Published in final edited form as:

Neuroimage. 2012 December ; 63(4): 1827–1832. doi:10.1016/j.neuroimage.2012.08.039.

Abnormal Network Topographies and Changes in Global Activity: Absence of a Causal Relationship

Vijay Dhawan, PhD, Chris C. Tang, MD, PhD, Yilong Ma, PhD, Phoebe Spetsieris, PhD, and David Eidelberg, MD

Center for Neurosciences, The Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, NY 11030, USA

Chris C. Tang: ctang@nshs.edu; Yilong Ma: yma@nshs.edu; Phoebe Spetsieris: pspetsie@nshs.edu; David Eidelberg: david1@nshs.edu

Abstract

Changes in regional brain activity can be observed following global normalization procedures to reduce variability in the data. In particular, spurious regional differences may appear when scans from patients with low global activity are compared to those from healthy subjects. It has thus been suggested that the consistent increases in subcortical activity that characterize the abnormal Parkinson's disease-related metabolic covariance pattern (PDRP) are artifacts of global normalization, and that similar topographies can be identified in scans from healthy subjects with varying global activity. To address this issue, we examined the effects of experimental reductions in global metabolic activity on PDRP expression. Ten healthy subjects underwent ^{18}F -fluorodeoxyglucose PET in wakefulness and following sleep induction. In all subjects, the global metabolic rate (GMR) declined with sleep (mean -34% , range: -17 to -56%), exceeding the test-retest differences of the measure ($p < 0.001$). By contrast, sleep-wake differences in PDRP expression did not differ from test-retest differences, and did not correlate ($R^2 = 0.04$) with concurrent declines in global metabolic activity. Indeed, despite significant GMR reductions in sleep, PDRP values remained within the normal range. Likewise, voxel weights on the principal component patterns resulting from combined analysis of the sleep and wake scans did not correlate ($R^2 < 0.07$) with the corresponding regional loadings on the PDRP topography. In aggregate, the data demonstrate that abnormal PDRP expression is not induced by reductions in

© 2012 Elsevier Inc. All rights reserved.

Address Correspondence To: Vijay Dhawan, PhD, 350 Community Drive, Manhasset, NY 11030, Phone: 1-516-562-1128; Fax: 1-516-562-1008; dhawan@nshs.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosure Statement

Dr. Dhawan has received research support from Neurologix, Inc., the NIH (NIDCD, NIAID, NINDS), the Dana Foundation, and the Thomas Hartman Foundation for Parkinson's Research, Inc.

Dr. Tang has received research support from Neurologix, Inc., and the NIH (NINDS).

Dr. Ma has received research support from the NIH (NINDS, NIDCD)

Dr. Spetsieris has received research support from the NIH (NINDS)

Dr. Eidelberg serves on scientific advisory boards for the Michael J. Fox Foundation and the Bachmann-Strauss Dystonia and Parkinson Foundation; Inc. and Merck & Co., Inc., serves on the editorial board of *Annals of Neurology* and *NeuroImage* and as Associate Editor for the *Journal of Neuroscience*; and is listed as coinventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same; has received research support from the NIH (NINDS, NIDCD, NIAID), High Q Foundation, the Dana Foundation, and the Bachmann-Strauss Dystonia and Parkinson Foundation; has served as an expert in medico-legal cases; and has served as scientific advisor for the Thomas Hartman Foundation for Parkinson's Research, Inc., and as a consultant for Neurologix, Inc.

global activity. Moreover, significant declines in GMR are not associated with the appearance of PDRP-like spatial topographies.

