

Analytic Methods for Determining Multimodal Biomarkers for Parkinson's Disease

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Acknowledgements



Research Team

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 - Anthony Pileggi, , *Biostatistics and Bioinformatics*
- **Kaiser Permanente Georgia.**
 - Daniel Huddleston, MD, *Also *Neurology* at Emory
 - Michele Marcus, PhD, *Also *Epidemiology* at Emory

General Overview

- Our project seeks to develop statistical tools to identify multimodal biomarkers of Parkinson's disease (PD).
 - Establish a PD risk profile to identify subjects to populate future clinical trials (e.g. assessing neuroprotective treatments).
 - Examine multimodal imaging (MRI-based), biologic, and clinical candidate biomarkers.
 - Hypothesis driven biomarkers
 - A massive number of exploratory biomarkers
- Develop software for the PD biomarker research community to help implement our planned statistical tools.
- Make our data publicly available to the research community.

Outline



EMORY
ROLLINS
SCHOOL OF
PUBLIC
HEALTH

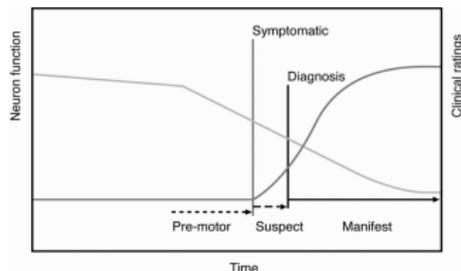
CBIS

Center for Biomedical
Imaging Statistics

- 1 Motivation
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- 3 Data
- 4 Preliminary Results

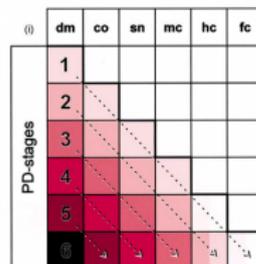
Motivation

The optimal window for neuroprotection in PD is during the **premotor period** before most neuronal death occurs.



Neurology 2009;72(Suppl 2):S21-S26.

Neuropathological evidence suggests that **locus coeruleus (LC)** may be involved with PD pathology before SNpc (Braak Hypothesis).

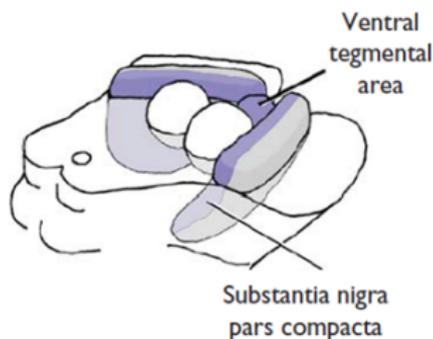


Neurobiology of Aging 24 (2003):197-211.

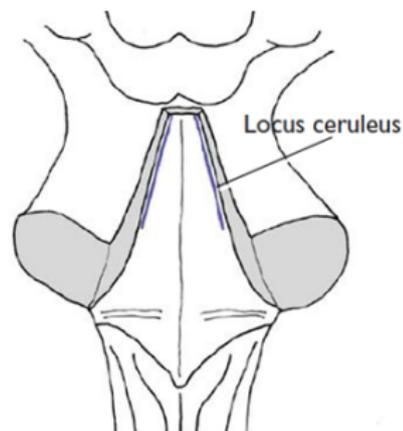
[**dm**: dorsal motor nucleus of the glossopharyngeal and vagal nerves; **co**: locus coeruleus (pons); **sn**: substantia nigra (midbrain); **mc**: anterior temporal mesocortex ; **hc**: high order sensory association areas and prefrontal fields ; **fc**: first order sensory association areas, premotor areas, and primary sensory and motor fields.]

Motivation

The catecholamine nuclei, substantia nigra (pars compacta) and locus coeruleus, degenerate in Parkinsons disease.



