Network correlates of disease severity in multiple system atrophy

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ABSTRACT

Objective: Multiple system atrophy (MSA), the most common of the atypical parkinsonian disorders, is characterized by the presence of an abnormal spatial covariance pattern in resting state metabolic brain images from patients with this disease. Nonetheless, the potential utility of this pattern as a MSA biomarker is contingent upon its specificity for this disorder and its relationship to clinical disability in individual patients.

Methods: We used [18 F]fluorodeoxyglucose PET to study 33 patients with MSA, 20 age- and severity-matched patients with idiopathic Parkinson disease (PD), and 15 healthy volunteers. For each subject, we computed the expression of the previously characterized metabolic covariance patterns for MSA and PD (termed MSARP and PDRP, respectively) on a prospective single-case basis. The resulting network values for the individual patients were correlated with clinical motor ratings and disease duration.

Results: In the MSA group, disease-related pattern (MSARP) values were elevated relative to the control and PD groups ($p < 0.001$ for both comparisons). In this group, MSARP values correlated with clinical ratings of motor disability ($r = 0.57$, $p = 0.0008$) and with disease duration ($r = -0.376$, $p = 0.03$). By contrast, MSARP expression in the PD group did not differ from control values ($p = 1.0$). In this group, motor ratings correlated with PDRP ($r = 0.60$, $p = 0.006$) but not with MSARP values ($p = 0.88$).

Conclusions: MSA is associated with elevated expression of a specific disease-related metabolic pattern. Moreover, differences in the expression of this pattern in patients with MSA correlate with clinical disability. The findings suggest that the MSARP may be a useful biomarker in trials of new therapies for this disorder. *Neurology*® 2012;78:1237-1244

GLOSSARY

FDG = [18 F]fluorodeoxyglucose; **MNI** = Montreal Neurological Institute; **MSA** = multiple system atrophy; **MSA-C** = multiple system atrophy cerebellar subtype; **MSA-P** = multiple system atrophy parkinsonian subtype; **MSARP** = multiple system atrophy-related spatial covariance pattern; **PDRP** = Parkinson disease-related spatial covariance pattern; **PD** = Parkinson disease; **ROI** = region of interest; **SPM** = Statistical Parametric Mapping; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Multiple system atrophy (MSA) is a progressive, adult onset neurodegenerative disorder characterized by autonomic dysfunction with varying degrees of parkinsonism and cerebellar ataxia. Currently, there is no disease-modifying therapy available for MSA and, unlike Parkinson disease (PD), only limited symptomatic treatment. Clinical trials for potential therapies have been hampered by the lack of validated, disease-specific biomarkers for this illness.

To address this need, we examined the previously characterized MSA-related spatial covariance pattern (MSARP) as a potential biomarker of this disease. [18 F]fluorodeoxyglucose (FDG) PET scans from a combined group of patients with MSA and healthy subjects were used in conjunction with spatial covariance analysis to identify a reproducible MSARP network.^{1,2} Indeed, prospectively computed measures of MSARP expression in individual patients were

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Supplemental Data

From the Stanford University Medical Center (K.L.P.), Stanford, CA; Center for Neurosciences (C.C.T., T.E., V.D., D.E.), The Feinstein Institute for Medical Research, Manhasset; Movement Disorders Division (S.F.), Mount Sinai School of Medicine, New York; and the Department of Pathology (J.-P.V.) and Neurological Institute (S.F.), Columbia University, New York, NY. T.E. is currently affiliated with the Department of Neurology, University of Magdeburg, Germany.

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found to discriminate patients with MSA from clinically similar individuals with PD, as well as other parkinsonian syndromes.^{2,3} In the current study, we assessed the MSARP as a potential disease-specific imaging biomarker by quantifying its expression in FDG-PET scans from a large prospective patient cohort. The specificity of this metabolic network for MSA was evaluated by computing MSARP expression, as well as the expression of the previously validated PD-related spatial covariance pattern (PDRP) in each member of the MSA cohort and in a prospective group of patients with PD of similar age and clinical severity.⁴ Additionally, network values computed in both patient groups were correlated with independent motor disability ratings obtained concurrently in the same individuals at the time of imaging.

