Parkinson's disease-More than just a movement disorder

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Disclosures

- No relevant financial relationships with commercial interests
- The following talk may include unlabeled/unapproved use of medications
- Dr. Pontone has consulted for Acadia Pharmaceuticals Inc

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I. Overview of Parkinson's as a 'disease' model for neuropsychiatric symptoms

II. Anxiety, Depression, and Psychosis in PD

III. Cognitive Impairment and Dementia in PD

Clinical Diagnosis of PD Requires only motor symptoms

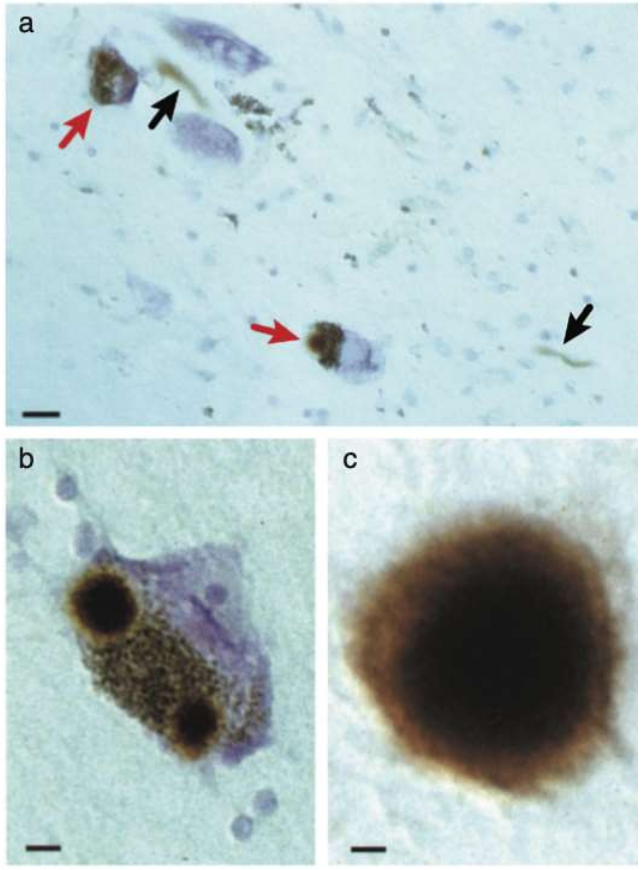
First essential criterion:

Slowing of physical movement (bradykinesia)

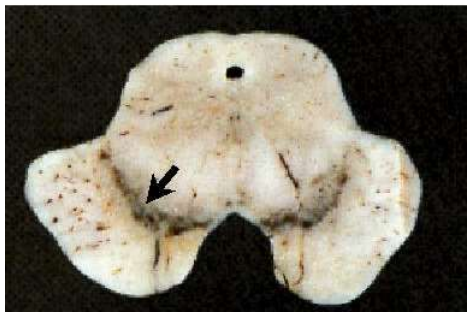
Plus at least one of the following:

- Tremor (4-7hz)
- Muscle rigidity

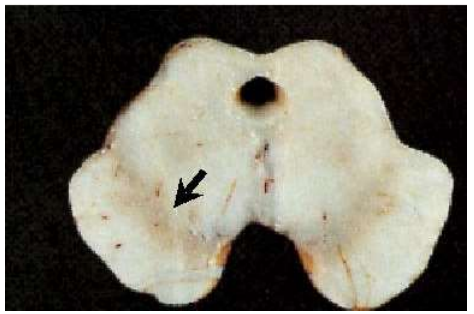
Parkinson's Disease – Substantia Nigra



Normal



Parkinson's



Stage and Severity of Parkinson's Disease

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Hoehn and Yahr Stage

- Stage 1 – unilateral involvement only
- Stage 2 – bilateral involvement without impairment of balance
- Stage 3 – bilateral involvement with impairment of postural reflexes (balance)
- Stage 4 – severely disabling disease; still able to walk with assistive device or stand unassisted
- Stage 5 – confinement to bed or wheelchair unless aided

Unified Parkinson's Disease Rating Scale – motor exam

- 0: normal: no rigidity
- 1: slight: rigidity detected only with activation maneuver
- 2: mild: rigidity detected without activation maneuver, but full range of motion easily achieved
- 3: moderate: rigidity detected without activation and full range of motion is achieved with effort
- 4: severe: rigidity detected without activation and full range of motion not achieved

Interventions for Parkinson's Disease

1. Prevention or delay of disease progression ('disease modifying')
2. Symptomatic monotherapy
3. Adjunctive therapies
4. Prevent or delay of motor complications
5. Motor complication therapies

Symptomatic Monotherapy

Efficacious – clinically useful

- Dopamine agonists – non-ergot, ergot
- Levodopa + peripheral decarboxylase inhibitor – immediate release, controlled release, extended release
- Monoamine oxidase inhibitors – B-selective, e.g., rasagiline, selegiline

Likely efficacious – clinically useful or possibly useful

- Anticholinergics
- Amantadine

Essay on the Shaking Palsy

"…the senses and intellects being uninjured."

