COGNITIVE CHANGES AND PSYCHOSIS IN PD

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DISCLOSURES

- I have no financial disclosures to declare

I WAS ASKED TO DISCUSS

- Cognitive changes,
- Dementia,
- Psychosis
- Management of cognitive changes
- Management of psychosis
- Prevention of PDD & PDP

OBJECTIVES

- To review:
  - PD with Dementia (PDD)
  - PD with Psychosis (PDP)
- To discuss:
  - Recurrent Complex Visual Hallucinations (RCVH's)
  - Extracampine Hallucinations (EH's)
  - Review possible causes

OBJECTIVES

- To highlight the role of the Default Mode Network (DMN)
- Review current and future treatment
- Discuss prevention

Unmet Needs in PD Treatment

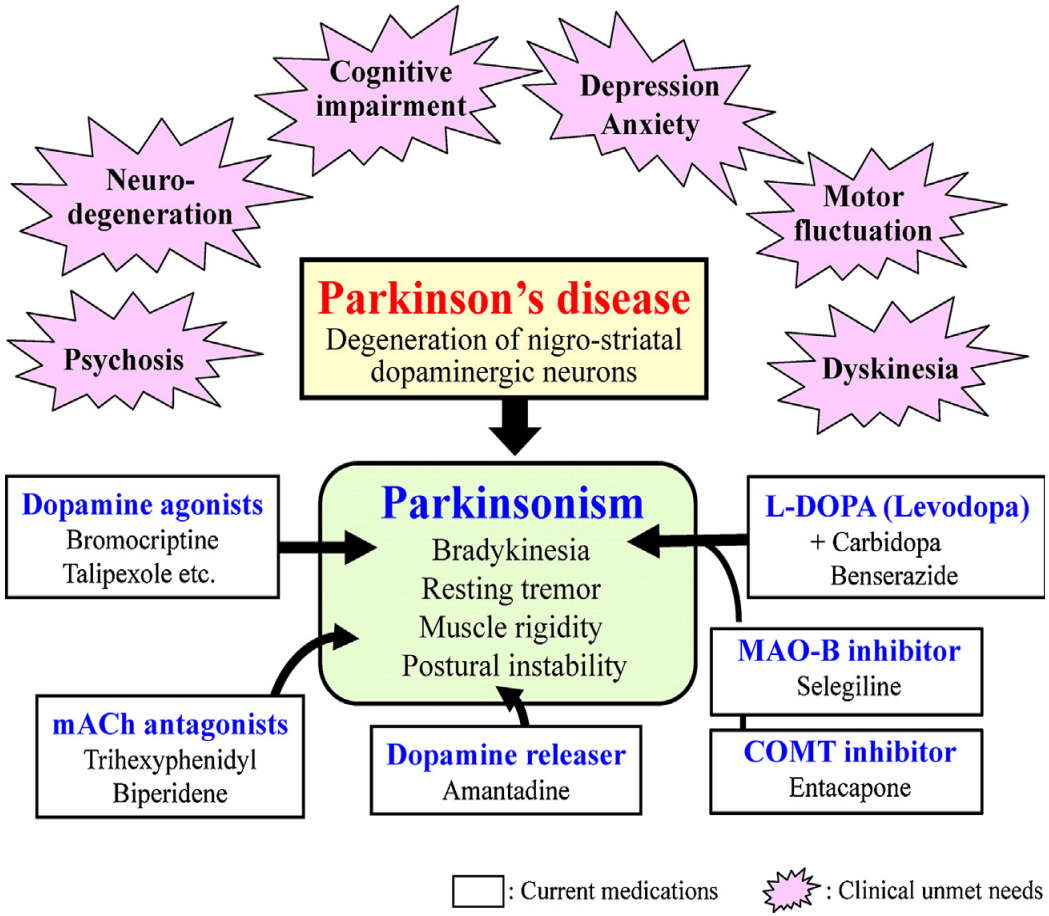

Fig. 3. Current medications for Parkinson's disease and clinical unmet needs. Various dopaminergic agents including L-DOPA and dopamine agonists are widely used to the treatment of Parkinson's disease. Although these agents are generally effective for most symptoms of Parkinson's disease, there are residual unmet needs, including a lack of effectual medications for neurodegeneration, cognitive impairments, mood disorders (e.g., depression and anxiety), dyskinesia or psychosis associated with chronic dopaminergic medications and motor fluctuation (e.g., wearing-off and on-off phenomena) in L-DOPA efficacy. mACh, muscarinic acetylcholine; MAO-B, monoamine oxidase-B; COMT, catechol-*O*-methyltransferase.