Keywords

Parkinson's disease; PET; Sleep

Introduction

Spatial covariance analysis of metabolic images has provided valuable insights into the network-level abnormalities that underlie different brain disorders (Eidelberg, 2009). In recent years, a rigorous computational framework has been developed to identify specific disease-related metabolic topographies, which can be used to track disease progression and monitor treatment responses (Habeck and Stern, 2010; Spetsieris and Eidelberg, 2011). Of the neurodegenerative disorders, Parkinson's disease (PD) has been the most extensively studied from a network standpoint (Poston and Eidelberg, 2011; Niethammer and Eidelberg, 2012). This disorder is associated with an abnormal metabolic network (Fig. 1A) characterized by increased activity in the putamen, globus pallidus, ventral thalamus, dorsal pons and cerebellum, with relative reductions in premotor and parietal association regions. This distinctive and highly replicable topography, known as the PD-related covariance pattern (PDRP), is thought to represent disease-specific abnormalities of local synaptic activity analogous to those described in experimental animal models of the disorder (e.g., Guigoni et al., 2005). Indeed, a topographically homologous metabolic network has recently been reported in non-human primates with experimental parkinsonism (Ma et al., 2007). The intimate relationship between the PDRP and the underlying disease process has been substantiated by the close correlation that has been observed between network activity and intraoperative cell recordings in PD patients (Lin et al., 2008). Further support for a biological interpretation of the PDRP topography is provided by the stereotyped distal changes that have been noted following surgical antiparkinsonian interventions targeting discrete elements of this network (Eidelberg et al., 1996; Fukuda et al., 2001; Su et al., 2001; Asanuma et al., 2006; Trost et al., 2006; Mure et al., 2011).

The PDRP topography has also been thought to be an artifact of global normalization (Borghammer et al., 2008; 2009a; b), a commonly utilized means of reducing intersubject variability in the analysis of brain imaging data. It is well appreciated that this preprocessing step, particularly ratio normalization by the global mean value for each scan, can potentially elevate measurements of local activity in healthy brain regions (e.g., Petersson et al., 1999), and also affect the magnitude and direction of resting state correlations (Fox et al., 2009; Murphy et al., 2009). This concern is particularly relevant in studies of progressive neurodegenerative disorders, in which global measurements can decline rapidly over time. Nonetheless, disease-related covariance topographies such as PDRP are notably less susceptible to this form of measurement bias (Petersson et al., 1999; Ma et al., 2009; Spetsieris and Eidelberg, 2011). The Scaled Subprofile Model (SSM), the earliest computational algorithm used to detect abnormal covariance patterns in resting-state metabolic imaging data (Moeller and Strother, 1991; Alexander and Moeller, 1994), was specifically designed to disambiguate global and topographic effects in combined scan data from patients and healthy control subjects. In this situation, measures of cerebral function often exhibit skewed log-normal distributions (Crow and Shimizu, 1988), and variability in resting brain activity can be modeled as the multiplicative product of the individual regional elements. Thus, the SSM represents global activity as the geometric mean of the voxel values, which is invariant under commonly used ratio scaling procedures (Spetsieris and Eidelberg, 2011). Moreover, substantial reductions in the global metabolic rate (GMR) were

not evident in scans obtained in a large group of non-demented PD patients (Spetsieris and Eidelberg, 2011). By contrast, SSM analysis of metabolic data from the more rapidly progressing atypical parkinsonian variant conditions, which are associated with larger global reductions, revealed highly specific disease-related covariance patterns that did not include regions of artifactually elevated activity as might have been expected as a consequence of ratio normalization (Eckert et al., 2008; Tang et al., 2010; Poston et al., 2012).

The question remains, however, whether artifactual increases in PDRP expression can occur in circumstances in which substantial reductions in global activity occur as observed in dementing illnesses. In a related vein, it has been suggested that spatial covariance patterns with subcortical hypermetabolic features resembling the pathological PDRP topography can be identified in healthy subjects as a consequence of the global reductions such as those associated with normal aging (Borghammer et al., 2012). To address these issues, we studied a group of healthy subjects in whom global metabolic activity was experimentally modulated by sleep induction. While the subjects experienced substantial declines in GMR during imaging, commensurate changes in PDRP expression were not observed. Moreover, despite substantial global differences in the sleep and wake scans, spatial covariance analysis failed to disclose the presence of PDRP-like metabolic topographies in the combined data from these subjects.

Methods

Subjects

Ten healthy volunteer subjects (age: 54.4 ± 16.1 years (mean $\pm$ SD), range: 31.6–72.6 years) were scanned with ^{18}F -fluorodeoxyglucose (FDG) PET in sleep and wakefulness (see below). Scans from the additional groups of subjects were used for reference: (1) a healthy control group comprised of 10 normal subjects (CN1; age: 53.2 ± 11.3 years, range: 32.8–70.8 years); (2) a PD patient control group comprised of 10 PD subjects (CN2; age: 56.8 ± 7.0 years, range: 38.5–65.8 years); and (3) a test-retest group of 10 PD subjects (age: 64.1 ± 8.9 years, range: 50.9–77.4 years) who underwent repeat metabolic imaging twice within three weeks as part of a previously published test-retest study (Ma et al., 2007). The reference studies were all conducted in wakefulness.

