Association of Ideomotor Apraxia With Frontal Gray Matter Volume Loss in Corticobasal Syndrome

Edward D. Huey, MD; Matteo Pardini, MD; Alyson Cavanagh, BS; Eric M. Wassermann, MD; Dimitrios Kapogiannis, MD; Salvatore Spina, MD; Bernardino Ghetti, MD; Jordan Grafman, PhD

Objective: To determine the brain areas associated with specific components of ideomotor apraxia (IMA) in corticobasal syndrome (CBS).

Design: Case-control and cross-sectional study.

Participants: Forty-eight patients with CBS and 14 control subjects.

Intervention: Administration of the Test of Oral and Limb Apraxia.

Main Outcome Measures: Differences between patients with CBS and healthy controls and associations between areas of gray matter volume and IMA determined by voxel-based morphometry in patients with CBS.

Results: Overall, IMA was associated with decreased gray matter volume in the left supplemental motor area, premotor cortex, and caudate nucleus of patients with CBS. The overall degree of apraxia was independent of the side of motor impairment. Praxis to imitation (vs command) was particularly impaired in the patients with CBS. Patients demonstrated equal impairment in transitive and intransitive praxis.

Conclusions: In patients with CBS, IMA is associated with left posterior frontal cortical and subcortical volume loss. Despite showing left frontal volume loss associated with IMA, patients with CBS have particularly impaired imitation of gestures. These findings suggest either that the IMA of CBS affects a route of praxis that bypasses motor engrams or that motor engrams are affected but that they exist in areas other than the inferior parietal cortex.

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Corticobasal syndrome (CBS) is a rare neurologic disorder characterized by progressive asymmetric apraxia and rigidity with other findings of cortical (eg, alien limb, cortical sensory loss, myoclonus, and mirror movements) and basal ganglia (eg, bradykinesia and increased resistance to passive movement) dysfunction.1,2 Corticobasal syndrome is defined as a clinical syndrome arising from dysfunction of specific brain areas. It is associated with the neuropathological changes of corticobasal degeneration; however, the clinical syndrome of CBS can be observed with other underlying pathological conditions.3

Apraxia is a core clinical feature of CBS, as well as the most studied. Several researchers have proposed that successful praxis often involves the use of motor engrams.12-14 The term engram has been variably defined in the literature. In this study, we define an engram as a “visuokinesthetic motor memory” of a previously performed action that facilitates reproduction of the action.13,14 It has been proposed that these engrams are contained in the left inferior parietal lobe and communicated to premotor and motor areas that are important in programming the movements coded for by the parietal representation.13 In support of this theory, the left parietal lobe is the lesion site most commonly associated with apraxia,17,22 and the left parietal lobe is activated with praxis in healthy individuals.23 However, damage to the left frontal cortex, especially the left middle frontal gyrus, and subcortical structures is also sufficient to cause IMA in the absence of parietal lesions.18

If motor engrams are damaged (from injury to the left inferior parietal lobe), par-
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients With CBS (n=48)</th>
<th>Healthy Controls (n=14)</th>
<th>Chi-Square or T Value for Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. M/F</td>
<td>25/23</td>
<td>8/6</td>
<td>χ²=0.001</td>
<td>.98</td>
</tr>
<tr>
<td>Age at onset, mean (SD), y</td>
<td>61 (9)</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at testing, mean (SD), y</td>
<td>66 (9)</td>
<td>60 (6)</td>
<td>t=2.44</td>
<td>.02</td>
</tr>
<tr>
<td>Handedness, No. R/L/ambidextrous</td>
<td>43/4/1</td>
<td>14/0/0</td>
<td>χ²=1.586</td>
<td>.45</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>15 (3)</td>
<td>17 (4)</td>
<td>t=1.99</td>
<td>.051</td>
</tr>
<tr>
<td>MDRS2 total raw score, mean (SD) (total possible, 144)</td>
<td>116 (24)</td>
<td>139 (3)</td>
<td>t=3.65</td>
<td>.006</td>
</tr>
<tr>
<td>Initial side of symptoms, No. L/R/unclear</td>
<td>25/21/2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Side tested, No. L/R/both</td>
<td>33/13/2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CBS, corticobasal syndrome; L, left; MDRS2, Mattis Dementia Rating Scale 2; NA, not applicable; R, right.

a Significant at a Bonferroni-corrected level of P<.05.

