Redefining the diagnostic and therapeutic window in Parkinson's disease

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The Modern History of Dopaminergic basis for Parkinson's disease

- 1950s: Greenfield draws attention to the importance of the substantia nigra in Parkinson's disease
- 1959: Carlson first suggests that Parkinson's disease is due a dopamine deficiency in the CNS
- 1960: Hornykiewicz demonstrates a profound striatal dopamine deficiency in the disease
- 1968: Cotzias successfully treats parkinsonian features of the disease with L-dopa

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The Modern History of Dopaminergic basis for Parkinson's disease

In the 1980s:

- 1980s Dopamine agonists therapy introduced
- MPTP Model for PD introduced (pure nigral lesion)

- 1990s: DBS introduced as a way to modulate basal ganglia circuitry
- Conclusion: To date, therapeutic approaches have focused on the dopaminergic nigrostriatal system

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Definition of Parkinson's Disease

- Clinical triad of bradykinesia (slowed movement), rigidity (stiffness), and rest tremor (collectively referred to as parkinsonism)
- Characterized pathologically by loss of pigmented dopaminergic neurons in the substantia nigra, and intraneuronal inclusions known as Lewy Bodies.
- Humans exposed to MPTP, a compound that is selectively toxic to the substantia nigra, results in the parkinsonian triad
- At the current time, the definition focuses on the dopaminergic nigrostriatal system

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How do we diagnose Parkinson's disease?

- There are three commonly used sets of diagnostic criteria:
  - CAPIT (Langston et al, Movement Disorders, 1992)
  - Gelb (Gelb et al, Arch Neurol, 1999)
  - British Brain Bank (Hughes et al, JNNP, 1992)

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PD Diagnostic Criteria

Dx Type	Gelb	CAPIT	British Brain Bank
Definite PD	2/4 cardinal signs, (1 is tremor or bradykinesia), other symptoms not >3 years or currently not present, response to l-dopa shown or l-dopa not tried, AND histopathology + at PM	*Dx criteria 2/4 cardinal signs, (1 is tremor or bradykinesia), clear-cut l-dopa response* *(NOTE: no CAPIT "definite" dx, see below for others)*	Bradykinesia + one of the following: rigidity, 4-6 Hz rest tremor, postural instability; AND other causes of PD excluded; AND three of the following: unilateral onset, rest tremor, progression, persistent asymmetry, 70-100% l-dopa response, l-dopa dyskinesia, l-dopa response> 5 yr, clin. course >10 yr
Probable PD	3/4 cardinal signs, no symptoms suggesting other neurologic disease lasting >3 years, sustained l-dopa response	Meets dx criteria (above) on history and exam	Bradykinesia + one of the following: rigidity, 4-6 Hz rest tremor, postural instability AND other causes of PD excluded
Possible PD	2/4 cardinal signs, (1 is tremor or bradykinesia), other symptoms not >3 years or currently not present, response to l-dopa shown or l-dopa not tried	1) Meets dx criteria (at top) except one: no rest tremor or bradykinesia; only rest tremor; l-dopa response uncertain. 2) Meets dx criteria, but has other non-PD neuro symptoms	Bradykinesia + one of the following: rigidity, 4-6 Hz rest tremor, postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)

Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases.

Hughes AJ, Daniel SE, Kilford L, Lees AJ.

J Neurol Neurosurg Psychiatry. 1992 Mar;55(3):181-4.

- The pathological findings in 100 patients
- Diagnosed prospectively consultant neurologists
- 76% had typical Lewy body parkinsonism
- In 24 cases without Lewy bodies, diagnoses included:
  - progressive supranuclear palsy,
  - multiple system atrophy,
  - Alzheimer's disease,
  - Alzheimer-type pathology,
  - and basal ganglia vascular disease.

What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study.

Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ.

Neurology. 1992 Jun;42(6):1142-6.

- Second analysis of the same cohort
- Then they applied selected criteria:
  - asymmetrical onset
  - no atypical features
  - no possible etiology for another parkinsonian syndrome
- The proportion of true PD cases identified was increased to 93%, but 32% of pathologically confirmed cases were rejected on this basis

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

What's wrong with this definition?

