

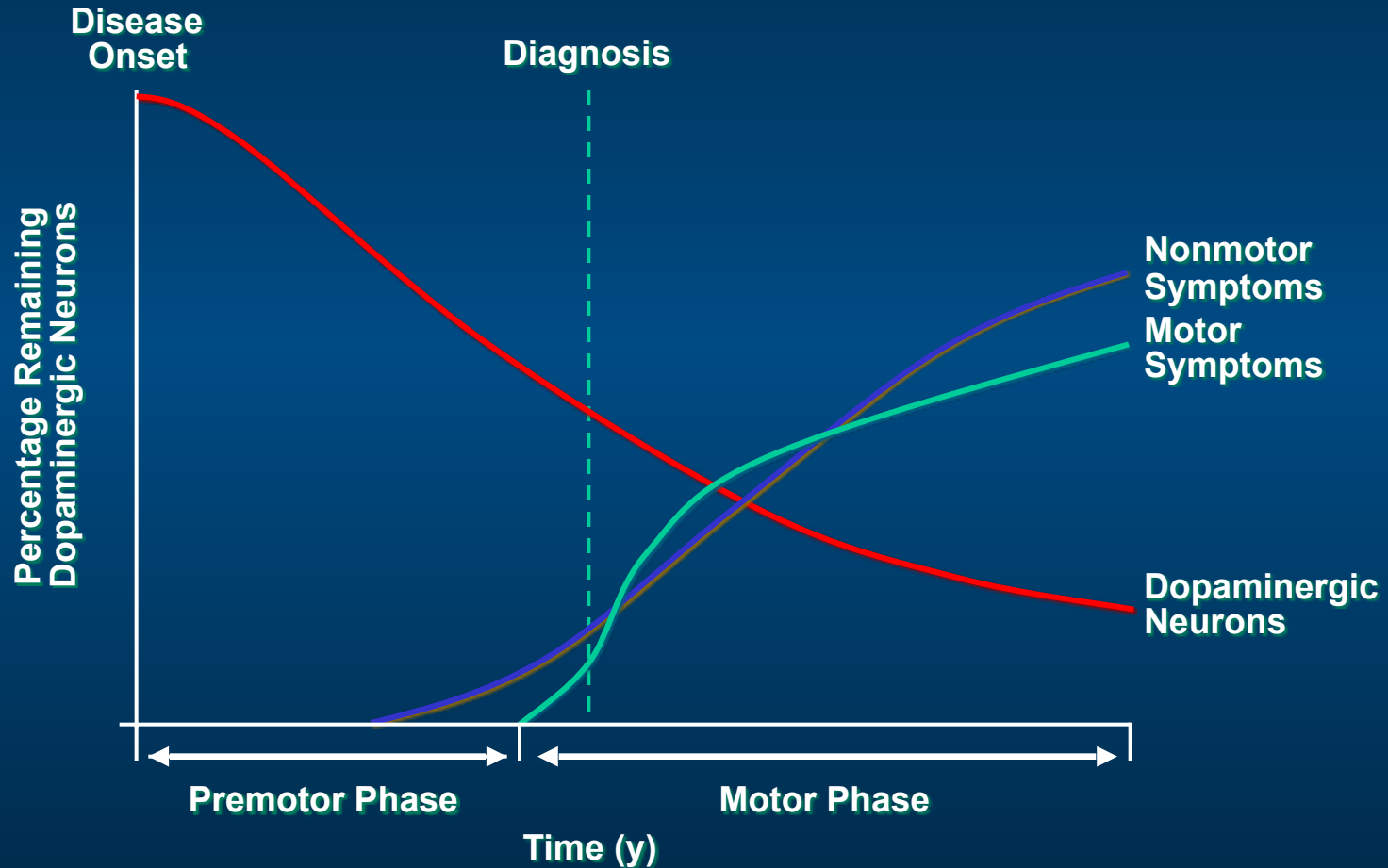
# **FOUNDATION OF UNDERSTANDING PARKINSON'S DISEASE**

- **DEE SILVER M.D MOVEMENT DISORDER  
SPECIALIST**
- **MEDICAL DIRECTOR -- PARKINSON  
ASSOCIATION OF SAN DIEGO 1980 TO  
PRESENT**
- **SCRIPPS MEMORIAL HOSPITAL, LA  
JOLLA CA. 1973 TO PRESENT**