Patients should have impairment of gesture recognition, whereas frontal lesions should be associated with apraxia with preserved gesture recognition. Thus, patients with IMA from frontal damage should be able to recognize gestures and perform them to imitation more easily than to command. Two studies found that patients with CBS had IMA to command to a greater degree than to imitation or recognizing actions, suggesting a relative preservation of movement representations implicating frontal rather than parietal damage (although this was not directly tested). A deficit of functions associated with the frontal lobe in patients with CBS has been linked with apraxia.

In the 2-route model, separate routes are proposed for gesture production and imitation depending on whether the gesture has meaning. The indirect or “lexical” route, associated with the inferior parietal lobe, is used to process meaningful gestures and has access to information about the gesture, including engrams. Damage to this route can produce “representation” IMA characterized by greater impairment of transitive (involving objects or tools) than intransitive (symbolic) gestures and equal impairment in the imitation of meaningful and meaningless gestures. The direct route, associated with frontoparietal structures, is used for the processing of meaningless gestures and bypasses engrammatic information. Damage to this route can produce “dynamic” IMA, which is characterized by equal impairment of transitive and intransitive gestures, but an advantage in imitating meaningful gestures. This model is similar to that proposed for language processing in which patients with transcortical sensory aphasia can repeat words without understanding them. Other researchers have also proposed models of praxis that posit the utilization of separate systems of action knowledge and perceptual and motor processes to perform actions.

This study attempts to better characterize IMA in CBS and elucidate its neuroanatomic basis. Corticobasal syndrome is a good system in which to examine the relative contributions of frontal and parietal cortices to IMA because the patients often have both posterior frontal and parietal dysfunction. A second goal is to integrate these findings into current theories of IMA. Specifically, we hypothesize that if the patients have IMA associated with dysfunction of engrams contained in the inferior parietal cortex, they should have especially poor praxis to imitation and equal impairment in the production of meaningful and meaningless gestures (ie, representational IMA). If their IMA is more associated with frontal dysfunction, they should show an advantage in producing gestures to imitation compared with command and meaningful gestures compared with meaningless gestures (ie, dynamic IMA).

METHODS

SUBJECTS

Forty-eight patients with CBS seen consecutively in the National Institute of Neurological Disorders and Stroke Cognitive Neuroscience Section clinic participated. All were enrolled in an ongoing natural history study of CBS and related disorders. Patients were referred by outside physicians or self-referred. The diagnosis was confirmed by a neurologist with expertise in movement disorders and behavioral neurology (E.M.W.) and a neuropsychologist (J.G.) according to published criteria. All patients assigned durable power of attorney before enrollment and assignees gave written informed consent for the study, which was approved by the institutional review board of the National Institute of Neurological Disorders and Stroke. Demographic and clinical data are presented in Table 1. Five patients died and their brains were obtained at autopsy. All of them had a neuropathological diagnosis of corticobasal degeneration, according to standard criteria. The healthy control subjects were recruited from the local community by advertisement and were age and education matched to the patients (Table 1). All healthy controls underwent an interview and neurologic examination. The exclusion criteria for the patients with CBS included a diagnosis of any neurodegenerative illness other than CBS, lack of a caregiver who could assist with participation in the study, behavioral symptoms that would preclude data collection, and any other medical or social condition that would, in the opinion of the investigators, preclude participation. The exclusion criteria for the healthy controls included any active neurologic or psychiatric condition, use of any neurologic or psychiatric medications, and significant abnormalities on neurologic examination, magnetic resonance imaging, or neuropsychological testing.