- It is the disease as seen through the lens of the neurologist
- All of these focus primarily if not exclusively on the dopaminergic nigrostriatal system
- This approach ignores the wide-spread nature of the disease, and the fact that many of the features may preceed the onset of parkinsonism
- It captures the disease at a very late stage which is likely to minimize our chances for successful therapeutic interventions aimed at slowing or halting disease progression

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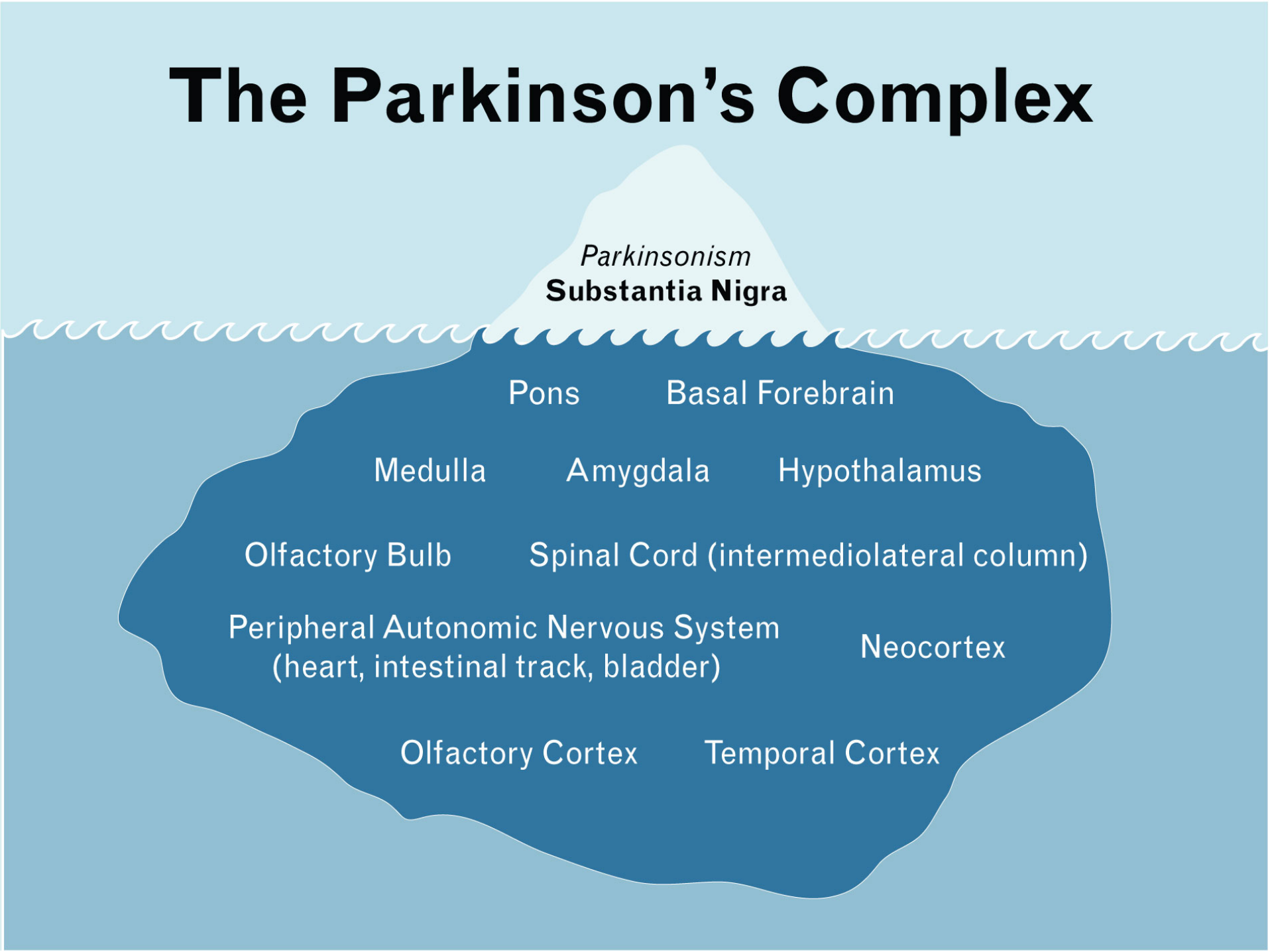
The Parkinson's Complex



Why are concepts finally coming togehter now?