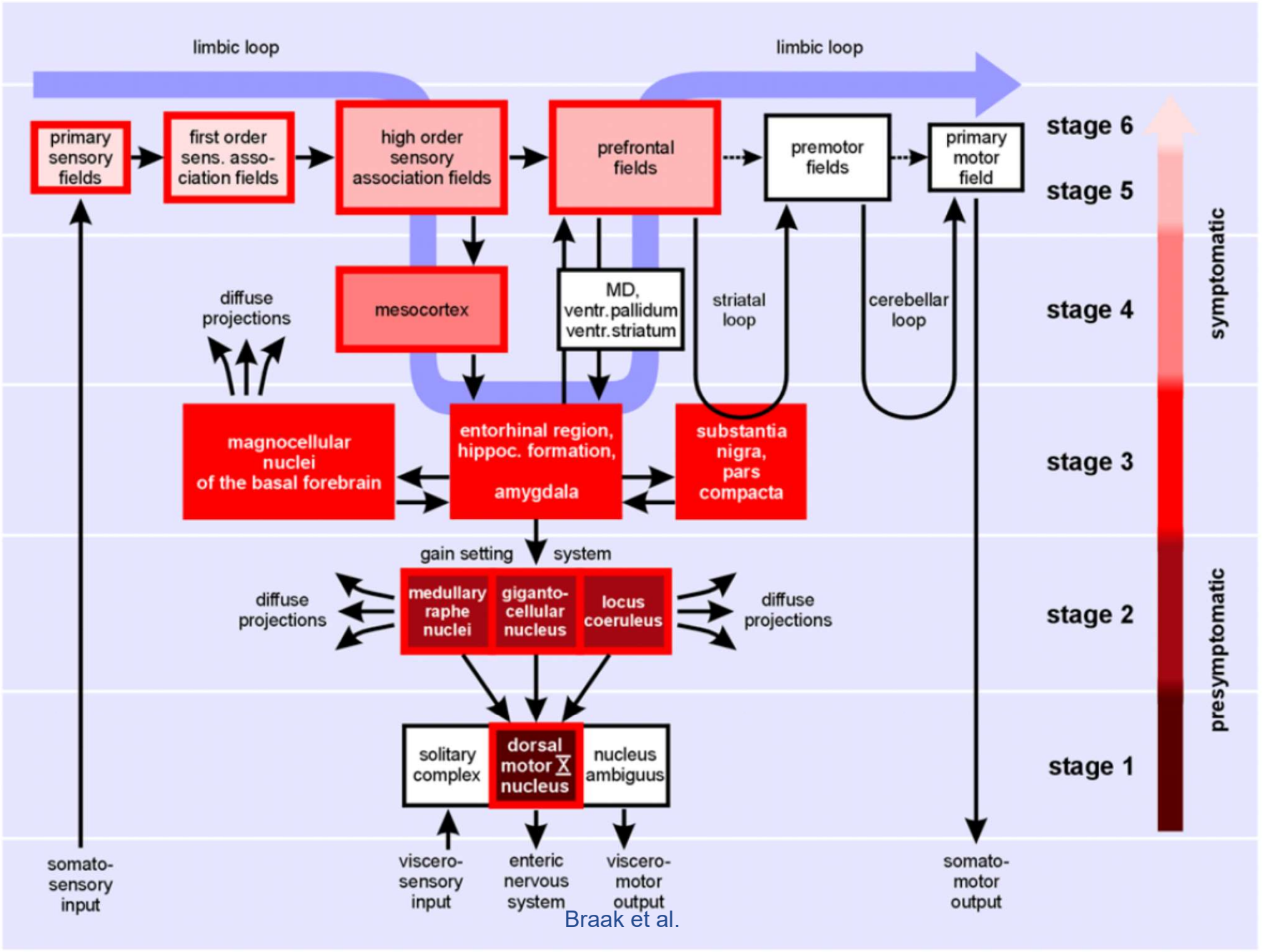
James Parkinson, 1817

PARKINSON'S DISEASE – A COMPLEX NEUROPSYCHIATRIC CONDITION

Non-motor symptoms of Parkinson's disease

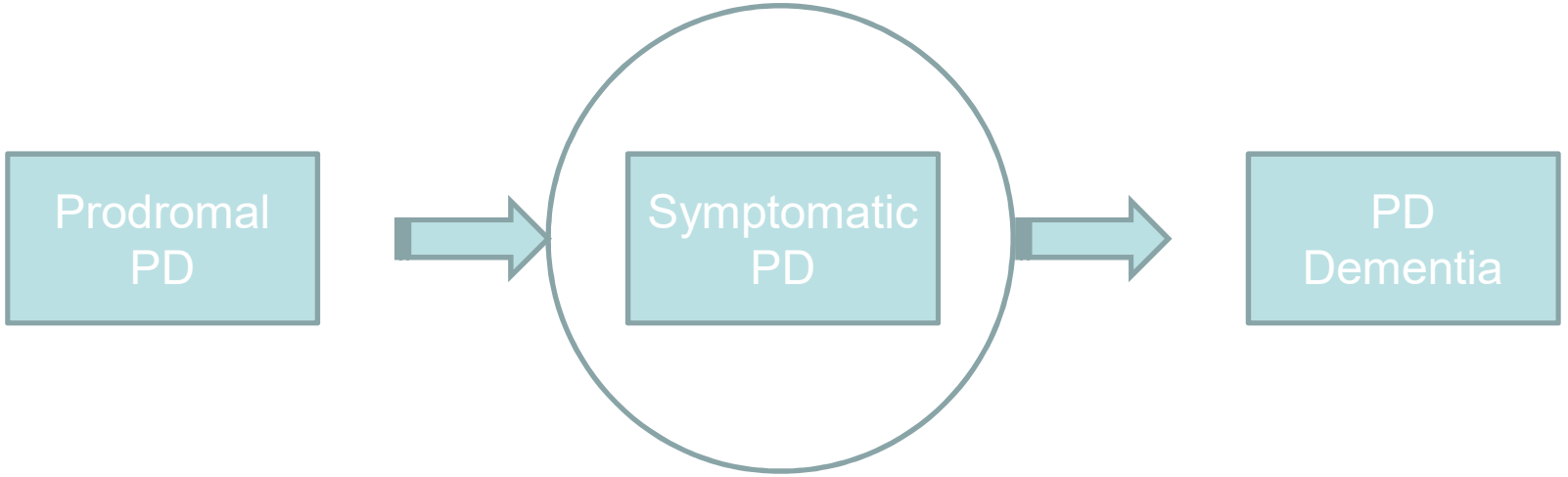
- Neuropsychiatric: apathy, anxiety, depression, psychosis, impulse control disorders
- Cognitive impairment, up to 40% have MCI at diagnosis and 80% demented within 20 years of motor symptom onset
- Olfactory loss, up to 90%
- Dysautonomia, up to 70%
- Sleep disturbances, >30%

Gonera et al 1997, Tolosa et al 2009, Yarnell et al 2014


limbic loop
limbic loop
primary sensory fields
first order sens. asso-ciation fields
high order sensory association fields
prefrontal fields
premotor fields
primary motor field
stage 6
stage 5
stage 4
stage 3
stage 2
stage 1
symptomatic
presymptomatic
diffuse projections
mesocortex
MD, ventr.pallidum ventr.striatum
striatal loop
cerebellar loop
magnocellular nuclei of the basal forebrain
entorhinal region, hippoc. formation, amygdala
substantia nigra, pars compacta
gain setting system
diffuse projections
medullary raphe nuclei
giganto-cellular nucleus
locus coeruleus
diffuse projections
solitary complex
dorsal motor X nucleus
nucleus ambiguus
somato-sensory input
viscero-sensory input
enteric nervous system
viscero-motor output
somato-motor output

Braak et al.

New Landscape of Parkinson's Disease



PD diagnosed by motor symptoms

New ‘stages’ of Parkinson’s disease

Prodromal: pre-motor, anxiety/depression, hyposmia, RBD, cardiac sympathetic denervation

Symptomatic: motor symptom onset and progression

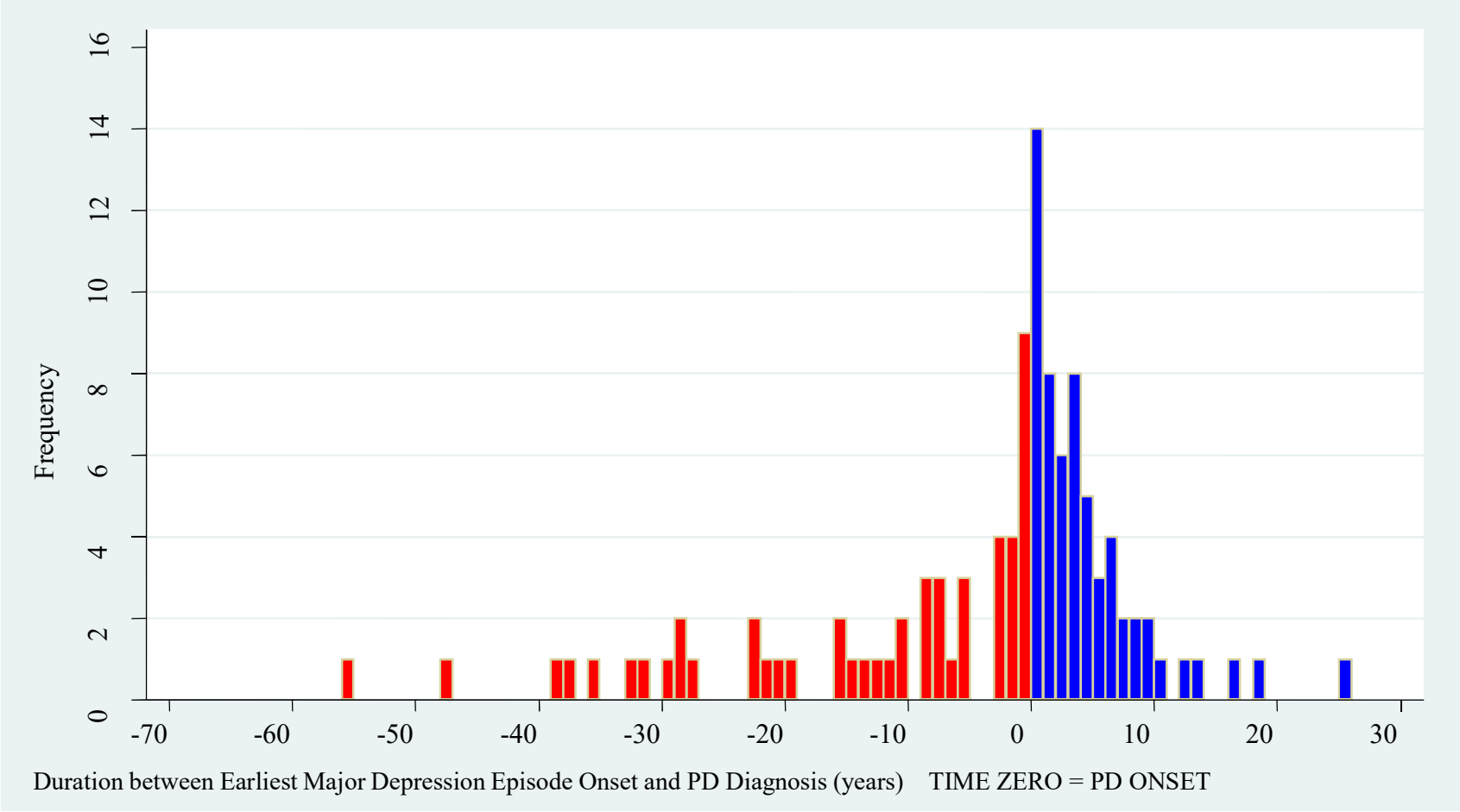
Dementia: progressive cognitive decline due to Lewy body disease or comorbidity

