Non-motor subtypes of Early Parkinson Disease in the Parkinson's Progression Markers Initiative

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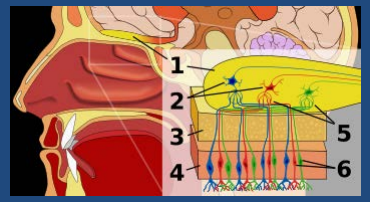
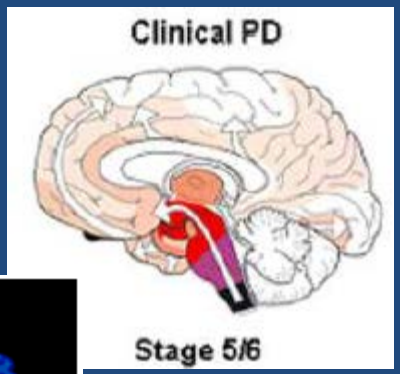
Background

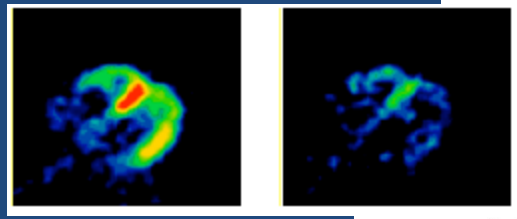
- Parkinson disease (PD) affects over 1 million Americans, with annual costs of $25 billion
- Diagnosis by clinical exam with characteristic movement disorder
  - Over half of neurons in the substantia nigra pars compacta affected
- Non-motor features occur in 90% of patients and manifest years prior to motor signs

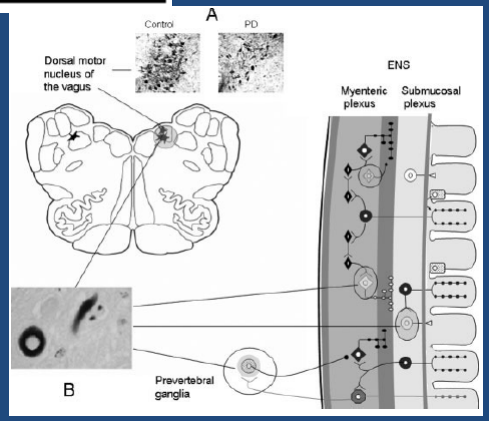
Background

- Non-motor features
  - Autonomic disorders
    - Blood pressure changes
    - Constipation
  - Cognitive impairment
  - Sleep and smell disorders
  - Psychiatric complications
- Non-specific, no biomarker
- Not ascribed to PD until motor features apparent









Background

- PD includes varied constellations of motor and non-motor features
- PD subtypes
  - Defined for motor phenotypes
    - Tremor-predominant
    - Postural Instability and Gait Disorders
    - Slow motor progression / Fast motor progression

Background

- Can PD subtypes be defined by non-motor features?
  - Non-motor features contribute more to morbidity, institutionalization and costs
  - More comprehensive and holistic management
- How early could non-motor subtypes be recognized?
  - Non-motor features occur before motor features
  - Earlier diagnosis
  - Earlier treatment

Objective

- To explore whether subtypes of Parkinson disease (PD) may be defined by non-motor features in a well-characterized cohort of recently diagnosed PD patients

Methods

The Parkinson's Progression Markers Initiative (PPMI)

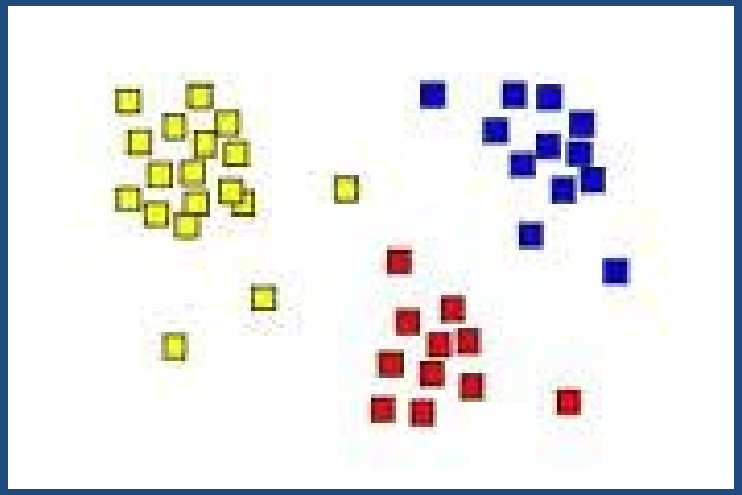
- Observational cohort which currently contains 345 individuals with PD:
  - at least 30 years old at baseline
  - diagnosed within last 2 years
  - not treated for PD (no medication effects)