Ethical permission to conduct these studies was obtained from the Institutional Review Board of the North Shore-Long Island Jewish Health System. Written informed consent was obtained from each participant following a detailed explanation of the procedures.

Positron Emission Tomography

Imaging in the waking state was performed in three-dimensional (3D) mode using the GE Advance tomograph (GE Medical Systems, Milwaukee, WI) at North Shore University Hospital, Manhasset, NY as detailed elsewhere (e.g., Ma et al., 2007; Lin et al., 2008). All subjects fasted overnight before PET imaging; in the PD patients, antiparkinsonian medications were withheld for at least 12 hours before the start of imaging. The studies were performed in a dimly lit room and with minimal auditory stimulation. Global and regional rates of cerebral glucose utilization were computed for each scan on a voxel-by-voxel basis.

Imaging during sleep was performed as described previously (Hutchinson et al., 2000). In the subjects undergoing both sleep and wake studies, scanning took place on consecutive days in random order. For sleep induction, subjects received 100 mg–200 mg of secobarbital orally approximately one hour before imaging. The sleep state during imaging was monitored with EEG recordings; radiotracer was injected only after the subjects were judged to be in stage II sleep.

Data Analysis

Metabolic images were standardized to the Montreal Neurological Institute template using an isotropic spatial smoothing filter (10 mm full width at half maximum); sleep and wake scans were aligned automatically. All image processing was performed using Statistical Parametric Mapping (SPM) software (Wellcome Department of Cognitive Neurology, London, UK) running in MATLAB (Mathworks, Natick, MA).

We first determined whether abnormal elevations in PDRP expression can be induced experimentally in healthy subjects by lowering global activity. To this end, we quantified PDRP expression in each subject/condition using an automated voxel-based algorithm (software available at <http://www.fil.ion.ucl.ac.uk/spm/ext/#SSM>) described previously (Ma et al., 2007; Eidelberg, 2009). These computations were performed blind to subject, group (PD/normal), and experimental condition (sleep/wake; test/retest). The resulting PDRP values were standardized by z-transformation with respect to the 33 healthy volunteer subjects used in deriving the pattern (Ma et al., 2007).

For each scan we computed GMR, which can be influenced by individual variation in injected activity, body weight, and the state of alertness of the subject during radiotracer uptake. Because it is possible for the measured GMR values to be influenced by large-scale topographic effects in the data, the SSM provides an additional global measure that is region independent, i.e., that scales all voxels equally in a given scan (Moeller and Strother, 1991; Alexander and Moeller, 1994; Moeller et al., 1996). That is, the SSM analysis partitions GMR variance into global and regional effects represented respectively by the global scaling factor (GSF) and the topographic profiles, i.e., the principal component (PC) patterns in the data. Operationally, the GSF is obtained by saving the unstandardized residuals of a multiple regression analysis where the PC scalars (i.e., the subject scores) are used to predict the GMR for each subject/condition. Hence in the current study, the GSF represented that aspect of GMR variance that was not explained by individual differences in the expression of the first several PCs (together accounting for the upper 50% of the subject $\times$ voxel variance in the combined sleep-wake data (see below). The significance of sleep-wake changes in PDRP expression and in global activity was respectively determined by comparing the between-condition differences to the test-retest differences of each measure using 2 $\times$ 2 repeated measures analysis of variance (RMANOVA) with post-hoc Bonferroni tests. This approach was also used to directly compare sleep-wake differences in PDRP expression with the concurrent changes in global activity. The relationship between changes in these variables was additionally evaluated by correlation analysis using Pearson product-moment correlation coefficients. These analyses were implemented in SPSS 17.0 for Windows (SPSS, Chicago, IL) and were considered significant for $p < 0.05$.

