

# **“Parkinson’s plus and minus”**

## **Cognitive decline and parkinsonism**

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# Objectives

- Identify what Parkinsonism is
- Generate a differential for Parkinsonism (besides Parkinson's disease)
- Describe clinical features that distinguish Lewy body dementia from Parkinson's Disease
- List 3 clinical findings to differentiate Progressive Supranuclear Palsy (PSP) from Parkinson's Disease

# What is Parkinsonism?

- An umbrella term covering a range of symptoms and signs similar to Parkinson's disease
  - Bradykinesia (slowness of movement) and/or hypokinesia (reduced movement amplitude)
  - Tremor at rest
  - Muscle stiffness (resistance to passive movement)
  - Postural instability, gait disorder
- Parkinson's disease accounts for ~80% of people with Parkinsonism

# Bradykinesia & Hypokinesia



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# Tremor at rest

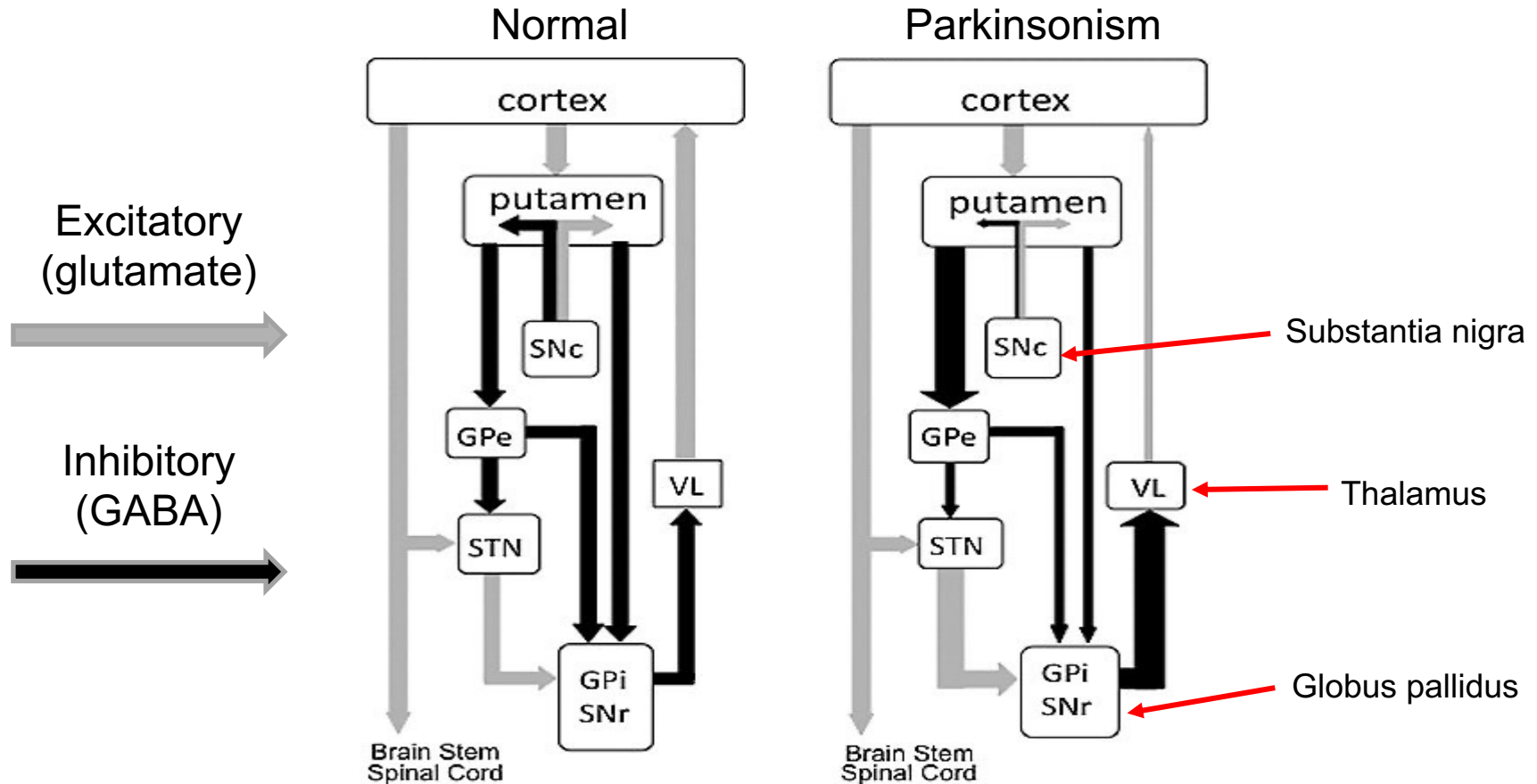


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# Dopamine deficiency & Parkinsonism

## reduced influence of Globus Pallidus on Thalamus (VL)



Thalamic excitation to cortex is inhibited by Globus Pallidus  
Low dopamine increases inhibition of Thalamus by Globus Pallidus



# Parkinsonism

## differential diagnosis

- Dementia with Lewy Bodies
- Progressive Supranuclear Palsy
- Small vessel ischemic injury
- Medication-induced (DA antagonists)
- Toxins (CO, methanol, Hg, Mn)
- And many more...
  - Chronic Traumatic Encephalopathy
  - Huntington's disease
  - Wilson's disease
  - Corticobasal syndrome
  - Prion disease
  - Multiple systems atrophy