Meta-analysis of anxiety and depression as risk factors for PD

- 11 Case-control studies OR 1.90 (95% CI 1.62-2.22)
- 2 Cohort studies OR 1.79 (95% CI 1.72-1.86)
- Combined OR 1.86 (95% CI 1.64-2.11)

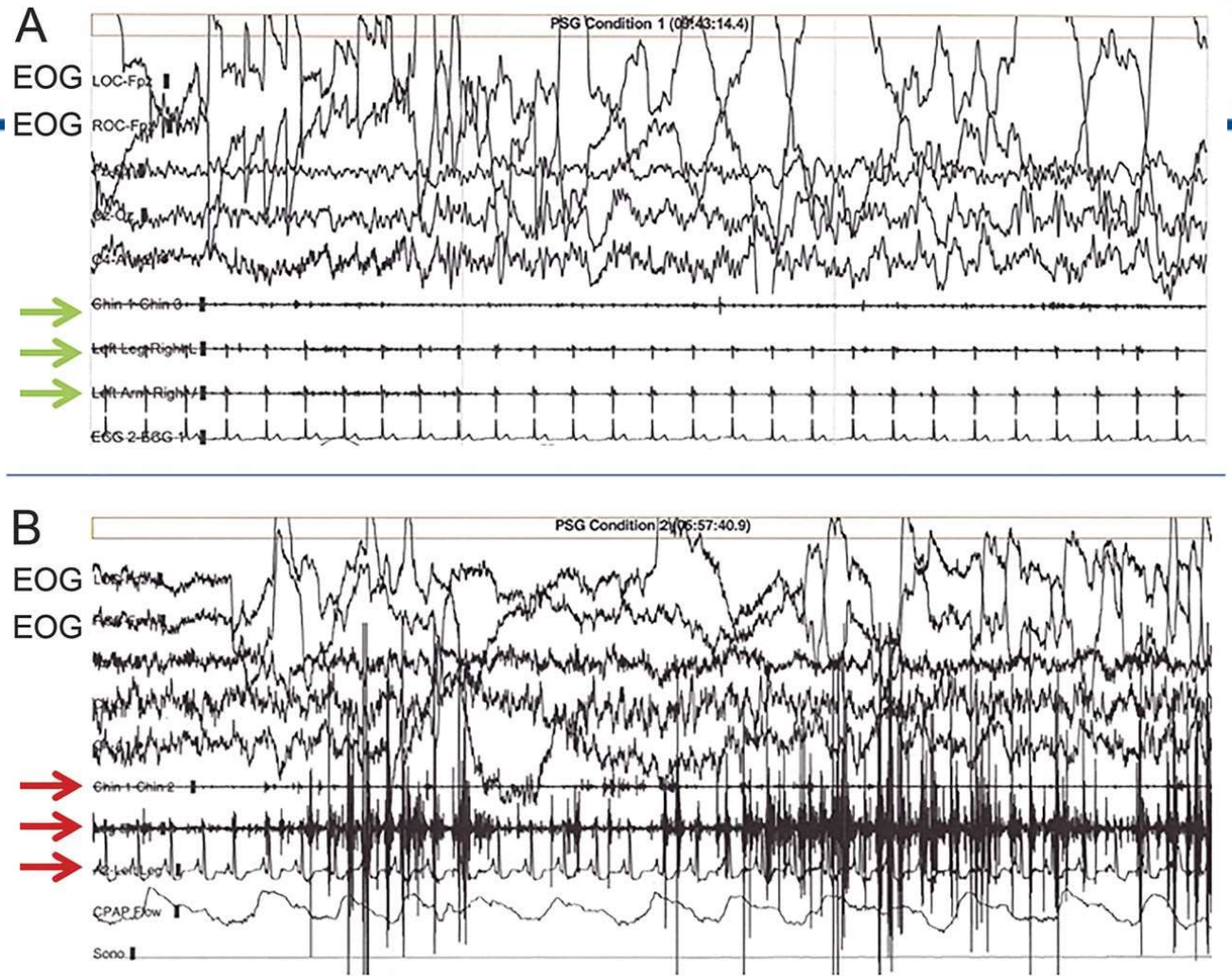
Noyce AJ et al. Ann Neurol 2012;72:893-901