- We now have new immunoshistochemical techniques that more precisely and comprehensively define the neuropathology of the disease
- The clinical syndromes associated with sites of neuroanatomical involvement other than the dopaminergic substantia nigra are becoming better recognized and characterized

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Large Multigenerational Italian Kindred with autosomal dominant parkinsonism (Contursi Kindred)

- Polymeropoulos et al. (1996): Linkage to 4q21-23
- In 1997, they reported an Ala53Thr mutation in the α–synuclein gene
- Two other mutations have now been identified
- These mutations are extremely rare

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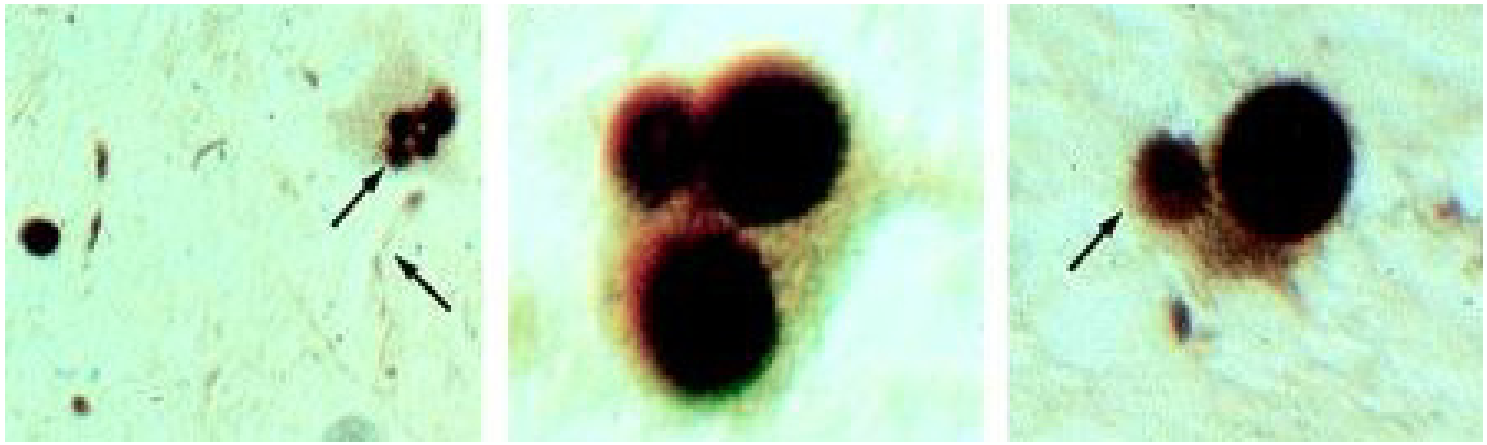
α-Synuclein and Sporadic PD

- **"α-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies"**

Spillantini M. G. et al. (1998) ***Proc. Natl. Acad. Sci. U S A*** **95:6469-6473.**



Impact of Synuclein Immunohistochemistry

- Traditionally we used H&E staining to identify Lewy bodies and Lewy neurites
- With synuclein staining, we can now obtain a an enhanced view of the neuritic pathology, in addition to obtaining a better visualization of Lewy bodies

