A disease-specific metabolic brain network associated with corticobasal degeneration

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Corticobasal degeneration is an uncommon parkinsonian variant condition that is diagnosed mainly on clinical examination. To facilitate the differential diagnosis of this disorder, we used metabolic brain imaging to characterize a specific network that can be used to discriminate corticobasal degeneration from other atypical parkinsonian syndromes. Ten non-demented patients (eight females/two males; age 73.9 ± 5.7 years) underwent metabolic brain imaging with 18F-fluorodeoxyglucose positron emission tomography for atypical parkinsonism. These individuals were diagnosed clinically with probable corticobasal degeneration. This diagnosis was confirmed in the three subjects who additionally underwent post-mortem examination. Ten age-matched healthy subjects (five females/five males; age 71.7 ± 6.7 years) served as controls for the imaging studies. Spatial covariance analysis was applied to scan data from the combined group to identify a significant corticobasal degeneration-related metabolic pattern that discriminated (P < 0.001) the patients from the healthy control group. This pattern was characterized by bilateral, asymmetric metabolic reductions involving frontal and parietal cortex, thalamus, and caudate nucleus. These pattern-related changes were greater in magnitude in the cerebral hemisphere opposite the more clinically affected body side. The presence of this corticobasal degeneration-related metabolic topography was confirmed in two independent testing sets of patient and control scans, with elevated pattern expression (P < 0.001) in both disease groups relative to corresponding normal values. We next determined whether prospectively computed expression values for this pattern accurately discriminated corticobasal degeneration from multiple system atrophy and progressive supranuclear palsy (the two most common atypical parkinsonian syndromes) on a single case basis. Based upon this measure, corticobasal degeneration was successfully distinguished from multiple system atrophy (P < 0.001) but not progressive supranuclear palsy, presumably because of the overlap (~24%) that existed between the corticobasal degeneration- and the progressive supranuclear palsy-related metabolic topographies. Nonetheless, excellent discrimination between these disease entities was achieved by computing hemispheric asymmetry scores for the corticobasal degeneration-related pattern on a prospective single scan basis. Indeed, a logistic algorithm based on the asymmetry scores combined with separately computed expression values for a previously validated progressive supranuclear palsy-related pattern provided excellent specificity (corticobasal degeneration: 92.7%; progressive supranuclear palsy: 94.1%) in classifying 58 testing subjects. In conclusion, corticobasal degeneration is associated with a reproducible disease-related metabolic covariance pattern that may help to distinguish this disorder from other atypical parkinsonian syndromes.
Keywords: brain networks; corticobasal degeneration; differential diagnosis; FDG PET; glucose metabolism

Abbreviations: CBD = corticobasal degeneration; CBDRP = corticobasal degeneration-related metabolic covariance pattern; FDG = 18F-fluorodeoxyglucose; MSA = multiple system atrophy; PDCP = Parkinson’s disease cognition-related metabolic covariance pattern; PDRP = Parkinson’s disease motor-related metabolic covariance pattern; PSP = progressive supranuclear palsy; PSPRP = progressive supranuclear palsy-related metabolic covariance pattern

Introduction

Parkinsonism is characterized by a combination of clinical features that include tremor, bradykinesia, rigidity, and postural instability. Idiopathic Parkinson’s disease is the most common cause of neurodegenerative Parkinsonism, whereas atypical parkinsonian syndromes, also referred to as ‘Parkinson plus syndromes,’ encompass several specific diseases with distinct pathology and prognosis, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). Atypical parkinsonian syndromes can represent as much as 15-20% of Parkinsonism seen in specialty practice (Fahn et al., 2004). Diagnosis of Parkinson’s disease and atypical parkinsonism is made based on clinical examination, relying on established consensus criteria. Parkinson’s disease and the different atypical parkinsonian syndromes can be differentiated by pathological examination, but post-mortem studies demonstrate only a 76% accuracy in the clinical diagnosis of Parkinson’s disease (Hughes et al., 2002). Although this accuracy does increase with longer follow-up evaluations by movement disorder specialists, it remains significantly lower for atypical syndromes (Hughes et al., 2002).

Pathologically, CBD and PSP are classified as tauopathies with significant overlap in motor and cognitive deficits (Sha et al., 2006), distinct from the alpha-synuclein aggregates that characterize Parkinson’s disease and MSA (Poston, 2010). Clinically, CBD is characterized by asymmetric, levodopa non-responsive Parkinsonism. The presentation typically includes progressive rigidity and limb apraxia, in conjunction with limb dystonia, stimulus-sensitive myoclonus, and/or cortical sensory loss (Boeve et al., 2003). However, predominantly cognitive presentations are also seen (Litvan et al., 1997; Mahapatra et al., 2004; Hu et al., 2009), potentially confounding the diagnosis.

With this in mind, one important aim of neuroimaging is to provide increased diagnostic accuracy, allowing for the selection of appropriate treatment strategies and more accurate long-term prognosis. Conventional neuroimaging such as MRI is of limited value in the diagnosis of the different atypical parkinsonian syndromes. Asymmetric atrophy of the prefrontal and parietal cortices is suggestive but neither sensitive nor specific for CBD, particularly at early disease stages (Mahapatra et al., 2004). As Parkinson’s disease and atypical parkinsonian syndromes are both associated with presynaptic nigrostriatal dopaminergic deficits, dopaminergic imaging has been of limited use in the differential diagnosis of these disorders (Vlaar et al., 2007).