Depressive disorders can occur at any stage of PD



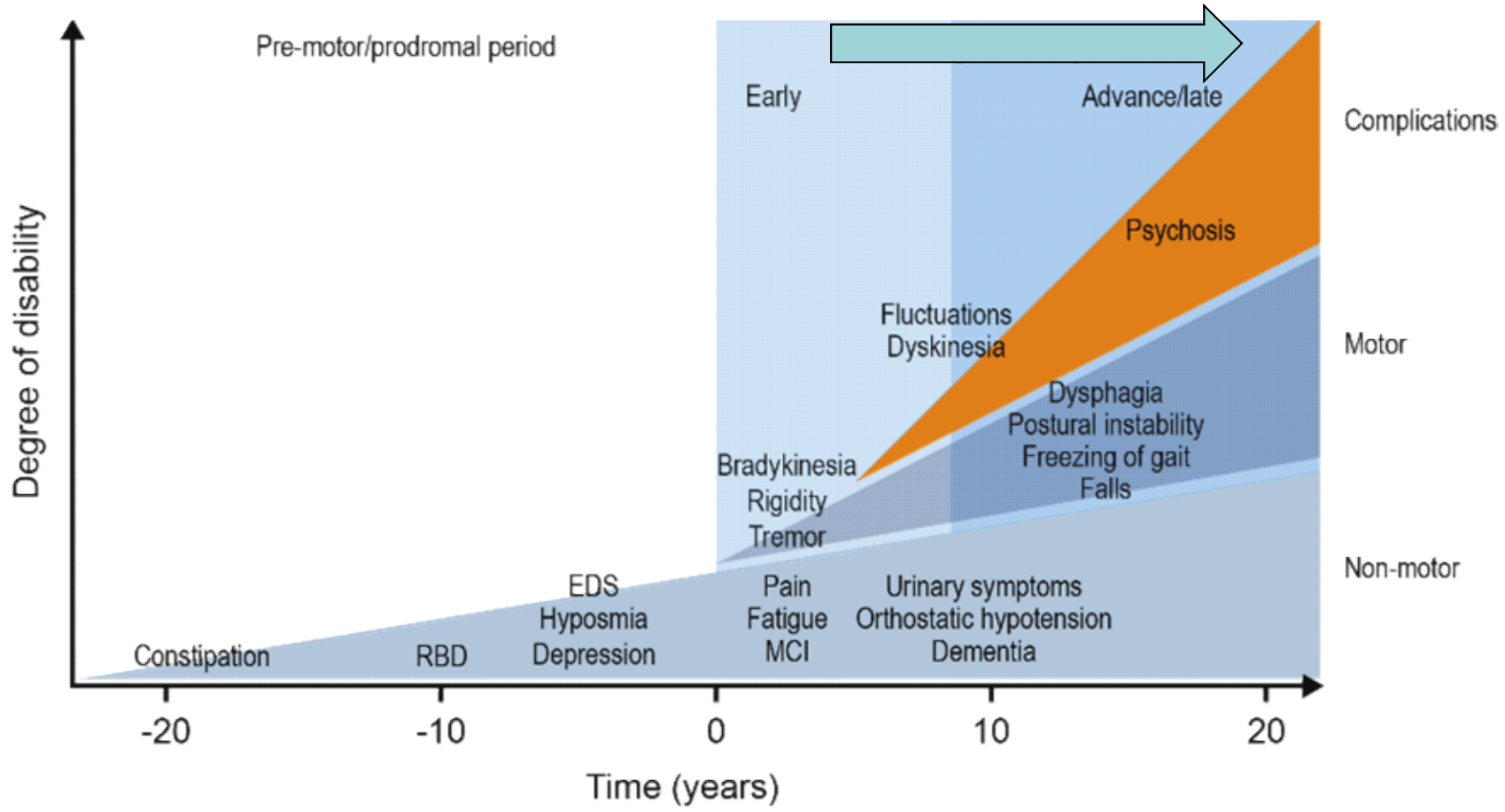
Ishihara and Brayne 2006

Figure 3 Polysomnographic (PSG) recordings



Ian G. McKeith et al. Neurology 2017;89:88-100

Parkinson's as a complex neuropsychiatric condition



Kalia and Lang et al.

Anxiety in Parkinson's disease

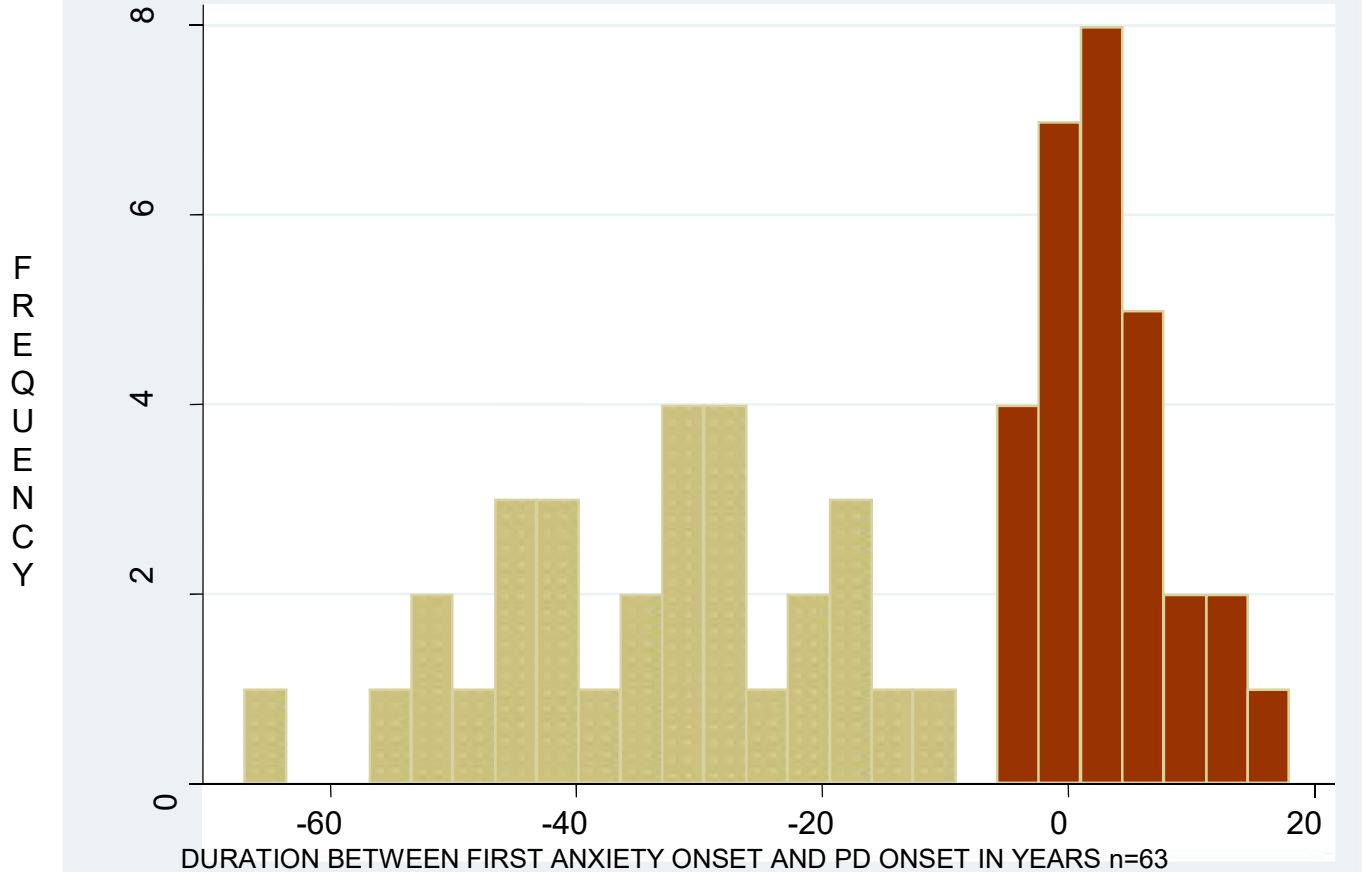
Prevalence of anxiety and anxiety disorders in PD

- Up to 55% have clinically significant anxiety symptoms
- 31% have an anxiety disorder (e.g. DSM)