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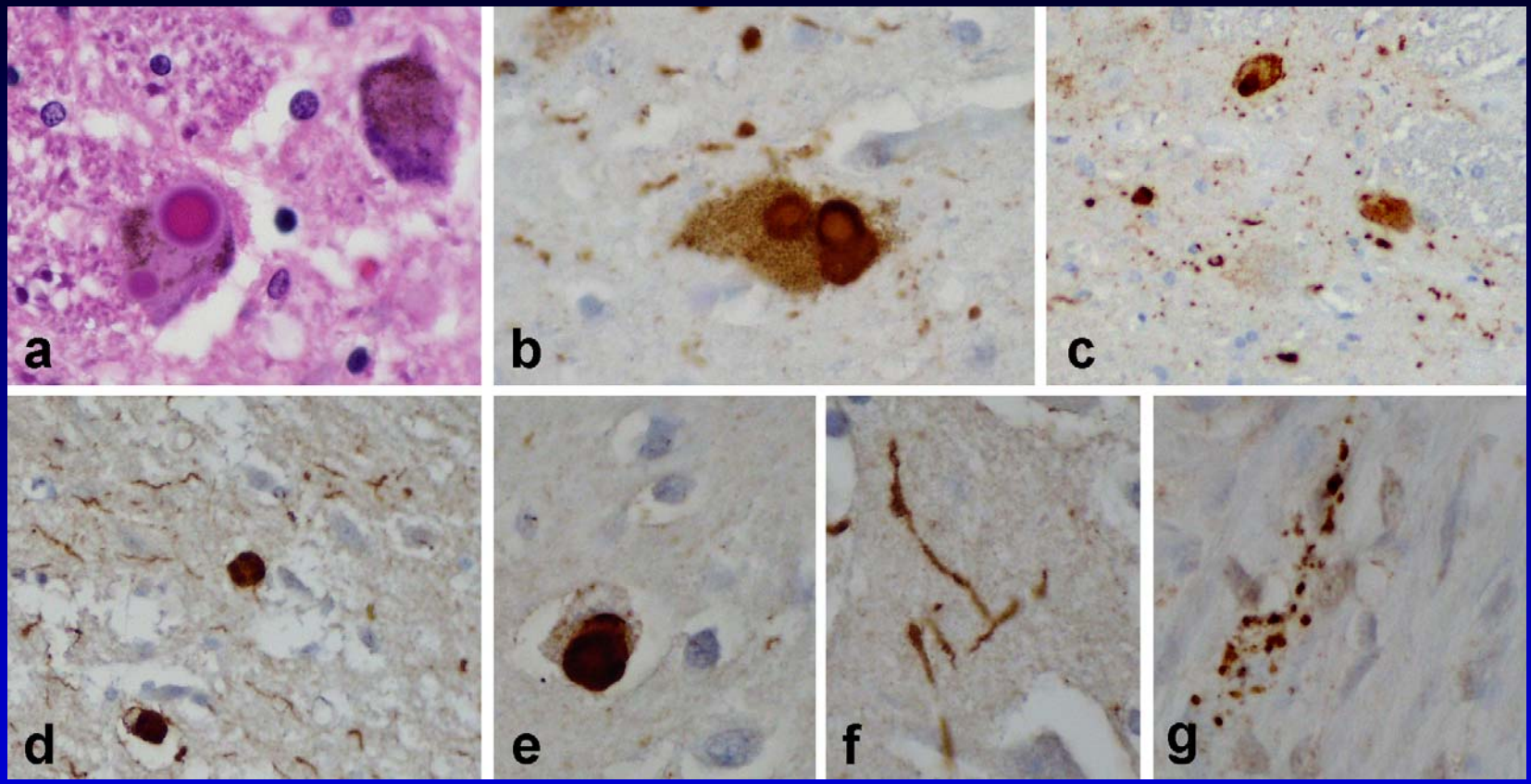
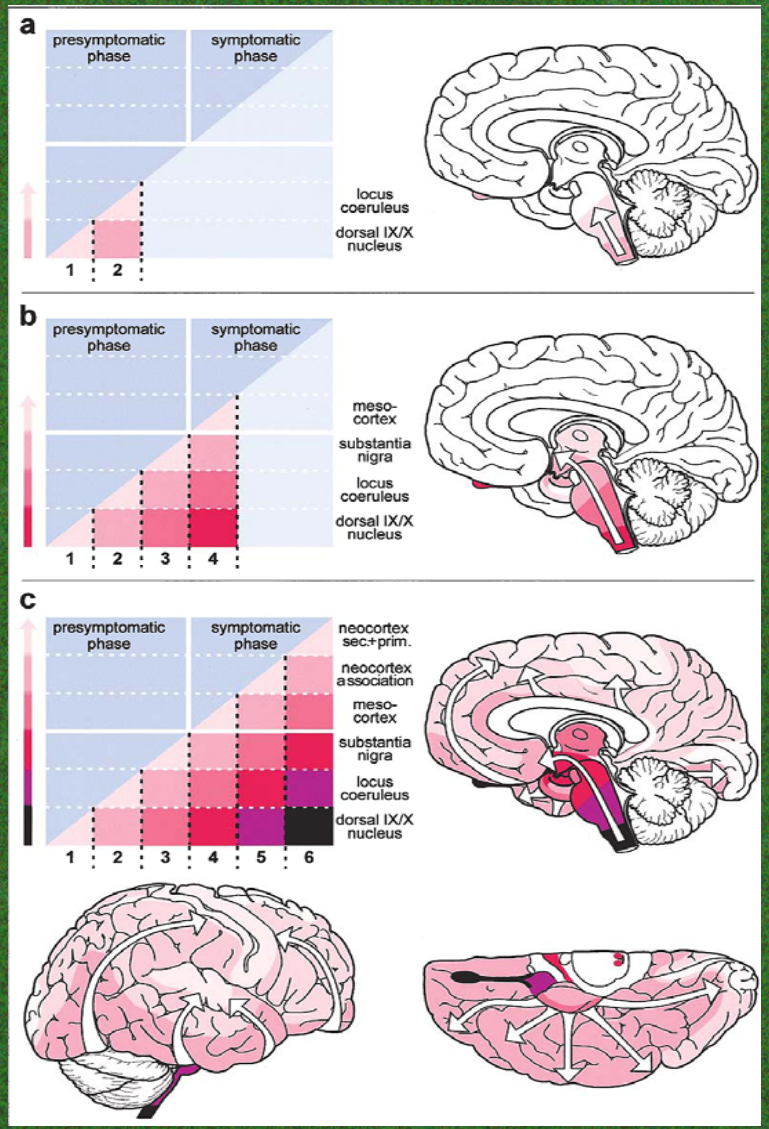