In a separate set of analyses, we determined whether PDRP-like topographies are expressed in healthy subjects with low global metabolic activity. To this end, we combined the sleep and wake scans into a single group and conducted a voxel-wise SSM analysis. In this analysis, the relationship between mean spatial image, global scaling factor and the PCA component is defined by the following equation:

$$P_{ij} = GMR_i + GMP_j + SRP_{ij}$$

where i is the subject index and j is the voxel index. The subject log data (P_{ij}) can be expressed as a sum of subject and spatial mean values and a subject residual profile term (SRP_{ij}) that is submitted to PCA. GMR_i is the subject whole brain mean log value. The subject GMR_i value is subtracted from the corresponding subject voxel values and the GMP_j

is then evaluated as the spatial group mean value of voxel j . Details of the SSM analysis have been reported elsewhere (Eidelberg, 2009; Spetsieris and Eidelberg, 2011).

Logistical regression analysis was then performed on subject scores for the patterns that account for the largest effects in the data (typically the first four or five PCs, together accounting for approximately 50% of the subject $\times$ voxel variance) to identify that which maximally discriminated between the wake and sleep conditions. Specifically, subject scores for each PC were entered singly and in all possible combinations as the independent variables into a series of logistical regression models with the experimental condition (wake/sleep) as the dependent variable. The model with the lowest Akaike Information Criterion (Burnham and Anderson, 2002) value was selected and significance was determined by the p -value of the likelihood ratio test.

Voxel weights on the PCs contributing to the selected model were linearly combined according to the regression coefficients on the respective subject scores (Moeller et al., 1996). Voxel weights on this topography were tested for reliability using bootstrap resampling with 1,000 iterations (Efron and Tibshirani, 1994; Habeck and Stern, 2010). Forward computations of pattern expression in prospective scan data from individual subjects were performed as described above. All subject scores for the resulting sleep/wake discrimination pattern were z -transformed with respect to the waking scans of the derivation cohort such that the mean value was zero with a standard deviation of one.

Following spatial covariance analysis, we interrogated the space spanned by the major pattern vectors for the presence of topographies with “PDRP-like” regional features. This was accomplished by correlating the loadings on each of these patterns with the corresponding PDRP weights using a voxel-wise routine described elsewhere (Mure et al., 2011). The R^2 -value for each correlation was computed across all voxels with non-zero region weights. For this calculation, images are assumed to be previously spatially normalized in 3D space and only voxels that are not zero in both images are considered. Voxel weights on both covariance patterns are represented as data vectors of equal size, involving approximately 150,000 voxels for the masked non-zero gray matter space common to the two patterns. Voxels from each image are formatted into a single vector by appending successive rows in each plane of the image. Voxel weights on each pattern, i.e., the regional elements of the respective data vectors, were z -scored as per our routine (Spetsieris and Eidelberg, 2011). The two vectors are input into the MATLAB statistical routine ‘corr’ to calculate the Pearson’s product-moment correlation coefficient. The same procedure was separately applied to the sleep/wake discrimination pattern to determine whether its regional loadings correlated with those on the PDRP.

Results

Sleep induction (Fig. 1B) produced a decline in GMR of $33.9 \pm 13.9\%$ (mean $\pm$ SD, range: -16.9 to -55.8%) relative to the baseline waking condition ($p < 0.001$). These changes were significantly greater than the test-retest differences of this measure ($F(1, 18) = 22.5$, $p < 0.001$; 2×2 RMANOVA). Waking GMR in this group did not differ from the corresponding values measured in the healthy and PD control cohorts ($p = 0.38$). By contrast, PDRP expression measured concurrently in these subjects (Fig. 1C) did not change significantly during sleep induction ($p = 0.11$). The changes in network activity observed during sleep induction did not differ from the test-retest differences of this measure ($F(1, 18) = 1.4$, $p = 0.26$; 2×2 RMANOVA). Indeed, the sleep-wake differences in PDRP expression observed in these subjects were substantially smaller in magnitude than the concurrent declines in GMR recorded from the same individuals ($F(1, 18) = 19.6$, $p < 0.001$; 2×2 RMANOVA). Similarly, the differences in network expression seen during sleep did not correlate with declining

global values ($R^2=0.04$, $p=0.59$). Of note, PDRP expression in these healthy subjects, whether measured in sleep or wakefulness, did not differ from reference values for waking normals in the healthy control group ($p=0.22$). On the other hand, PDRP values measured in either condition, were lower than reference values for waking patients in the PD control group ($p<0.001$).