    ~30% had more than one anxiety disorder

Yamanishi et al 2013, Broen M et al 2016

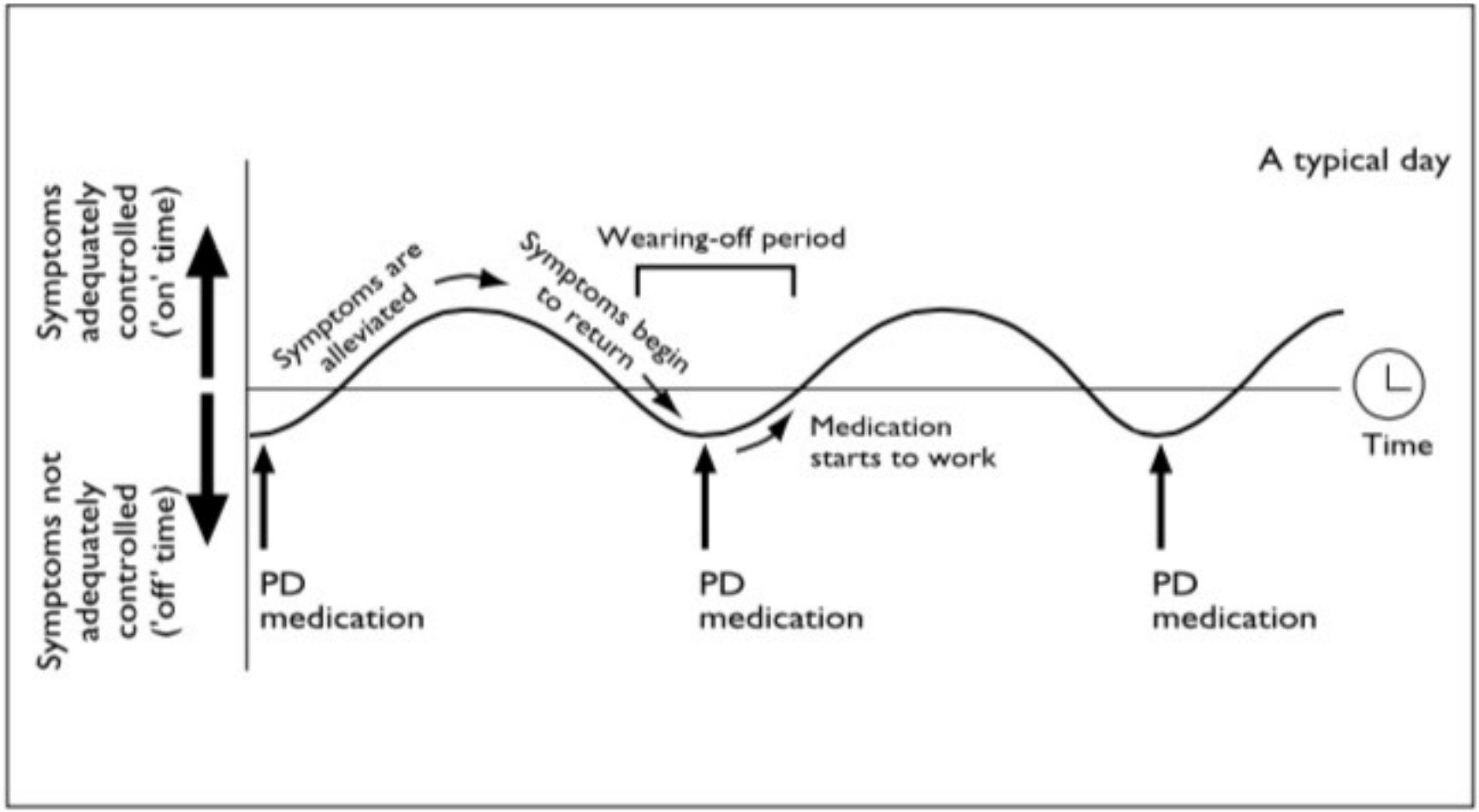
First Anxiety Disorder Onset Relative to Parkinson's Onset



Bimodal distribution of anxiety disorder onset compared to PD onset

Pontone et al 2009

Dopaminergic medication on-off fluctuations in PD



Stacey M. and Hauser R. 2007

Mood and motor fluctuation with levodopa infusion

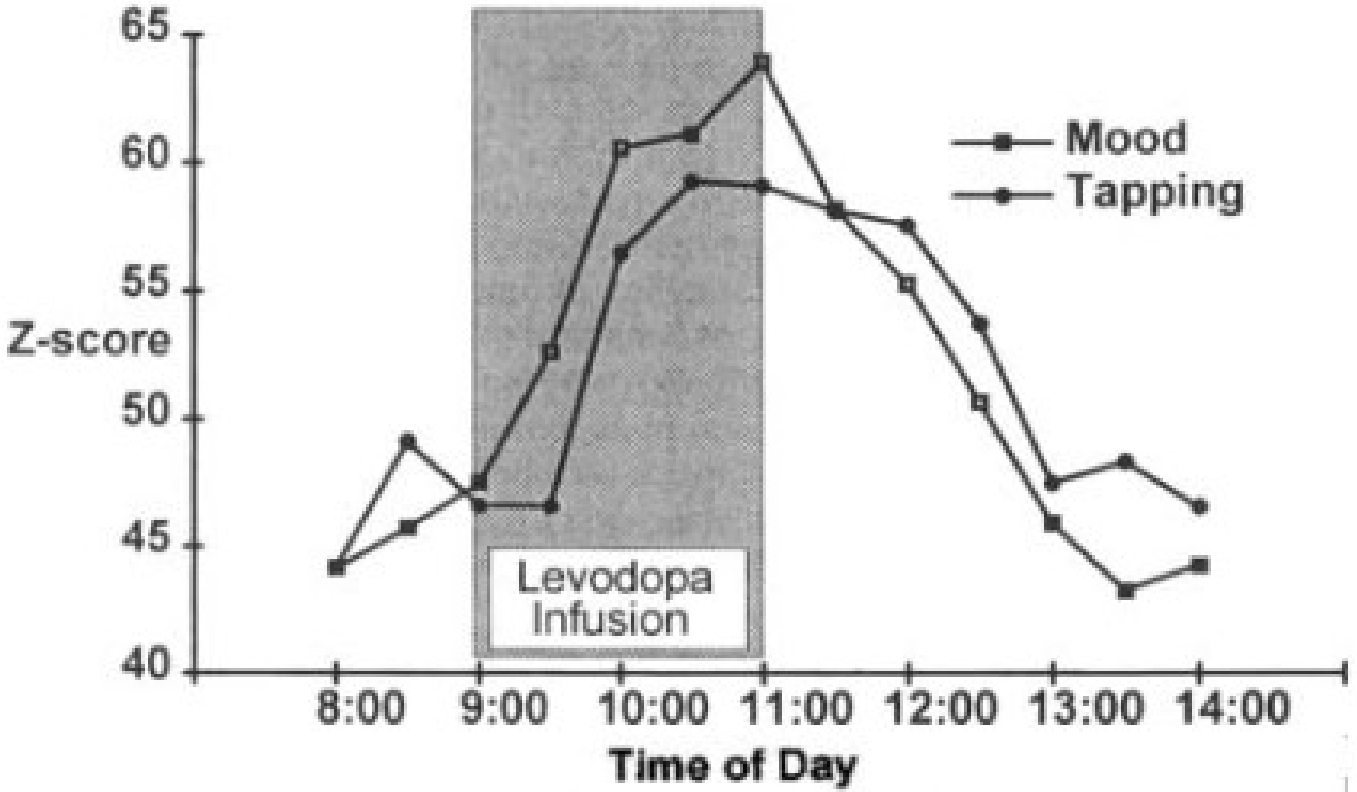
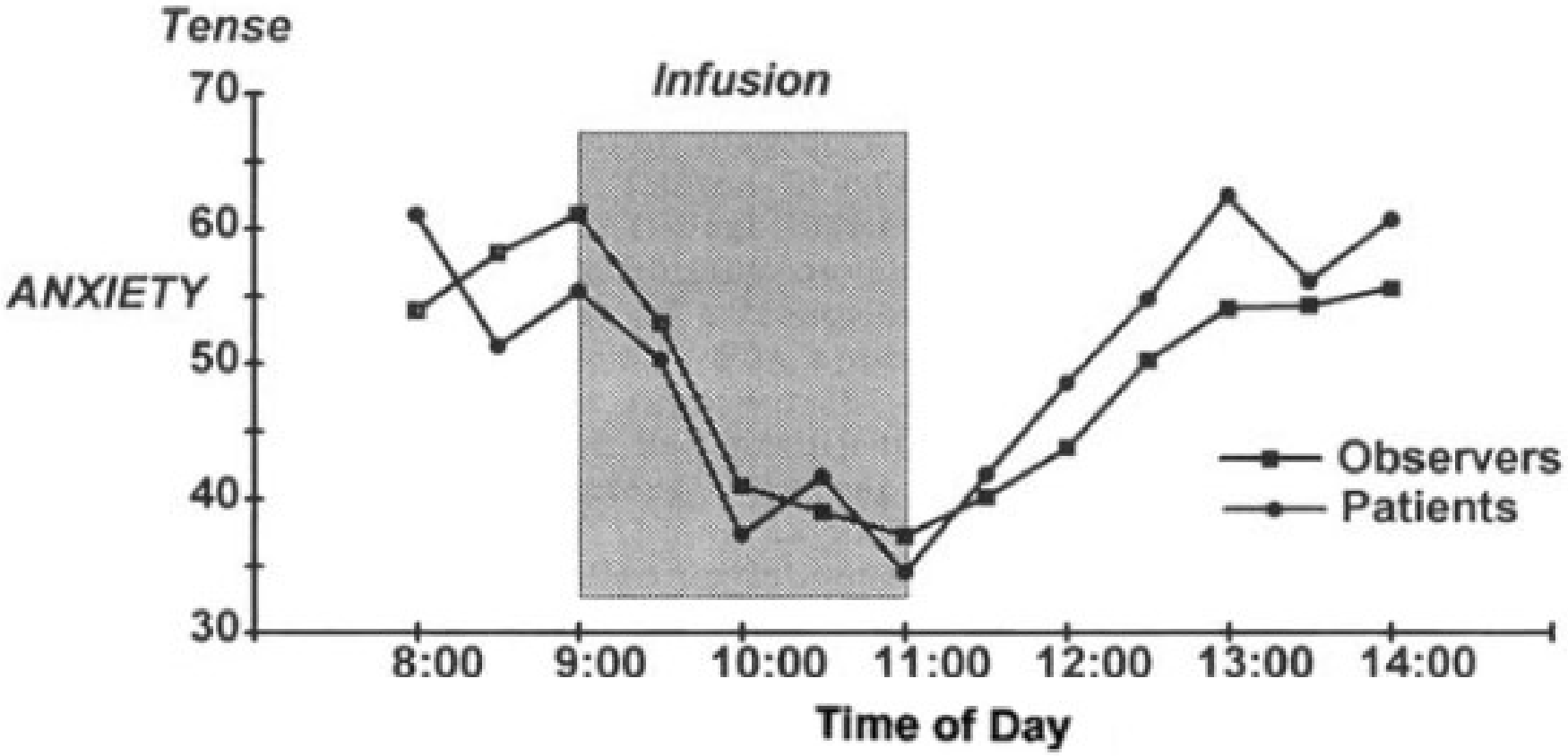