a) Locus cereleus,
b) LBs and dot-like neurite in intermedial column of the spinal cord
c) Pathology in olfactory bulb,
d) Cortical LBs temporal cortex
e) CA2 Lewy body
f) CA 2 Lewy neurites,
g) Dot-like Lewy neurites in the myenteric plexus of the large intestine



Braak et al, J Neurol, 2002

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Many of these other pathological features can clearly cause signs and symptoms that may precede the onset of parkinsonism, and thereby expand the diagnostic and therapeutic window in of Parkinson's disease

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Olfaction

- A high prevalence of decrease olfactory function PD by numerous groups (up to 70% to 100%)
- Many patients report a loss or change in their sense of smell years before the onset of parkinsonism
- Corresponds with Braak Stage I

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REM Sleep Behavior Disorder

- Burst of motor activity during sleep
- May be violent and lead to injury
- Thought to be dream-enacting behaviour associated to REM sleep without atonia

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REM Sleep Behavior Disorder

- Schenk et al (1996) followed a group of men over age 50 with RBD and reported that 40% went on to develop Parkinson's disease
- The average interval between onset of RBS and the appearance parkinsonism was 13 years
- This corresponds with Braak Stage 2 Parkinson's disease

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Case Report: Uchiyama et al.

- 84-year-old man who had a 20-year history of RBD but no evidence of parkinsonism during life
- Autopsy: Typical Parkinson's disease
  - Brainstem Lewy bodies
  - Cell loss in the substantia nigra and locus ceruleus
- RBD may be the only manifestation of pathologically typical Parkinson's disease

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REM Sleep Behavior Disorder

- 18% of PD patients will give a history of RBD prior to on set of PD
- 45% will have RBD when studied in a sleep lab (Shannon, 2005)
- Gagnon, Bedard et al. (2002) reported REM sleep without atonia, regardless of the behavioral disorder, in 60% of patients with PD

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James Parkinson, 1817

"… sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm"

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Cardiac Sympathetic Denervation

- More than 20 studies have agreed that virtually all patients with PD have a loss of sympathetic innervation of the heart
- This is documented by heart imaging studies (sympatho-neuronal imaging agents ^{123}I-MIBG and 6-[^{18}F]fluorodopamine)
- It has also been measured by neurochemical assessments during catheterization
- Indicates that peripheral sympathetic nervous system involvement is a universal feature of the disease (early feature?)

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Iwanaga and colleagues , 1999

- This group examined cardiac tissue from patients with both incidental Lewy bodies and typical Parkinson's disease
- They found synuclein-positive neurites in the myocardium in:
  - 7 of 7 patients with incidental Lewy bodies
  - 9 of 11 patients with Parkinson's disease
- Both extrinsic and intrinsic sympathetic neurons were affected.
- This is a very consistent feature of Parkinson's disease

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Parkinson's disease as an intestinal disorder

- Lewy Bodies were first described the myenteric plexus of the gut nearly 30 years ago
- Braak has recently reported abundant Lewy neurites in the enteric nervous system using synuclein immunohistochemistry

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Constipation

- Major complaint in the management of PD
- Usually attributed to immobility, dehydration, or PD medications
- Could it be the earliest feature of PD?