METHODS Subjects. We identified 41 patients with a clinical diagnosis of MSA who were referred for FDG-PET as part of a larger study of metabolic pattern analysis for the differential diagnosis of parkinsonian movement disorders.³ Of these, 33 patients (15 men, 18 women; age 60.6 ± 8.4 years; off-state Unified Parkinson's Disease Rating Scale [UPDRS] motor scores 34.2 ± 13.8) were selected based upon the following inclusion criteria: 1) the treating movement disorders specialist established a diagnosis of MSA based on best clinical diagnosis after at least 6 months of follow-up; 2) the diagnosis of MSA was confirmed by a second movement disorders specialist (K.L.P.) on chart review using published criteria⁵; 3) UPDRS motor ratings were obtained in a practically defined "off-state" within 1 month of imaging; and (4) there was no evidence of structural brain abnormalities (i.e., mass lesions, white matter changes, ischemia) on routine MRI to explain the clinical findings.

The patients were classified as having either the parkinsonian (MSA-P) or cerebellar (MSA-C) disease subtype based upon the predominant clinical feature that was evident at the time of initial movement disorders evaluation.⁶ Of the patients enrolled in this study, 26 were classified as MSA-P and 7 as MSA-C. Two of the participants underwent repeat metabolic imaging: one patient (patient 1) was scanned at baseline and again 4 and 7 years later; the other (patient 2) was scanned at baseline and 7 years. In 3 patients, the clinical diagnosis of MSA was confirmed on post-mortem assessment by an experienced neuropathologist using established histologic criteria.⁷

Scan data from the MSA group were compared with those from 20 age- and severity-matched patients with PD (10 men, 10 women; age 60.1 ± 8.7 years; off-state UPDRS motor scores 33.1 ± 13.1). In these subjects, the diagnosis of idiopathic PD was made according to published criteria.⁸ Scans from 15 healthy volunteer subjects (8 men, 7 women; age 58.8 ± 6.4 years) were used as controls in comparisons of the imaging data from the MSA and PD groups.

PET. PET imaging with FDG was performed in 3-dimensional mode using a GE Advance tomograph (General Electric; Milwaukee, WI) at North Shore University Hospital, as described in

detail elsewhere.^{9,10} The subjects fasted overnight and antiparkinsonian medication was withheld for at least 12 hours before the start of the imaging session. Images of relative cerebral glucose utilization were acquired in a single 10-minute frame, beginning 35 minutes after the IV injection of a 5 mCi dose of radiotracer. An isotropic spatial smoothing kernel (10 mm full width at half maximum) was applied to the images, which were standardized according to the Montreal Neurological Institute (MNI) template. Image processing was performed using Statistical Parametric Mapping (SPM) software (Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB (Mathworks, Natick, MA).

Data analysis. We quantified the expression of the MSARP and PDRP metabolic networks (figure 1, A and B) in each of the MSA, PD, and control scans using an automated voxel-based algorithm (software available at <http://www.fil.ion.ucl.ac.uk/spm/ext/#SSM>) as described elsewhere.^{3,4,11} These spatial covariance patterns represent disease-related biological signals that can be detected and quantified in metabolic brain images. The expression of a given disease pattern (i.e., the "subject score" for the pattern) can be computed prospectively from an individual's brain scan. The resulting value represents the magnitude of network activity expressed in the metabolic image of that particular subject. All network computations were performed blind to subject, disease group, and clinical disability ratings. MSARP and PDRP subject scores were *z* transformed with respect to the corresponding healthy control values such that network activity in the normal group had a mean value of zero and a SD of 1.

In addition to comparing PDRP and MSARP expression across the 3 groups, we measured regional metabolic activity in the lentiform nucleus and cerebellum of each subject using an automated region of interest (ROI) template as described previously.¹² These particular regions were selected because of prior data demonstrating consistent reductions in local glucose utilization in these brain regions in metabolic scans from patients with MSA.^{13–15} For each region, glucose metabolism was averaged across hemispheres. To reduce intersubject variability, both regional measures were normalized by the global metabolic rate.

Group differences in whole-brain pattern expression and in lentiform and cerebellar regional metabolic activity were assessed using analysis of variance with post hoc Bonferroni tests. Dichotomous variables (e.g., gender) were evaluated using the χ^2 statistic. Multiple regression analysis was used to examine relationships between the network- and region-level metabolic measures (MSARP/PDRP scores; lentiform/cerebellar glucose metabolism) and clinical severity (UPDRS motor ratings). Statistical analyses were implemented in SPSS 17.0 for Windows (SPSS, Chicago, IL). Group differences were considered significant for $p < 0.05$.

