**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, supratemporal 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 parieto-frontal 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. Neuroimaging studies 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. 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.
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 χ2 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 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-dimen-

<table>
<thead>
<tr>
<th>Table 1. Neuropsychological Assessment in 20 Patients With CBDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Short story</td>
</tr>
<tr>
<td>Raven progressive colored matrices</td>
</tr>
<tr>
<td>Rey figure copy</td>
</tr>
<tr>
<td>Rey figure recall</td>
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<tr>
<td>Phonemic fluency</td>
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<tr>
<td>Semantic fluency</td>
</tr>
<tr>
<td>Token test</td>
</tr>
<tr>
<td>Digit span</td>
</tr>
<tr>
<td>Trail Making Test A, s</td>
</tr>
<tr>
<td>Trail Making Test B, s</td>
</tr>
</tbody>
</table>

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

cional 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; 3-mm thickness; and voxel size, 1.7 × 1.7 × 5.0 mm. Three acquisitions were averaged. Diffusion weighting was performed along 6 independent directions with a b value of 1000 s/mm². A T2-weighted image with no diffusion weighting was also obtained (b = 0 s/mm²).

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 Optimized 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-
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 al8 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-

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

<table>
<thead>
<tr>
<th>Brain Region (Patients With CBDS vs Controls)</th>
<th>Peak Coordinates, mm&lt;sup&gt;a&lt;/sup&gt;</th>
<th>t Statistic</th>
<th>z Value</th>
<th>Cluster Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left dorsolateral frontal cortex</td>
<td>−46 23 8</td>
<td>4.30</td>
<td>3.85</td>
<td></td>
</tr>
<tr>
<td>Left premotor cortex</td>
<td>−50 17 36</td>
<td>4.01</td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>Left parietal operculum</td>
<td>−45 3 35</td>
<td>5.05</td>
<td>4.38</td>
<td></td>
</tr>
<tr>
<td>Left superotemporal gyrus</td>
<td>−57 −18 11</td>
<td>4.83</td>
<td>4.23</td>
<td></td>
</tr>
<tr>
<td>Left insula</td>
<td>−48 −11 3</td>
<td>4.39</td>
<td>3.91</td>
<td></td>
</tr>
<tr>
<td>Left uncus</td>
<td>−34 6 −20</td>
<td>4.13</td>
<td>3.72</td>
<td></td>
</tr>
<tr>
<td>Left supratoryl cortex</td>
<td>−23 −47 60</td>
<td>3.47</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td>Right dorsolateral frontal cortex</td>
<td>46 30 9</td>
<td>4.41</td>
<td>3.93</td>
<td></td>
</tr>
<tr>
<td>Right superotemporal gyrus</td>
<td>51 10 −4</td>
<td>5.00</td>
<td>4.34</td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>46 10 −4</td>
<td>5.00</td>
<td>4.34</td>
<td></td>
</tr>
<tr>
<td>Right/left thalamus–pulvinar</td>
<td>8 −31 2</td>
<td>5.78</td>
<td>4.85</td>
<td></td>
</tr>
<tr>
<td>Right cerebellar cortex</td>
<td>18 −83 −30</td>
<td>4.22</td>
<td>3.79</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: See Table 1.

<sup>a</sup>The x, y, and z values localize the areas of gray matter reduction according to the Talairach stereotactic coordinates.
sorimotor associative fibers in the hand cortical repres-
sentations, 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 parieto-
frontal 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 (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 hypoth-

esis of an involvement of frontoparietal connecting fi-
bers, we lowered the threshold to \(P < .01\) and found a posi-
tive correlation between total scores on the test of De Renzi
et al and FA only in the left dorsolateral parietofrontal
associative fibers. We further explored the correlation with
complex and simplex gesture subscroes: for complex ges-
ture subscroes, a correlation with the left parietofrontal
associative fibers and intraparietal associative fibers was
found, whereas for simple gesture subscroes, a signifi-
cant correlation with local FA value of the fibers con-
necting the premotor and parietal areas bilaterally was
found. The limb-kinetic component of apraxia showed a
correlation with hand sensorimotor connecting fibers
(Figure 3).

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

<table>
<thead>
<tr>
<th>Fasciculus (Patients With CBDS vs Controls)</th>
<th>Peak Coordinates, (\text{mm}^3)</th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(t) Statistic</th>
<th>(z) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsolateral parietofrontal associative fibers and intraparietal associative fibers</td>
<td>Left</td>
<td>-30</td>
<td>-53</td>
<td>25</td>
<td>5.19</td>
<td>4.47</td>
</tr>
<tr>
<td></td>
<td>-50</td>
<td>-14</td>
<td>21</td>
<td>5.35</td>
<td>4.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>-57</td>
<td>27</td>
<td>6.47</td>
<td>5.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor associative fibers (hand cortical area)</td>
<td>Left</td>
<td>-20</td>
<td>-46</td>
<td>43</td>
<td>5.21</td>
<td>4.44</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>18</td>
<td>-47</td>
<td>37</td>
<td>4.72</td>
<td>4.15</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>Body</td>
<td>4</td>
<td>-4</td>
<td>19</td>
<td>4.65</td>
<td>4.10</td>
</tr>
<tr>
<td>Splenium</td>
<td>-8</td>
<td>-14</td>
<td>22</td>
<td>5.13</td>
<td>4.43</td>
<td></td>
</tr>
<tr>
<td>Left fornix</td>
<td>-18</td>
<td>-33</td>
<td>-5</td>
<td>5.00</td>
<td>4.35</td>
<td></td>
</tr>
<tr>
<td>Right ventrolateral parietofrontal fibers</td>
<td>46</td>
<td>5</td>
<td>-14</td>
<td>5.22</td>
<td>4.49</td>
<td></td>
</tr>
</tbody>
</table>

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.
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). 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 space12 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-
cantly greater than those observed in progressive supranuclear palsy and Pick disease. The present study provides new hints into the WM correlates of limb apraxia in CBD. 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. The bilateral degeneration of the sensorimotor fibers in the hand areas for sensorimotor representations (Figure 3) might be the neutral 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 dorso-lateral parietofrontal associative fibers and the intraparial 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. 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 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, Belleri, 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, Belleri, Gasparotti, Padovani, and Perani. Statistical analysis: Borroni and Garibotto. Obtained funding: Padovani and Perani. Study supervision: Borroni, Agosti, Brambati, Belleri, Gasparotti, Padovani, and Perani.

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