NEUROIMAGING OF DEGENERATIVE DISEASES

Silvina G Horovitz, PhD,
Staff Scientist
Human Motor Control Section
NINDS, National Institutes of Health
Bethesda, MD, USA
Aim: To understand
- Pathophysiology of the disease
- Disease progression
- Differential diagnosis
- Treatment assessment
Parkinson’s Disease

belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells.

https://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page
https://www.nia.nih.gov/health/parkinsons-disease
Parkinson’s Disease (PD)

Cardinal symptoms:
- tremor,
- rigidity,
- bradykinesia,
- postural instability

Treatment:
- Dopamine replacement
  Over time treatment wears off.
  Deep brain stimulation is an alternative

Non-motor symptoms:
- Sensory symptoms
  Voice, speech and swallowing disorders
- Gastrointestinal problems
- Autonomic dysfunction
- Sleep disorders
- Behavioral (apathy, amotivation; impulse control, executive function)
- Psychiatric (anxiety and panic, dementia, depression)
Behind the PD symptoms

- Genetic risk factors
- Protein misfolding and accumulation
- Toxins

Clinical manifestation

DISEASE MECHANISMS

PD symptoms
Behind the PD symptoms

- Genetic risk factors
- Protein misfolding and accumulation
- Toxins

Neuroimaging studies
- Inflammatory processes
- Mitochondrial dysfunction
- Protein misfolding and accumulation

Free water, structural
- 31P MRSI

Neuronal dysfunction and degeneration
- DTI, GRE, morphometry fMRI

Clinical manifestation
- PD symptoms
Multimodal approach:

Structural changes
- High resolution T1 weighted MRI
- Diffusion MRI
- Susceptibility weighted images
- Neuromelanin

Metabolic changes
- MR Spectroscopy / PET / SPECT

Functional changes
- Functional MRI (task and steady state)

integrated with clinical data, electrophysiology, and neuro-stimulation

Imaging & Clinical manifestation
Uses of neuroimaging to understand disease

- Identify changes
  - *Distinguish whether changes are cause or consequence of the disorder*
- Understand/Predict the onset of a disorder
- Differential diagnosis
- Understand/predict the disease progression
- Assess treatment

Cross-sectional studies

Imaging modality and type of analysis based on the research question

Populations with similar manifestations
Towards imaging biomarkers for PD

- Cross-sectional studies
- Longitudinal studies
- Populations at risk
- Healthy populations
- Differential diagnosis
CASE STUDY: Parkinson’s Disease

“Issues” to be aware when studying this population

- Elderly population
- Brain atrophy
- Neurodegeneration
- Enlarged ventricles
- Vascular issues

- Rigidity (difficult to accommodate head in coil)
- Tremor, dyskinesia (possible extra movement)
- Heterogeneity of symptoms
CASE STUDY:

Parkinson’s Disease

Outline:

• Pathophysiology of the disease
  • fmri
  • morphometry

• Disease progression
  • longitudinal studies

• Differential diagnosis
  • MRS

• Treatment assessment
  • DBS
(Dys)functional networks in PD
resting state fMRI studies
Basal ganglia circuitry in Parkinson's disease

Expert Reviews in Molecular Medicine © 2003 Cambridge University Press
Patients with Parkinson’s disease have difficulties with self-initiating a task and maintaining a steady task performance.
Network analysis

- Pre-processing AFNI
- Graph theory analysis:
  - Brain Connectivity Toolbox

- NETWORK DEFINITION

TABLE 2. Graph metric definitions

- Functional segregation of a neural network refers to its ability for specialized processing within clusters of nodes.
- Functional integration is related to a neural network's ability to bind information efficiently from distributed regions.
- Degree is the number of connections that link a node to the rest of the nodes in the network.
- Node strength is computed as the sum of weights of the connections that link a node to the rest of the nodes. It indicates how strongly one node is connected to the rest of the nodes in the network.
- Path is the shortest distance (i.e., minimum number of connections) between a node and every other node in the network. Efficiency is inversely related to path length.
- Global efficiency is calculated as the inverse of the average shortest path length between all pairs of nodes in the network. It is a measure of functional integration.
- Node Betweenness Centrality indicates how central a node is to the communication among other nodes in the network. It is computed as the fraction of all shortest paths in the network that contain a given node. Nodes with high values of betweenness centrality participate in a large number of shortest paths and potentially function as hubs.
- Clustering coefficient is computed as the number of connections that exist between the nearest neighbors of a node as a proportion of the maximum number of possible connections. It measures the density of connections between neighboring nodes. High clustering is associated with high local efficiency of information transfer.
- Local efficiency is computed as the inverse of the average shortest path connecting all neighbors of a node. It reflects how relevant a node is for the communication among other nodes within a local neighborhood, and is related to the clustering coefficient.
Deficits beyond motor network

Sensorimotor network
Execution
(motor output)

Cingulo-opercular network
Task-set maintenance
(maintaining the mental state)

Fronto-parietal network
Adaptive control
(cues and feedback; top-down)

Network: 86 nodes
FPN: 21 nodes
CON: 32 nodes
SMN: 33 nodes

Subjects:
30 HV
30 PD off medication (H&Y 2-3)

Tinaz, Lauro, Hallett, Horovitz; *Brain Struct Funct* 2015
Deficits in task-set maintenance and execution networks in Parkinson’s disease

Sule Tinaz

Network: 86 nodes
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Data pre-processing: AFNI
Network analysis: Matlab and Brain Connectivity Toolbox

Tinaz et al, 2015 Brain Struct Funct
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Tinaz et al., 2015 Brain Struct Funct

Cingulo-opercular network

Task-set maintenance
(maintaining the mental state)
How extensive are the changes in PD?