Unanswered Q's

- Why are hallucinations from non L-DOPA drugs like amantadine and anticholinergics **the same** as seen with DA-stimulating drugs?
- Why does effectiveness differ for some antipsychotics (e.g. clozapine is effective; quetiapine and olanzapine are not) when they all share an affinity for the 5HT2A receptors?

Friedman J. et al. EXP REV NEUROTHER, 2016

Unanswered Q's

- What is the relationship between dopaminergic agents that cause psychosis, and pimavanserin which *does not affect dopamine*?
- Why are hallucinations in DLB patients without medications identical to the hallucinations with dopaminergic agents in people with PD?

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Unanswered Q's

- Clozapine doses ***1-2 orders of magnitude lower*** than used in schizophrenia improve PDP without worsening motor function
- For unknown reasons, not likely related to anticholinergic effects, clozapine improves tremor, often dramatically.

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Unanswered Q's

- Why does clozapine improve PDP but not olanzapine or quetiapine?
- Why is the DA-induced psychotic syndrome the same as that occurring in DLB, a dopamine deficiency state?

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MY OBSERVATIONS

- Individuals with PDP/DLB are not fully "asleep" when they are dreaming
- PDP/DLB patients *behave like they are dreaming* while they are awake
- PDP/DLB pts "keep two sets of books"
- Changes in the eye may be involved in hallucinations

COGNITION IN PD/DLB

TIME COURSE

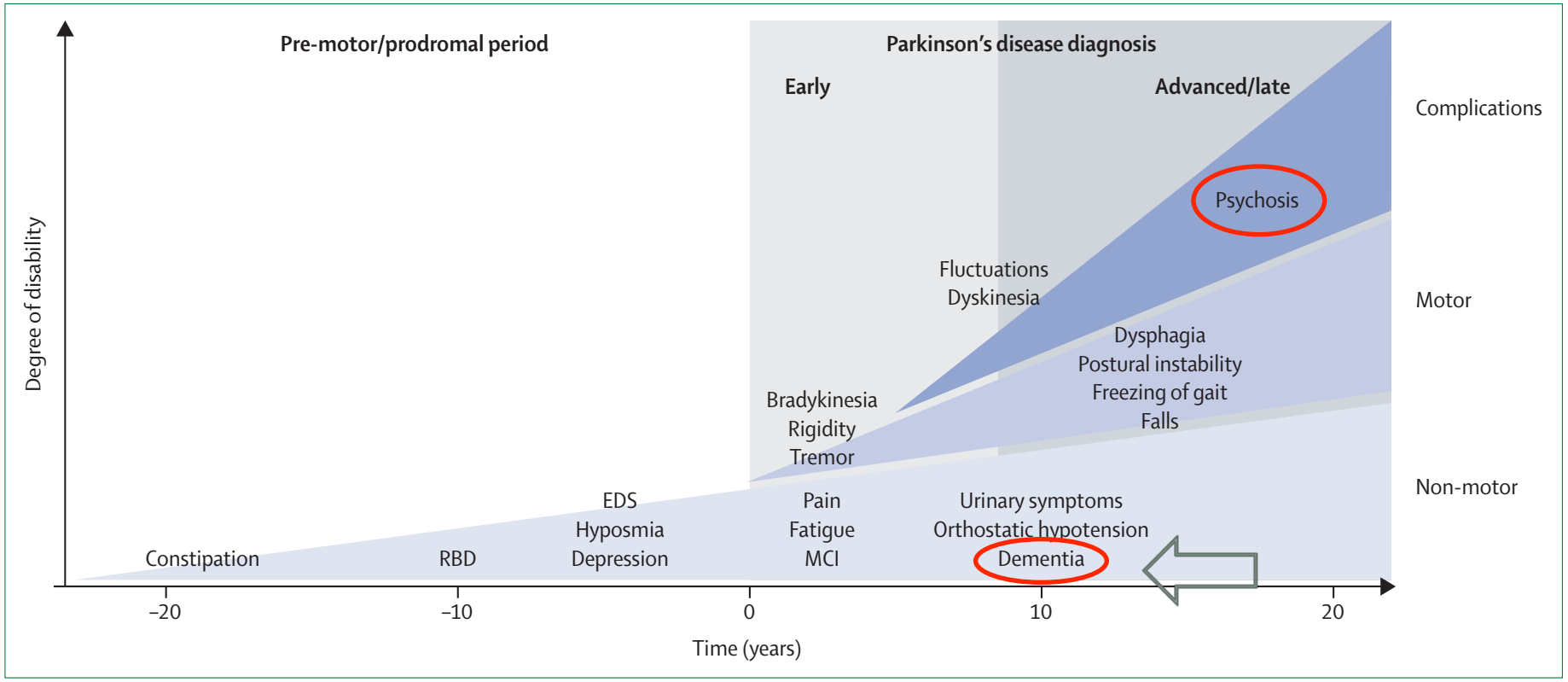


Figure 1: **Clinical symptoms and time course of Parkinson's disease progression**
Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