Standard protocol approvals, registrations, and patient consents. Ethical permission to conduct this retrospective analysis was obtained from the Institutional Review Board of the North Shore–Long Island Jewish Health System.

RESULTS Group differences. Clinical measures. Clinical data from all patients are summarized in table 1. The MSA and PD groups did not differ with respect to age ($p = 0.78$) or to off-state UPDRS motor ratings ($p = 0.97$). The patients with MSA were found to have shorter symptom duration than their PD counterparts, with a similar level of motor disability ($p = 0.001$).^{16,17}

Figure 1 Multiple system atrophy (MSA)- and Parkinson disease (PD)-related metabolic patterns

(A) Multiple system atrophy-related pattern (MSARP) identified by spatial covariance analysis of FDG-PET scans from 10 patients with MSA and 10 healthy controls.¹ This pattern was characterized by covarying metabolic reductions in the putamen and the cerebellum. The covariance map was overlaid on T1-weighted magnetic resonance template images. The display represents regions that contributed significantly to the network at $p \leq 0.001$ and were demonstrated to be reliable ($p < 0.0001$) by bootstrap resampling. (B) PD-related pattern (PDRP) identified by spatial covariance analysis of FDG-PET scans from 33 patients with PD and 33 age-matched normal volunteer subjects.¹⁰ This pattern was characterized by relative metabolic increases in the pallidum and thalamus, in the pons and cerebellum, and in sensorimotor cortex. These changes covaried with metabolic decreases in the lateral premotor cortex and in parieto-occipital association regions. The display represents regions that contributed significantly to the network at $p \leq 0.001$ and were demonstrated to be reliable ($p < 0.001$) by bootstrap resampling. Voxels with negative region weights (metabolic decreases) are color-coded blue; voxels with positive region weights (metabolic increases) are color-coded red.

The proportion of male to female participants did not differ across groups ($p = 0.87$, χ^2 test). When MSA-P, MSA-C, and PD were considered as discrete clinical categories, no group differences were observed in subject age at the time of imaging (MSA-P: 61.5 ± 8.9 years, mean $\pm$ SD; MSA-C: 57.5 ± 5.7 ; PD: 60.1 ± 8.7 , $p = 0.15$). Nonetheless, disease duration was shorter in the MSA-C group (MSA-P: 4.2 ± 2.6 years, mean $\pm$ SD; MSA-C: 2.9 ± 1.5 , $p = 0.04$), and a trend was noted toward relatively lower (less severe) motor ratings in the MSA-C group (MSA-P: 36.8 ± 14.1 , mean $\pm$ SD; MSA-C: 23.5 ± 7.3 , $p = 0.07$).

Network activity. MSARP subject scores (figure 2A) differed for the 3 groups ($F_{2,65} = 68.48$, $p < 0.001$), with higher pattern expression in the MSA group compared to the PD and normal control groups ($p <$

0.001 , post hoc Bonferroni tests). MSARP values computed in the patients with PD did not differ from the corresponding measures determined in the healthy control subjects ($p = 1.0$). When the MSA cohort was separated into discrete MSA-P and MSA-C subgroups, MSARP scores were likewise found to differ from PD and normal controls ($F_{2,50} = 53.19$, $p < 0.001$). Pattern expression was elevated in both MSA-P and MSA-C when each subgroup was separately compared to PD and healthy control subjects ($p < 0.001$, post hoc Bonferroni tests). MSARP expression was marginally elevated in MSA-P relative to MSA-C ($p = 0.08$).

PDRP scores (figure 2B) also differed across the 3 groups ($F_{2,65} = 57.81$, $p < 0.001$), with higher expression in patients with PD compared to patients with MSA ($p < 0.001$) and healthy control subjects ($p < 0.001$). PDRP scores did not differ for the MSA and healthy control groups ($p = 0.34$). Moreover, PDRP values did not differ across the MSA subgroups ($p = 1.0$).