In contrast, functional imaging techniques aimed at measuring cerebral blood flow or metabolism have been used extensively to identify disease-specific changes in local neural activity (Eidelberg, 2009). In the past several years, voxel-based spatial covariance analysis has been successfully applied to 18F-fluorodeoxyglucose (FDG) PET images to identify metabolic patterns relating to specific neurodegenerative diseases (Eidelberg, 2009). Using this approach, we have previously identified and validated patterns that can discriminate Parkinson’s disease, MSA, and PSP not only from healthy subjects but also from each other (Spetsieris et al., 2009; Tang et al., 2010b; Niethammer and Eidelberg, 2012).

To date, we have not applied this network-based method to the study of CBD, although metabolic asymmetries can readily be seen in patients with this disorder (Eidelberg et al., 1991). In the present study, we identified and validated a disease-specific metabolic pattern that can separate patients with CBD from healthy controls, and patients with other atypical parkinsonian syndromes.

Materials and methods

Subjects

Demographic data for the patient cohorts and the healthy control groups are presented in Table 1. Patients were referred to the respective institution to aid in clinical diagnosis between January 1995 and December 2006 (North Shore University Hospital, NY, USA), March 2009 and October 2010 (Stanford University, CA, USA), July 2008 and January 2011 (University of Freiburg, Freiburg, Germany), and between January 1998 and December 2008 (University Medical Centre Groningen, The Netherlands). All patients had Parkinsonian signs and were followed by movement disorder specialists at each institution for at least 6 months after PET imaging. Inclusion required a final clinical diagnosis of probable CBD, PSP, or MSA that was supported by the clinical impression of the trained movement disorder specialists, who evaluated the patients, chart review (M.N., K.L.P., E.H., L.H., K.L.L., S.H., F.A.) using published clinical criteria (Litvan, 2003; Poston, 2010; Armstrong et al., 2013), and the absence of dementia as well as structural brain abnormalities on MRI (i.e. mass lesions, white matter changes, or ischaemia) that could have explained the clinical findings. Diagnosis was confirmed pathologically (J.P.V.) in 10 patients (three CBD, three PSP, and four MSA). Scan data from some of the patients have appeared previously as part of different analyses (Tang et al., 2010b; Teune et al., 2010; Hellwig et al., 2012).

To identify a CBD-related metabolic covariance pattern (CBDRP), we studied 10 patients (CBDNS: eight females/two males; age 73.9 ± 5.7 years (mean ± standard deviation [SD]); disease duration 3.5 ± 1.5 years; Table 2) who met diagnostic criteria for probable CBD, with limb asymmetry and apraxia on clinical examination and without evidence of eye movement abnormalities. Three of 10 subjects with CBD were pathologically confirmed cases. Eight of the patients with CBD in this group and 10 age-matched normal control subjects (NLNS: five females/five males; age 71.7 ± 6.7 years) were scanned at North Shore University Hospital; two patients with CBD were scanned at Stanford University. Six of 10 patients with CBD had symptoms predominately on the right, and four on the left.

To date, we have not applied this network-based method to the study of CBD, although metabolic asymmetries can readily be seen in patients with this disorder (Eidelberg et al., 1991). In the present study, we identified and validated a disease-specific metabolic pattern that can separate patients with CBD from healthy controls, and patients with other atypical parkinsonian syndromes.
To validate the pattern, we studied independent testing cohorts of atypical parkinsonian syndromes subjects who had uncertain diagnoses at the time of FDG PET and were then followed clinically by movement disorder specialists for at least 6 months until a final clinical diagnosis was made. We studied 10 patients with CBD (CBDGR: seven females/three males; age 68.9±9.3 years; disease duration 2.0±0.82 years) and 10 normal control subjects (NLGR: five females/five males; age 65.0±10.1 years) who were scanned at the University of Freiburg. We also measured CBDRP expression in an additional atypical parkinsonian syndromes cohort comprised of patients diagnosed with PSP (PSPGR: 5 males/5 females; age 70.5±7.6 years; disease duration 2.9±2.0 years) and MSA (MSAGR: 5 males/5 females; age 65.1±7.2 years; disease duration 3.6±2.0 years) who were scanned at the University of Freiburg. All of these patients had uncertain diagnoses of atypical parkinsonian syndromes at the time of imaging, and their final clinical diagnoses were made after clinical follow-up (PSPGR: 1.9±1.1 years; PSPGR: 1.0±0.4 years; MSAGR: 3.2±2.6 years; MSAGR: 0.8±0.3 years) (Tang et al., 2010b; Hellwig et al., 2012).

Ethical permission for the procedures was obtained from the Institutional Review Board at North Shore University Hospital and Stanford University, and the local ethics committee at University of Freiburg and the University Medical Centre Groningen. Written consent was obtained at each institution from each subject following detailed explanation of the scanning procedures.

