.

Patients with CBDS had visuospatial (Rey figure copy), psychomotor dexterity (Trail Making Test A), and executive function (Trail Making Test B) deficits (Table 1). A standardized examination of language functions showed mean scores within the reference range. Behavioral disturbances were present in some patients with CBDS, and the most common disorder was apathy, which was present in 25% (5 of 20) patients.

The affected limb at onset was on the right side in 55% (11 of 20) patients and on the left side in 45% (9 of 20) patients. At the MRI study, most patients, despite an asymmetrical onset, showed bilateral apraxia: only 3 patients presented with right unilateral apraxia. Mean (SD) test scores on the test of De Renzi et al[8] were 51.0 (23.8) for the right limb and 52.6 (21.9) for the left limb. The Frontal Behavioral Inventory item of praxis was referred to as pathologic (score ≥1) by the caregiver in 75% (15 of 20) patients.

VOXEL-BASED MORPHOMETRY

There was an asymmetrical pattern of cortical atrophy in CBDS, which was greater in the left hemisphere (cluster size in **Table 2**). In patients with CBDS compared with controls, significant clusters of reduced GM on VBM were found in the dorsolateral frontal cortex, premotor cortex, parietal operculum, parietal cortex, superotemporal gyrus, and hippocampal uncus. Regarding subcortical brain regions, there was reduced GM density in the pulvinar bilaterally. The right cerebellar cortex showed GM reductions (Table 2 and **Figure 1**). The WM comparison on VBM showed significant clusters of reduction in only the body and the splenium of the corpus callosum. The opposite comparison (greater atrophy in healthy controls compared with patients) in VBM for GM and WM did not reveal voxels above the threshold.

DTI ANALYSIS

The DTI analysis revealed significant and extensive FA changes in the dorsolateral parietofrontal associative fibers and the intraparietal associative fibers and in the sen-

sorimotor associative fibers in the hand cortical representations, all bilaterally. The body and the splenium of the corpus callosum showed a significant decrease in FA. The left fornix fibers and the right ventrolateral parietofrontal fibers showed significant FA reductions (**Table 3** and **Figure 2**).

VBM AND FA CORRELATIONS WITH APRAXIA

Using VBM, we found a positive correlation between total scores on the test of De Renzi et al[8] (sum of both limbs) and GM density in the parietal operculum bilaterally ($P<.001$).

Regarding FA, at a high statistical threshold ($P<.001$), no correlations emerged. Based on an a priori hypothesis of an involvement of frontoparietal connecting fibers, we lowered the threshold to $P<.01$ and found a positive correlation between total scores on the test of De Renzi et al[8] and FA only in the left dorsolateral parietofrontal associative fibers. We further explored the correlation with complex and simplex gesture subscores: for complex gesture subscores, a correlation with the left parietofrontal associative fibers and intraparietal associative fibers was found, whereas for simple gesture subscores, a significant correlation with local FA value of the fibers connecting the premotor and parietal areas bilaterally was found. The limb-kinetic component of apraxia showed a correlation with hand sensorimotor connecting fibers (**Figure 3**).

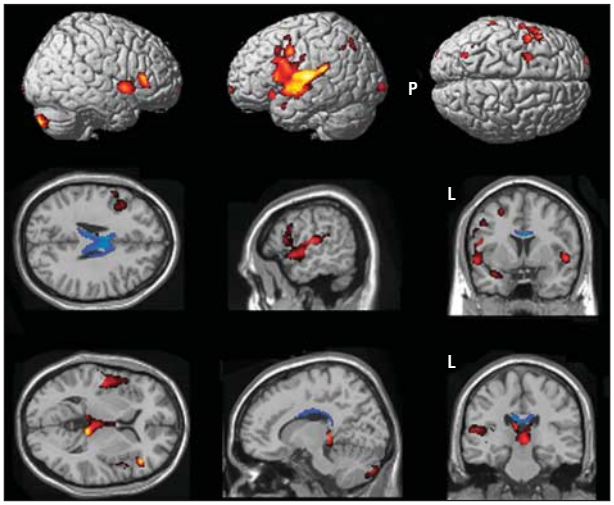

Figure 1. Regions of brain atrophy in patients with corticobasal degeneration syndrome (CBDS) relative to control subjects. Voxel-based morphometry–identified regions of decreased gray matter (red) and white matter (blue) volume relative to age-matched controls in patients with CBDS are displayed on a healthy adult brain template (row 1). The Talairach coordinates are as follows. For row 2, x=−53, y=0, and z=25; and for row 3, x=15, y=−26, and z=13. The threshold was set at $P<.001$. Table 2 provides the coordinates. L indicates left; P, posterior.