Dopaminergic nuclei

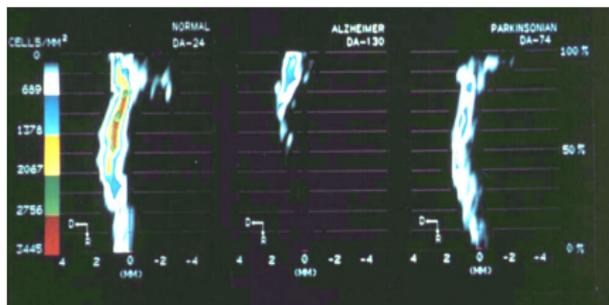


Noradrenalinergic nuclei

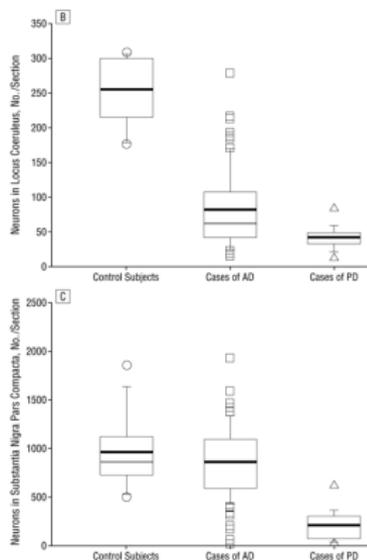
NeuroReport 9:1649-1654.

Motivation

Locus Coeruleus Cell Loss



German et al. (1992). Disease-specific patterns of locus coeruleus cell loss, *Ann Neurol* 32:667-676.



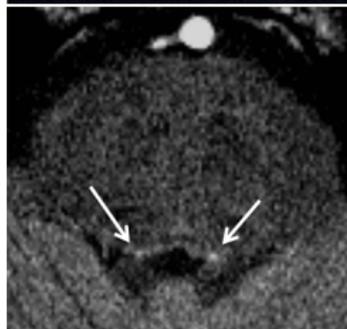
[AD (n=86) ; PD (n=19) ; HC (n=13)]

Zarow et al. (2003). Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases, *Arch Neurol* 60(3):337-341.

Motivation

Why MRI?

- **Safe, non-invasive**, longitudinal assessment in living subjects.
- **Multimodality**: can acquire multiple types of information in a single scanning session.
 - **MRI, fMRI, DTI, NM-MRI, CSI**
- **Translational application**: MRI is widely available and familiar technology in clinical settings.
- **Inexpensive** (relative to PET/SPECT) and **no radionuclide exposure**.



Motivation

Neuromelanin MRI reveals *decreased contrast* with neurodegeneration.

Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease

Makoto Sasaki^a, Eri Shibata^a, Koujiro Tohyama^b, Junko Takahashi^c, Kotaro Otsuka^d, Kuniaki Tsuchiya^e, Satoshi Takahashi^f, Shigeru Ehara^a, Yasuo Terayama^g and Akio Sakai^d

NEUROREPORT Vol 17 No 11 31 July 2006

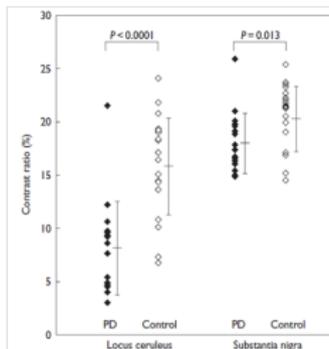
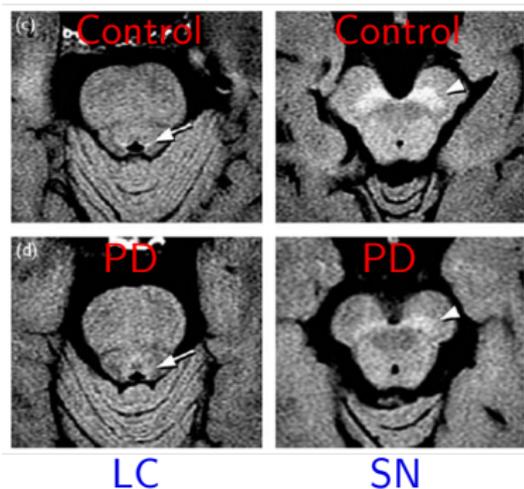


Fig. 2 Contrast ratios of the locus ceruleus (LC) and substantia nigra pars compacta (SNc) in patients with Parkinson's disease (PD) and age-matched healthy volunteers. The contrast ratio of the LC in PD patients ($8.3 \pm 4.3\%$) is markedly decreased as compared with that in the controls ($15.8 \pm 4.6\%$). The contrast of the SNc in PD patients ($18.0 \pm 2.8\%$) is also smaller than that in the controls ($20.3 \pm 3.0\%$). The decrease is statistically significant, although there is substantial overlap between the PD and control values.