FIG. 3. Relationship of mood change and motor change.

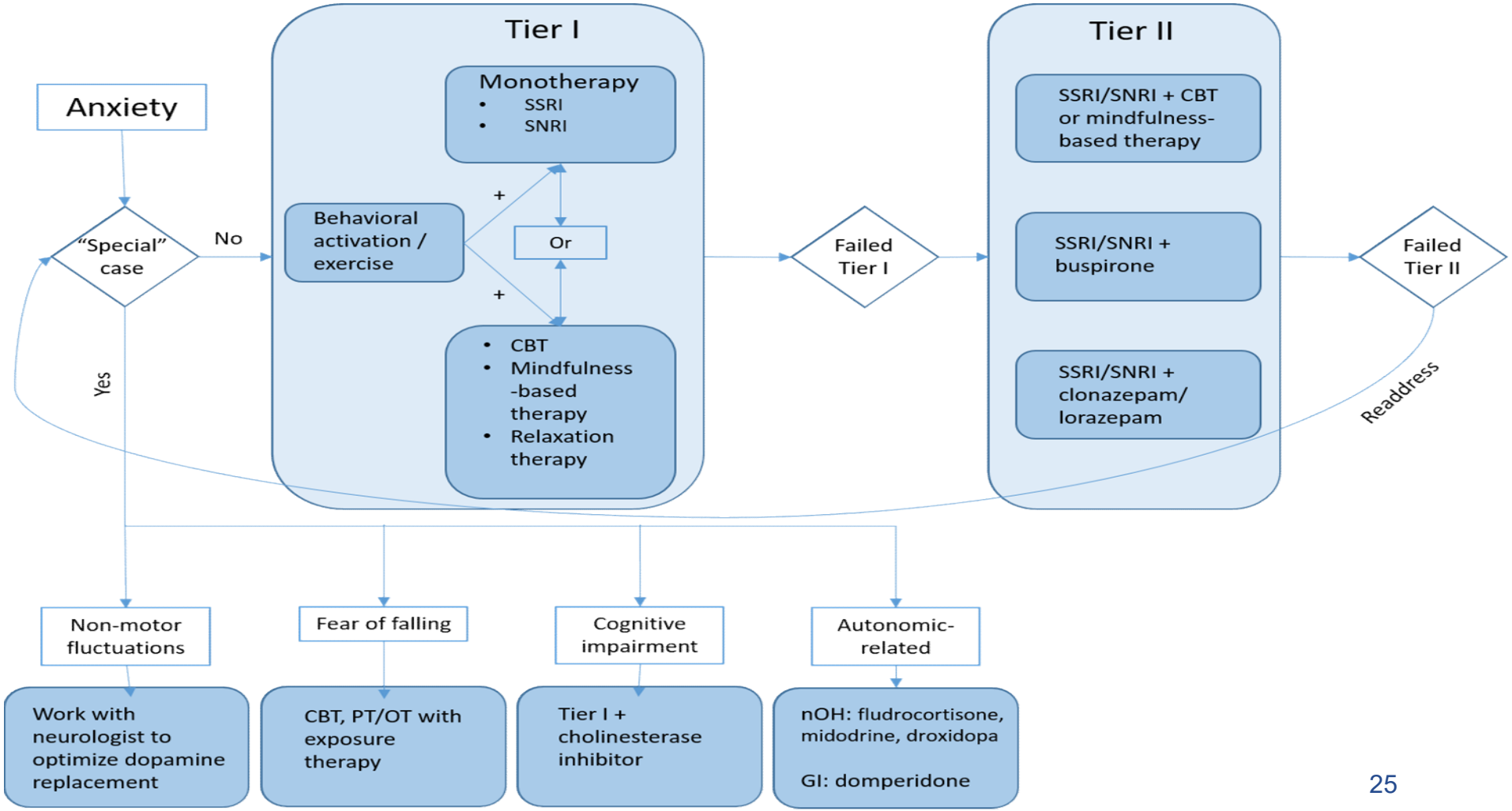
Maricle RA et al 1995

Anxiety fluctuation with levodopa infusion



Maricle RA et al 1995

PD anxiety treatment algorithm



Depression in Parkinson's disease

National Parkinson Foundation

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- **Parkinson's Outcomes Project**, a longitudinal look at which treatments produce the best health outcomes in PD n=12,000+
- **The impact of depression on quality of life is almost twice that of the motor impairments**

Prevalence of Depression in Parkinson's disease

- 25% for major depression up to 50% for 'minor' depression/dysthymia
- Anxiety disorders often co-occur

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004; Even 2012; Shakeri 2015; Ghaddar 2016; Reidel 2016

NET- PD Study/Neuroprotective Treatment Trials

Depressive symptoms predicted

- Increased need for symptomatic PD therapy (HR 1.86; 95% CI 1.29-2.68)
- Increased impairment in ADLs ($p<0.0001$)