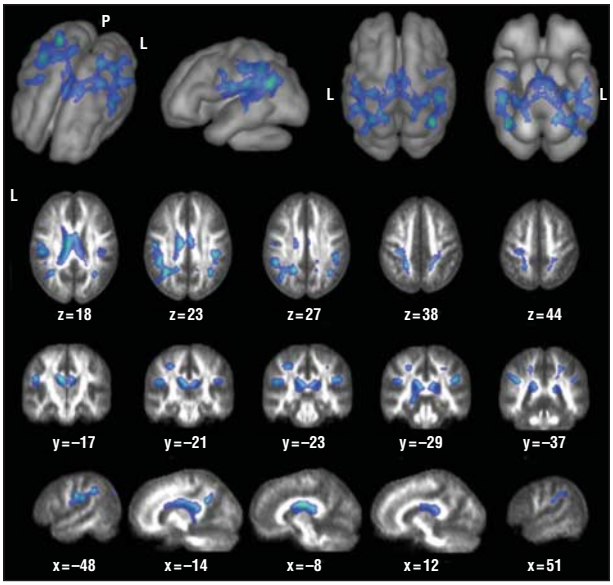

Figure 2. Regions of reduction in fractional anisotropy (FA) in patients with corticobasal degeneration syndrome relative to control subjects. Clusters of statistically significantly decreased FA relative to age-matched controls are displayed on a 3-dimensional rendering of a healthy white matter template (row 1) and on transaxial, coronal, and sagittal sections of a healthy FA template (rows 2, 3, and 4, respectively). The "DTI Analysis" subsection of the "Results" section provides details. The threshold was set at $P<.001$. Table 3 provides the coordinates. L indicates left; P, posterior.

Table 3. Locations of the Peaks of Regional Reduction in Fractional Anisotropy in Patients With CBDS Compared With Controls

Fasciculus (Patients With CBDS vs Controls)	Peak Coordinates, mm[a]			*t* Statistic	*z* Value
	x	y	z		
Dorsolateral parietofrontal associative fibers and intraparietal associative fibers					
Left	−30	−53	25	5.19	4.47
	−50	−14	21	5.35	4.43
Right	38	−57	27	6.47	5.26
Sensorimotor associative fibers (hand cortical area)					
Left	−20	−46	43	5.21	4.44
Right	18	−47	37	4.72	4.15
Corpus callosum					
Body	4	−4	19	4.65	4.10
Splenium	−8	−14	22	5.13	4.43
Left fornix	−18	−33	−3	5.00	4.35
Right ventrolateral parietofrontal fibers	46	5	−14	5.22	4.49

Abbreviation: See Table 1.
[a]The x, y, and z values localize the areas of fractional anisotropy reduction according to the Talairach stereotactic coordinates. Only peaks with the highest significance are reported.

DTI AND FIBER TRACKING IN INDIVIDUAL PARTICIPANTS

Selective reduction of WM bundles in the parietal corticocortical connections and in the posterior corpus callosum is illustrated in a single patient with CBDS (**Figure 4**). For this purpose, a control (a 60-year-old woman with a UPDRS-III score of 0 and a Mini-Mental State Examination score of 30 [of a possible 30]) and a patient with CBDS (a 64-year-old man with a Mini-Mental State Examination score of 19 [of a possible 30] and a UPDRS-III score of 37 [bilateral apraxia]) were chosen. Fiber tracking was obtained using the FACT algorithm implemented in the computer software (BrainVISA 1.6).