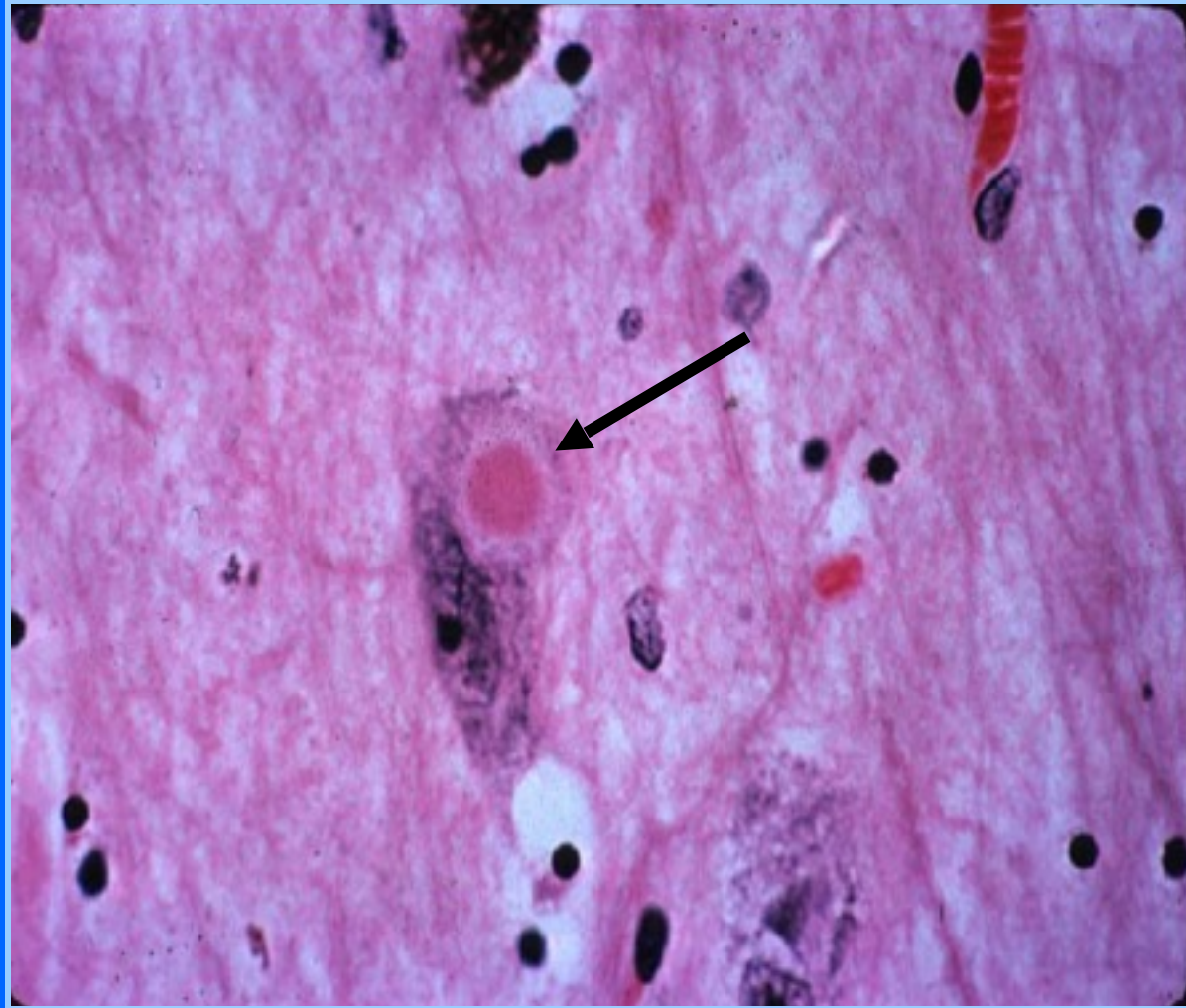
## **OUTLINE OF FOUNDATION TALK KNOWLEDGE IS POWER**

- **SIGN & SYMPTOMS OF IPD**
- **RED FLAGES FOR APD**
- **DIAGNOSTIC ACCURACY**
- **TREATMENT**
- **MAKE IT HAPPEN FOR Q OF LIFE, ACTIVITIES OF DAILY LIVING, REDUCED CAREGIVER BURDEN**