Motivation

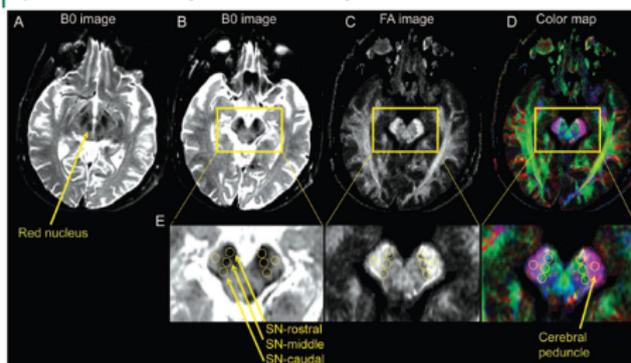
DTI in Substantia Nigra

High-resolution diffusion tensor imaging in the substantia nigra of de novo Parkinson disease

Neurology® 2009;72:1378-1384

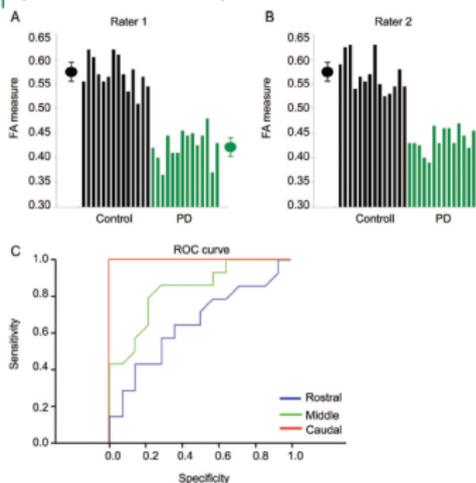
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Figure 1 Procedure used to draw regions of interest in the substantia nigra



A) B0 image with the red nucleus and substantia nigra. This slice was first identified. B) B0 slice just inferior to the slice shown in A, and this slice is where we draw the three regions of interest. C) shows the fractional anisotropy image and D) shows the colormap of the same slice in B. The region of interest for the cerebral peduncle is also shown. E) Larger image of the three regions of interest in the rostral, middle, and caudal substantia nigra as well as the region of interest in the cerebral peduncle. All images were generated in DtiStudio.

Figure 3 Differences between individual subjects

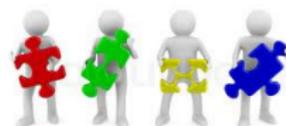


A) Fractional anisotropy values from rater 1 for patients with Parkinson disease (PD) (green) and healthy controls (black) from the caudal region of interest. The black symbol represents the average plus/minus 1 SD for control subjects. The green symbol represents the average plus/minus 1 SD for patients with PD. B) Same as in A but data are from rater 2. C) Receiver operating characteristic plots from the rostral (blue), middle (green), and caudal (red) region of interest. The caudal region had the greatest sensitivity and specificity.

Objectives

Multimodal biomarker detection

- Numerous findings suggest links between PD and **single** genetic, imaging, and biologic factors.
 - Many of these are non-specific or insensitive.
 - Single modality biomarkers may not fully address the complexity of PD.
- We regard PD as a complex, systems-level, multi-dimensional disorder with discrete, but functionally integrated manifestations.
- We will develop methods to define **multimodal PD biomarkers** from a massive number of hypothesis driven and exploratory candidate markers.



Specific Aims



Aim 1: To Develop new statistical techniques to reveal multimodal biomarkers for PD including imaging, clinical, and biologic variables.