# Dementia with Lewy Bodies

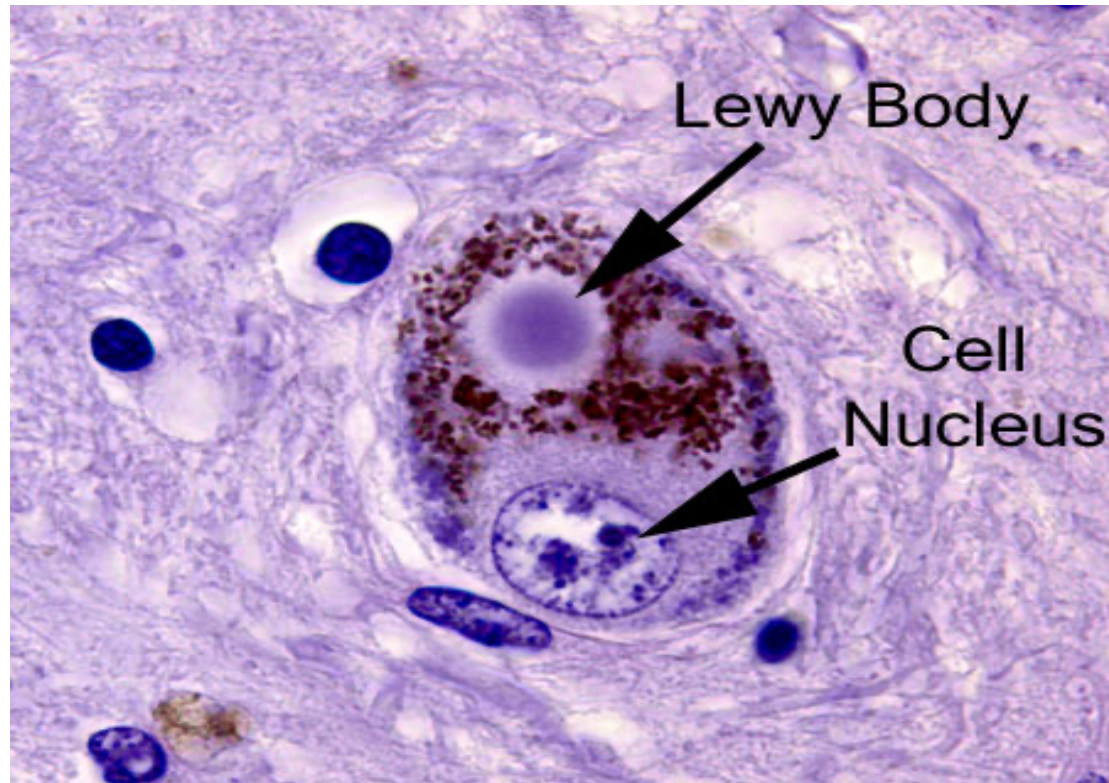


# Dementia with Lewy Bodies

## evolution of concept

- Psychiatrists reported late-onset psychosis with parkinsonism aggravated by neuroleptic
- Neurologists reported parkinsonism with psychotic reactions to carbidopa/levodopa
- Pathologists reported a spectrum of findings with Lewy Bodies as common feature
  - Lewy Body variant of Alzheimer's disease
  - Pure Lewy Body disease

# The Lewy Body



Aggregates of protein (mainly alpha synuclein) in cytoplasm of vulnerable neurons (substantia nigra above) or their extensions

# Dementia with Lewy Bodies criteria – DLB consortium

- Central feature – dementia
- Core features
  - Spontaneous parkinsonism
  - Fluctuation in alertness/attention
  - Visual hallucinations
  - REM sleep behavior disorder
- Supportive features
  - Severe neuroleptic sensitivity
  - Postural instability/repeated falls
  - Severe autonomic dysfunction
  - Nonvisual hallucinations or systematized delusions
  - Syncope/transient LOC

# Dementia with Lewy Bodies

## spontaneous parkinsonism

- More often bilateral signs
- Tremor – resting less common, “atypical”
- Other features “same as PD”