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Honolulu Heart Program Study Design

Longitudinal study of heart disease and stroke originally funded by NHLBI

Target population: all Japanese-American men born 1900-1919 and living on the island of Oahu in 1965 from selective service records (N=12000)

8006 Japanese-American men agreed to participate

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HHP Study Design

Baseline exam 1965-1968,

follow-up exams:

- **1967 (N=7498)**
- **1971 (N=6860)** → ***Honolulu-Asia Aging Study (HAAS) begins***
- **1991 (N=3734)**
- **1994 (N=2500)**
- **1997 (N=1800)**

Longitudinal follow-up through hospital and death records (2 lost to follow-up)

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HAAS: Evaluation Methodology

- All Participants → structured interview
- History of PD
  - IPD Medications
  - Signs of parkinsonism noted
- Screen positive → evaluation by neurologist
- Symptom questionnaire
- Unified Parkinson's Disease Rating Scale
- N=96

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Parkinson's disease Diagnostic criteria*

- parkinsonism (any two of - rest tremor, bradykinesia, rigidity, postural instability)
- progressive disorder
- any 2 of - marked response to levodopa, asymmetry of signs, asymmetry at onset, initial onset tremor
- absence of other etiology

*Ward and Gibb, 1990

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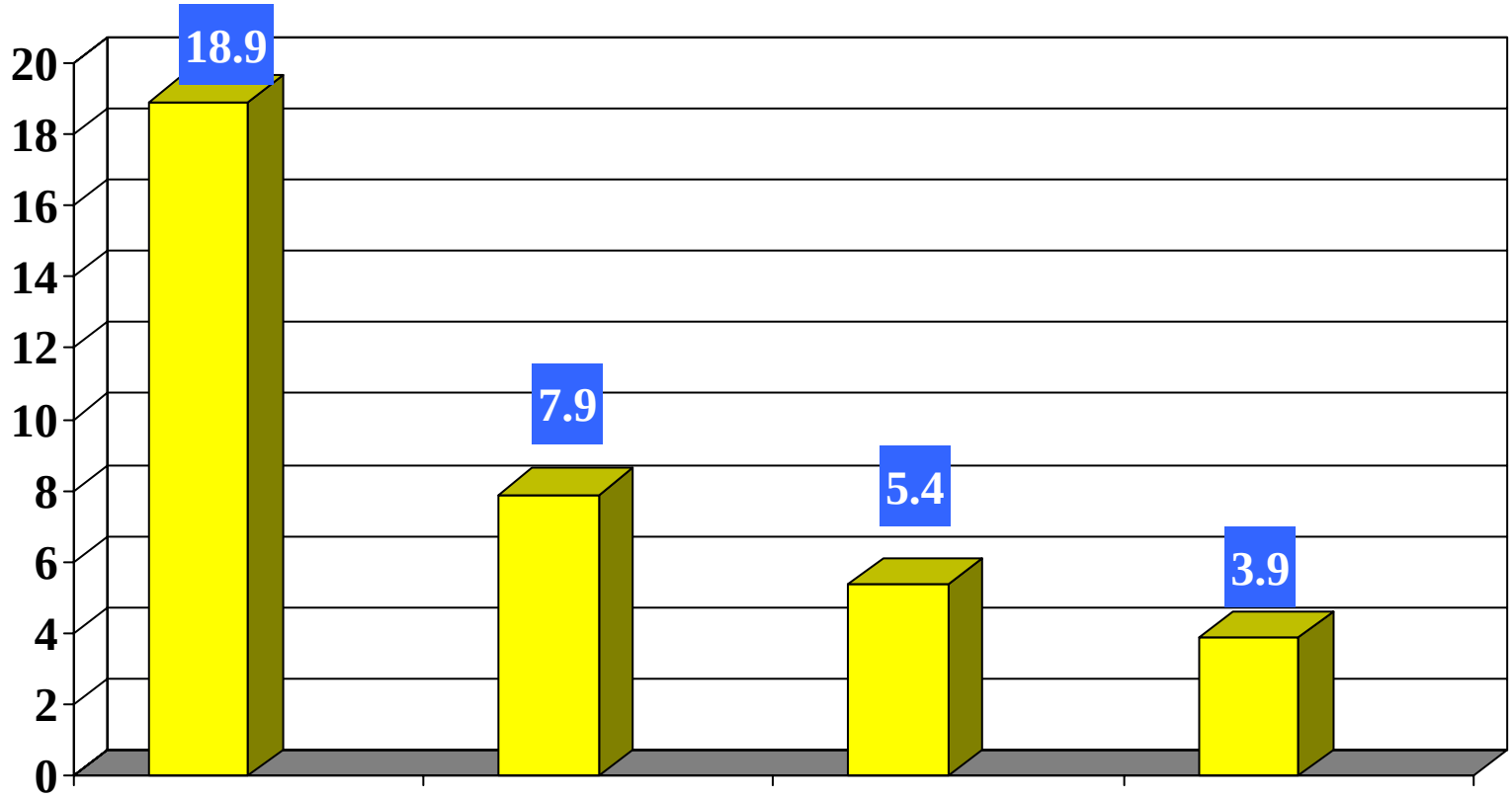
Age-adjusted incidence of PD* according to frequency of bowel movements in midlife