Spatial covariance analysis of the combined sleep and wake scan data revealed four linearly independent principal components (PCs 1–4) that together accounted for 58.9% of the subject $\times$ voxel variance. Comparison of these covariance topographies with the PDRP disclosed no spatial homology between these PCs and the PDRP network ($R^2<0.07$, voxel-wise correlation analysis). Further analysis revealed the presence of a specific spatial covariance pattern for which subjects expression differed across experimental conditions. This topography (Fig. 2A), representing a linear combination of the PCs 1–4 (23% variance accounted for), was characterized by covarying reductions in metabolic activity in the cerebellum, mediodorsal thalamus, posterior cingulate area, and inferior parietal lobule, and occipital cortex. Voxel weights on the pattern in these brain regions (Table 1) were found to be reliable by bootstrap resampling (1,000 iterations, $p<0.001$). These values did not correlate ($R^2=0.01$) with the corresponding regional loadings on the PDRP network.

In all subjects, the expression of this pattern (Fig. 2B) increased in sleep relative to the baseline waking condition ($p=0.002$, binomial test). Of note, pattern expression during wakefulness was found to be similar (Fig. 2C) to the corresponding values computed in the healthy and PD control cohorts ($p>0.41$) and in the test and retest PD groups ($p>0.43$). The increases in pattern expression observed during sleep did not correlate with concurrent changes in PDRP expression ($R^2=0.06$, $p=0.50$) or global activity (GMR: $R^2=0.02$, $p=0.73$; GSF: $R^2=0.06$, $p=0.48$).

Discussion

The data reported in this study demonstrate that experimentally induced reductions in global metabolic activity are not associated with increased PDRP expression. We found that the changes in PDRP expression that took place during sleep induction were significantly smaller than the concurrent declines in global metabolism that were observed, and did not differ from the test-retest differences of the measure. Indeed, despite the consistent global reductions that occurred with sleep, PDRP expression remained within one SD of the normal mean reference value. In this vein, no correlation was evident between the reductions in global activity that were induced by sleep and concurrent changes in PDRP expression. Lastly, contrary to the proposed hypothesis, declining global activity in healthy individuals was not associated with the appearance of artifactual spatial covariance patterns resembling the disease-related topography.

While PDRP-like topographies were not detected, spatial covariance analysis did reveal a consistent sleep-related metabolic topography in the combined sleep-wake data. This covariance pattern was characterized by reduced metabolic activity in the medial thalamus, and in posterior cingulate, inferior parietal, and occipital cortex. These regions accord well with the changes in regional cerebral blood flow and glucose utilization reported previously in healthy subjects scanned during non-REM sleep (Braun et al., 1997; Nofzinger et al., 2002). While not previously described in relation to physiological sleep, prominent cerebellar metabolic reductions were also noted as part of the currently observed covariance topography. The changes observed in this region as part of the network are likely attributable to the barbiturate sedative that was used for sleep induction (Hutchinson et al., 2000). In any event, the expression of this brain network during sleep proved to be independent of changes in both GMR and GSF, a model-based estimator of the region-free

global effect. In fact, sleep-wake changes in these measures of global activity were closely inter-related ($R^2=0.96$). Thus, the observed global changes are unlikely to have been driven by topographic (i.e., region-specific) effects associated with the transition to non-REM sleep, the administration of a barbiturate sedative, or both. Moreover, the independence of the observed global and topographic effects suggests that the conclusions of the study can be generalized beyond the context of the sleep induction paradigm that was employed.

On a final note, we draw attention to recent reports confirming the presence of basal ganglia hypermetabolism in early stage PD patients scanned on a high resolution PET instrument (Eggers et al., 2009; Borghammer et al., 2012). These findings, resulting from mass-univariate analyses of the data incorporating different normalization schemes, lend further credence to the validity of the PDRP as a quantitative network biomarker of the disease process. Future studies employing spatial covariance analysis of data acquired on such platforms will help specify the precise anatomy of this abnormal topography.