  - Bradykinesia
  - Limb rigidity
  - Gait disorder / Postural instability

*Table 3 EPS noted at the onset of parkinsonism in Parkinson's disease (PD) and Lewy body dementia (LBD)*

	PD (n = 11) n (%)	LBD (n = 12) n (%)	$\chi^2$ test
Tremor at rest	9 (82%)	8 (67%)	$\chi^2 = 0.9$ ; P = 0.4
Rigidity	9 (82%)	9 (75%)	$\chi^2 = 0.1$ ; P = 0.8
Bradykinesia	7 (64%)	7 (58%)	$\chi^2 = 0.1$ ; P = 0.8
Asymmetry of motor symptoms:			
Left/right asymmetry	11 (100%)	5 (42%)**	$\chi^2 = 9.2$ ; P < 0.01
Upper/lower limb asymmetry	8 (73%)	6 (50%)	$\chi^2 = 0.8$ ; P = 0.4

# Dementia with Lewy Bodies

## hallucinations

- Present in 58-85% (c/w AD 11-28%)
- Hallucinations start early in course
- Fully formed, detailed – objects/people
  - Auditory hallucination occur (not without VH)
- Associated with greater cognitive deficit
- May also relate to REM dysregulation

# Dementia with Lewy Bodies

## “fluctuations”

- Present in 60-85% at onset
- Variable
  - Duration – seconds to hours
  - Subtle “daydream” → unresponsive
  - Context independent
- Features distinguishing DLB from AD
  - Daytime drowsiness/lethargy
  - Daytime sleep >2 hours
  - Episodes of “staring into space”
  - Episodes of “disorganized speech”