Ravina et al 2007; Paumier KL et al 2012

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

The longitudinal impact of depression on disability in Parkinson disease

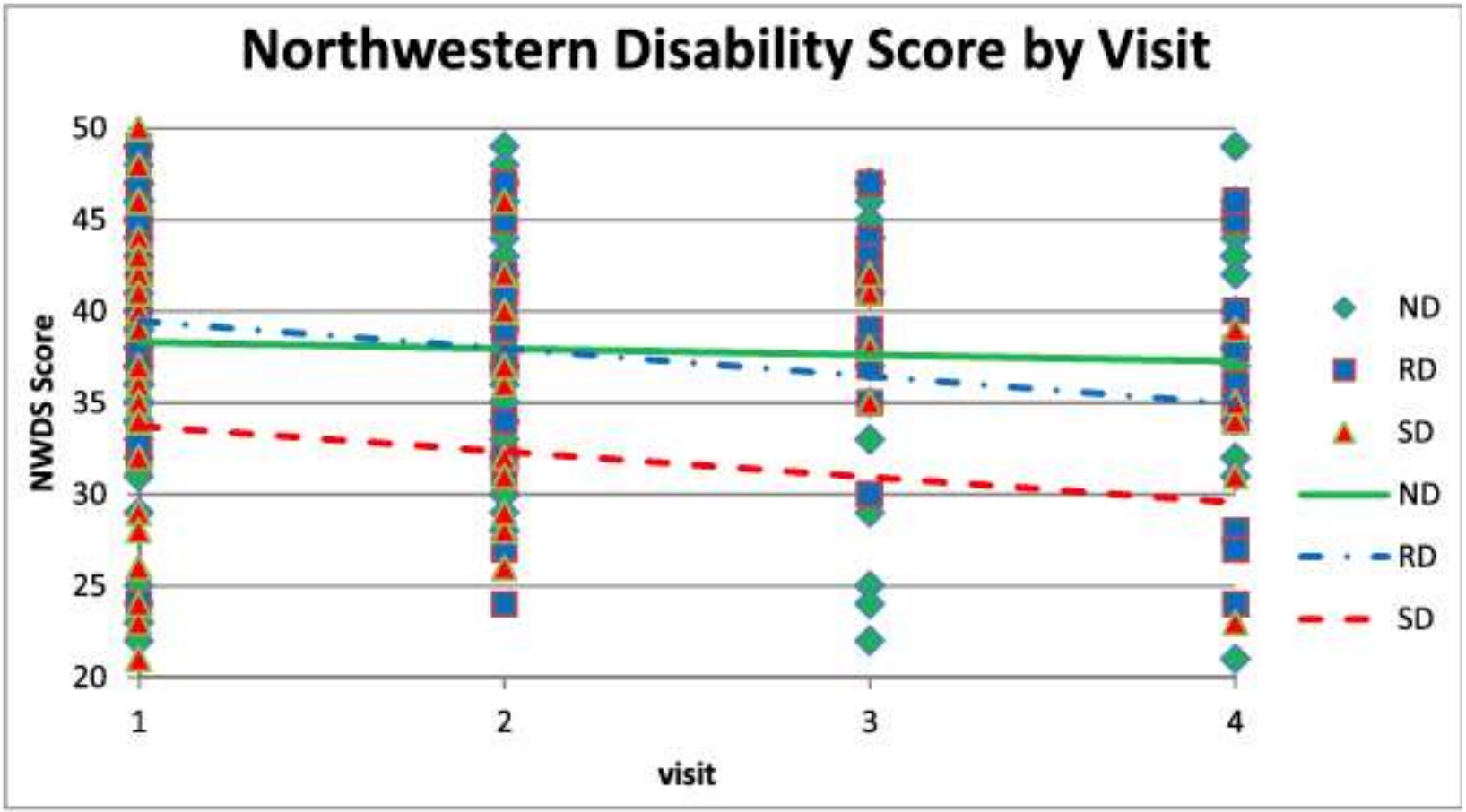
Gregory M. Pontone[1,2], Catherine C. Bakker[1,2], Shaojie Chen[3], Zoltan Mari[2,4], Laura Marsh[1,2†,‡], Peter V. Rabins[2,1], James R. Williams[1§] and Susan S Bassett[1,2]

Objective: This study examined the association between physical disability and DSM-IV-TR depression status across six years

Methods: 137 adults with idiopathic PD. A generalized linear mixed model with Northwestern Disability Scale score as dependent variable to determine the effect of baseline depression status on disability

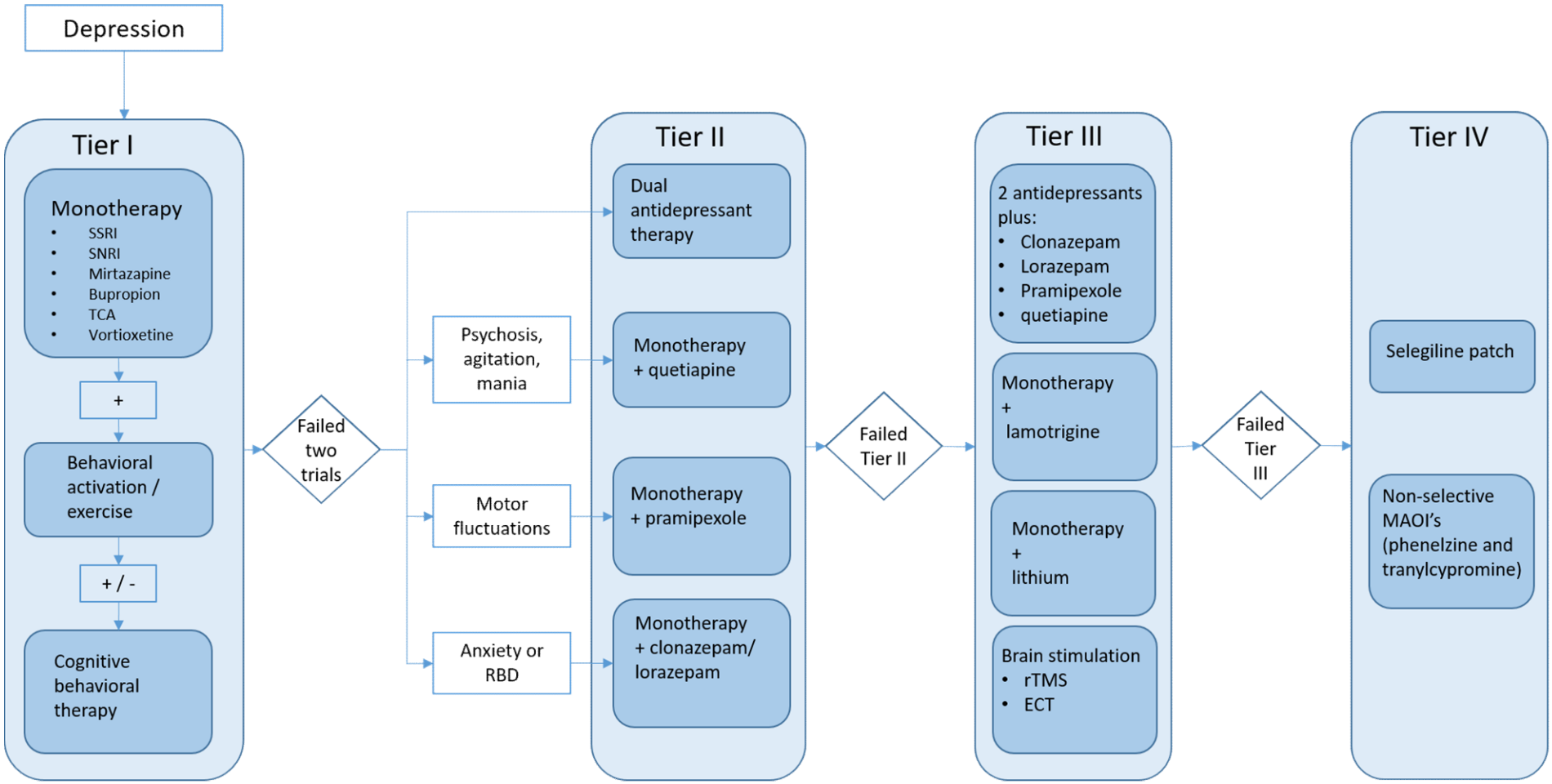
Results: 43 depressed at baseline vs 94 without depression. Symptomatic depression predicted greater disability compared to both never depressed (p=0.0133) and remitted depression (p=0.0009) after controlling for sex, education, dopamine agonist use, and motor fluctuations.