Regional metabolism. At a regional level, metabolic activity in the lentiform nucleus and cerebellum were also found to differ across groups (lentiform: $F_{2,65} = 28.5$, $p < 0.001$; cerebellum: $F_{2,65} = 5.44$, $p = 0.007$, see table e-1 on the *Neurology*[®] Web site at www.neurology.org). Regional metabolic activity in the lentiform nucleus was lower in MSA relative to PD and healthy control subjects ($p < 0.001$, post hoc Bonferroni tests). In the cerebellum, metabolic activity was lower in patients with MSA relative to patients with PD ($p = 0.01$), but was only marginally reduced with respect to healthy controls ($p =$

Table 1 Demographic features

	IPD	MSA	Control	p Value ^a
No. subjects	20	33	15	
No. male/female	10/10	15/18	8/7	0.87
Age, y ^b	60.1 $\pm$ 8.7	60.6 $\pm$ 8.4	58.8 $\pm$ 6.4	0.78
Symptom duration, y ^b	6.3 $\pm$ 4.5	3.9 $\pm$ 2.4		0.001
Hoehn & Yahr stage ^b	2.8 $\pm$ 0.9	3.3 $\pm$ 1.2		0.08
UPDRS (motor) ^b	33.1 $\pm$ 13.1	34.2 $\pm$ 13.8		0.97

Abbreviations: IPD = idiopathic Parkinson disease; MSA = multiple system atrophy; UPDRS = Unified Parkinson's Disease Rating Scale.

^a For gender, p values reflect the Pearson χ^2 test; for age, p values reflect analysis of variance; for symptom duration, UPDRS, and Hoehn & Yahr stage, p values reflect t tests.

^b Values are means $\pm$ SD.

Figure 2 Pattern expression in multiple system atrophy (MSA) and Parkinson disease (PD)

(A) MSA-related spatial covariance pattern (MSARP) expression was elevated ($p < 0.001$) in the current MSA group ($n = 33$) compared to the PD ($n = 20$) and the normal ($n = 15$) control groups. MSARP scores for patients with PD did not differ from control values ($p = 1.0$). (B) Parkinson disease-related spatial covariance pattern (PDRP) expression was elevated ($p < 0.001$) in the current PD group ($n = 20$) compared to both the MSA ($n = 33$) and the normal control ($n = 15$) groups. PDRP scores for patients with MSA did not differ from control values ($p = 0.34$). Error bars represent standard error.

0.09). In both regions, metabolic activity did not differ between patients with PD and healthy control subjects ($p = 1.0$). A marginal reduction in cerebellar metabolic activity was observed in MSA-C relative to PD ($p = 0.06$), but no group difference was observed with respect to MSA-P ($p = 1.0$) and healthy control subjects ($p = 0.19$).

Clinical-metabolic relationships. Network-level correlations. In the MSA group, increased MSARP expression correlated with greater clinical disability ($r = 0.57$, $p = 0.001$) as determined by higher UPDRS motor ratings (figure 3A). By contrast, in these patients,

more severe clinical disability (i.e., higher UPDRS motor ratings) correlated with lower PDRP expression values ($r = -0.53$, $p = 0.002$). An inverse relationship was noted between MSARP and PDRP subject scores ($r = -0.44$, $p = 0.01$). Further analysis disclosed that MSARP and PDRP subject scores together accounted for 42% of the variability in motor disability ratings across the subjects with MSA ($p = 0.0017$, multiple linear regression). Each of the 2 disease patterns contributed to the predictive model (MSARP: $p < 0.02$; PDRP: $p < 0.05$) without interaction effect ($p = 0.85$).

Figure 3 Relationship between pattern expression and motor ratings

(A) In the multiple system atrophy (MSA) group, increased MSA-related spatial covariance pattern (MSARP) expression (red circles) correlated with greater clinical disability as measured by increased Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings ($r = 0.57$, $p = 0.001$). By contrast, increased motor disability in these subjects was associated with lower Parkinson disease-related spatial covariance pattern (PDRP) expression values (blue triangles; $r = -0.53$, $p = 0.002$). (B) By contrast, in the Parkinson disease (PD) group, PDRP expression (blue triangles) correlated with UPDRS motor ratings ($r = 0.60$, $p = 0.006$), and no correlation was present between MSARP scores (red circles) and clinical severity ratings ($r = 0.038$, $p = 0.88$). Bars represent the mean (0) and SD (1) of normal control values.

Figure 4 Relationship between multiple system atrophy–related spatial covariance pattern (MSARP) expression and symptom duration

In patients with multiple system atrophy, there was a linear correlation between MSARP expression and symptom duration ($r = 0.38$, $p = 0.03$).