**PET**

All subjects were scanned with FDG PET under resting conditions. All anti-parkinsonian medications were withheld at least 12 h before imaging. PET imaging was performed using a GE Advance tomograph (4.0 mm, full-width at half-maximum (FWHM), North Shore University Hospital), a GE PET/CT Discovery LS (5 mm FWHM, Stanford University), a Siemens ECAT HR+ PET scanner (4.1 mm FWHM, University Medical Centre Groningen), or a Siemens ECAT EXACT 922/47 scanner (5.5 mm FWHM; University of Freiburg) as described previously (Huang et al., 2007; Teune et al., 2010; Meyer et al., 2011). Scans from each subject were realigned and spatially normalized to a standard Talairach-based FDG PET template, and smoothed with an isotropic Gaussian kernel (10 mm) in all directions to improve the signal-to-noise ratio (Feigin et al., 2007; Huang et al., 2007). All image processing was performed using Statistical Parametric Mapping (SPM5) software (Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB (MathWorks).

**Network analysis**

**CBDRP identification**

To identify a specific metabolic pattern associated with CBD, we applied a spatial covariance mapping algorithm (Eidelberg, 2009; Niethammer and Eidelberg, 2012; Spetsieris et al., 2013) to the FDG PET data from the 10 CBDNS patients and 10 NLNS subjects that comprised the derivation set. This method is based on a principal component analysis that can be used to identify specific disease-related spatial covariance patterns with significantly greater expression (denoted by higher subject scores) in patients than in control subjects. A detailed description of this approach has appeared elsewhere (Habeck and Stern, 2010; Spetsieris and Eidelberg, 2011). In brief, principal component analysis was performed on scans from the

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### Table 1 Patient cohorts

<table>
<thead>
<tr>
<th>Site</th>
<th>Category</th>
<th>n</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North Shore University Hospital/Stanford University (NS)</td>
<td>NL (NLNS)</td>
<td>10</td>
<td>71.7±6.7</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>CBD (CBDNS)</td>
<td>10</td>
<td>73.9±5.7</td>
<td>3.5±1.5</td>
</tr>
<tr>
<td></td>
<td>PSP (PSPNS)</td>
<td>30</td>
<td>69.4±5.6</td>
<td>2.7±1.2</td>
</tr>
<tr>
<td></td>
<td>MSA (MSANS)</td>
<td>40</td>
<td>61.4±8.7</td>
<td>3.9±2.2</td>
</tr>
<tr>
<td>University Medical Centre Groningen (GR)</td>
<td>NL (NLGR)</td>
<td>10</td>
<td>65.0±10.1</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>CBD (CBDGR)</td>
<td>10</td>
<td>68.9±9.3</td>
<td>2.0±0.8</td>
</tr>
<tr>
<td>University of Freiburg (FR)</td>
<td>CBD (CBDFR)</td>
<td>7</td>
<td>65.8±6.0</td>
<td>2.3±1.6</td>
</tr>
<tr>
<td></td>
<td>PSP (PSPFR)</td>
<td>21</td>
<td>70.5±7.6</td>
<td>2.9±2.0</td>
</tr>
<tr>
<td></td>
<td>MSA (MSAFR)</td>
<td>12</td>
<td>65.1±7.2</td>
<td>3.6±2.0</td>
</tr>
</tbody>
</table>

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### Table 2 Patient characteristics: derivation cohort (CBDNS)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Disease duration (years)</th>
<th>Clinically worse side</th>
<th>Pathologically confirmed</th>
<th>CBDRP score (z-scored)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>74.5</td>
<td>3</td>
<td>Left</td>
<td>Yes</td>
<td>5.02</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61.9</td>
<td>1</td>
<td>Right</td>
<td>Yes</td>
<td>5.59</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>81.0</td>
<td>3</td>
<td>Right</td>
<td>Yes</td>
<td>12.01</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>78.2</td>
<td>2</td>
<td>Right</td>
<td>No</td>
<td>5.26</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>73.2</td>
<td>5</td>
<td>Right</td>
<td>No</td>
<td>6.41</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>77.6</td>
<td>6</td>
<td>Right</td>
<td>No</td>
<td>8.04</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>76.0</td>
<td>3</td>
<td>Right</td>
<td>No</td>
<td>4.07</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>72.5</td>
<td>6</td>
<td>Left</td>
<td>No</td>
<td>5.50</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>68.2</td>
<td>1</td>
<td>Left</td>
<td>No</td>
<td>8.14</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>79.2</td>
<td>5</td>
<td>Left</td>
<td>No</td>
<td>6.75</td>
</tr>
</tbody>
</table>
combined group of patients and normal controls (n = 20) using an automated voxel-based routine (software freely available at http://feinsteinneuroscience.org/imaging-software) in a common stereotaxic space. The combination of principal component patterns that best discriminated patients from controls in the derivation set was identified using pre-specified subject score criteria (Spetsieris and Eidelberg, 2011). To delineate a specific CBD-related topography, we limited the analysis to the set of principal components that in aggregate accounted for the top 50% of subject × voxel variability, and for which each individual principal component contributed at least 10% to the total variance in the scan data. Region weights for the resulting disease-related topography (denoted by voxel loadings on the pattern) were tested for reliability using bootstrap resampling (Habeck and Stern, 2010). Coordinates were reported in the standard anatomical space developed at the Montreal Neurological Institute. The cytoarchitectonic localization of each reported network-related region was confirmed using the Talairach space utility available at http://www.tls.hsp.ru/~pet_lab/TSU/TSUMain.html. For pattern derivation, the scans from the CBD patients with predominantly left-sided symptoms were flipped so that all subjects had the left hemispheres of the brain as their most affected side.