Kalia LV. Lancet 2015; 386: 896–912

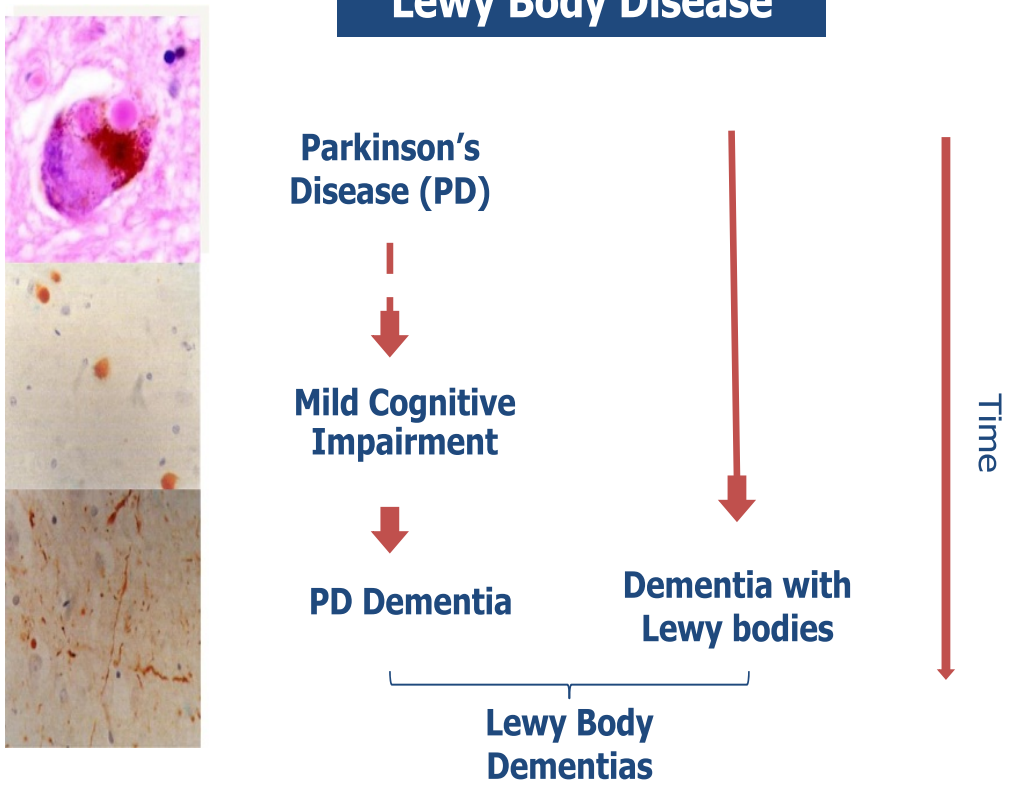


Figure 2 Nomenclature of Lewy body diseases. Parkinson's disease dementia is diagnosed when cognitive impairment develops a year or more after the onset of parkinsonism. Dementia with Lewy bodies is diagnosed when cognitive symptoms appear without parkinsonism or less than 1 year after the onset of parkinsonism.

COGNITIVE DEFICITS IN PD

- Most patients with PD develop cognitive impairment over time.
- By 20 years of disease duration, up to 83% of patients develop dementia

Berlyand Y. et al. 2016 PLoS ONE 11(1)

- Mean time from onset of PD to dementia is 10 years

Baggio HC. CNS Neuroscience & Therapeutics 21 (2015) 793–801 .

NON MOTOR SYMPTOMS

nonmotor symptoms of PD include:

- depression,
- sleep disturbance,
- sensory abnormalities,
- autonomic dysfunction, and
- cognitive decline

D.T. Dexter, P. Jenner / Free Radical Biology and Medicine 62 (2013) 132–144

PD WITH DEMENTIA (PDD)

- PD pts with dementia (PDD) patients have:
  - reduced Q of L
  - Less independence,
  - increased cost of care,
  - additional stress for families & caregivers.