≥ 3 features – positive predictive value 83%



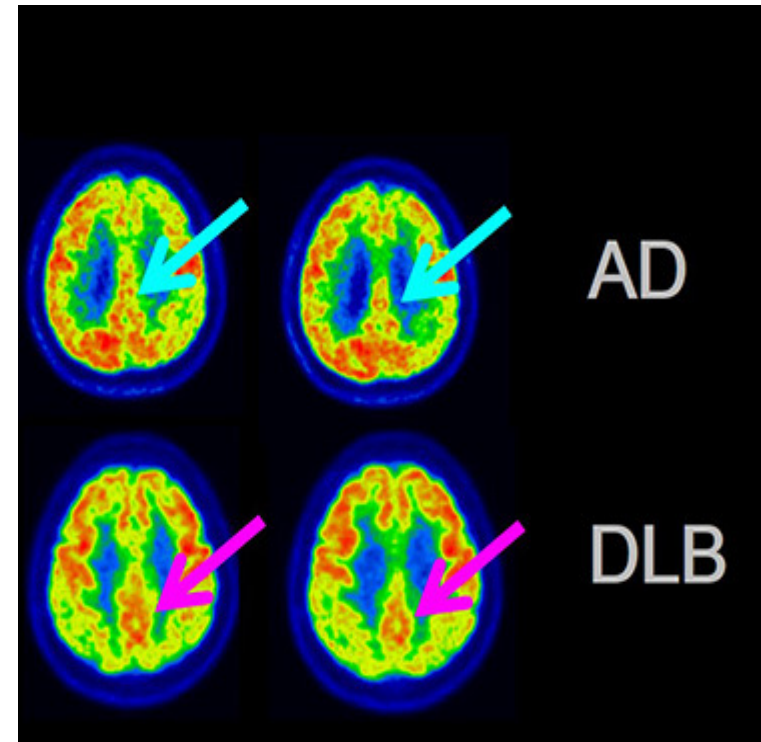
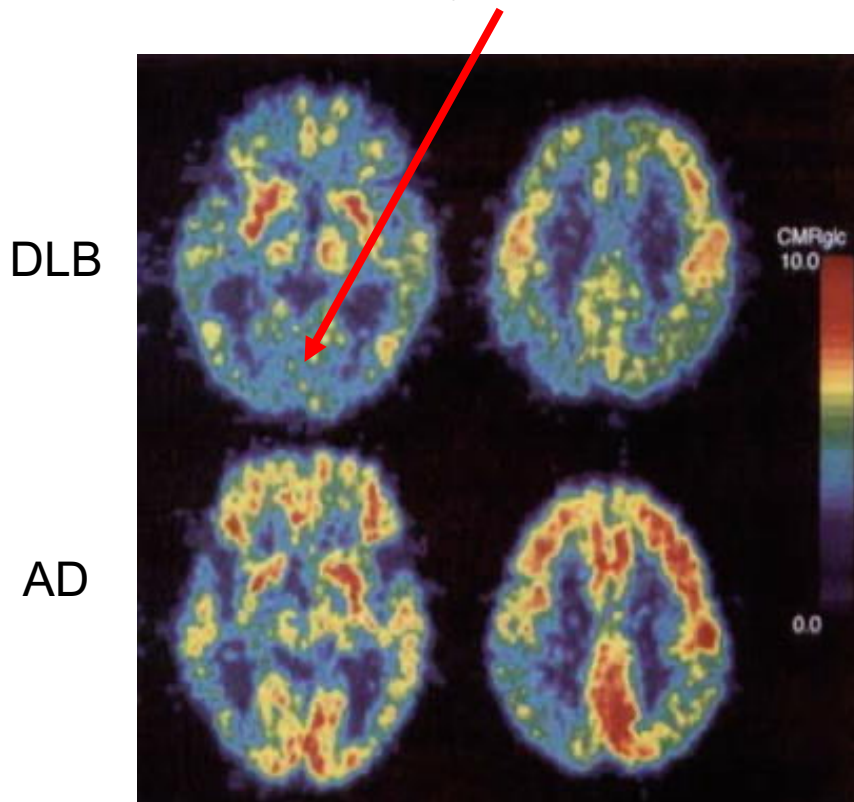
# Dementia with Lewy Bodies

## supportive biomarkers

- Generalized low perfusion (SPECT) or metabolism (FDG PET) with reduced occipital uptake and/or the cingulate island sign
- Reduced basal ganglia dopamine transporter uptake
- Polysomnogram showing REM sleep without atonia
- Relative preservation of medial temporal lobe on MRI
- Prominent posterior slow-wave activity on EEG

# Dementia with Lewy bodies FDG PET Scan

Occipital hypometabolism



Normal metabolism posterior cingulate  
“cingulate island sign”