Methods

- PPMI to be carried out over five years
  - 24 sites in United States, Europe, and Australia
  - 400 PD and 200 controls
  - Mean rates change and variability in clinical, imaging, and biomic measures
  - Comparisons between PD, controls and SWEDD's
  - Prodromal cohort recently added
  - http://www.ppmi-info.org

Methods

- Cluster Analysis
  - Grouping objects so that objects in the same group are more similar in some way to each other than those in other groups
  - Defined similarity by non-motor features



Methods

Variables used to cluster	
Sleep Disturbance Epworth Sleepiness Scale REM Sleep Disorder Questionnaire	Non-motor Questionnaire (MDS_UPRDS 1)
Psychiatric Disturbance Geriatric Depression Scale Impulsive-Compulsive disorders screen Anxiety State and Trait	Cognitive Measures Benton Judgement of Line Orientation Hopkins Verbal Learning Test Letter Number Sequencing Test Montreal Cognitive Assessment Test Semantic Fluency Symbol Digit Modalities Test
Autonomic dysfunction (SCOPA-AUTO)	
Disease Progression (MDS-UPDRS 1-3/mo)	Age of onset
University of Pennsylvania Smell ID Test	

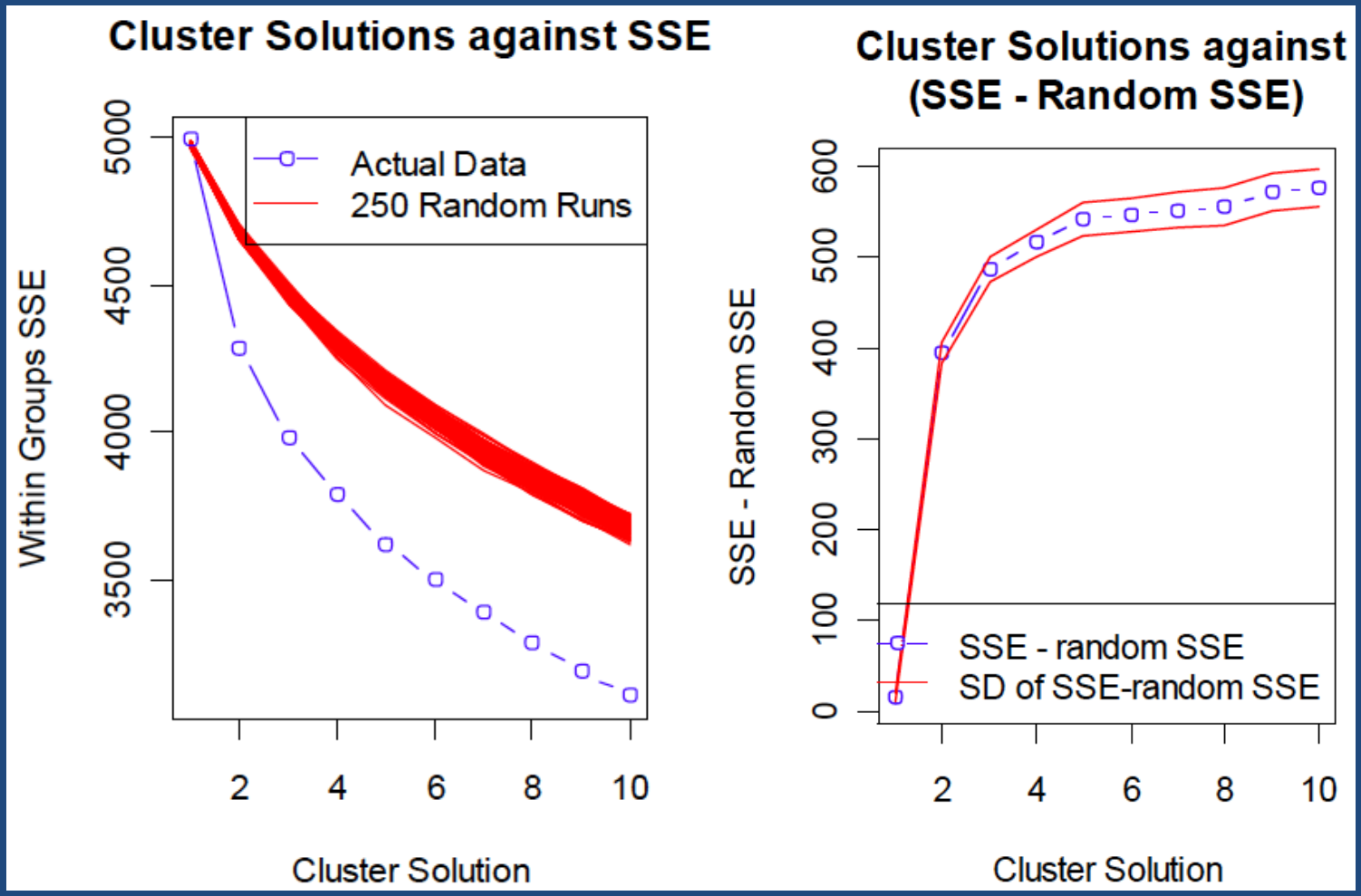
Methods

- K-means clustering
  - Partition observations into a pre-specified number of clusters in which each observation belongs to the cluster with the nearest mean
  - Means = Non-motor variables
- How do we decide the number of clusters?

Methods

- Sum of squared error (SSE)
  - Used to see if clusters exist, and the # of clusters
  - SSE = sum of squared distance between each member of a cluster and its mean
  - Compare the SSE of randomized data to SSE of actual data for an increasing number of clusters
  - If a data set has strong clusters, the SSE of the actual data should decrease more quickly than random data
  - The point at which difference between the SSE of random vs. actual data stops increasing determines the number of clusters