In the MSA group, increased MSARP expression correlated ($r = 0.38$, $p = 0.03$) with longer symptom duration (figure 4). Longitudinal metabolic data were available from 2 patients with MSA. In patient 1, MSARP scores increased over time (year 2 = 2.91, year 9 = 7.27). PDRP expression values for this subject remained in the normal range, declining minimally (-0.63 units) over time. In patient 2, MSARP expression increased continuously over the 3 time points (year 2 = 0.43, year 6 = 0.91, year 9 = 1.82), while PDRP scores fluctuated within the normal range over the same time period (year 2 = 0.17, year 6 = -0.43 , year 9 = 0.76).

In the PD group, increased PDRP expression correlated ($r = 0.60$, $p = 0.006$) with greater clinical disability, i.e., higher UPDRS motor ratings (figure 3B). MSARP expression did not correlate with clinical disability in these patients ($r = 0.038$, $p = 0.88$). In this group, the correlation between UPDRS motor ratings and PDRP scores was not improved by including MSARP expression values in the regression model ($p = 0.99$, interaction effect).

Region-level correlations. In the MSA group, increased UPDRS motor ratings correlated with reduced local metabolic activity in the lentiform nucleus ($r = -0.37$, $p = 0.04$) but not in the cerebellum ($r = -0.10$, $p = 0.58$). There was no correlation between regional measures and individual differences in symptom duration (lentiform: $p = 0.065$; cerebellum: $p = 0.64$).

DISCUSSION In this study, we quantified the expression of 2 previously characterized disease-related metabolic patterns, the MSARP and PDRP, in a sizeable cohort of patients with MSA, and compared the

resulting network values to those from a group of patients with PD with a similar degree of motor disability. As expected for an MSA biomarker, MSARP expression was elevated in patients diagnosed clinically with this disorder, while PDRP expression was normal in the same subjects. Analogously, the patients with PD were characterized by elevated PDRP expression and normal MSARP scores. The specificity of the group differences seen for the 2 networks, and their distinctive relationships with clinical disability ratings, underscores the “disease-relatedness” of the MSARP and PDRP as functional imaging biomarkers.

Natural history studies in MSA have found that the time from symptom onset to death varies widely between patients with MSA with survival ranging from 3 to 15 years.¹⁸ By contrast, functional disability is closely associated with the severity of motor symptoms,¹⁶ and standardized rating scales are currently being used to measure disease progression in MSA experimental trials.^{19–21} Given the variability inherent in such clinical descriptors, alternative quantifiers of disease severity/progression may enhance the accuracy and speed of experimental trials of new MSA therapies. In this study, cross-sectional analysis of the MSA cohort indicated that the expression of the corresponding disease-related pattern increased in patients with longer symptom duration and worse motor disability. Similarly, the 2 patients with MSA who underwent longitudinal imaging studies exhibited increasing MSARP expression over time, while PDRP expression fluctuated within the normal range. These data suggest the MSARP is likely to be a disease-specific and clinically sensitive biomarker of MSA progression. Nonetheless, a systematic longitudinal study of early-stage MSA is required prior to adopting this network as an outcome measure in clinical trials.

The subjects with MSA included in this study represent patients who initially presented to a movement disorders specialist with an uncertain parkinsonian diagnosis, including patients with early symptoms. Indeed, 30% of the patients with MSA had symptoms for 2 years or less at the time of imaging. Certainly, objective disease biomarkers are most valuable in patients who are early in the disease course, as this is the target population for inclusion into clinical trials. However, diagnostic accuracy can be challenging in such subjects. Therefore, we took several measures to verify the diagnosis of MSA in this cohort. Clinicopathologic studies suggest the sensitivity for initial clinical diagnosis in MSA is comparatively low (22%–56%).^{22,23} Nonetheless, after follow-up by a movement disorders specialist, the sensitivity for an MSA diagnosis is as high as 88%–

100%.^{23,24} For this reason, we included only patients who both met diagnostic criteria for MSA²³ on the last evaluation after PET and in whom the clinical diagnosis was confirmed by a movement disorders specialist after at least 6 months, with an average of 2.1 ± 0.5 years of follow-up after PET. In addition, in 9% of the patients with MSA included in our cohort, the diagnosis was confirmed by post-mortem examination, providing further diagnostic verification.