Conclusion

The data indicate that reductions in global activity, as observed with sleep induction, do not lead to concomitant changes in PDRP expression. Moreover, network analysis of scan data from healthy subjects studied in both sleep and wakefulness did not disclose the presence of artifactual “PDRP-like” spatial topographies. Thus, the network-related increases in subcortical activity that characterize this disease-related covariance pattern cannot be ascribed to group differences in global metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank Ms. Yoon Young Choi and Ms. Patricia J. Allen for valuable assistance with manuscript preparation/editing.

Funding

This work was supported in part by Grant No. P50NS071675 (Morris K. Udall Center of Excellence in Parkinson's Disease Research at The Feinstein Institute for Medical Research) to D.E. from the National Institute of Neurological Disorders and Stroke. 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.

Abbreviations

PDRP	Parkinson's disease-related pattern
SSM	scaled subprofile model
GMR	global metabolic rate
SPM	statistical parametric mapping
GSF	global scaling factor
PC	principal component

References

- Alexander GE, Moeller JR. Application of the scaled subprofile model to functional imaging in neuropsychiatric disorders: A principal component approach to modeling brain function in disease. *Hum Brain Mapp.* 1994; 2:1–16.
- Asanuma K, Tang C, Ma Y, Dhawan V, Mattis P, Edwards C, Kaplitt MG, Feigin A, Eidelberg D. Network modulation in the treatment of Parkinson's disease. *Brain.* 2006; 129:2667–2678. [PubMed: 16844713]
- Borghammer P, Cumming P, Aanerud J, Forster S, Gjedde A. Subcortical elevation of metabolism in Parkinson's disease--a critical reappraisal in the context of global mean normalization. *Neuroimage.* 2009a; 47:1514–1521. [PubMed: 19465133]
- Borghammer P, Cumming P, Aanerud J, Gjedde A. Artefactual subcortical hyperperfusion in PET studies normalized to global mean: lessons from Parkinson's disease. *Neuroimage.* 2009b; 45:249–257. [PubMed: 18718541]
- Borghammer P, Hansen SB, Eggers C, Chakravarty M, Vang K, Aanerud J, Hilker R, Heiss WD, Rodell A, Munk OL, Keator D, Gjedde A. Glucose metabolism in small subcortical structures in Parkinson's disease. *Acta Neurol Scand.* 2012; 125:303–310. [PubMed: 21692755]
- Borghammer P, Jonsdottir KY, Cumming P, Ostergaard K, Vang K, Ashkanian M, Vafaee M, Iversen P, Gjedde A. Normalization in PET group comparison studies--the importance of a valid reference region. *Neuroimage.* 2008; 40:529–540. [PubMed: 18258457]
- Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, Selbie S, Belenky G, Herscovitch P. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. *Brain.* 1997; 120(Pt 7):1173–1197. [PubMed: 9236630]
- Burnham, KP.; Anderson, DR. Model selection and multimodel inference. New York: Springer Verlag; 2002.
- Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr.* 1994; 18:192–205. [PubMed: 8126267]
- Crow, EL.; Shimizu, K., editors. Lognormal distributions: theory and applications. New York: Dekker; 1988.
- Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, Feigin A, Eidelberg D. Abnormal metabolic networks in atypical parkinsonism. *Mov Disord.* 2008; 23:727–733. [PubMed: 18186116]
- Efron, B.; Tibshirani, R. An introduction to the bootstrap. New York: CRC Press, LLC; 1994.
- Eggers C, Hilker R, Burghaus L, Schumacher B, Heiss WD. High resolution positron emission tomography demonstrates basal ganglia dysfunction in early Parkinson's disease. *J Neurol Sci.* 2009; 276:27–30. [PubMed: 18835490]
- Eidelberg D. Metabolic brain networks in neurodegenerative disorders: a functional imaging approach. *Trends Neurosci.* 2009; 32:548–557. [PubMed: 19765835]
- Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Silbersweig D, Stern E, Woods RP, Fazzini E, Dogali M, Beric A. Regional metabolic correlates of surgical outcome following unilateral pallidotomy for Parkinson's disease. *Ann Neurol.* 1996; 39:450–459. [PubMed: 8619523]
- Fox MD, Zhang D, Snyder AZ, Raichle ME. The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol.* 2009; 101:3270–3283. [PubMed: 19339462]
- Fukuda M, Mentis MJ, Ma Y, Dhawan V, Antonini A, Lang AE, Lozano AM, Hammerstad J, Lyons K, Koller WC, Moeller JR, Eidelberg D. Networks mediating the clinical effects of pallidal brain stimulation for Parkinson's disease: a PET study of resting-state glucose metabolism. *Brain.* 2001; 124:1601–1609. [PubMed: 11459751]
- Guigoni C, Li Q, Aubert I, Dovero S, Bioulac BH, Bloch B, Crossman AR, Gross CE, Bezard E. Involvement of sensorimotor, limbic, and associative basal ganglia domains in L-3,4-dihydroxyphenylalanine-induced dyskinesia. *J Neurosci.* 2005; 25:2102–2107. [PubMed: 15728850]
- Habeck C, Stern Y. Multivariate data analysis for neuroimaging data: overview and application to Alzheimer's disease. *Cell Biochem Biophys.* 2010; 58:53–67. [PubMed: 20658269]