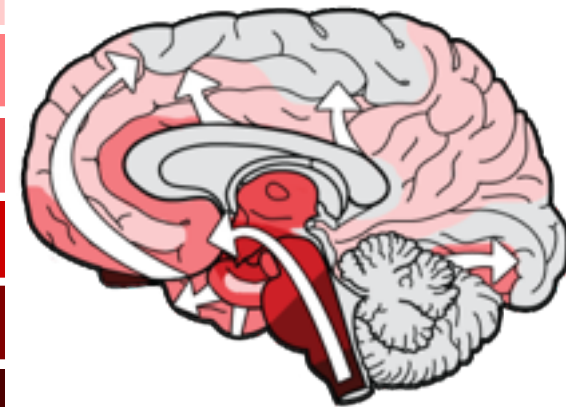
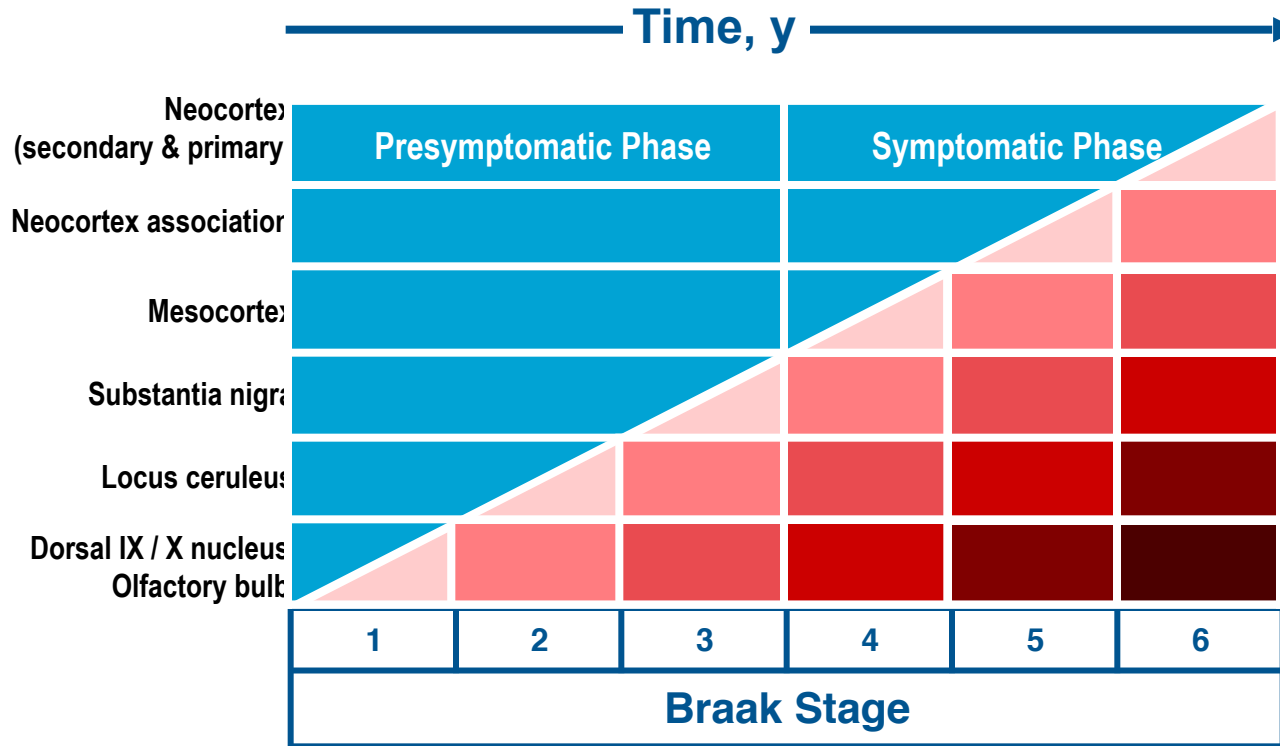
# Conceptual Diagram of the Phases of PD



# Lewy Body



# The Braak Hypothesis: An Evolving Concept of Disease Progression and Timing



Braak H et al. *Cell Tissue Res.* 2004;318:121-134.