Methods



A 4 cluster solution was selected

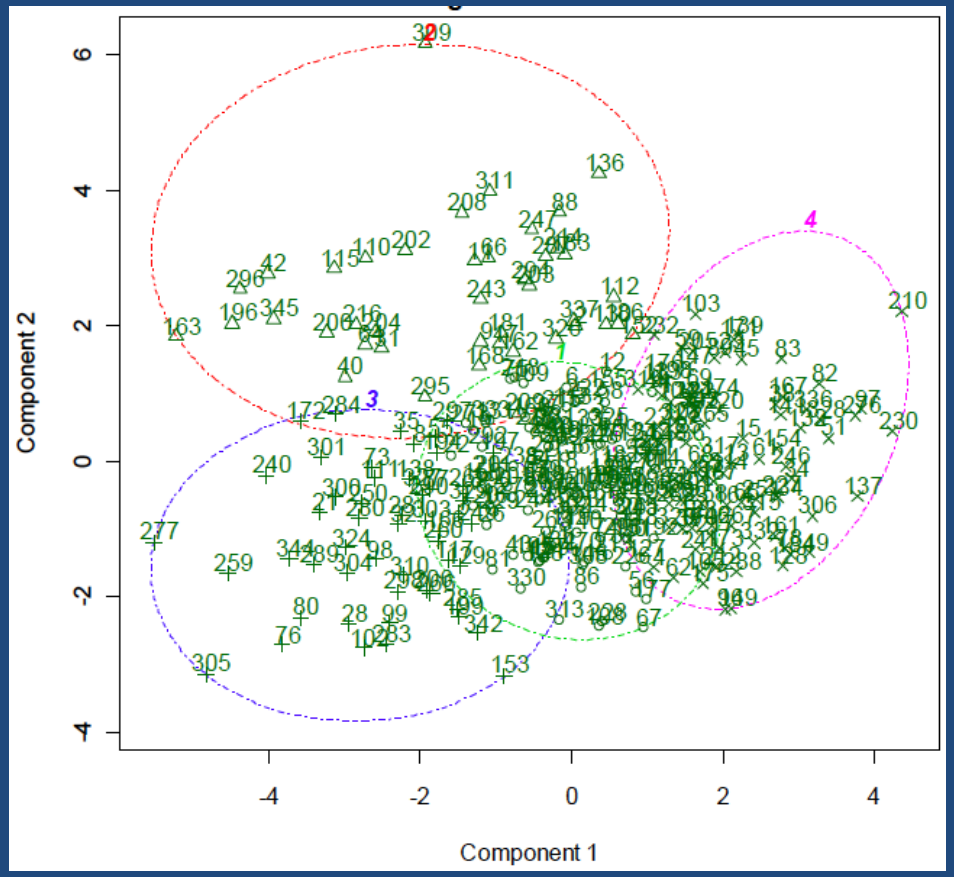
Methods

- Is there a way to graphically demonstrate clusters?
- Principal Components Analysis (PCA) scree plot
  - Orthogonal transformation = convert a set of observations of possibly correlated variables into linearly uncorrelated variables = principle components
  - The first principle component accounts for as much of the variability as possible
  - Each succeeding component accounts for as much variability as possible provided it be orthogonal to (uncorrelated with) preceding components
- Different linear combinations (coefiicients) of all cluster variables form each component

Results

Variable	Component 1	Component 2
Age	-0.332	-0.225
REM	-0.183	0.303
SCOPA-AUTO	-0.206	0.396
MDS-UPDRS 1	-0.177	0.520
Epworth	-0.150	0.379
Disease Progression	-0.194	0.080
Impulsivity	-0.074	0.303
Depression	-0.043	0.151
Anxiety	0.016	-0.201
Smell ID Test	0.195	0.199
Benton Line	0.219	-0.004
MOCA	0.281	0.146
Semantic Fluency	0.357	0.124
Letter Number	0.362	0.063
Verbal Learning	0.374	0.141
Digit Symbol	0.387	0.157

Coefficients of linear combinations comprising principal components and PCA plot



The first 2 components account for 34.36% of the point variability

Results

PD Participant Characteristics, Mean (SD)

Non-motor characteristics	N=313
Age	59.6
Hoehn and Yahr	1.6
MDS-UPDRS-1	6.0
MDS-UPDRS-2	6.0
MDS-UPDRS-3	20.0
# women (%)	109 (35%)
SWEDD	39 (12%)