Berlyand Y. et al. 2016 PLoS ONE 11(1)

DLB & PDD

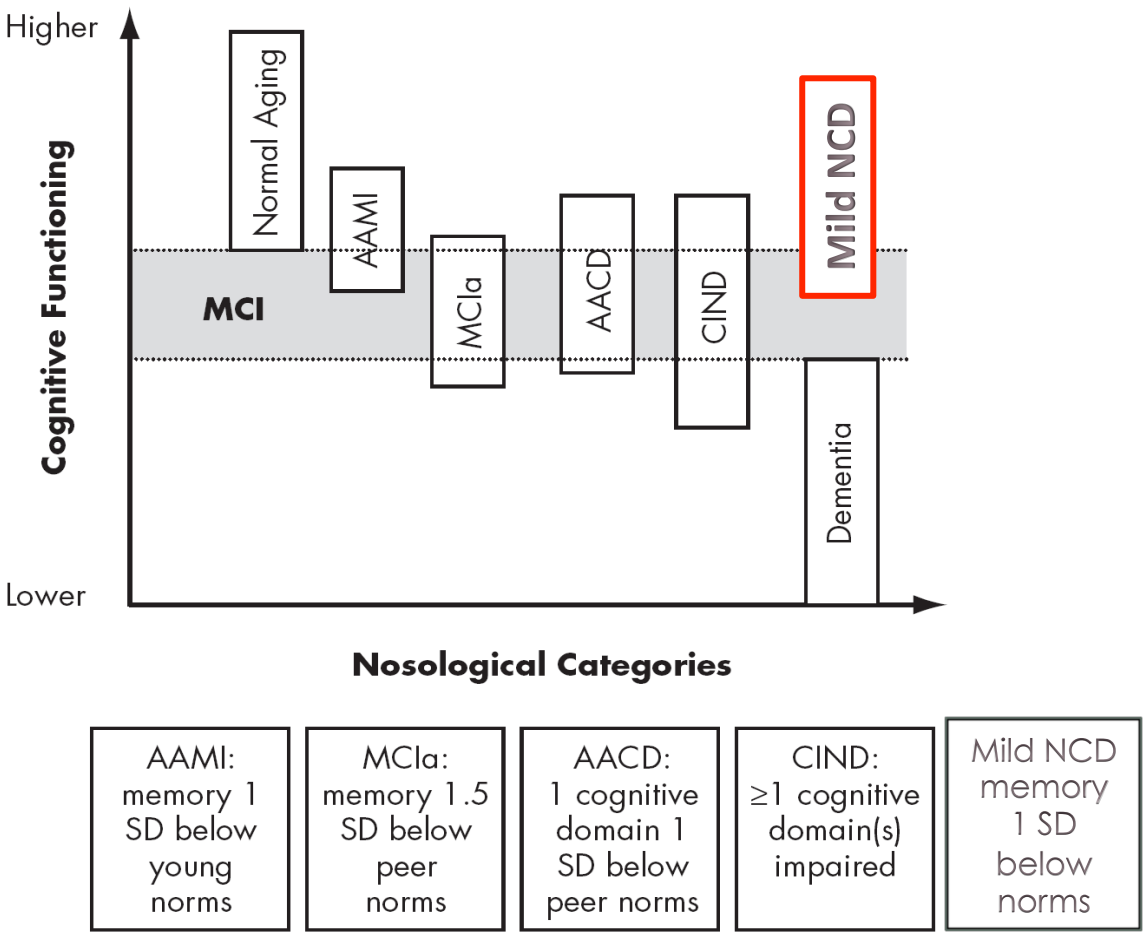
- DLB is best conceptualized as a ***dominant dementia syndrome*** with multiple pathologies that include Lewy bodies and AD

- In contrast to DLB, PD is a ***dominant movement disorder*** characterized by the presence of bradykinesia, rigidity, resting tremor, gait instability that is responsive to levodopa therapy

Kim et al. Alzheimer's Research & Therapy 2014, 6:73

MCI/MILD NCD

FIGURE 1. Conceptual Model of the Cognitive Continuum From Normal Aging to Dementia



Note: AAMI: age-associated memory impairment
MCIa: (amnestic) mild cognitive impairment
AACD: age-associated cognitive decline
CIND: cognitive impairment not dementia.

Feldman, L. Am J Ger Psych 2005;13:8

PROGRESSION FROM MCI

- In general population studies, some MCI cases remain stable, or revert to normal cognition.
- Reversion rates of 30–40% from MCI to normal cognition suggest MCI is not a stable diagnosis

Hobson P. Int J Geriatr Psychiatry 2015 30: 1048–1055

PROGRESSION FROM MCI

- A 2015 study examined PD patients with cognitive impairment over 16 years,
  - > 90% progressed to PDD.
- This confirmed the findings of the Sydney Multicenter Study (2008)
  - nearly all PD patients developed significant cognitive impairment or dementia.

Hobson P. Int J Geriatr Psychiatry 2015 30: 1048–1055

COGNITIVE DEFICITS IN PD

PD-related cognitive deficits affect:

- Attention
- Executive function,
- Memory,
- Psychomotor speed ,
- Visuospatial &
- Perceptual abilities
- .

Baggio HC. CNS Neuroscience & Therapeutics 21 (2015) 793–801 .