Braak H et al. *J Neurol.* 2002;249(suppl 3):III/1-5.

Braak H et al. *Neurobiol Aging.* 2003;24:197-211.

Adaptation of figure reprinted with kind permission from Springer Science+Business Media: *Cell Tissue Res*, Stages in the development of Parkinson's disease-related pathology, 318, 2004, page 122, by Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K, Figure 1. Copyright ©2004 Springer Berlin Heidelberg.

# DX OF IPD—TRIO + ONE

- BRADYKINESIA—AKINESIA
- RIGIDITY
- RESTING TREMOR
- ASMMERTY
  - POSTURAL INSTABILITY-- LATER
    - NO KNOWN MARKER—YET
    - PROBABLY WILL NEED MORE THAN ONE MARKER BECAUSE OF THE HETEROGENITY OF IPD

# S & S OF ADVANCED IPD

- **RESTING TREMOR**
- **AKINESIA**
- **RIGIDITY**
- **POSTURAL INSTABILITY, FREEZING GAIT**
- **DYSKINESIAS; PEAK & DIPHASIC**
- **WEARING OFF (END DOSE FAILURE-EDF)**
- **DELAYED ON & NEVER ON**
- **SPEECH & SWALLOWING DSYFUNCTION**
- **BEHAVIOR & COGNITIVE DECLINE**

# RED FLAGS FOR APD

- Early falling, as postural instability
- With out robust response to L-Dopa or waning effect; taper off
- Dysphagia, dysarthria, lack of asymmetry
- Early cognitive loss
- Early orthostatic hypotension
- Early Neurogenic bladder
- Neuropsych and behavior changes
- Antiflexion, Retroflexion



# GENETICS-ABOUT 15

- **SNCA-alpha synuclein prone to aggregate**
- **LRRKS- leucine-rich repeat kinase-2**
- **GBA-beta-glucocerebrosidase**
- **DNAJC13, Parkin, PINK**
- **Others, CHCHD2, VPS35, ATP13A2, C9ORF72, SCA2, SCA3, FBX07, MAPT (tau)**