Feature (Mean(SD)) Worst= Best=	ALL N=313 (100%)	Cluster 1 N=119 (38%)	Cluster 2 N=42 (13%)	Cluster 3 N=52 (17%)	Cluster 4 N=100 (32%)
MDS-UPRDS-1	6.0 (4.3)	5.2 (3.2)	13.3 (4.1)	5.1 (2.9)	4.4 (2.9)
Sleep - Epworth - REM	 6.3 (3.9) 5.3 (2.7)	 6.0 (3.1) 5.1 (2.5)	 10.6 (4.1) 7.4 (2.9)	 6.3 (4.4) 6.2 (3.0)	 5.0 (3.1) 4.3 (1.9)
Autonomic-SCOPA	13.7 (10.0)	13.4 (7.1)	26.7 (15.2)	13.4 (7.2)	8.8 (6.0)
Depression (>5 abnormal)	5.3 (1.4)	4.9 (1.1)	6.2 (2.1)	5.2 (1.3)	5.4 (1.2)
Impulsivity/Compulsivity	68 (22%)	19 (16%)	24 (57%)	8 (15%)	17 (17%)
Anxiety	46.6 (3.8)	46.2 (3.5)	45.2 (4.5)	48.3 (3.9)	46.7 (3.7)
Cognitive - Line Judgment - Verbal Learning - Letter-number - MOCA (>26 normal) - Sematic Fluency - Symbol Digit	 12.9 (2.2) 14.7 (2.5) 10.5 (2.7) 27.2 (2.2) 48.0 (11.1) 41.6 (9.9)	 13.3 (1.7) 14.8 (2.0) 10.3 (2.0) 27.2 (1.9) 47.2 (8.4) 41.3 (6.5)	 12.2 (2.5) 14.2 (2.3) 9.4 (2.5) 27.3 (2.3) 45.2 (9.3) 39.1 (10.4)	 11.2 (2.5) 11.9 (2.3) 8.0 (2.2) 25.1 (2.6) 37.4 (7.8) 29.6 (7.4)	 13.6 (1.6) 16.4 (1.8) 12.6 (2.1) 28.3 (1.5) 55.8 (10.8) 48.5 (7.7)
Smell ID	23.0 (8.5)	21.3 (7.4)	25.6 (8.7)	17.3 (8.1)	26.9 (7.8)
Age	59.6 (10.1)	63.3 (6.8)	59.7 (9.7)	68.3 (7.1)	50.8 (8.3)
Progression (per mo)	2.4 (2.5)	2.3 (2.0)	3.6 (3.3)	3.2 (3.5)	1.6 (1.4)
1st symptom to diagnosis (mo)	16.9 (22.5)	15.3 (13.9)	15.8 (15.6)	12.6 (15.6)	21.5 (33.2)
Women (N(%))	109 (35%)	34 (29%)	18 (43%)	14 (37%)	43 (43%)
SWEDD (N) (% of SWEDD's)	39 (12% of total)	7 (18%)	14 (36%)	5 (13%)	13 (33%)

Results

Motor features of clusters

Feature (Mean(SD))	ALL N=313 (100%)	Cluster 1 N=119 (38%)	Cluster 2 N=42 (13%)	Cluster 3 N=52 (17%)	Cluster 4 N=100 (32%)
Posture	0.3	0.4	0.5	0.5	0.2
Hypokinesia	0.7	0.8	0.8	0.8	0.7
Tremor	0.4	0.5	0.4	0.5	0.4
Motor Features at diagnosis	N (%)				
- Tremor	245 (81%)	98 (92%)	37 (88%)	41 (79%)	78 (78%)
- Rigidity	222 (71%)	89 (75%)	25 (56%)	33 (63%)	75 (75%)
- Bradyknesia	256 (82%)	98 (82%)	35 (83%)	40 (77%)	83 (83%)
- Postural Instability	27 (8.6%)	12 (10%)	8 (19%)	2 (4%)	5 (5%)
- Left side affected	119 (38%)	51 (43%)	12 (29%)	16 (31%)	40 (40%)
- Right side affected	182 (58%)	60 (50%)	28 (67%)	36 (39%)	58 (58%)
- Both sides affected	11 (3.5%)	8 (7%)	2 (5%)	0	1(1%)
Hoehn and Yahr Stage	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	1.7 (0.5)	1.4 (0.5)

- Tremor and bradykinesia are common at the time of diagnosis
- Bilateral involvement of motor features in early PD is rare

Results

- Main Findings in untreated early PD
  - 4 PD subtypes based on non-motor features
    1. Intermediate burden of non-motor features (38%)
    2. Non-cognitive, non-motor impairments with fastest progression (13%)
       - Most severe sleep, depressive and autonomic symptoms with highest prevalence of impulsive/compulsive features
    3. Cognitive and olfactory most impaired (17%)
       - Most severe olfactory and cognitive deficits across all measures
    4. Younger onset, mildest non-motor features and slowest progression (32%)

Summary

- Results support the concept that PD is a multi-system, multi-organ disease
  - Not just movement
  - Not just brain, involves other end-organs
- Such patterns of non-motor features may be present prior to diagnostic motor signs in longitudinal cohorts with incident PD cases
- Future plans:
  - Cluster with motor only, both motor/non-motor features
  - 2, 3 or 5 cluster solutions
  - Follow PD subtypes longitudinally
  - Biomic and imaging data