As previously reported, we found that MSA was associated with significant localized reductions in basal ganglia and cerebellar metabolic activity, which were not present in patients with PD.^{13,25} However, in contrast to the network-based MSARP measurements, these regional changes exhibited only a weak correlation with clinical motor ratings. While patients with MSA can have clinical parkinsonism without ataxia, and vice versa, data from a recent clinicopathologic study from 100 patients with MSA suggest that basal ganglia and cerebellar regional pathology do not exist in isolation.²⁶ Furthermore, although the putamen and cerebellum are key elements of the MSARP topography, this metabolic network includes significant contributions from other brain areas.¹ Thus, this spatial covariance pattern is likely to be more representative of the widespread neurodegenerative changes that underlie this disorder. We note that for our primary analysis, patients with MSA-P and MSA-C were analyzed together as one pathologic disease group. However, when these clinically defined subgroups were considered separately, only the patients with MSA-P exhibited significant reductions in putamen metabolism—and neither subgroup displayed significant metabolic reductions in the cerebellum. Indeed, despite the modest degree of regional change seen in these patients, both MSA subgroups exhibited substantial MSARP elevations compared to the PD and normal control groups. In aggregate, these observations are consistent with the notion that network biomarkers based on whole brain imaging data provide more robust descriptors of neurodegenerative processes than measurements derived from one or more isolated brain regions.⁴

To evaluate the specificity of the relationships between these metabolic networks and disease severity, we correlated MSARP and PDRP subject scores with corresponding motor disability ratings obtained at the time of imaging. Indeed, the correlations between network expression and motor ratings were observed to be fundamentally different in the MSA and PD patient groups. In the MSA group, we noted a correlation with higher MSARP expression in patients with more severe motor dysfunction.

An analogous correlation was evident in the PD group, with greater expression of the relevant disease-related pattern (i.e., PDRP) in the more advanced patients. In keeping with the disease specificity of the MSARP, the expression of this pattern in patients with PD failed to correlate with individual motor ratings.

Interestingly, a significant clinical–network correlation was also observed in the MSA group, in which higher (more severe) motor ratings were associated with lower PDRP values. Of note, PDRP expression was normal in the MSA group and individual differences in the corresponding network values were relatively small. This is consistent with our observations in the 2 MSA patients with longitudinal imaging, in whom PDRP scores fluctuated within the normal range over the 4–7 years of follow-up. By contrast, in the MSA group, concurrently measured MSARP scores were abnormally elevated and increased with worsening motor symptoms. In this vein, the magnitude of the slope of the line correlating clinical ratings with MSARP scores was twice that for the corresponding correlation with declining PDRP values.

Finally, we note that there was no interaction effect between the 2 sets of network values in their prediction of the clinical severity ratings. Thus, the distinct clinical–network correlations observed for the 2 patterns in the MSA cohort are unlikely to represent the divergent effects of disease on basal ganglia glucose metabolism.^{13,15} This point is supported by an exploratory analysis in which we prospectively measured MSARP and PDRP expression in the individual scan data following the removal of the putamen using an anatomically standardized volume of interest mask.²⁷ We found that the resulting pattern scores in the MSA group continued to correlate with the motor ratings (MSARP: $r = 0.42$, $p = 0.02$; PDRP: $r = -0.51$, $p = 0.004$). Similarly, a priori removal of the putamen from the PD scans did not substantially alter the clinical–network correlations observed in this group (PDRP: $r = 0.60$, $p = 0.005$; MSARP: $r = 0.10$, $p = 0.69$). An interesting possibility is that the correlation observed between decreased PDRP expression and increased motor ratings in patients with MSA is attributable to a predominance of nigral over striatal cell loss early in the disease process. While speculative, such an effect is consistent with the transient presence of a dopaminergic treatment response in some patients with early-stage MSA.¹⁸

The findings we describe support the proposition that network analysis of rest-state metabolic imaging data can provide robust, useful biomarkers for the diagnosis and assessment of patients with neurodegenerative disorders.^{3,28} Nonetheless, longitudinal

imaging studies in patients with early MSA will be necessary to confirm the relationship between pattern expression and disease progression, and to quantify the annual rate of network change in these subjects.

AUTHOR CONTRIBUTIONS

D.E. and C.C.T. designed the research; K.L.P., C.C.T., T.E., and V.D. performed the research; K.L.P. and C.C.T. analyzed the data; K.L.P., C.C.T., and D.E. wrote the manuscript; J.-P.V., S.F., T.E., and V.D. provided critical revision of the manuscript; and V.D., J.-P.V. and S.F. provided administrative, technical, or material support.