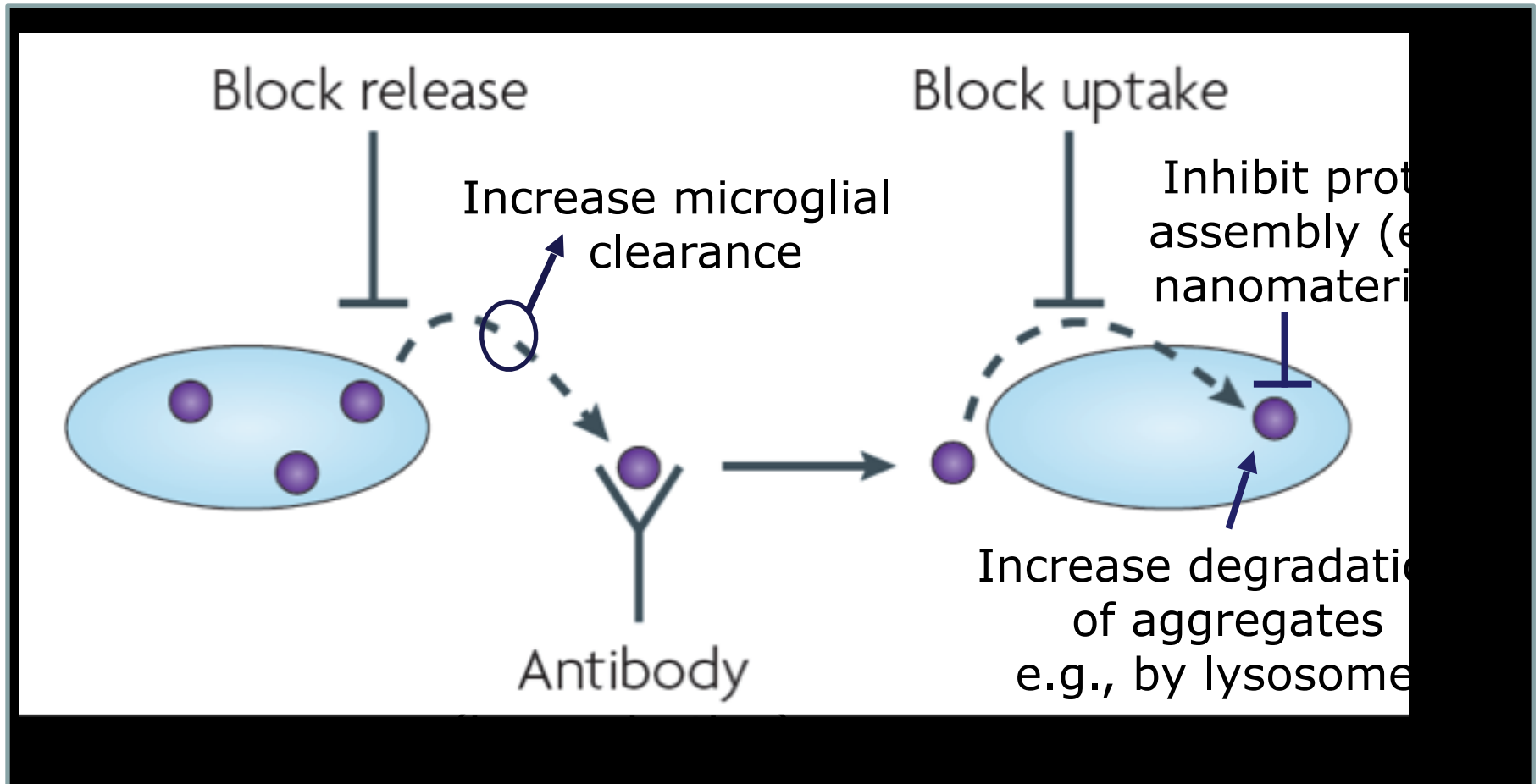
# Etiology of PD

- Specific causative factor unknown, but genetic and environmental factors probably involved
- Rare families with inheritance of abnormal genes
- Major epidemiologic study suggests:
  - Genetic factors play larger role in young-onset patients
  - Environmental insults play larger role in patients with onset after age 50
  - Age major risk factor

# RISK FACTORS

- AGE
- GENETICS
- ENVIROMENTAL
  - HERBISIDES
  - PESTISIDES
  - RURAL LIVING

# New Therapeutic Approaches Based on Trans-cellular Propagation of Protein Misfolding



# ANTICIPATION OF IPD

- **Hyposmia-85%**
- **RBD-alpha synuclein syndromes – IPD, LBD, MSA—early predictor, as much as 15 yrs, 85%**
- **Depression**
- **Constipation-30 to 50%**

# Non-motor Symptoms

## Cognitive/ Psychiatric

- Anxiety
- Depression
- Fatigue
- Slow thinking
- Hallucinations
- Sleep dysfunction\*
- Sleep fragmentation
- RBD & OSA

Neuropathy

RLS

Melanoma

## Autonomic

- Drenching sweats
- Dyspnea
- Orthostatic hypotension
- Sexual dysfunction
- Seborrhea
- Constipation
- Urinary urgency