- Collect **MRI**, **fMRI**, **DTI**, **NM-MRI**, **CSI** imaging data along with **genetic**, **clinical**, and **CSF**-based measures.
 - **NM-MRI** uses an *in-house optimized pulse sequence*, which captures both the LC and SN in ≈ 16 minute scan, and we apply a **contour segmentation algorithm** to generate LC volume estimates.
- **Develop statistical model** for high-dimensional data to pool strength across multiple data modalities for classifying subgroup membership (e.g. PD or HC).
 - $\ell_p(\beta, \lambda) = -\ell(\beta) + \sum_k \lambda_k P_k(\beta_k)$
 $\ell(\beta) = \sum_i [y_i \log \pi_i + (1 - y_i) \log(1 - \pi_i)]$
 - **Variable selection** using modality-specific penalties
 - Model **development**, **training**, **testing**, and **validation**
- Apply our developed tools to data from imaging-based studies.

Specific Aims



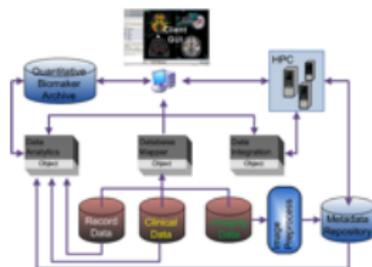
Aim 2: To identify prediagnosis clinical predictors of PD from a massive database obtained from an integrated, closed cohort healthcare system.

- Utilize **Kaiser Permanente Georgia patient database** to select PD patients (with medical history at KP) and healthy controls.
- Data will include **patient subgroup** (PD or not) along with **diagnoses**, **medication history**, and **lab results**.
- Develop regularized logistic predictive model to select significant clinical factors for predicting the probability of PD.
 - **Cross-sectional** clinical factors
 - **Longitudinal** clinical factors
- Generate risk score for development of PD.
 - Eligibility criterion for enrollment into future studies (e.g. clinical trials of neuroprotective treatments).

Specific Aims

Aim 3: To develop software equipped with a friendly graphical user interface to implement the multimodal biomarker detection methods.

- **Data management** system for storing, sharing, and securing data.
- **Data integration** component for fusing the different multimodal data and implementing preprocessing algorithms
- **Analysis** GUI for biomarker exploration, which supports execution of the approaches proposed in Aims 1 and 2.



Data

Multimodal Imaging-based Studies

- The data will include **81 subjects** across three studies
 - 38 Parkinson's disease patients
 - 32 Healthy control subjects
 - 11 Alzheimers disease patients
- Potential Biomarkers
 - Imaging
 - Genetic
 - Neurocognitive Testing
 - Questionnaire-Derived Scores
 - Clinical
 - CSF Neuroinflammation
 - CSF Catecholamine Metabolites

Data Measure	Udall	ADRC	Bumpus
Sample Size			
Parkinson's Disease (PD)	23	-	15
Healthy Controls (HC)	17	-	15
Alzheimer's Disease (AD)	-	11	-
Imaging			
Neuromelanin MRI (NM-MRI)	35	11	30
Resting-state fMRI (rs-fMRI)	39	11	-
Diffusion Tensor Imaging (DTI)	30	10	30
Chemical Shift Imaging (CSI)	36	10	-
Genotype			
DNA	40	11	30
Neurocognitive Testing			
MOCA	40	11	30
Questionnaires			
Beck Depression II	40	11	-
Beck Anxiety Index	40	11	-
RBD Questionnaire	40	11	30
Non-Motor Symptoms Ques.	40	11	-
Epworth Sleepiness	40	11	30
Freezing of Gait	40	11	-
Apathy Questionnaire	40	11	-
SCOPA-AUT	-	-	30
Clinical			
UPDRS-III Motor	40	11	30
MDS-UPDRS	-	-	30
UPSIT (Smell Test)	-	-	30
CSF Neuroinflammatory Markers			
Millipore 42-Plex Panel	-	-	30
CSF Catecholamine Metabolites			
DOPAC, DHPG	-	-	30

Table 1: Summary of the imaging-based datasets for use in Aim 1 of our project. Data shaded green have already been collected. Data shaded light blue will be collected and ready for processing and analysis by February 2014. The measures shaded orange will be made available for public access by 6 months after the close of our project.