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# Dementia with Lewy Bodies

## pharmacological management

- Cognitive impairment
  - Cholinesterase inhibitors: “first-line” therapy
  - Donepezil (off label), Rivastigmine (FDA)
  - Memantine-less evidence for benefit
- Psychiatric symptoms
  - Psychosis: Quetiapine, Clozapine, and Pimavanserin
  - Depression/anxiety: SSRI, SNRI, mirtazapine
- Parkinsonism
  - Sinemet least likely to aggravate psychosis
  - Adjunctive zonisamide

# Dementia with Lewy Bodies

## management of psychosis

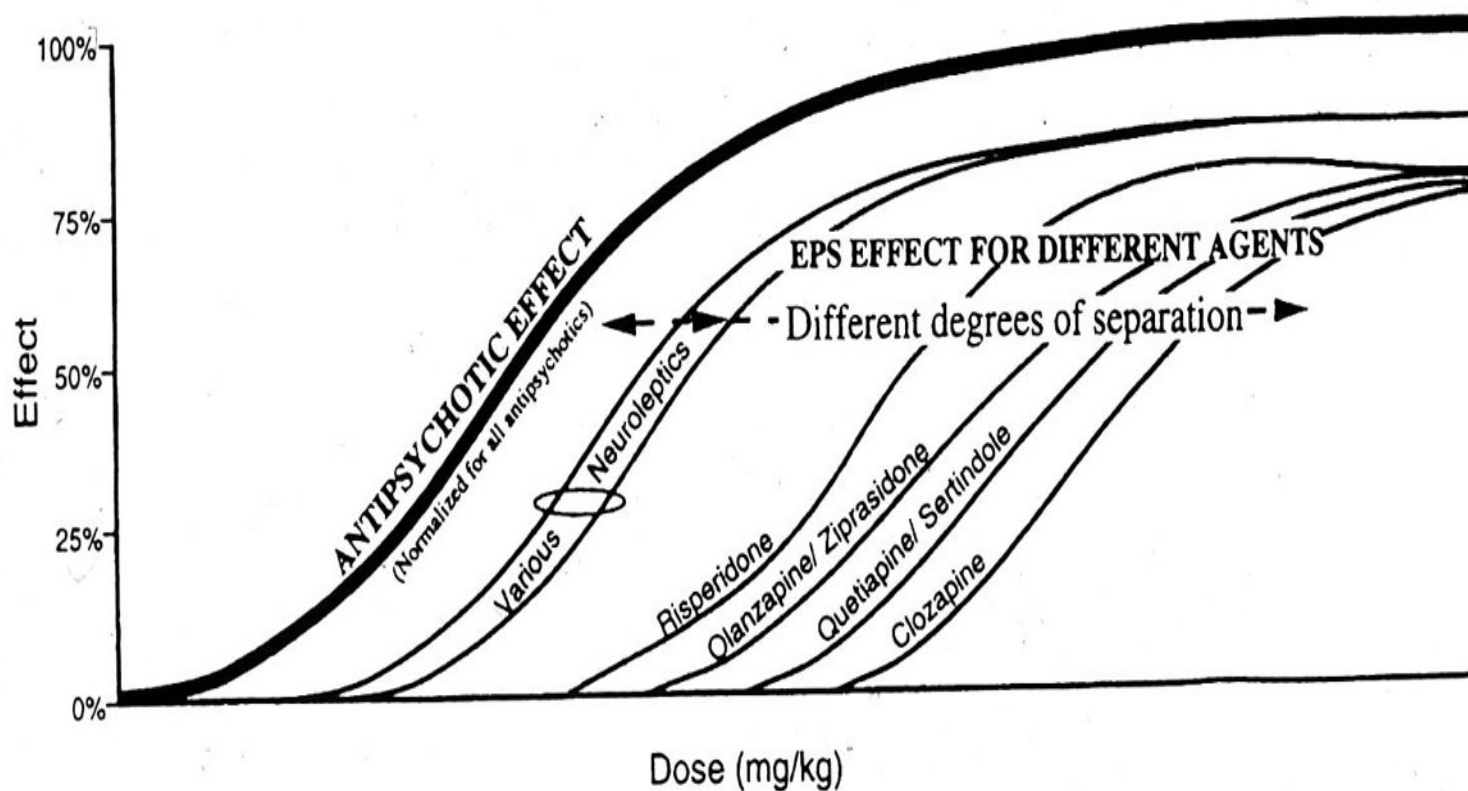


Fig. 5. Dose-response curves for antipsychotic and EPS effects for neuroleptics and atypical antipsychotics.