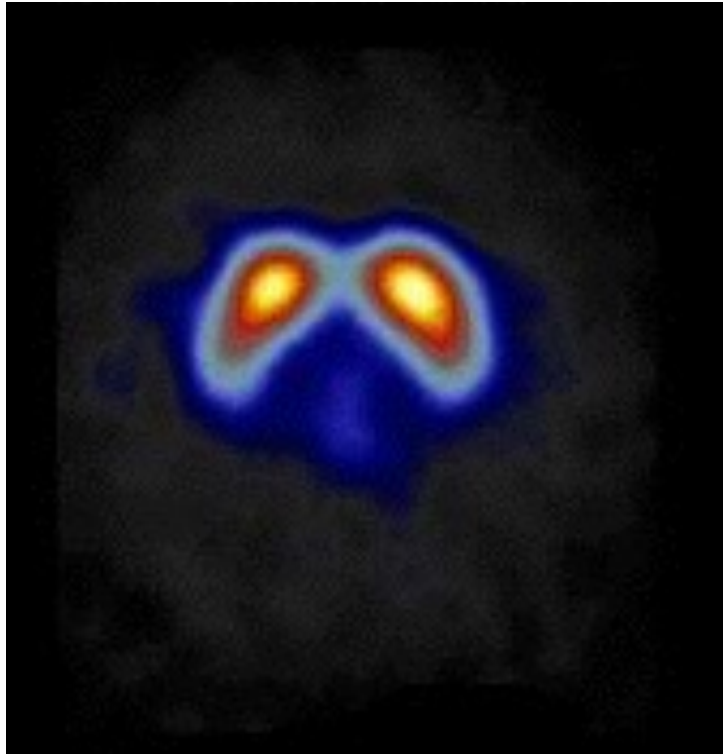
## Sensory/ Pain

- Tingling sensation
- Akathisia
- Olfactory deficit
- Diffuse pain
- Back & shoulder
- Hot-cold sensations
- Burning

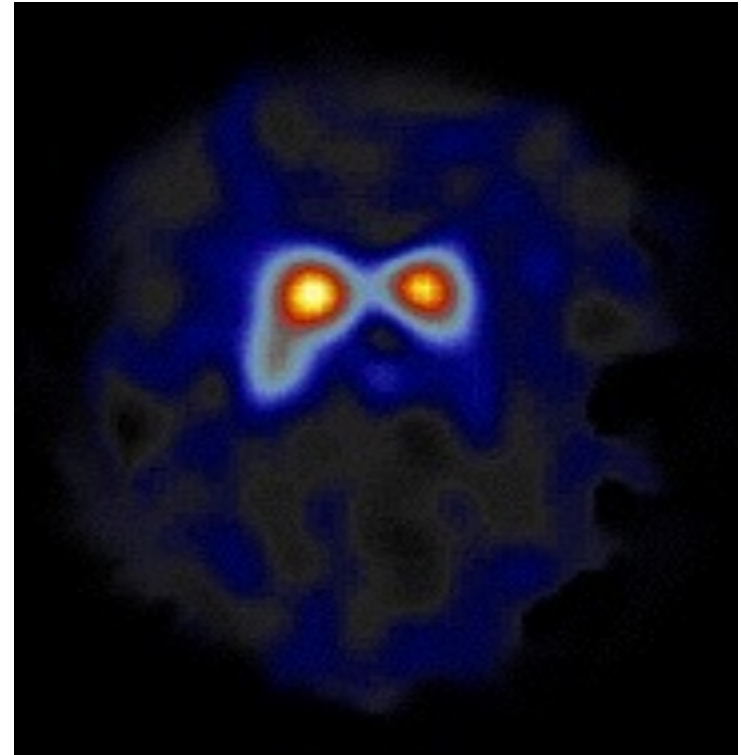
## **ACCURACY OF DIAGNOSIS COMPARED WITH AUTOPSY**

- **London Brain Bank—75% at initial exam ; and 90 to 95 % final diagnosis**
- **Mayo—At 5 years into care, 50% and at final diagnosis 80 to 85%**
- **Reports of patients with MSA, PSP, CBS; diagnosis only 60% correct with autopsy**