- How to parcel the brain?  
  - Craddock 200

- Functional and structural analysis
  - Resting state
  - DTI

The connectome (whole brain analysis)

Data pre-processing: AFNI; TORTOISE; FATCAT
Network analysis: Matlab and Brain Connectivity Toolbox
Breakdown in the functional modular organization of the PD connectome

Network: 200 nodes
Whole brain
Subjects:
20 HV
20 PD on medication

Tinaz, Lauro, Ghosh, Lungu, Horovitz; Neuroimage: Clinical, 2017
Breakdown in the functional modular organization of the PD connectome

Alterations in functional modularity in:
- core cognitive networks:
  - default mode network
  - dorsal attention networks,
- sensorimotor network

lack of modular distinction in the orbitofrontal and basal ganglia nodes in PD group

DTI: reduced node strength, clustering coefficient, and local efficiency in a small group of nodes mostly in the frontoparietal regions

**Dopaminergic treatment does not improve the functional network properties unanimously, on the contrary, may even be disruptive.**

Tinaz Lauro, Ghosh, Lungu, Horovitz; *Neuroimage: Clinical, 2017*
Effect of medication

Berman et al. Mov Dis 2016
How to parcel the brain?

- Whole brain parcellation (for example Craddock 200)
- Nodes from pre-defined networks
Limitations on "resting state"

- Comparison of clinical metrics defined on activity with brain at “rest”
- How much “rest” is in “rest”?
- How much motion or active motion suppression is present?
  - some control from looking at fluctuations properties of the motor areas.
- How much alertness variability?
  - *State or trait?*
Parkinson Disease affects brain networks beyond the motor system
- Connectivity studies can aid at identifying complexity of the disorder

Deficits are related to disease progression and affected by medication
- Are these deficits cause or consequence?

Functional changes are seen earlier than structural changes observed with tractographic methods
- Due to disease course or limitation on methods?
Parkinson’s disease (PD) is a progressive neurodegenerative disorder, characterized in histopathologic studies by dopaminergic cell loss in the substantia nigra (SN).

SN degeneration as a landmark

Lee et al. Neuroimage, 2018
Shapes and contrasts

- Longitudinal studies
- Cross-sectional studies
The ‘Swallow Tail’ Appearance of the Healthy Nigrosome – A New Accurate Test of Parkinson’s Disease: A Case-Control and Retrospective Cross-Sectional MRI Study at 3T

Schwarz et al. PLOS One 2014

\[\text{https://doi.org/10.1371/journal.pone.0093814}\]
Lateral Boundaries of the SN

https://doi.org/10.1002/ana.22592

Cho et al. Mov. Disorders 2011
Parkinson's disease related signal change in the nigrosomes 1–5 and the substantia nigra using T2* weighted 7T MRI

Longitudinal white matter microstructural change in Parkinson's disease

**Measure** | **Contrast direction** | **T-statistic** | **Location(s)** | **Cluster extent (mm³)**
--- | --- | --- | --- | ---
FA | PD decrease > control | 3.94 | B. midbrain tegmentum, periaqueductal gray matter | 344
MD | PD increase > control | 4.14 | B. midbrain tegmentum, L. thalamus | 896
RD | PD increase > control | 4.39 | B. midbrain tegmentum, B. pontine crossing tract, L. thalamus | 1,624
AD | PD increase > control | 4.29 | L. post. limb of internal capsule, L. thalamus, L. midbrain tegmentum | 1,240
Increased free water in the substantia nigra of Parkinson’s disease

Ofori et al. Neurobiology of Aging 2015
MRS to differentiate Parkinsonian syndromes

Quantitative magnetic resonance spectroscopic imaging in Parkinson’s disease, progressive supranuclear palsy and multiple system atrophy
Guevara et al. 2010 European Journal of Neurology V17,19

MRS to differentiate Parkinsonian syndromes

S. Zanigni et al.
Parkinsonism and Related Disorders 21 (2015) 929e937

Watanabe, Fukatsu, Katsuno, et al
J Neurol Neurosurg Psychiatry 2004;75:103–109
Treatment assessment

- On-off medication studies (as mentioned before)
  - DBS (our approach individual; M Fox: database)
  -
- tremor dominant (TD) and postural instability/gait difficulty (PIGD) subtype
Connectivity from databases to predicts DBS Outcome in Parkinson Disease

Horn et al. ANN NEUROL 2017;82:67–78
Big data

- PPMI (Parkinson’s progression markers initiative)
  - [http://www.ppmi-info.org/study-design/research-documents-and-sops/1](http://www.ppmi-info.org/study-design/research-documents-and-sops/1)

- Human connectome project
Methods: DBSproc

- Identify contacts from the CT scan
- Estimate Volume of Tissue Activated (VTA)
- Images Registration (target: T2w pre- AC-PC aligned)
  - pre-op: T1w, T2w, DWI 33dir
  - post-op: T1w, CT
- Connectivity from individual subject to predicts DBS Outcome in Parkinson Disease

Individual subject
Single contact Tractography

VTA - Thalamic Nuclei connectivity

Horovitz et al. ISMRM 2016

Binary analysis  (195 EC)
Threshold: 105 streamlines