APRAXIA ASSESSMENT

The measure of apraxia used in this study was the Test of Oral and Limb Apraxia (TOLA). In the TOLA, each subject was asked to perform each gesture first to verbal command (eg, “show me how...
you would wave ‘goodbye’ †) and then to imitation (eg, “I want you to imitate the following gesture”). The gestures were all meaningful (ie, nonsense gestures were not evaluated). The TOLA consists of 6 categories of tasks performed to both command and imitation: proximal intransitive (eg, salute), proximal transitive (eg, stir a gallon of paint), distal intransitive (eg, make an “OK” sign), distal transitive (eg, dial a telephone), oral nonrespiratory (eg, bite an apple), and oral respiratory (eg, blow out a candle). In addition, subjects were shown pictures of an object and told, “Now I’m going to show you some pictures. Each picture shows an object that can be represented with a gesture. For example, here is a picture of a pen. If I were to represent it with a gesture without talking, I would do this.” (Make an appropriate gesture.) ‡ Now, you make a gesture to represent this picture.”31 For this “gestured pictures” task, 3 categories were tested: proximal (eg, a meat grinder), distal (eg, tweezers), and oral (eg, toothbrush). Patients were instructed to use the nondominant hand to perform the actions. If this hand was too impaired to perform the task, the dominant hand was used. Table 1 shows the distribution of hands tested. On all transitive oral gestures (eg, licking an ice cream cone), the patient was restrained from cueing himself or herself by pretending to hold the object. The TOLA was administered and scored by trained bachelor’s- to master’s-level research assistants (including A.C.). All subject gestures were given a score of 0 to 3, where 3 represents normal performance; 2 represents noticeable errors, hesitancy, or self-correction; 1 represents a movement that retains some basic elements but is largely disordered; and 0 represents a movement that lacks all crucial elements of the gesture. The TOLA has been tested on healthy controls and patients with apraxia and has been demonstrated to have content, predictive, concurrent, and construct validity for the measurement of IMA.31 Patients who did not appear to understand the TOLA instructions were not included in the analysis, although this excluded only 1 subject.

In a previous study, the TOLA was normed in a sample of 145 patients with apraxia (139 from stroke, 6 from other causes) and 21 healthy subjects.31 A “standard score” was developed for the total score and several subtests (see Table 2 for a comparison of the patients with CBS from our study with the patients and healthy controls from the normative TOLA sample). The TOLA composite standard score is derived from the raw scores and assigned a mean of 100 and a standard deviation of 15 in the normative patient sample. The standard subscores have a mean of 10 and a standard deviation of 3 in the normative patient sample. We compared the patients with CBS vs the healthy controls and patient populations from the TOLA normative sample with 1-tailed (between patients with CBS and healthy controls) and 2-tailed (between patients with CBS and the standardization sample of patients) t tests on 5 of the TOLA summary measures (Table 2).

### Table 2. TOLA Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean (SD)</th>
<th>Healthy Controls</th>
<th>Patients With CBS</th>
<th>Standardization Sample</th>
<th>Comparison Between CBS and Standardization Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOLA composite standard score</td>
<td>121 b</td>
<td>100 (9)</td>
<td>100 (15)</td>
<td>100 (15)</td>
<td>.01</td>
</tr>
<tr>
<td>Imitation standard score</td>
<td>14 (0.40)</td>
<td>8 (2)</td>
<td>10 (3)</td>
<td>4.31</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Command standard score</td>
<td>15 (0.10)</td>
<td>10 (2)</td>
<td>10 (3)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Oral standard score</td>
<td>14 (0.03)</td>
<td>10 (3)</td>
<td>10 (3)</td>
<td>0</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Limb standard score</td>
<td>14 (0.30)</td>
<td>8 (2)</td>
<td>10 (3)</td>
<td>4.31</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: CBS, corticobasal syndrome; TOLA, Test of Oral and Limb Apraxia.

a Scores on the TOLA composite and subtests for the 48 patients with CBS compared with the standardized sample and healthy controls of the TOLA standardization sample.31 The standardization sample was composed of 145 patients with ideomotor apraxia, mostly from stroke. The healthy control sample was composed of 21 healthy volunteers.31 A higher score reflects more intact praxis.

b The normative data do not allow the computation of a standard deviation on this derived measure for the healthy controls.

To determine whether severity of apraxia differed between patients with CBS with predominantly left vs right hand affected, the TOLA composite standard score was compared in right-handed subjects with left-hand impairment (25 patients) vs right-handed subjects with right-hand impairment (21 patients) by the use of a 2-tailed t test.

### Imaging

A 1.5-T magnetic resonance imager (GE Medical Systems, Milwaukee, Wisconsin) and standard quadrature head coil were used to obtain all images. A T1-weighted spoiled gradient-echo sequence was used to generate 124 contiguous 1.5-mm-thick axial sections (repetition time, 6.1 milliseconds; echo time, minimum full; flip angle, 20°; field of view, 240 mm; 124 sections; section thickness, 1.5 mm; matrix size, 256 × 256 × 124).