# Dopamine Transporter Imaging in PD



Healthy subject

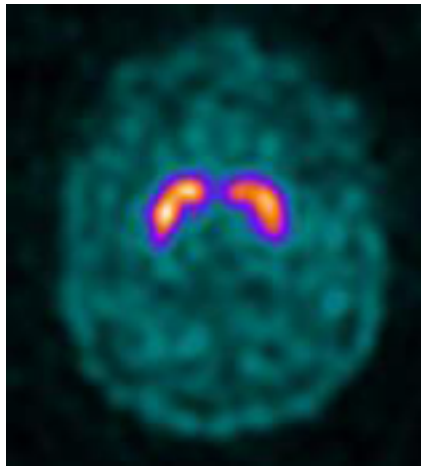


PD patient – Hoehn-Yahr  
Stage 1



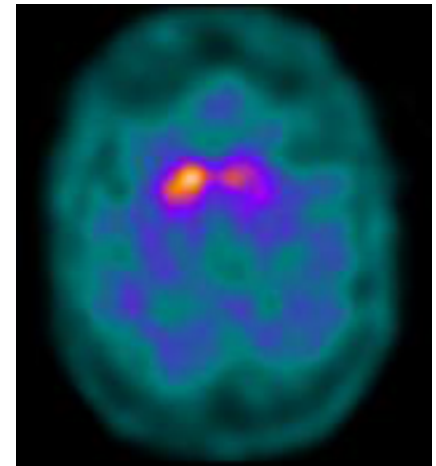
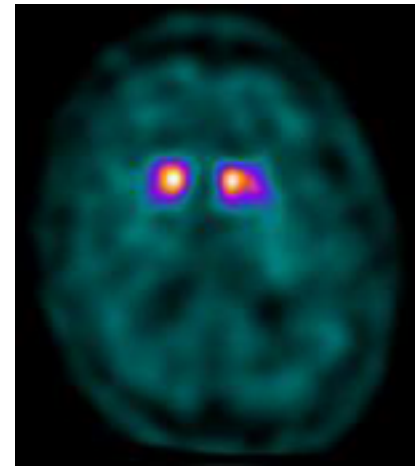
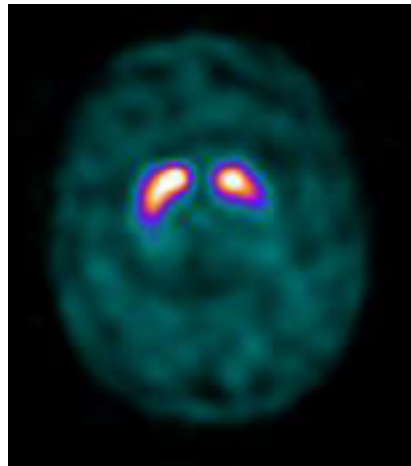
# DaTscan™ (Ioflupane I 123 Injection) SPECT Images