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REFERENCES

- Eckert T, Tang C, Ma Y, et al. Abnormal metabolic networks in atypical parkinsonism. *Mov Disord* 2008;23:727–733.
- Spetsieris PG, Ma Y, Dhawan V, Eidelberg D. Differential diagnosis of parkinsonian syndromes using PCA-based functional imaging features. *Neuroimage* 2009;45:1241–1252.
- Tang CC, Poston KL, Eckert T, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol* 2010;9:149–158.
- Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. *Trends Neurosci* 2009;32:548–557.
- Litvan I, Bhatia KP, Burn DJ, et al. SIC Task Force appraisal of clinical diagnostic criteria for parkinsonian disorders. *Mov Disord* 2003;18:467–486.
- Geser F, Wenning GK, Seppi K, et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA Study Group (EMSA SG). *Mov Disord* 2006;21:179–186.
- Papp MI, Lantos PL. The distribution of oligodendroglial inclusions in multiple system atrophy and its relevance to clinical symptomatology. *Brain* 1994;117:235–243.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
- Asanuma K, Tang C, Ma Y, et al. Network modulation in the treatment of Parkinson's disease. *Brain* 2006;129:2667–2678.
- Ma Y, Tang C, Spetsieris PG, et al. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. *J Cereb Blood Flow Metab* 2007;27:597–605.
- Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: methodological issues. *Neuroimage* 2011;54:2899–2914.
- Moeller JR, Nakamura T, Mentis MJ, et al. Reproducibility of regional metabolic covariance patterns: comparison of four populations. *J Nucl Med* 1999;40:1264–1269.
- Eidelberg D, Takikawa S, Moeller JR, et al. Striatal hypometabolism distinguishes striatonigral degeneration from Parkinson's disease. *Ann Neurol* 1993;33:518–527.
- Antonini A, Kazumata K, Feigin A, et al. Differential diagnosis of parkinsonism with [18F]fluorodeoxyglucose and PET. *Mov Disord* 1998;13:268–274.
- Eckert T, Barnes A, Dhawan V, et al. FDG PET in the differential diagnosis of parkinsonian disorders. *Neuroimage* 2005;26:912–921.
- Tison F, Yekhelef F, Chrysostome V, et al. Parkinsonism in multiple system atrophy: natural history, severity (UPDRS-III), and disability assessment compared with Parkinson's disease. *Mov Disord* 2002;17:701–709.
- Seppi K, Yekhelef F, Diem A, et al. Progression of parkinsonism in multiple system atrophy. *J Neurol* 2005;252:91–96.
- O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain* 2008;131:1362–1372.
- Bensimon G, Ludolph A, Agid Y, et al. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS Study. *Brain* 2009;132:156–171.
- Dodel R, Spottke A, Gerhard A, et al. Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [11C] (R)-PK11195 PET (MEMSA-trial). *Mov Disord* 2010;25:97–107.
- May S, Gilman S, Sowell BB, et al. Potential outcome measures and trial design issues for multiple system atrophy. *Mov Disord* 2007;22:2371–2377.

22. Litvan I, Goetz CG, Jankovic J, et al. What is the accuracy of the clinical diagnosis of multiple system atrophy? A clinicopathologic study. *Arch Neurol* 1997;54:937–944.
23. Osaki Y, Wenning GK, Daniel SE, et al. Do published criteria improve clinical diagnostic accuracy in multiple system atrophy? *Neurology* 2002;59:1486–1491.
24. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;125:861–870.
25. Lyoo CH, Jeong Y, Ryu YH, et al. Effects of disease duration on the clinical features and brain glucose metabolism in patients with mixed type multiple system atrophy. *Brain* 2008;131:438–446.
26. Ozawa T, Paviour D, Quinn NP, et al. The spectrum of pathological involvement of the striatonigral and olivopontocerebellar systems in multiple system atrophy: clinicopathological correlations. *Brain* 2004;127:2657–2671.
27. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003;19:1233–1239.
28. Huang C, Tang C, Feigin A, et al. Changes in network activity with the progression of Parkinson's disease. *Brain* 2007;130:1834–1846.

Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.¹⁻³

REFERENCES

1. French J, Gronseth G. Lost in a jungle of evidence: we need a compass. *Neurology* 2008;71:1634–1638.
2. Gronseth G, French J. Practice parameters and technology assessments: what they are, what they are not, and why you should care. *Neurology* 2008;71:1639–1643.
3. Gross RA, Johnston KC. Levels of evidence: taking *Neurology*® to the next level. *Neurology* 2009;72:8–10.

Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population where outcome is independently assessed or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specific population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specific population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specific population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.