COMMENT

In the present study, we characterized CBDS by using the combination of 2 different techniques of structural brain imaging (VBM and DTI), in an attempt to shed light on the GM and WM abnormalities in the early stage of the disease and to explore the relationship of the structural changes and upper limb apraxia.

VBM RESULTS

In agreement with previous data,[3,4] we showed that CBDS is characterized by bilateral asymmetrical (left-sided prevalence) GM reductions in frontal, parietal, and temporal regions and in subcortical gray structures, such as the pulvinar, bilaterally, and in the right cerebellar cortex (Figure 1).

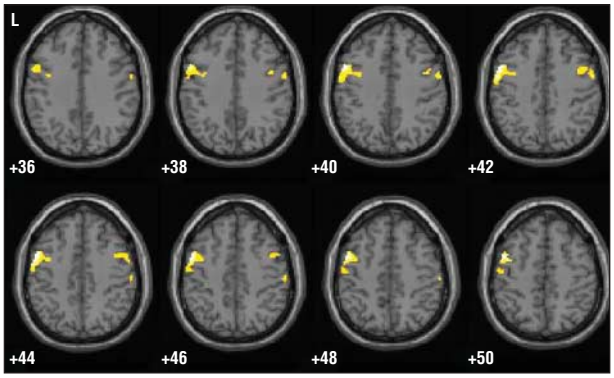

Figure 3. Correlation of the limb-kinetic component of apraxia with fractional anisotropy reduction of hand sensorimotor connecting fibers. Statistically significant clusters are displayed on a healthy adult brain template. The threshold was set at $P < .01$. L indicates left.

Investigating specifically the pathologic changes associated with praxic performance, we found a significant correlation between apraxia and GM atrophy at symmetrical loci in the parietal operculum. The VBM results suggest that in CBDS, the dysfunction could be considered at the level of decoding the inner representation of movements.[11] The hypothesis of an involvement of the parietal operculum in praxis was advanced in neuroimaging experiments of visually guided movements and mental transformation of the body in space[12] and also in neuropsychological studies of patients with cerebrovascular disease during elaboration and maintenance of the working representation of the gesture to perform.[13]

The frontal cortex is the other most prominent region of atrophy reported in the literature,[3] and the finding of selective atrophy in the left dorsolateral frontal and dorsal premotor cortices is likely to be related to complex deficits in voluntary movement. As for the subcortical structures, the atrophy in the pulvinar may further account for apraxia in patients with CBDS. In fact, several lines of evidence indicate that the pulvinar is part of a distributed network subserving visuospatial attention.[14]

The finding of cerebellar atrophy contralateral to the prevalent left-sided cerebral GM reduction might be related to the mild and moderate τ abnormalities usually documented in the cerebellum and to a distant effect possibly related to retrograde fiber degeneration.

DTI RESULTS

The DTI allows the precise identification of fibers, and it has been successfully applied to other neurodegenerative diseases, such as progressive supranuclear palsy and frontotemporal dementia.[6,7] The present DTI analysis revealed a significant reduction in the frontoparietal connecting fibers and the intraparietal associative fibers and in the sensorimotor fibers of the hand cortical representations. The commissural connections (the body and splenium of the corpus callosum) were involved as well.

The present findings fit well with autopsy data in CBDS that report a wide burden of WM abnormalities signifi-