**CBDRP validation**

Following derivation, the CBDRP candidate network was validated by computing its expression in patient and control testing data from the CBDGR, CBDFR, and NLCR cohorts. The Freiburg data set did not include scans from healthy control subjects. As in the derivation set, scans of patients with CBD with predominantly left-sided symptoms in the testing cohorts were flipped so that the most affected hemisphere was on the left side. Subject scores for the candidate CBDRP identified in the derivation set were computed in the testing scans using an automated voxel-based algorithm to quantify the expression of known patterns on a prospective single scan basis (Spetsieris et al., 2006, 2013; Eidelberg, 2009) and were compared across groups. In addition, CBDRP expression values were computed in scans from the testing cohorts with PSP (PSPNS and PSPFR) or MSA (MSANS and MSAMSA). The resulting subject scores were compared with values from the corresponding CBD cohorts (CBDNS and CBDFR).

**CBDRP asymmetry index**

To obtain a quantitative measure of the pattern asymmetry in individual subjects, we generated a hemi-CBDRP from the left side (most affected hemisphere) of the whole-brain pattern. For each subject, hemi-CBDRP expression values were computed separately for the two hemispheres (hemi-CBDRP was flipped to calculate the value for the right hemisphere). The difference in hemispheric values was calculated and used as an asymmetry index of CBDRP expression. Values from the diagnostically relevant patient groups (CBD and PSP) were compared with each other and with measures from the healthy volunteer group.

**Differential diagnosis**

In addition to assessing group differences in the expression of covariance patterns relating to CBD and PSP in the testing populations, we developed an automated logistic algorithm to discriminate between these disorders at the individual patient level. To this end, we extended the pattern-based classification strategy that we previously developed to distinguish patients with Parkinson’s disease from MSA and PSP (Tang et al., 2010b). A training sample was constructed using scans from the 10 CBDNS subjects used for CBDRP derivation (age 73.9 ± 5.7 years) and scans from 10 PSPNS patients (age 69.9 ± 8.2 years) closely matched in age to their CBDNS counterpart subjects. Logistic regression analysis was performed on the scan data from this combined training sample to determine which of the three network measures [i.e. CBDRP expression, CBDRP asymmetry index, and PSP-related metabolic covariance pattern (PSPRP)] expression] could, singly or in combination, best differentiate between the two diseases. The model with the best between-group discrimination was selected based on the lowest Akaike information criterion value (Burnham and Anderson, 2002).

For validation, this algorithm was used prospectively to classify each of 58 independent subjects. This testing set was comprised of 17 CBD (10 CBDGR and seven CBDFR) and 41 PSP patients (20 remaining PSPNS and 21 PSPFR). For each subject, probability values for CBD (PCBD) or PSP (PPSP) were computed using the original logistic equation from the training sample and then compared to the optimal cut-off probabilities for classifying a given subject as CBD or PSP (i.e. cut-offCBD or cut-offPSP). The cut-off probability for each condition was determined by identifying an inflection point on each receiver-operating characteristic (ROC) curve corresponding to high specificity and sensitivity (Tang et al., 2010b). Because in a clinical setting FDG PET is used primarily as a confirmatory test rather than for screening, high specificity (i.e. >90%) rather than high sensitivity was preferred in determining a suitable inflection point for each curve and, correspondingly, the cut-off probability for each disease. By comparing the individual case probabilities (PCBD and PPSP) to the cut-off probabilities, each subject was classified as CBD if PCBD > cut-offCBD, PSP if PPSP > cut-offPSP, or as an indeterminate case if PCBD ≤ cut-offCBD and PPSP ≤ cut-offPSP. We then calculated discriminative measures (sensitivity, specificity, positive predictive value and negative predictive value) for the CBD and PSP groups.

**Statistical analysis**

Because of the relatively small sample size of some groups (e.g. n = 7 in CBDNS), the non-normal distribution of the data in some groups, and unequal sample sizes, non-parametric tests were used to compare network measures between (Mann-Whitney U-tests) and among (Kruskal-Wallis tests) the different groups. For all patients and control subjects, individual pattern scores were standardized (z-scored) with respect to the original NKS group used in pattern derivation. Thus, for each of these normal reference samples, mean pattern expression was zero with an SD of one. Logistic regression analysis was performed in SAS 9.2 (SAS Institute Inc.) and other statistical tests were performed in SPSS 14.0 (SPSS Inc.). All tests were considered significant for P < 0.05.