DIFFERENCES FROM AD

- DLB differs from AD by showing relative preservation of:
  - Confrontation naming
  - Recognition
  - Short and medium term recall
- DLB pts exhibit impaired :
  - Verbal fluency
  - Visual perception
  - Performance tasks
- Pronounced memory deficits are more characteristic of AD

COGNITIVE DEFICITS IN PD

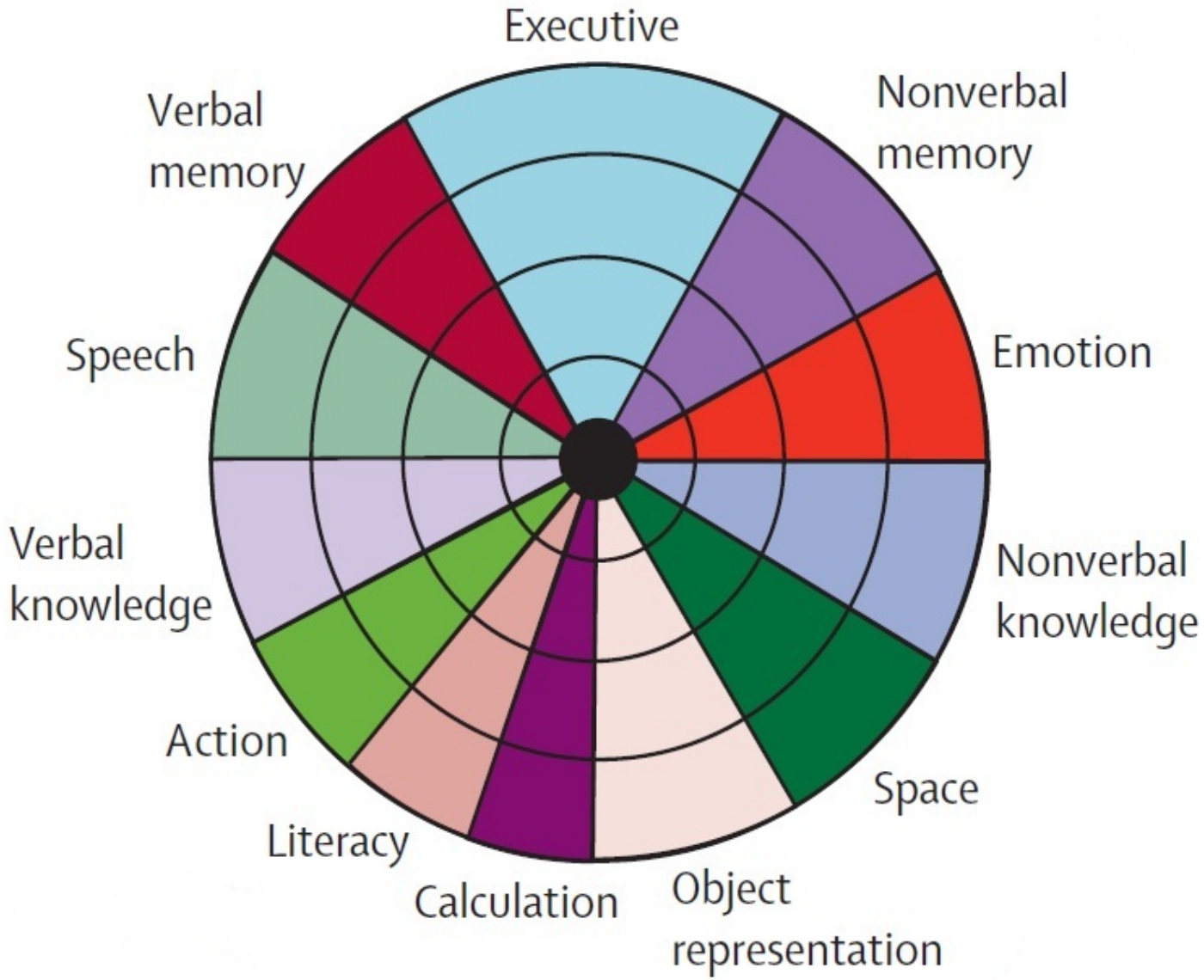
- There are two overlapping cognitive syndromes in PD with different clinical presentations, tx response, & prognosis
  - **Frontal-striatal executive deficits** related to dopaminergic imbalances
  - **posterior cortical syndrome**, not related to dopamine deficiency, & more likely to progress to dementia

Baggio HC. CNS Neuroscience & Therapeutics 21 (2015) 793–801 .