Voxel-based morphometry (VBM) analysis of the data was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5) and followed the principles outlined by Ridge et al.31 Except as noted subsequently, all default SPM5 options were used. Images were segmented into gray matter, white matter, and cerebrospinal fluid. In SPM5, spatial normalization, segmentation, and modulation are processed by means of a unified segmentation algorithm.32 This algorithm, in contrast to optimized VBM used in SPM2 (in which the steps are completed sequentially), simultaneously calculates image registration, tissue classification, and bias correction by using our participants’ structural magnetic resonance images combined with the tissue probability maps provided in SPM5. The segmented and modulated normalized gray matter images were smoothed with a 12-mm full-width at half-maximum gaussian kernel. An explicit mask encompassing the entire brain was used in the analyses to control for background signal outside the brain. This mask was downloaded from the SPM5 Anatomic Automatic Labeling toolbox (http://www.cyceron.fr/web/aal__anatomical_automatic_labeling.html). A 0.05 explicit absolute threshold for masking was used in the SPM second-level model interface.34 Total intracranial volume was calculated in SPM5 from the unsmoothed, modulated gray matter, white matter, and cerebrospinal fluid images from each patient and used as a nuisance variable to account for the possible effect of varying brain volumes. We corrected the statistical significance thresholds for multiple comparisons correction by 2 methods widely used in the neuroimaging community: the false discovery rate and the family-wise error correction. The false discovery rate is the proportion of false-positive results among those tests for which the null hypothesis is rejected,35 whereas the family-wise error correction, which computes a correction for all voxels controlling for the chance of any false-positive results, is the most stringent correction for multiple comparisons available in SPM.36
The TOLA composite standard score (total IMA) correlated with decreased gray matter volume in the left middle frontal and precentral gyri and the left caudate nucleus of patients with CBS (Figure 2, Table 3). The TOLA limb score showed areas of decreased gray matter very similar to those associated with the TOLA composite standard score, likely reflecting the large contribution of limb IMA to total IMA. The VBM analyses of TOLA proximal, distal, transitive, intransitive, and oral scores did not show associations with areas of gray matter volume loss that survived false discovery rate correction (data not shown).

IMAGING

The VBM analysis showed patients with CBS to have reduced gray matter volume in the posterior frontal lobes (including supplemental motor area and dorsal premotor and prefrontal cortex) and anterior parietal lobes (including postcentral gyrus and superior parietal lobule) compared with healthy controls (Figure 1, Table 3). Significantly reduced gray matter densities were also found in the superior temporal and fusiform gyri, caudate nucleus, thalamus, and cerebellum (Figure 1, Table 3).

First, the images from the patient group were compared with the images of a group of 14 age-matched healthy controls by means of a 2-sample t test. Statistical threshold for this analysis was set at $P < .05$, family-wise error–corrected for multiple comparisons. All subsequent analyses were limited to these areas of significant gray matter volume reduction. Especially stringent significance and voxel thresholds were used when patients with CBS were compared with healthy controls because the differences between the patients with CBS and the controls were sufficiently large that using less stringent significance and voxel thresholds resulted in much of the brain being detected as significantly different between patients and controls. Figure 1 shows images and areas of significant differences between the patients with CBS and the healthy controls. The relationship between voxel values and TOLA composite standard score was examined by means of a separate 1-tailed t test, assuming that worsening praxis would be associated with decreased tissue volume. Total intracranial volume was added as a covariate of no interest. For this analysis, we considered as significant those voxels surviving a threshold of both $P < .001$ uncorrected at voxel level and $P < .05$ false discovery rate–corrected for multiple comparisons. All clusters reported were composed of at least 20 voxels (Figure 2).

RESULTS

APRAXIA ASSESSMENT

As shown in Table 2, patients with CBS performed significantly worse than the healthy controls on the TOLA measures (TOLA imitation: $t = 13.6, P = .01$; command: $t = 11.4, P = .01$; oral: $t = 6.1, P = .01$; limb: $t = 13.6, P = .01$). We were unable to perform a t test on the TOLA composite standard score between the patients with CBS and healthy controls because the normative data do not allow the computation of a standard deviation on this derived measure for the healthy controls. However, the mean for the healthy controls on this measure is greater than 2 standard deviations above that of the patients with CBS. When compared with the TOLA standardization sample, patients with CBS had significantly lower scores on the imitation ($t = 4.31, P = .01$) and limb ($t = 4.31, P = .01$) measures. Within the CBS patient group, the limb scores were depressed compared with the oral scores ($t = 6.3, P < .05$) and the imitation scores were depressed compared with the command scores ($t = 10.3, P < .05$). No other significant differences were observed.