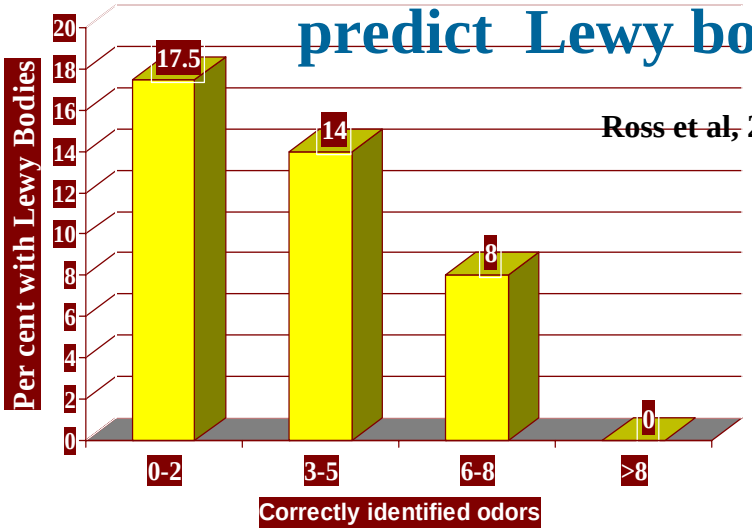
*** Rate/10,000 person-years**
Test for Trend - p=0.005

When Should Risk Factor Investigations Begin?

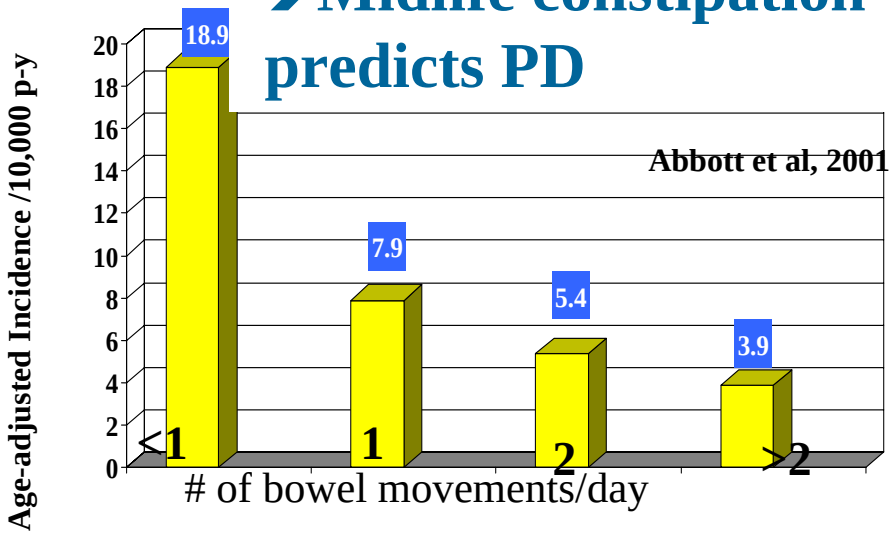
Does PD Start in Midlife?