**Results**

**Corticobasal degeneration-related metabolic pattern**

Spatial covariance analysis of the metabolic imaging data from the derivation set revealed a significant CBDRP (principal component 1, accounting for 18.4% of the total subject × voxel variance of the data). This pattern (Fig. 1A and Table 3) was characterized by metabolic reductions in the primary motor (BA4), lateral premotor (BA6), prefrontal (BA9) and parietal (BA40) cortical regions, cingulate gyrus (BA24, BA31) and in the thalamus (mediodorsal, ventrolateral and lateroposterior nuclei). The changes in these...
network regions were more pronounced in the left hemisphere (i.e. opposite the more affected body side), although abnormal changes were also present in the other hemisphere, albeit at lower significant levels (not shown in Fig. 1A). Voxel weights on CBDRP were stable in these regions (inverse coefficient of variation range = 2.22 to 2.26, \( P = 0.01 \); bootstrap estimation, 1000 iterations). In the derivation set, pattern expression values (Fig. 1B and D) significantly separated the patients with CBD from the healthy control subjects (\( P < 0.001 \); permutation test). The clinical diagnosis of CBD was confirmed post-mortem in three of 10 subjects (Fig. 1B and Table 2) used to identify the pattern. In each of the autopsied cases, subject scores were
Table 3 Brain regions with significant contributions to the CBD-related pattern

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Coordinates(^a)</th>
<th>Zmax (\times) (\times) (\times)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Network-related metabolic reductions (negative region weights)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus MD/VL/LP nuclei,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>–2</td>
<td>–22</td>
</tr>
<tr>
<td>Right</td>
<td>6</td>
<td>–14</td>
</tr>
<tr>
<td>Left inferior parietal lobule, BA40</td>
<td>–4</td>
<td>–38</td>
</tr>
<tr>
<td>Left precuneus gyrus, BA4/6</td>
<td>–32</td>
<td>–16</td>
</tr>
<tr>
<td>Left cingulate gyrus, BA31</td>
<td>–10</td>
<td>–24</td>
</tr>
<tr>
<td>Left inferior frontal gyrus, BA9</td>
<td>–52</td>
<td>14</td>
</tr>
<tr>
<td>Left middle frontal gyrus, BA6</td>
<td>–28</td>
<td>16</td>
</tr>
<tr>
<td>Left cingulate gyrus, BA24</td>
<td>–8</td>
<td>–8</td>
</tr>
<tr>
<td>Network-related metabolic increases (positive region weights)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lingual gyrus, BA18</td>
<td>–26</td>
<td>–70</td>
</tr>
<tr>
<td>Right inferior occipital gyrus, BA18</td>
<td>40</td>
<td>–92</td>
</tr>
<tr>
<td>Right lingual gyrus, BA17</td>
<td>20</td>
<td>–102</td>
</tr>
</tbody>
</table>

\(^a\) Montreal Neurological Institute standard space. MD = mediodorsal; VL = ventrolateral; LP = lateroposterior; BA = Brodmann area.

Pattern validation

To validate the CBDRP, we prospectively computed the expression of this pattern in an independent testing cohort comprised of 10 patients with CBD (CBD\(_{\text{CR}}\)) and 10 age-matched normal control subjects (NL\(_{\text{CR}}\)) scanned at University Medical Centre Groningen. Subject scores for this pattern were computed on a prospective single scan basis in each of testing scans using an automated voxel-based algorithm that was blind to diagnostic category (i.e. CBD\(_{\text{CR}}\) or NL\(_{\text{CR}}\)). In this testing sample (Fig. 1D) CBDRP expression was also elevated \((P < 0.001\); Mann-Whitney test\) in the patients (CBD\(_{\text{CR}}\)) relative to the healthy (NL\(_{\text{CR}}\)) control subjects. Of note, subject scores in both cohorts were standardized with respect to CBDRP expression values from the healthy NL\(_{\text{NS}}\) subjects in the derivation sample. Nevertheless, the mean for the prospectively computed NL\(_{\text{CR}}\) values (–0.24) was near the zero mean \((P = 0.36\); Mann-Whitney test\) that was set for the NL\(_{\text{NS}}\) (see ‘Materials and methods’ section).

Lastly, we computed CBDRP expression in an additional testing cohort comprised of seven patients with CBD (CBD\(_{\text{FR}}\)) scanned at the University of Freiburg. Although no scans from healthy control subjects were available at this site, subject scores for CBD\(_{\text{FR}}\) patients (Fig. 1D) were significantly elevated \((P < 0.001\); Mann-Whitney test\) relative to healthy NL\(_{\text{NS}}\) and NL\(_{\text{CR}}\) control values. Indeed, the expression of this pattern in CBD\(_{\text{FR}}\) patients (CBD\(_{\text{NS}}\): 6.68 ± 0.89) did not differ \((P = 0.55\); Kruskal-Wallis test\) from corresponding measurements in CBD\(_{\text{CR}}\) and CBD\(_{\text{GR}}\) patients (CBD\(_{\text{NS}}\): 6.68 ± 0.72 (derivation); CBD\(_{\text{GR}}\): 5.35 ± 1.27).

CBDRP expression in other forms of atypical parkinsonism

To determine the specificity of the pattern for CBD, we measured its expression in other forms of atypical parkinsonian syndromes. Specifically, we quantified CBDRP scores in 30 PSP patients (PSP\(_{\text{NS}}\)) and 40 MSA patients (MSA\(_{\text{NS}}\)) scanned at North Shore University Hospital. The patients in the CBD\(_{\text{NS}}\) group showed higher CBDRP expression than both the PSP\(_{\text{NS}}\) \((P < 0.05\); Mann-Whitney test\) and MSA\(_{\text{NS}}\) \((P < 0.001\) patient groups. Right: CBDRP expression in independent groups of seven CBD (CBD\(_{\text{FR}}\)), 21 PSP (PSP\(_{\text{FR}}\)) and 12 MSA (MSA\(_{\text{FR}}\)) patients scanned with FDG PET at the University of Freiburg. In these groups, CBDRP expression was significantly elevated in the patients with CBD compared with the patients with MSA \((P < 0.001\); Mann-Whitney test\), but was not different from the patients with PSP \((P = 0.96)\). In addition, both PSP\(_{\text{NS}}\) and PSP\(_{\text{FR}}\) patients showed higher CBDRP expression \((P < 0.001\); Mann-Whitney test\) than the normal (NL\(_{\text{NS}}\)) control subjects. Error bars represent SE. **P < 0.001, Mann-Whitney tests, compared to normal control subjects.
to PSP in both differential diagnosis sets (P < 0.003 for CBDNS versus PSPNS and CBDFR versus PSPFR).