POSTERIOR CORTICAL SYNDROME

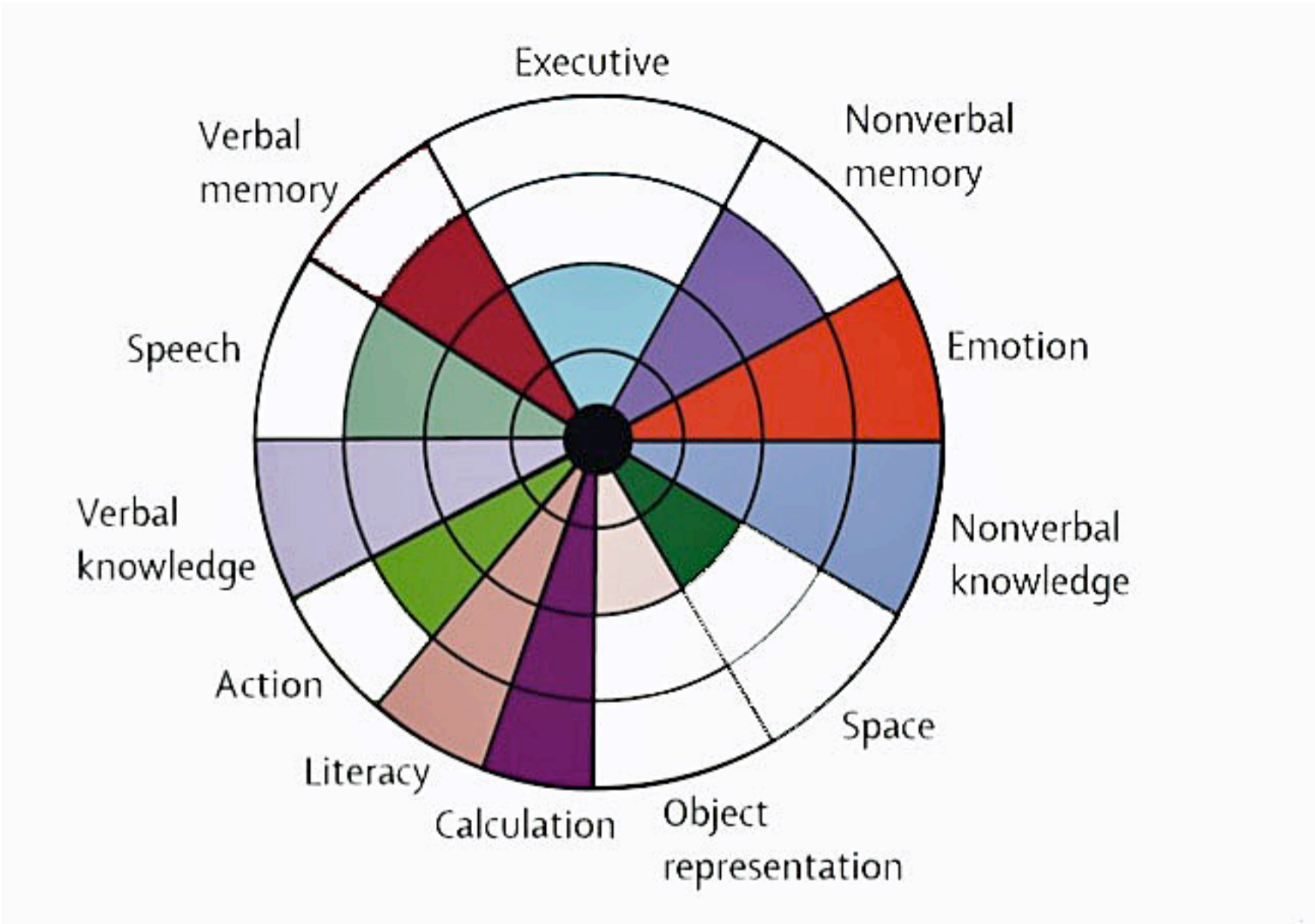
- Posterior cortical syndrome is associated with:
  - A higher risk of dementia
  - Impaired semantic fluency
  - visuospatial/visuoperceptual deficits

Baggio HC. CNS Neuroscience & Therapeutics 21 (2015) 793–801 .



Normal Cognition

Rossor MN. Lancet Neurol 2010;9:793-806



PD with Dementia

Rossor MN. Lancet Neurol 2010;9:793-806

Panel 3: Recommended guidelines for cognitive test selection in Lewy body disorders[3]

Brief screening tools

Montreal Cognitive Assessment,[63] Parkinson's Disease Cognitive Rating Scale,[64] Parkinson's Neuropsychometric Dementia Instrument,[65] Scales for Outcomes in Parkinson's Disease—Cognition[66]

Visuospatial

Figure copy tests (eg, cube, clock, interlocking pentagons, or complex figures), spatial judgment tests that do not rely on motor functions (eg, Visual Object Space Perception Battery,[67] Benton Judgment of Line Orientation)[68]

Executive or attention

Measures of working memory, selective attention, set-shifting, planning, and verbal fluency (eg, Wisconsin Card Sorting Test,[69] NIH EXAMINER,[70] trail making test,[71] Stroop[72])

Memory

Word list, figure, or associative learning with delayed recall and recognition (eg, Rey Auditory Verbal Learning Test,[73] California Verbal Learning Test,[74] Free and Cued Selective Reminding Test,[75] Brief Visuospatial Memory Test-Revised[76]); visual memory might be poor for reasons of visual perceptual or memory deficit.