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# Progressive Supranuclear Palsy (PSP)



Jennifer Wexton D-Va

# Progressive Supranuclear Palsy

## diagnostic criteria

- Inclusion

- Gradually progressive akinetic-rigid syndrome

- Symmetric

- Onset at age > 40

- Supranuclear ophthalmoparesis

- Early postural instability with falls

- Exclusion

- History of encephalitis lethargica

- Alien hand syndrome, cortical sensory deficits

- Prominent cerebellar signs or dysautonomia

- Hallucinations or delusions



# What is supranuclear ophthalmoparesis?

- Restricted range of ocular pursuit
  - PSP: Vertical before horizontal  
Downgaze before upgaze
- Normal cranial nerve 3/4/6 and extraocular muscle function by oculoccephalic reflex
- Caveat: axial rigidity can make neck movement difficult



# Vertical Gaze Impairment in Progressive Supranuclear Palsy



RS Supranuclear Ocular Motor Pathways Part 2 - Vertical Saccades



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# Other oculomotor findings in PSP

- Decreased blink rate
- Saccadic intrusions at fixation  
(‘square wave jerks’)
- Saccades
  - Delayed initiation/increased latency
  - Hypometric (vertical before horizontal)
  - Curvilinear downward path-“round the house”
- Eyelids
  - Blepharospasm
  - Eyelid opening apraxia-levator inhibition

# Square wave jerks



# Other motor findings in PSP

- Dystonia
  - Face – “startled” expression, furrowed brow
  - Neck – retrocollis, anterocollis
- Rigidity is axial (neck/trunk > extremities)
  - Posture extended rather than flexed
- Dysphagia

# Neurobehavioral features of PSP

- Speech
  - “Dysarthrophonia” → apraxia of speech
  - Less spontaneous speech → nonfluent aphasia
  - Palilalia → keening/wailing
- Executive/personality-presenting symptom ~20%
  - Apathy, loss of interest
  - Loss of empathy-“self-centered”
- Mood disorder
  - Depression (20-40%)>Anxiety>OCD
  - Pseudobulbar affect can look like mood disorder
- Sleep disorders
  - Sleep disordered breathing (~1/3)
  - Periodic Leg Movements (~1/2), Restless Leg