**Normal Uptake,  
No Dopaminergic Deficit**



**Consistent with:  
Essential Tremor**

**3 Patients With  
Abnormal Uptake,  
Dopaminergic Deficit**

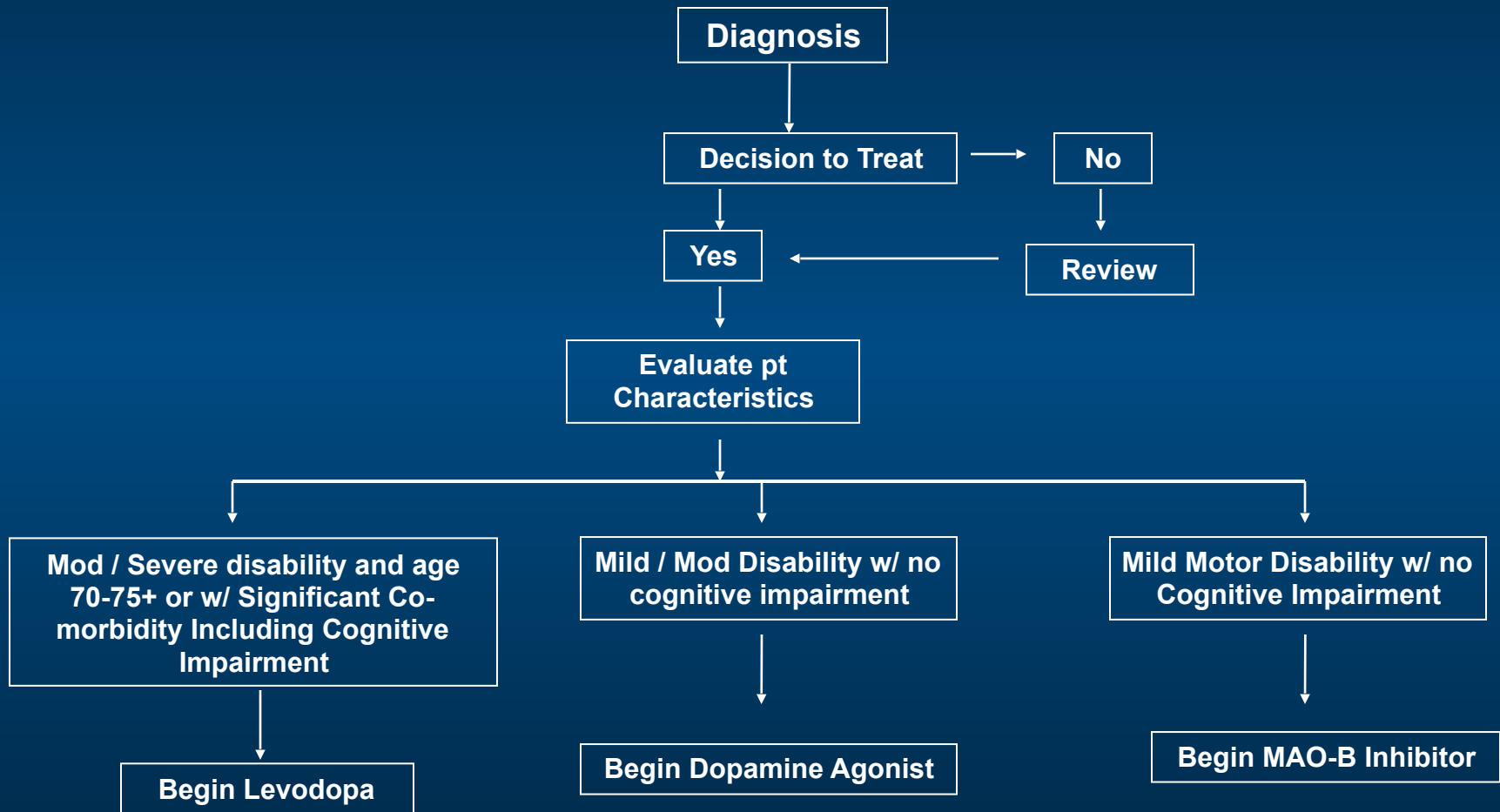


**Consistent with:  
Parkinson's Disease  
Multiple System Atrophy  
Progressive Supranuclear Palsy**

# **MRI AND THE SWALLOW TAIL**

- **3 TESLA MRI**
- **NeuroQuant analysis-volumetric**
- **Absence of the Swallow Tail sign**
- **Absent high signal with in the posterior third of the substantia nigra**
- **Indicates loss of dopamine neurons.**
- **Correlates clinically at about 85%**

# Algorithm for the Treatment of Early Parkinson's Disease



# SIDE EFFECTS OF DA

- Drowsiness, sleepiness, fatigue
- Sudden sleep events
- Nausea
- Orthostatic hypotension, new or worsening
- Confusion, hallucinations, delusions,
- Ankle swelling,
- Red and swollen hands
- Compulsive, impulsive disorders (ICD), ie gambling, pornography etc.
- Possible fibrosis

# L-DOPA RX MOST ROBUST THERAPY BUT FREQUENT MOTOR COMPLICATIONS- 2 TYPES-

- Wearing-off; End dose failure, Morning off
  - Delayed on, Never on

## Drug-induced dyskinesias

- Peak dyskinesias
- Diphasic dyskinesias

## Dystonias- On & Off

AM & HS Dystonia

# Disease-Related Symptom Evolution Despite Optimal Levodopa Therapy

- Postural imbalance, freezing

Dysarthria, dysphagia

Nonmotor symptoms-Cognition

Neuropsych symptoms

Comorbidity (45% at autopsy have DAT)

# MANAGEMENT OF BEHAVIOR DISORDERS

- SSRI'S
- SNRI'S
- TRICYCLICS
- Quetiapine (Seroquel)
- Pimavanserin (Nuplazid); first drug released for hallucinations and delusions.

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