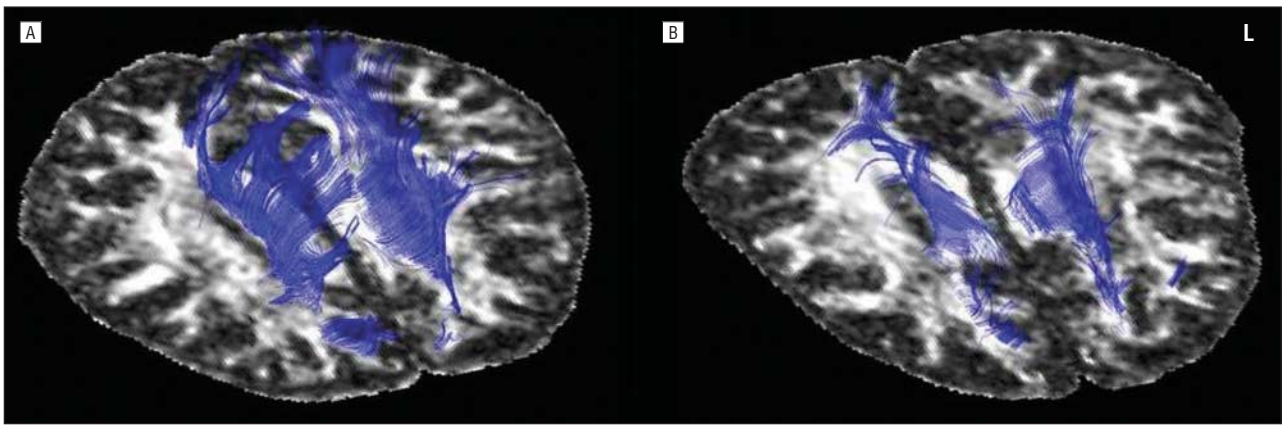

Figure 4. Diffusion tensor imaging in a representative control subject (A) and a patient with corticobasal degeneration syndrome (B) illustrates the selective fiber tract changes. The parietal corticocortical connections and the posterior corpus callosum are displayed and the severe fiber tract reduction in the patient is shown. L indicates left.

cantly greater than those observed in progressive supranuclear palsy and Pick disease.[15] The present study provides new hints into the WM correlates of limb apraxia in CBDS. The degeneration of specific fiber tracts in the associative parietal and frontoparietal connecting bundles can explain ideomotor apraxia. A fludeoxyglucose F 18 positron emission tomography study in CBDS specifically attributed the visuoimitative upper limb apraxia to a functional impairment of the parietofrontal neural network.[2]

The bilateral degeneration of the sensorimotor fibers in the hand areas for sensorimotor representations (Figure 3) might be the neural basis for motor disturbance consistent with the difficulty in performing individual finger movements. Interference at the level of decoding the innervatory patterns of movements might, thus, result in limb-kinetic apraxia.

Correlating specifically the structural changes with praxic performance, we found a significant correlation between apraxia scores and reduced FA in the left dorsolateral parietofrontal associative fibers and the intraparietal associative fibers. The correlation analysis, therefore, confirms that ideomotor apraxia resides in left hemispheric structural changes according to the classic neuropsychological theories.

We also demonstrated that these fiber bundles are subserving mostly complex gesture performance, whereas simple gesture performance correlates with FA reduction in fibers connecting the parietal and premotor areas bilaterally. The present DTI evidence of an impairment of left dorsolateral parietofrontal associative fibers refers to ideomotor apraxia as the classic disconnection syndrome.[16] Three sets of fiber connections have been proposed as those underlying praxis (the dorsolateral parietofrontal, the dorsomedial parietofrontal, and the ventrolateral parietofrontal fibers), as well as interhemispheric fibers located in the body of the corpus callosum (Leiguarda and Marsden[17] provide a review). According to the present results, we suggest that the dorsolateral parietofrontal fibers and the interhemispheric fibers are principally involved in causing ideomotor apraxia in CBDS even in the early stages of the disease.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Borroni and Garibotto equally contributed to this study. *Study concept and design:* Borroni, Garibotto, Agosti, Padovani, and Perani. *Acquisition of data:* Borroni, Garibotto, Agosti, Bellelli, Gasparotti, and Padovani. *Analysis and interpretation of data:* Borroni, Garibotto, Agosti, Brambati, and Perani. *Drafting of the manuscript:* Borroni, Garibotto, and Agosti. *Critical revision of the manuscript for important intellectual content:* Agosti, Brambati, Bellelli, Gasparotti, Padovani, and Perani. *Statistical analysis:* Borroni and Garibotto. *Obtained funding:* Padovani and Perani. *Study supervision:* Borroni, Agosti, Brambati, Bellelli, Gasparotti, Padovani, and Perani.
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