# Progressive Supranuclear Palsy

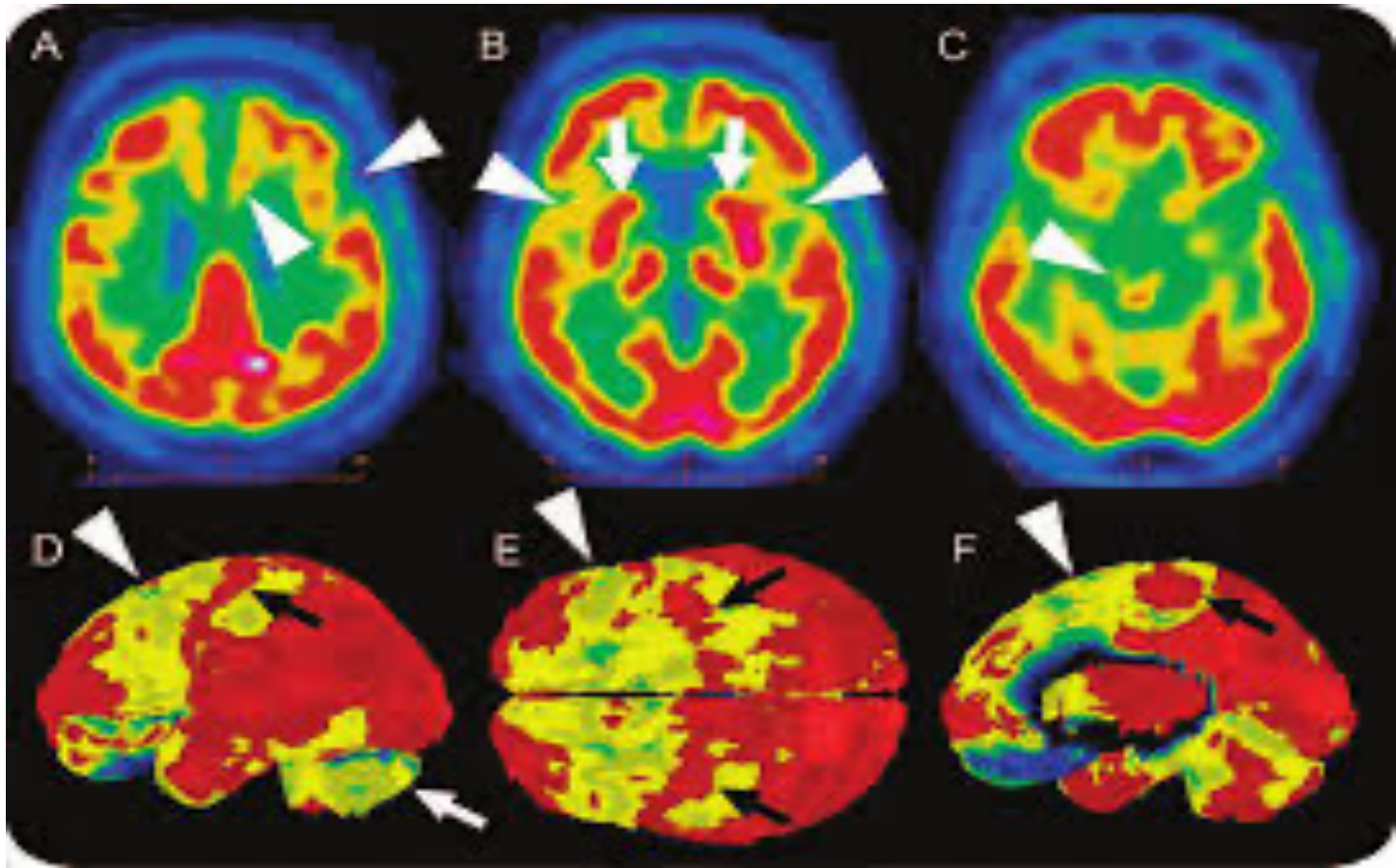
## supportive biomarkers

- Clinical diagnosis-all other studies less helpful
- Reduced basal ganglia dopamine transporter uptake
  - Just like Parkinson's disease
- Hypometabolism on brain FDG PET scan
  - Just like frontotemporal dementia
- Brain MRI shows midbrain atrophy



# Progressive Supranuclear Palsy

## FDG PET scan



Reduced metabolism in dorsolateral/paramedian frontal lobes, insula, and midbrain

# Progressive Supranuclear Palsy

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# Midbrain atrophy

hummingbird/penguin sign



# Management of PSP

- Motor symptoms
  - Trial of levodopa – patients with akinetic rigidity
  - Carbidopa/levodopa: 25/100 TID x 2 weeks then 25/100 x2 tabs TID x 2 weeks then 25/250 TID
  - Patient/care partner global impression 2-3 months
  - If no benefit, taper over 4-6 weeks
  - Trial of amantadine – patients with akinetic rigidity
  - 100 mg QAM, increase by 100 mg every two weeks
  - Up to 400 mg divided BID, 2<sup>nd</sup> dose not after midday
  - Younger patient less likely to have adverse effects
- Dystonia → botulinum toxin + PT

# Summary points

- Consider other causes of Parkinsonism besides Parkinson's disease if atypical features (cognitive impairment)
- Think dementia with Lewy bodies instead of Parkinson's Disease for patients with early cognitive decline, hallucinations and complex movements in sleep
- Think progressive supranuclear palsy rather than Parkinson's Disease if patients have early falls, cognitive/behavior symptoms and eye movement abnormalities