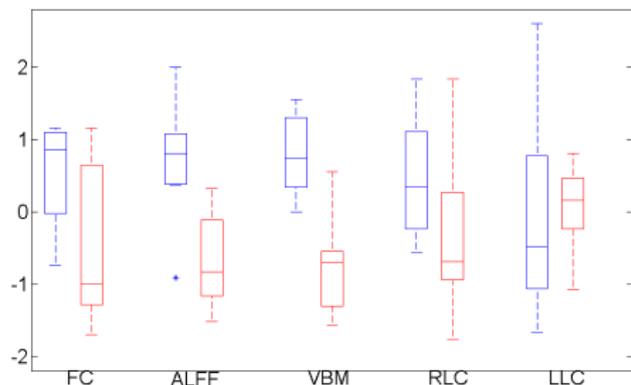
Data

Clinical Database from Kaiser Permanente Georgia Healthcare System

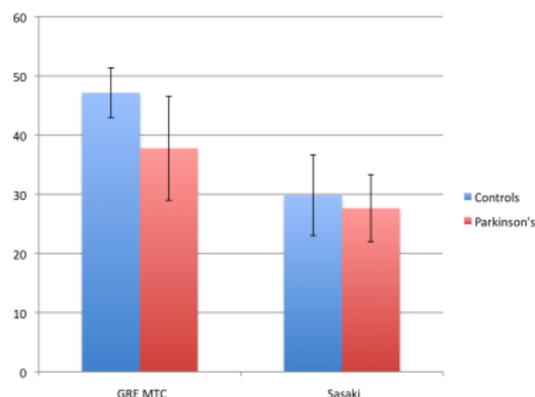
- The KP Georgia system includes over **235,000 patients**
- Approximately **530 Parkinson's disease patients** with at least one year of clinical observation prior to PD diagnosis
- Clinical chart database (Epic) allows data pulls for research.
- Potential PD Predictors
 - **ICD9 Codes:** depression, anxiety, constipation, anosmia, orthostatic hypotension, REM sleep behavior disorder
 - **Medications** used to treat these disorders: antidepressants, anxiolytics, constipation medications, fludrocortisone/midodrine, clonazepam
 - **Labs:** Anemia, EKG, electrolytes, liver function, etc.
- Very inexpensive to identify large numbers of potential pre-motor PD subjects.

Preliminary Results

Selected features from multiple imaging modalities.



[Blue represents PD patients and red represents HC subjects.
 Networks: FC; Local activity: ALFF; Volumetric: VBM;
 Chemical shift imaging: RLC and LLC].

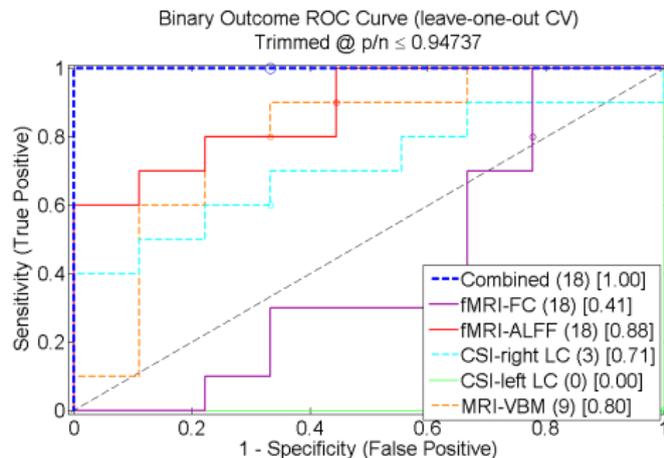


[NM-MRI Estimated Locus Coeruleus Volume.
 Controls: N=6; PD: N=9].

Preliminary Results

Multimodal classification of PD patients versus HCs

- Networks: FC
- Local activity: ALFF
- Volumetric: VBM
- Chemical shift imaging: RLC and LLC
- Multimodal dataset (blue)



Number of predictors and the AUC are given.

Acknowledgements



Thank you!

- Emory University and CBIS Collaborators:
 - Lijun Zhang, PhD, *Biostatistics and Bioinformatics*
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