DIFFERENCES FROM AD

Table 2. Comparison of Clinical Features of Lewy-body Dementia, PD Dementia, and Alzheimer's Disease

	Lewy-body Dementia	PD Dementia	Alzheimer's Disease
Clinical features			
Common presentation	Psychotic symptoms and/or parkinsonian features	Parkinsonian features	Memory decline
Psychotic symptoms	Early visual hallucinations with or without delusions	Associated with exposure to PD pharmacotherapy	Usually later in disease process
Memory decline	As disease progresses, particularly in accessing memories	Difficulty accessing memories	Earlier, global, and progressive difficulty in forming memories
Speech impairment	Usually late	Hypophonia, dysarthria	Aphasia, paraphasia
Parkinsonian features			
Tremors at rest	Present in 20%-50%	Present in 75%	Only late in disease
Rigidity	Common	Common	Only late in disease
Gait abnormality	Early in disease	Early or late in disease	Late in disease
Response to levodopa	Variable	Common	NA
Antipsychotic sensitivity	Can be extreme	Variable, increased parkinsonism at higher dosages	Development of parkinsonism at higher dosages
Efficacy of cholinesterase inhibitors	One positive efficacy study	One positive efficacy study	Established

PD WITH PSYCHOSIS (PDP)

AWAKENINGS

- Neurologist Oliver Sacks (1933-2015) wrote about the early trials of L-Dopa
- He was among the first to recognize the side effects of L-Dopa treatment
- His patient Leonard was the subject of a radio documentary ~1986
  - It reenacted his experiences on L-Dopa and an emotional roller coaster of highs and lows

AWAKENINGS

- His medical reports, describing their "awakenings" on the drug, received very positive responses when published in The Lancet and JAMA.
- Dr. Sacks reported that, within months, *his patients experienced major side effects on L-dopa,*

DOIDGE N. The Globe and Mail Mar. 28, 2016

AWAKENINGS

- He cautioned that these people may be sensitive "canaries in the coal mine,"
- He suggested L-dopa might best be used with caution on more typical Parkinson's patients.
- Some said he was "off his head," and that no such side effects occurred.

DOIDGE N. The Globe and Mail Mar. 28, 2016

AWAKENINGS

- L-Dopa can increase or cause psychosis, but it is rarer than with other drugs
  - Pramipexole
  - Ropinirole
  - Pergolide