Longitudinal impact of depression on disability in PD (Pontone et al 2016)



ND=never depressed, RD=remitted depression, SD=symptomatically depressed

PD depression treatment algorithm



Pontone G and Mills K 2021

Psychosis in Parkinson's disease

NINDS/NIMH - Diagnostic criteria Parkinson's psychosis

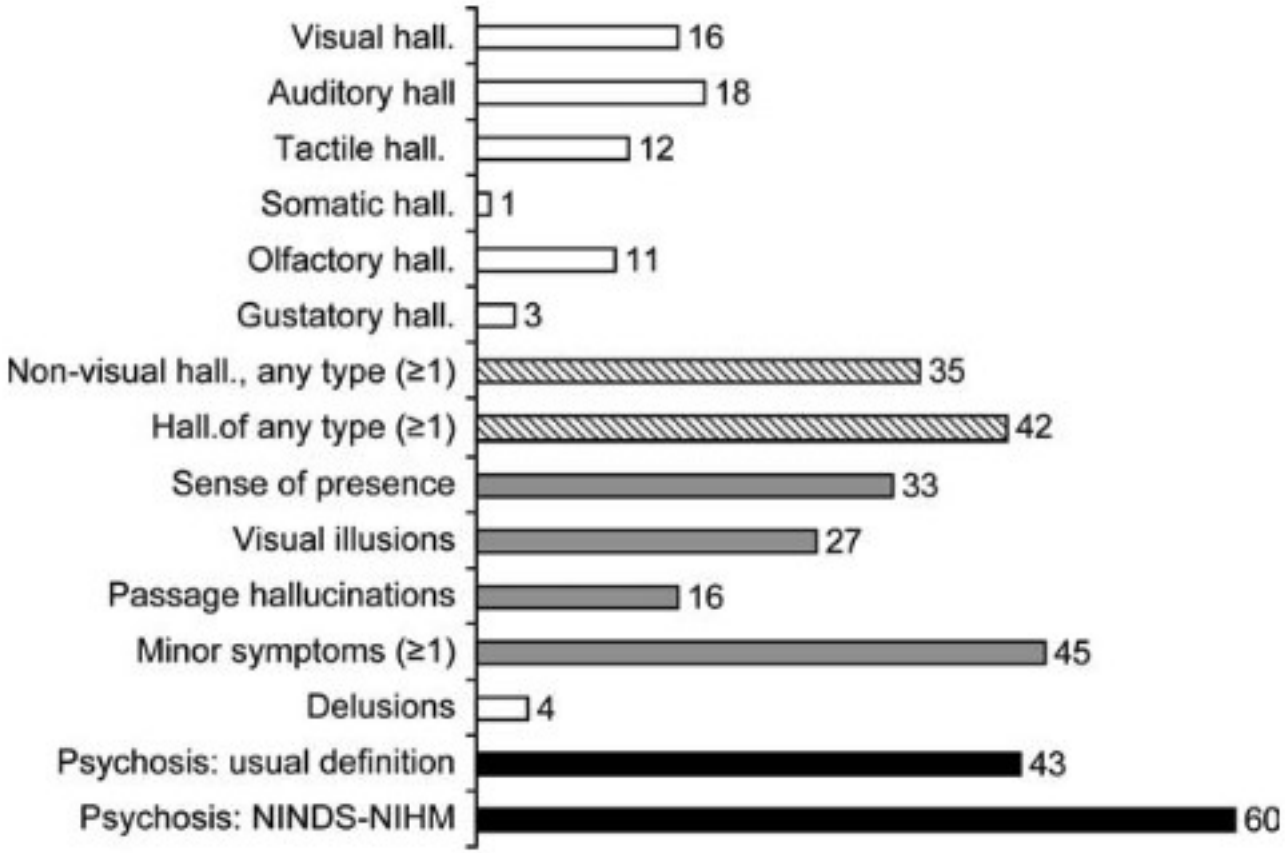
- Include ≥ 1 of the following
  - ✓ Illusions
  - ✓ False sense of presence
  - ✓ Hallucinations (visual and nonvisual)
  - ✓ Delusions
- Symptoms of psychosis
  - ✓ Occur after the onset of PD
  - ✓ Recurrent or continuous for 1 month
- Exclude alternate causes of PDP

Ravina B, et al. *Mov Disord*. 2007;22(8):1061-1068.

Parkinson's disease psychosis "Minor phenomena"

- **Illusions** – misperception of actual stimuli
- **Passage hallucinations** – indefinite object passing through the peripheral visual field
- **Sense of presence hallucination** – a 'feeling' (or idea) of someone close by

Prevalence of psychotic symptoms in Parkinson's



Fenelon G et al Movement Disorders 2010.

Dopamine replacement therapies and Parkinson's psychosis

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Support

- 3x increased incidence after starting dopamine in prospective cohort
- OR of 1.26 per 100mg LEDD increase in psychosis risk

Refute

- Lack of direct causal role, levodopa infusion did not induce hallucinations
- Psychosis in absence of exogenous dopamine
- Dose-response relationship is inconsistent across studies

Ffythche D et al 2017 Nature Reviews

Treatment of psychosis in PD

Drug	Efficacy	Safety	Practice implications
Clozapine	Efficacious	Acceptable, with specialized monitoring	Clinically useful
Pimavanserin	Efficacious	Acceptable, without specialized monitoring	Clinically useful
Quetiapine	Insufficient evidence	Acceptable, without specialized monitoring	Possibly useful

Seppi K et al 2019

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Dementia with Lewy Bodies and Parkinson's disease dementia

LEWY BODY DEMENTIAS

September 3, 2009

Parkinson's disease with dementia and dementia with Lewy bodies

- Dementia with Lewy-body like inclusions was first reported in the early 1960's (Okazaki et al 1961)
- Lewy-body-related dementias (PDD and DLB) are the second most frequent cause of primary degenerative dementia; 15-20% of dementias

Dementia in Parkinson's disease (PDD) MDS Task Force on PDD

1) Meets diagnostic criteria for PD (except for criterion re lack of dementia)
2) Motor symptoms developed prior to the onset of dementia
3) PD *associated* with decreased global cognitive efficiency (exclude other causes)
4) Progressive cognitive deficits in > one cognitive domain (2 or more of 4 domains)
5) Cognitive deficits severe enough to impair daily life

Emre et al 2007

DLB and PDD: clinical contrasts

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DLB

- Onset before or < 1 year after motor symptoms
- Faster course
- Hallucinations without dopamine meds; multimodality more likely
- Fluctuations in cognition more likely early

PDD

- Onset > 1 year after motor symptoms
- Usually >=10 years after PD onset/slower course
- Often, can't distinguish clinically from DLB, especially in later stages

Epidemiology of Parkinson's disease dementia (PDD)

- Incidence – annually 10% of a PD population progress from non-demented to demented
- not uniform, as incidence and prevalence increase with age (e.g., incidence 0.6/100K age 50-59 to 47/100K age 80-99)

Aarsland et al 2003, Hely et al 1999,
Hobson et al 2015

Epidemiology of Parkinson's disease dementia (PDD)

- Point prevalence ~30% (95% CI 20.1-42.1)
- Cumulative prevalence of 75% of PD surviving >10 years
- 83% after 20 years
- Up to 95% by age 90 years

Aarsland et al 2003, Butler et al 2008, Hely et al 1999, 2008, Hobson et al 2015, Marder K 2010, Williams-Gray et al 2013

Treatments for Lewy body dementias

Drug	Efficacy	Safety	Practice implications
Rivastigmine	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Donepezil	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Memantine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational

Questions?