- Hutchinson M, Nakamura T, Moeller JR, Antonini A, Belakhlef A, Dhawan V, Eidelberg D. The metabolic topography of essential blepharospasm: a focal dystonia with general implications. *Neurology*. 2000; 55:673–677. [PubMed: 10980732]
- Lin TP, Carbon M, Tang C, Mogilner AY, Sterio D, Beric A, Dhawan V, Eidelberg D. Metabolic correlates of subthalamic nucleus activity in Parkinson's disease. *Brain*. 2008; 131:1373–1380. [PubMed: 18400841]
- Ma Y, Tang C, Moeller JR, Eidelberg D. Abnormal regional brain function in Parkinson's disease: truth or fiction? *Neuroimage*. 2009; 45:260–266. [PubMed: 18992824]
- Ma Y, Tang C, Spetsieris P, Dhawan V, Eidelberg D. Abnormal metabolic network activity in Parkinson's disease: test-retest reproducibility. *J Cereb Blood Flow & Metab*. 2007; 27:597–605. [PubMed: 16804550]
- Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Mandel F, Alexander GE, Grady C, Pietrini P, Eidelberg D. The metabolic topography of normal aging. *J Cereb Blood Flow Metab*. 1996; 16:385–398. [PubMed: 8621743]
- Moeller JR, Strother SC. A regional covariance approach to the analysis of functional patterns in positron emission tomographic data. *J Cereb Blood Flow Metab*. 1991; 11:A121–A135. [PubMed: 1997480]
- Mure H, Hirano S, Tang CC, Isaia IU, Antonini A, Ma Y, Dhawan V, Eidelberg D. Parkinson's disease tremor-related metabolic network: characterization, progression, and treatment effects. *Neuroimage*. 2011; 54:1244–1253. [PubMed: 20851193]
- Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage*. 2009; 44:893–905. [PubMed: 18976716]
- Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: concepts and applications. *Ann Neurol*. 2012 in press.
- Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, Price JC, Sembrat RC, Ombao H, Reynolds CF, Monk TH, Hall M, Kupfer DJ, Moore RY. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. *Brain*. 2002; 125:1105–1115. [PubMed: 11960899]
- Petersson KM, Nichols TE, Poline JB, Holmes AP. Statistical limitations in functional neuroimaging: Non-inferential methods and statistical models. *Philos Trans R Soc Lond B Biol Sci*. 1999; 354:1239–1260. [PubMed: 10466149]
- Poston KL, Eidelberg D. Functional brain networks and abnormal connectivity in the movement disorders. *Neuroimage*. 2011
- Poston KL, Tang CC, Eckert T, Dhawan V, Frucht S, Vonsattel JP, Fahn S, Eidelberg D. Network correlates of disease severity in multiple system atrophy. *Neurology*. 2012; 78:1237–1244. [PubMed: 22491861]
- Schmahmann, JD.; Doyon, J.; Toga, AW.; Petrides, M.; Evans, AC. *MRI atlas of the human cerebellum*. San Diego: Academic Press; 2000.
- Spetsieris PG, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: methodological issues. *Neuroimage*. 2011; 54:2899–2914. [PubMed: 20969965]
- Su PC, Ma Y, Fukuda M, Mentis MJ, Tseng HM, Yen RF, Liu HM, Moeller JR, Eidelberg D. Metabolic changes following subthalamotomy for advanced Parkinson's disease. *Ann Neurol*. 2001; 50:514–520. [PubMed: 11601502]
- Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, Dhawan V, Lesser M, Vonsattel JP, Fahn S, Eidelberg D. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol*. 2010; 9:149–158. [PubMed: 20061183]
- Trost M, Su S, Su P, Yen RF, Tseng HM, Barnes A, Ma Y, Eidelberg D. Network modulation by the subthalamic nucleus in the treatment of Parkinson's disease. *Neuroimage*. 2006; 31:301–307. [PubMed: 16466936]