Clues from the Honolulu Asian Aging Study

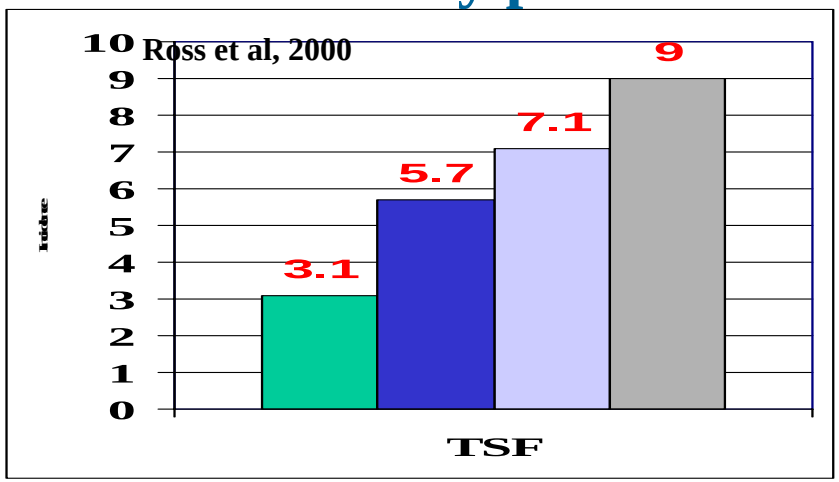
➔Midlife olfactory deficits predict Lewy bodies



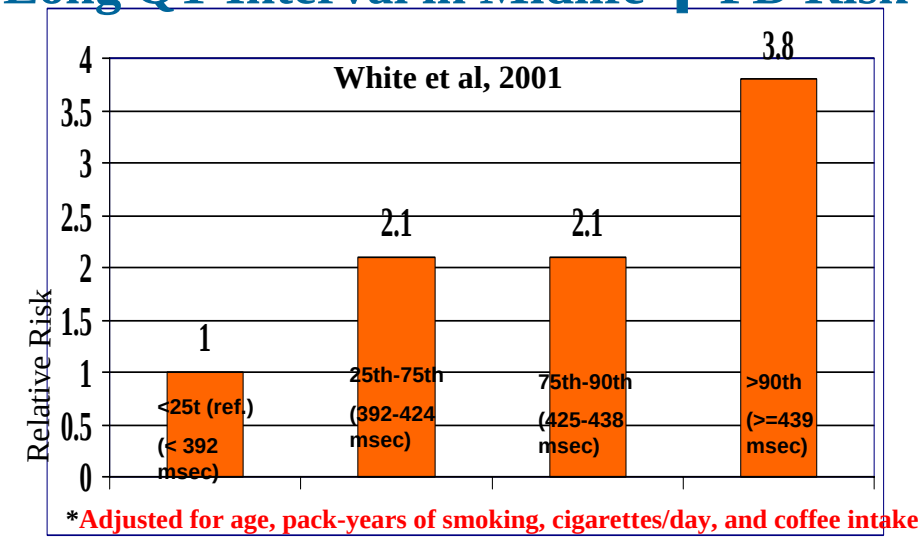
➔Midlife constipation predicts PD



➔Midlife obesity predicts PD



➔Long QT Interval in Midlife ↑ PD Risk



*Adjusted for age, pack-years of smoking, cigarettes/day, and coffee intake

Conclusions

- **Investigating neuroprotective strategies must take all aspects of the clinico-pathological spectrum of the disease (the Parkinson's complex) into consideration if we are to succeed in slowing or halting disease progression**
- **It woefully inadequate to focus just the dopaminergic nigrostriatal system**
- **Neuroprotective strategies probably need to be started much earlier if they are to succeed**
- **But - we don't yet have a way to unequivocally identify the disease process during life before patients meet the full British Brain Bank Criteria (which may be too late for the successful testing of neuroprotective drugs)**

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Future Research Needs

- It is probably premature to change current diagnostic criteria, but that may change as we better define non-motor features, particularly those that precede parkinsonism (but many are not specific for PD)
- Or, we must develop a biomarker for the disease tracks it from its inception
- Back to the drawing board with more observational studies, focusing on clinicopathological correlations
- Both clinical and basic research must move beyond the dopaminergic system at all levels, taking into consideration the disease in it entirety
- We have to find a new way of conceptualizing the disorder that doesn't involve just parkinsonism or the nigrostriatal dopaminergic system (TAKE HOME MESSAGE)

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