We also computed PSPPRP expression in each of these subjects. PSPPRP scores were indeed elevated in both PSP groups (P < 0.001; Mann-Whitney tests for PSPNS versus NLNS and PSPFR versus NLNS), and also in the two CBD samples (P < 0.005 for CBDNS versus NLNS, P = 0.07 for CBDFR versus NLNS). Moreover, PSPPRP expression was significantly higher in PSPNS compared to CBDNS (Fig. 3B, left; P < 0.01), but was not different for the PSPFR and CBDFR groups (Fig. 3B, right; P = 0.27). Indeed, voxel-wise correlation of CBDRP and PSPPRP revealed moderate overlap between the two patterns (R² = 0.24, P < 0.001). There was also a significant correlation between expression of CBDRP and PSPPRP in individual subjects with CBD (Spearman’s r = 0.58, P = 0.001, n = 27; combined group of CBDNS, CBDGR and CBDFR) or PSP (Spearman’s r = 0.57, P < 0.001, n = 51; combined group of PSPNS and PSPFR). These findings suggest that, singly, the two whole-brain network measures are insufficient for prospective discrimination between the two diseases. That said, adequate differentiation between these conditions may be possible using multiple network measures in combination.

Automated algorithm for differential diagnosis of corticobasal degeneration versus progressive supranuclear palsy

For accurate differential diagnosis of CBD and PSP, we next employed a logistic classification algorithm to determine whether the three network measures (the whole-brain CBDRP expression, the CBDRP asymmetry index, and the whole-brain PSPPRP expression), individually or in combination, provided accurate discrimination between clinically diagnosed CBD and PSP patients at the single case level. In the training sample comprised of the 10 CBDNS and the 10 age-matched PSPNS cases (Fig. 4A), a logistic regression model based on the CBDRP asymmetry index and whole-brain PSPPRP expression values produced better group separation (Y² = 15.6, P = 0.0004; likelihood ratio test) than any individual univariate model as well as the other multivariate models. Receiver-operating characteristic (ROC) analysis of this selected bivariate model revealed that the area under-the-curve (AUC) was 0.94 (P < 0.0001), indicating excellent differentiation between the CBD and PSP patients. Odds ratio estimates for this model were 1.84 [95% confidence interval (CI) = 1.06–3.20, P = 0.03] for CBDRP asymmetry and 0.42 (95% CI = 0.15–1.19, P = 0.10) for PSPPRP expression. Thus, greater asymmetry occurring in concert with lower PSPPRP expression suggests a higher likelihood of CBD relative to PSP in a given subject.

To validate this algorithm, we applied the discriminant function of the model prospectively to individual subjects in an independent testing set of 17 CBD (CBDGR + CBDFR) and 41 PSP (PSPNS + PSPFR) subjects (Fig. 4B). The classification probabilities of CBD and PSP in each case were computed using the algorithm with the individual CBDRP asymmetry index and the whole-brain PSPPRP expression value for that individual. The probabilities of all subjects were illustrated in a frequency distribution diagram

Figure 3 CBDRP asymmetry index and PSPPRP expression.

(A) The CBDRP asymmetry index was found to be greater in both CBD patient cohorts (CBDNS versus PSPNS; P < 0.002; CBDFR versus PSPFR; P < 0.003; Mann-Whitney tests) than for the respective PSP patient cohorts. (B) Expression of a previously identified PSP-related pattern (PSPPRP) (Eckert et al., 2008) was significantly higher in the PSPNS group relative to the CBDNS group (P < 0.01; Mann-Whitney test), but was not different between the PSPFR and CBDFR groups (P = 0.27). Error bars represent SE.

CBDPRP asymmetry index and PSPPRP expression

We used the inherent asymmetries that characterize the CBDRP topography to define a hemispheric pattern. The hemi-CBDRP topography was defined by the left hemisphere of the original whole-brain pattern. As the side opposite the more affected limbs in patients with CBD, the left hemisphere contained the bulk of the local metabolic reductions that constitute this disease topography. The expression of the left hemi-CBDRP was separately computed in the two hemispheres of each subject (see ‘Materials and methods’ section). The left-right difference in these values was used to compute a CBDRP asymmetry index for each subject. Relative to the normal control group (NLNS), the asymmetry index was greater in the CBD (CBDNS: P < 0.001; CBDFR: P < 0.001; Mann-Whitney tests) and the PSP (PSPNS: P < 0.005; PSPFR: P = 0.005; Mann-Whitney tests) samples. However, unlike the original whole-brain pattern, the CBDRP asymmetry index (Fig. 3A) was significantly greater in CBD relative to PSP in both differential diagnosis sets (P < 0.003 for CBDNS versus PSPNS and CBDFR versus PSPFR).