Fig. 1. Parkinson's disease-related metabolic pattern (PDRP)

A. This metabolic network was identified by spatial covariance analysis of ^{18}F -fluorodeoxyglucose (FDG) PET images from 33 PD patients and 33 age-matched healthy volunteer subjects (Ma et al., 2007). This pattern was characterized by increased metabolic activity (*red*) in the putamen, globus pallidus (GP), thalamus, pons, cerebellum and sensorimotor cortex, associated with relative reductions (*blue*) in the lateral premotor cortex (PMC) and parieto-occipital association regions.

[In this combined group analysis, the PDRP was represented by the first principal component pattern (PC1, accounting for 21.4% of the subject $\times$ voxel variance), which

constituted the largest effect in the data. The display of the voxel weights on the pattern was thresholded at $Z=3.61$, $p<0.001$ and overlaid on T1-weighted MR-template images].

B. Global metabolic rate (GMR) for healthy subjects scanned in wakefulness (*gray bar*) and in sleep (*black bar*), and for a reference group (*white bar*) comprised of healthy control (CN1) subjects scanned in wakefulness. Analogous values are displayed for PD patients scanned as part of a test (*gray bar*)/retest (*black bar*) study (Ma et al., 2007), and for a separate reference group (*white bar*) of waking PD controls (CN2). A significant decline in GMR ($p<0.001$) was observed during sleep induction, whereas no change was evident between test and retest ($p=0.71$).

C. The corresponding sleep-wake changes in PDRP expression did not differ from the test-retest differences of this measure ($p=0.26$).

Fig. 2. Sleep-related metabolic pattern

A. This pattern was identified in the spatial covariance analysis of sleep and wake scans from 10 healthy subjects (see text). The resulting topography was characterized by covarying reductions in the cerebellum, medial thalamus, occipital cortex, posterior cingulate gyrus, and in parietal association regions. Voxel weights for the pattern were demonstrated to be reliable by bootstrap resampling ($p<0.001$; 1,000 iterations). [The covariance map was overlaid on T1-weighted MR-template images. The display of the pattern was thresholded at $Z=2.58$, $p=0.01$. Voxels with negative region weights (metabolic decreases) are color-coded blue.]

B. The expression of this pattern increased consistently in all subjects during sleep induction ($p=0.002$, binomial test). [Error bar represents one standard error of the mean. Values in sleep are represented by closed symbols; values in wakefulness by open symbols.]

C. Pattern expression was elevated in sleep relative to wakefulness in both the healthy control group (CN1), the PD control group (CN2), and the test-retest PD cohort ($p<0.001$).

Table 1
Brain regions with significant loadings on the sleep-related spatial covariance pattern

Brain region	Coordinates ^d			Zmax	c
	x	y	z		
Reduced activity (sleep < wake)					
Cerebellum, Hemisphere (Crus I, II) ^b	Left	-6	-84	-32	5.50***
	Right	14	-84	-32	4.38***
Cerebellum, Vermis ^b		0	-46	-34	2.67*
Inferior/Middle Occipital Gyrus (BA 17/18/19)		-6	-98	-8	3.01**
Posterior Cingulate (BA 23/30/31)					
Superior/Inferior Parietal Lobe (BA 40)		-30	-52	36	3.15***
Thalamus (mediodorsal)		4	-18	12	3.13**

^aMontreal Neurological Institute (MNI) standard space (Collins et al., 1994)

^bAccording to Atlas of Schmahmann (Schmahmann et al., 2000)

^cRegions with significant loadings on the sleep-related metabolic pattern. Z-values at peak voxel are given for each region (*p<0.05, **p<0.01, ***p<0.001). Voxel weights for each region were found to be reliable by bootstrap estimation (p<0.001; 1,000 iterations).
BA=Brodman Area