No significant difference ($t = 0.89, P = .38$) in TOLA composite standard score was observed between right-handed patients with primarily right-hand impairment (mean [SD] score, 98.4 [9.0]) and right-handed patients with primarily left-hand impairment (101.3 [11.3]).
Our data are consistent with previous imaging\textsuperscript{1,37-39} and autopsy\textsuperscript{1,3} studies on patients with CBS; compared with the healthy subjects, the patients showed the greatest decrease of gray matter surrounding the dorsal precentral and postcentral gyri bilaterally, with additional volume decreases in the caudate nucleus, cerebellum, and frontal, temporal, and parietal lobes. The frontal and occipital poles were spared. Although the basal ganglia are commonly affected in CBS, cerebellar atrophy is less commonly observed.\textsuperscript{1}

Within the regions found to have decreased gray matter volume in the patients with CBS compared with healthy controls, greater total IMA was associated with lower volume in the left supplemental motor area, dorsal premotor cortex, and caudate nucleus (Figures 2 and 3, and Table 3). The predominance of left hemisphere findings in Figure 2 (even though, as seen in Figure 1, the patients with CBS as a group showed bilateral volume changes) is consistent with the dominant role of the left hemisphere in praxis,\textsuperscript{18} especially since the left hand was tested in most patients (Table 1). Damage to the left posterior frontal lobe (see Leiguarda and Marsden\textsuperscript{18} for a review) and basal ganglia\textsuperscript{24} have been associated with apraxia in illnesses other than CBS. The specific role of the basal ganglia in apraxia remains unclear. However, damage to the basal ganglia usually results in apraxia with preservation of imitation and discrimination, suggesting that the basal ganglia do not contain motor engrams.\textsuperscript{24} The lack of significant imaging findings associated with most of the TOLA submeasures may reflect that this study did not have sufficient subjects to adequately power these analyses. Future studies may disclose informative associations between these measures and gray matter volume.

Previous studies of IMA (mostly from patients with stroke) have found the strongest association between left inferior parietal damage and IMA.\textsuperscript{18} Our data suggest that patients with CBS have a more “frontal” form of IMA than patients who are apraxic secondary to other neurologic disorders. However, the patients with CBS did not show preservation of praxis to imitation compared with the stan-

<table>
<thead>
<tr>
<th>Cluster Dimension, Voxels</th>
<th>Voxel T Value</th>
<th>Voxel Z Value</th>
<th>Peak MNI Coordinates x, y, z</th>
<th>Anatomic Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>5690</td>
<td>7.68</td>
<td>6.37</td>
<td>0, 2, 64</td>
<td>Left cerebrum, superior frontal gyrus, BA 6</td>
</tr>
<tr>
<td>7.42</td>
<td>6.21</td>
<td>–2, –46, 66</td>
<td>Left paracentral lobe, BA 5</td>
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</tr>
<tr>
<td>7.37</td>
<td>6.18</td>
<td>0, –14, 62</td>
<td>Left medial frontal gyrus, BA 6</td>
<td></td>
</tr>
<tr>
<td>501</td>
<td>7.10</td>
<td>6.01</td>
<td>58, –62, –30</td>
<td>Right cerebrum, fusiform gyrus, BA 37</td>
</tr>
<tr>
<td>5.43</td>
<td>4.87</td>
<td>52, –66, –20</td>
<td>Right fusiform gyrus, BA 19</td>
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<tr>
<td>801</td>
<td>5.66</td>
<td>28, –2, 68</td>
<td>Right cerebrum, middle frontal gyrus, BA 6</td>
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<td>5.82</td>
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<td>58, –4, 50</td>
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<tr>
<td>799</td>
<td>5.62</td>
<td>5.64</td>
<td>6, 10, 12</td>
<td>Right caudate nucleus</td>
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<tr>
<td>5.63</td>
<td>5.02</td>
<td>2, –18, 14</td>
<td>Right thalamus</td>
<td></td>
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<td>66</td>
<td>6.13</td>
<td>5.37</td>
<td>–26, 18, –44</td>
<td>Left cerebrum, superior temporal gyrus, BA 38</td>
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<td>125</td>
<td>6.12</td>
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<td>–68, –20, 14</td>
<td>Left postcentral gyrus, BA 40</td>
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<td>Left postcentral gyrus, BA 43</td>
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<td>4.57</td>
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<td>Left inferior parietal lobe, BA 40</td>
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<td>683</td>
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<td>5.14</td>
<td>–40, 12, –12</td>
<td>Left insula, BA 13</td>
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<td>127</td>
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<td>4.99</td>
<td>–58, 2, 42</td>
<td>Left cerebrum, middle frontal gyrus, BA 6</td>
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<td>4.72</td>
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<td>Left precentral gyrus, BA 6</td>
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<td>4.90</td>
<td>4.47</td>
<td>–52, –12, 54</td>
<td>Left postcentral gyrus, BA 3</td>
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</tr>
<tr>
<td>538</td>
<td>5.57</td>
<td>4.97</td>
<td>44, –8, 6</td>
<td>Right insula, BA 13</td>
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<tr>
<td>73</td>
<td>5.52</td>
<td>4.94</td>
<td>70, –20, 18</td>
<td>Right postcentral gyrus, BA 43</td>
</tr>
</tbody>
</table>