Multiple prospective CBD cohorts, the testing data also revealed significant pattern elevations in PSP patients.

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The subjects with higher CBD probabilities clustered on the right and those with higher PSP probabilities clustered on the left. ROC curve analysis (Fig. 5B) further revealed an AUC of 0.92 ($P < 0.0001$) indicating a high accuracy for the correct classification of CBD and PSP subjects. Based on these curves, the optimum cut-off probability for classifying CBD was 0.78 and for PSP was 0.63. Thus, patients whose probability values for CBD were $>0.78$ were classified as CBD and those whose probability values for PSP were $>0.63$ as PSP; patients whose probability values for CBD and PSP were both lower than their corresponding cut-off values were classified as indeterminate.

The image-based classification for each testing subject was compared to the ultimate clinical diagnosis of that individual. For the subjects diagnosed clinically with CBD, the image-based classifications had sensitivity of 76.5% (13/17, number of subjects), specificity of 92.7% (38/41), positive predictive value of 81.3% (13/16), and negative predictive value of 90.5% (38/42). For the PSP patients, the imaging classifications had 78.0% (32/41) sensitivity, 94.1% (16/17) specificity, 97.0% (32/33) positive predictive value, and 64.0% (16/25) negative predictive value. Nine of 58 testing subjects (15.5%) were classified as indeterminate by comparison of their probability values with the corresponding cut-offs. Of these, six were ultimately diagnosed as having PSP and three as CBD.

**Discussion**

In this study, we describe and validate a specific metabolic covariance pattern associated with CBD, termed CBDRP. Expression of this pattern reliably differentiated patients with clinical CBD from healthy control subjects in two independent samples. The CBDRP metabolic topography characterized by asymmetrical reductions (worse in the left hemisphere, i.e. contralateral to the more affected body side) in the cerebrum, lateral parietal and frontal regions and thalamus, with relative bilateral increases in occipital regions. This abnormal spatial covariance topography is consistent with previously reported metabolic (Eidelberg et al., 1991; Eckert et al., 2005; Teune et al., 2010; Hellwig et al., 2012; Zhao et al., 2012) and structural (Soliveri et al., 1999; Boxer et al., 2006; Erbetta et al., 2009) imaging changes in CBD identified using simple region-level analytical methods. Indeed, the pattern reflects the often marked asymmetry that is characteristic of the clinical presentation of CBD (Poston, 2010).

We acknowledge that derivation of a disease-specific pattern has to rely on the accuracy of the clinical diagnosis. This may be particularly problematic in CBD, where patients with the clinical diagnosis of CBD may be found to have another underlying pathology on post-mortem examination, mainly PSP, but including Alzheimer’s disease, vascular parkinsonism, and Pick’s disease (Litvan et al., 1997; Josephs et al., 2006; Hu et al., 2009). This has prompted some investigators to propose the term corticobasal syndrome to describe the clinical findings in living patients, while reserving CBD for the definitive diagnosis made at post-mortem. That said, to derive and validate a metabolic pattern that is highly specific to CBD, we only included probable CBD patients who had parkinsonism with limb asymmetry and apraxia on clinical examination, without extracocular movement abnormalities (Litvan et al., 1997). Thus, it is likely that the majority of the patients in our cohorts did indeed have CBD, as was confirmed by post-mortem examination of the brains of three of the patients whose scans were used to derive the CBDRP metabolic topography.
The clinical presentation of CBD may be quite heterogeneous. Indeed, the specific CBDRP topography described in this study may not be a consistent feature of variant phenotypes of the disorder, such as those with early dementia, which can be confused with Alzheimer’s disease (Alexander et al., 2014). Validation of this pattern as a specific diagnostic tool for CBD will ultimately be dependent on the accrual of additional cases with pathological confirmation. A separate possible problem is the low sensitivity in the diagnosis, a situation where neuroimaging could potentially be of benefit. It is well recognized that patients with the pathological diagnosis of CBD frequently may have different clinical syndromes and the true diagnosis is missed, as can occur in individuals diagnosed clinically as having PSP, Alzheimer’s disease, progressive aphasia, symmetrical parkinsonism, or frontotemporal dementia (Litvan et al., 1997; Hu et al., 2009; Boeve, 2011; Hassan et al., 2011). To assess the use of CBDRP expression in this context, it will be necessary to identify patients with pathologically confirmed CBD but with a different clinical diagnosis – and who had also undergone metabolic imaging in life.

In our cohorts, CBDRP expression was abnormally elevated in established CBD patients compared with healthy control subjects. Interestingly, one patient did undergo imaging twice. At the first time point, the clinical diagnosis was one of focal dystonia, without other features of CBD. CBDRP expression at the time was mildly elevated, only to become significantly elevated 3 years later, when the clinical diagnosis was established. We have previously shown that in Parkinson’s disease, expression of motor- and cognition-related patterns (PDRP and PDCP, respectively) increase in individual patients over time (Huang et al., 2007; Tang et al., 2010a). Indeed, expression of PDCP is within the normal range.
early in the disease course (Tang et al., 2010a). Our finding in this one patient, coupled with a similar report in two patients with MSA (Poston et al., 2012), suggests that disease-specific patterns may be useful markers of disease progression in individual patients in all forms of neurodegenerative parkinsonism. Nevertheless, longitudinal studies will be required to confirm this finding. Given the clinical uncertainty early in the disease process, it will be of special interest to define the earliest point at which abnormal pattern expression can reliably aid in the diagnosis of these disorders.