| Associated With TOLA Composite Standard Score (Figure 2)\textsuperscript{b} | |
|---------------------------|--------------|--------------|-----------------------------|----------------------|
| 44                        | 4.55         | 4.08         | –38, 10, 60                 | Left middle frontal gyrus, BA 6 |
| 49                        | 4.03         | 3.69         | –6, –2, 12                  | Left caudate nucleus  |
| 398                       | 3.98         | 3.65         | –62, –2, 38                 | Left precentral gyrus, BA 6 |

Abbreviations: BA, Brodmann area; CBS, corticobasal syndrome; MNI, Montreal Neurological Institute; TOLA, Test of Oral and Limb Apraxia.

\textsuperscript{a}Areas significant at a threshold of 50 voxels when corrected for multiple comparisons with the family-wise error correction at the .05 level.

\textsuperscript{b}Areas significant at an uncorrected $P < .001$ level and a threshold of 20 voxels that survived false discovery rate correction.

Figure 3. Correlation between Test of Oral and Limb Apraxia (TOLA) composite standard score and gray matter density in patients with corticobasal syndrome in brain areas found to have significantly reduced volume associated with the TOLA composite standard score in the voxel-based morphometry analysis ($r = 0.53$, $P = .01$). The TOLA composite standard scores have been normalized to the mean.
and apart from the attitudes of the sponsor. Study concept and design: Huey and Grafman. Acquisition of data: Huey, Cavanagh, Wassermann, Kapogiannis, Spina, and Ghetti. Analysis and interpretation of data: Huey, Pardini, and Grafman. Drafting of the manuscript: Huey and Grafman. Critical revision of the manuscript for important intellectual content: Huey, Pardini, Cavanagh, Wassermann, Kapogiannis, Spina, Ghetti, and Grafman. Statistical analysis: Huey and Pardini. Obtained funding: Spina, Ghetti, and Grafman. Administrative, technical, and material support: Ghetti and Grafman. Study supervision: Wassermann and Grafman.

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Author Affiliations: Cognitive Neuroscience Section (Drs Huey, Pardini, Wassermann, Kapogiannis, and Grafman and Ms Cavanagh) and Brain Stimulation Unit (Drs Wassermann and Kapogiannis), National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; Litwin-Zucker Research Center for the Study of Alzheimer’s Disease and Memory Disorders, The Feinstein Institute for Medical Research, Manhasset, New York (Dr Huey); Magnetic Resonance Research Centre on Nervous System Diseases and Department of Neurosciences, Ophthalmology, and Genetics, University of Genoa, Genoa, Italy (Dr Pardini); Department of Neurological, Neurosurgical, and Behavioral Sciences, University of Siena, Siena, Italy (Dr Spina); and Indiana Alzheimer Disease Center, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis (Drs Spina and Ghetti).

Correspondence: Jordan Grafman, PhD, Cognitive Neuroscience Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bldg 10, Room 7D43, MSC 1440, Bethesda, MD 20892-1440 (grafman@ninds.nih.gov).

Author Contributions: Dr Huey takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; he had full access to all the data; and he has the right to publish any and all data, separate

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Author Affiliations: Cognitive Neuroscience Section (Drs Huey, Pardini, Wassermann, Kapogiannis, and Grafman and Ms Cavanagh) and Brain Stimulation Unit (Drs Wassermann and Kapogiannis), National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; Litwin-Zucker Research Center for the Study of Alzheimer’s Disease and Memory Disorders, The Feinstein Institute for Medical Research, Manhasset, New York (Dr Huey); Magnetic Resonance Research Centre on Nervous System Diseases and Department of Neurosciences, Ophthalmology, and Genetics, University of Genoa, Genoa, Italy (Dr Pardini); Department of Neurological, Neurosurgical, and Behavioral Sciences, University of Siena, Siena, Italy (Dr Spina); and Indiana Alzheimer Disease Center, Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis (Drs Spina and Ghetti).

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