Expression values for CBDRP were not abnormally elevated in two MSA cohorts. However, while abnormal in the three CBD cohorts that we studied, these values were also elevated in PSP. Expression values for the previously characterized PSPRP (Eckert et al., 2008; Tang et al., 2010b) likewise are elevated in independent populations of both CBD and PSP. Moreover, CBDRP and PSPRP expression correlated in individual patients. While CBD and PSP are clinically and pathologically thought to be distinct, both are classified as tauopathies and share deposition of four repeat tau. This contrasts with the mixture of three repeat and four repeat isoforms seen in Alzheimer’s disease, suggesting perhaps a shared pathogenesis for the two disorders (Dickson, 1999; Boeve et al., 2003). It is intriguing to speculate that abnormally elevated expression of both patterns in PSP and CBD is also a consequence of regional overlap in their respective neuropathological landscapes. A significant portion of patients with clinical PSP are found to have CBD pathology and vice versa (Josephs et al., 2006; Murray et al., 2007; Ling et al., 2010). Indeed, the correlation between the two patterns, in terms of both spatial topography and subject expression, suggests that the current finding is not simply one of missed diagnoses. Rather, there is true regional overlap between their metabolic profiles.

In addition, despite different pathologies, recent studies have suggested that Alzheimer’s disease is a common clinical mimic of CBD (Alexander et al., 2014). Patients with Alzheimer’s disease have similar cognitive deficits to CBD, with less rigidity and dystonia (Hu et al., 2009; Hassan et al., 2011). Thus, we performed a preliminary analysis of CBDRP expression in Alzheimer’s disease patients, showing that this pattern is not abnormally expressed in these patients relative to healthy controls (personal communication). Indeed, a prior study has demonstrated that the metabolic deficits in Alzheimer’s disease tend to involve cortical regions (Habeck et al., 2008) that are rather distinct from those that define the CBDRP topography. Nonetheless, because non-demented subjects exclusively were used to identify and validate the CBDRP topography, it is not clear whether this pattern can effectively differentiate patients with CBD from clinical ‘look alike’ syndromes with underlying Alzheimer pathology. Further investigation is needed to determine the accuracy of network-based classification in CBD and in clinical mimics of this disorder.

Taking advantage of the clinical asymmetry of CBD, which is a distinctive feature of the disease and its metabolic topography, we measured the degree of hemispheric asymmetry that was present at the network level in the individual subjects. We reasoned that this measure would be more specific in differentiating CBD from the more symmetrical metabolic profile of PSP. Indeed, hemispheric asymmetry for CBDRP expression separated the CBD and PSP groups with greater accuracy than whole-brain CBDRP expression. Ultimately, the classification algorithm based on CBDRP asymmetry index and whole-brain PSPRP expression accurately discriminated between CBD and PSP subjects in whom the precise clinical diagnosis was uncertain at the time they were referred for the imaging study. Classifications of these individuals based upon these imaging measures accorded well with final clinical diagnoses reached independently by movement disorder specialists at clinical follow-up (Tang et al., 2010b; Teune et al., 2010; Hellwig et al., 2012). As a result, high specificity and positive predictive value were achieved for image-based classification of CBD on an individual case basis, with all three pathologically confirmed PSP cases classified as non-CBD. These findings provide strong support for the specificity of the CBDRP network and the validity of the classification algorithm that we have identified in this study.

The accuracy of prediction using this automated approach is in line with previously reported values using trained readers (Eckert et al., 2005; Hellwig et al., 2012), but does not require visual judgement whether trained or not. We have previously described an automated algorithm that can differentiate Parkinson’s disease from atypical parkinsonian syndromes (excluding CBD), and further subdivide atypical parkinsonian syndromes into MSA and PSP (Tang et al., 2010b; Niethammer and Eidelberg, 2012; Tripathi et al., 2012). With the data presented in the present study, we aim to refine this algorithm to include CBD, thereby improving the accuracy of diagnosis in clinically ambiguous cases. We recognize, however, given the protean clinical presentation of CBD, blinded, prospective imaging studies involving larger validation samples and longitudinal network measurements, ideally with post-mortem confirmation, will be necessary to establish the use of CBDRP to assist in diagnosis and for screening potential participants in clinical trials.

Funding

This work was supported in part by the National Institute of Neurological Disorders and Stroke Morris K. Udall Centre of Excellence for Parkinson’s Disease Research at The Feinstein Institute for Medical Research (P50 NS071675 to D.E.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the National Institutes of Health. The sponsor did not play a role in study design, collection, analysis and interpretation of data, writing of the report or in the decision to submit the paper for publication.

Conflict of interest

Dr Eidelberg serves on the scientific advisory board and has received honoraria from the Michael J. Fox Foundation for Parkinson’s Research; is listed as co-inventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same, without financial gain; has received research support from the NIH (NINDS, NICHD, NIAID) and the Dana Foundation; and has served as a consultant...
for Pfizer. All other authors declare no competing financial interests.

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