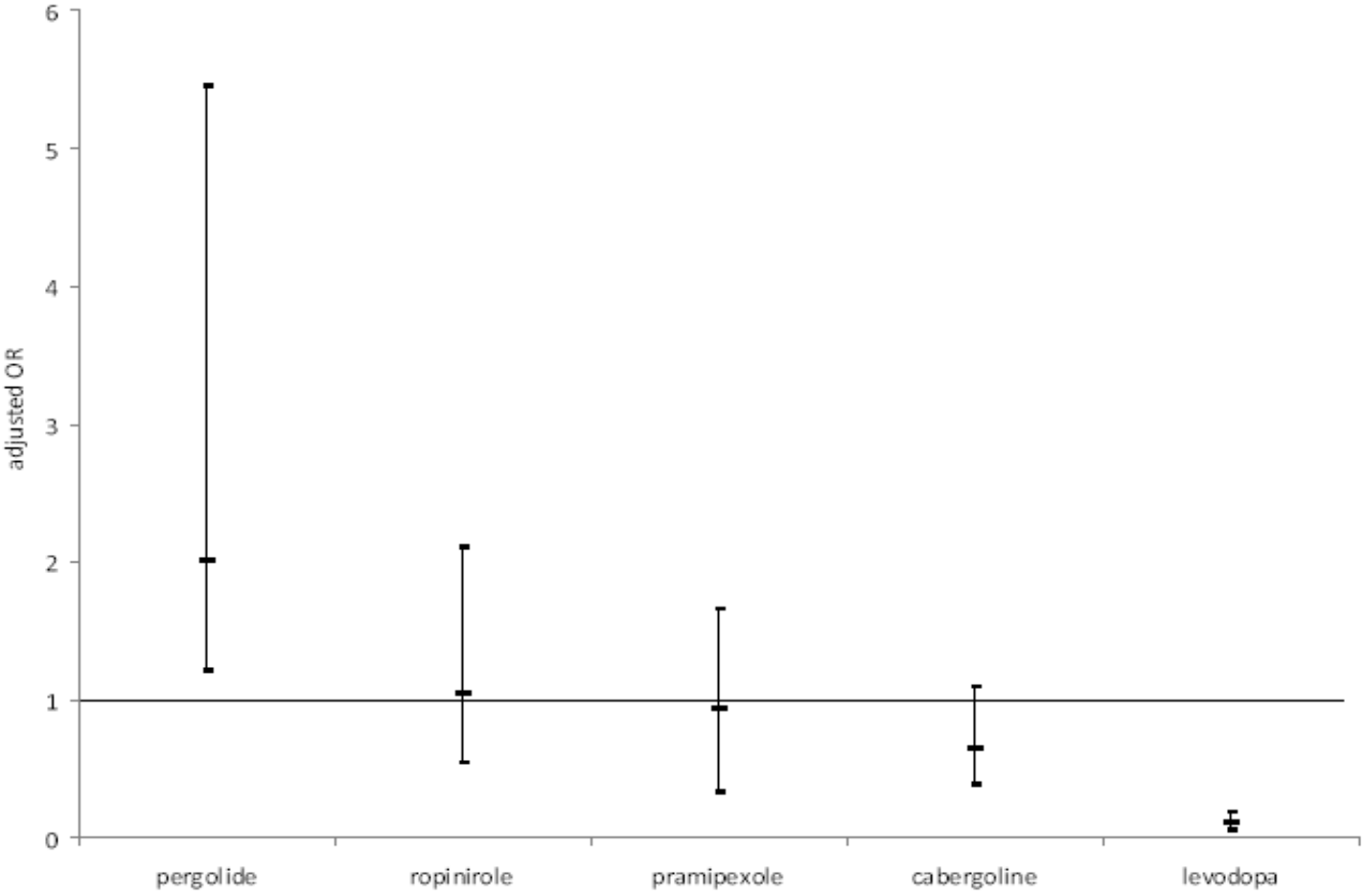


Figure 1
Adjusted odds ratios for levodopa, cabergoline, pramipexole ropinirole and pergolide. Results of the logistical regression model adjusted for sex, dementia, concomitant medication and concomitant disorders. Box marks indicate odds ratio, vertical bars indicate confidence intervals. Horizontal line indicates odds ratio of 1.

PSYCHOSIS IN PD (PDP)

- A 12-year prospective study of 230 individuals with PD found **60%** of the patients developed psychosis,
- Baseline predictors were:
  - Higher age at onset of PD
  - More severe parkinsonism
  - Depression
  - Higher use of antiparkinsonian medication,
  - Presence of REM behavioral disorder (RBD)

Starkstein SE. Curr Opin Psychiatry 2012, 25:468

PDP

- **Hallucinations** are the hallmark features of PDP, & DLB.
- ~ 30% of drug-treated PD patients have visual hallucinations
- The lifetime prevalence of visual hallucinations is approximately 50%

Friedman J. et al. EXP REV NEUROTHER, 2016

PDP

- Symptoms range from mild visual distortions and the sense of a presence (extracampine hallucinations), to fully formed, complex hallucinations.
- Visual images of people or animals are the most common type of hallucination
- other sensory modalities may also be affected.

Cooney JW. Curr Neurol Neurosci Rep (2016) 16: 49

PDP

- Auditory hallucinations have been reported in 8 % of patients with PD psychosis (PDP)
- Grandiose, religious, and/or persecutory hallucinations are rare in PDP.
- Delusions are less common in PD and affect a subset of 5–30 % patients, but these fixed beliefs are often refractory to treatment.

Cooney JW. Curr Neurol Neurosci Rep (2016) 16: 49

PDP

- **Delusions** are usually paranoid in nature,
- Frequently of spousal infidelity or abandonment
- These are more stressful for caregivers than motor symptoms,
- Delusions are often cited as a precipitant for nursing home placement

Friedman J. et al. EXP REV NEUROTHER, 2016

TABLE 1. Criteria Used for PD-Associated Psychosis According to *DSM-5* and the NINDS, NIMH Work Group[a]

Criteria for PD-Associated Psychosis
NINDS, NIMH Work Group: Proposed Diagnostic Criteria for PD-Associated Psychosis
A. Characteristic symptoms
Presence of at least one of the following symptoms:
Illusions
False sense of presence
Hallucinations
Delusions
B. Primary diagnosis
U.K. Brain Bank criteria for PD
C. Chronology of the onset of symptoms of psychosis
The symptoms in criterion A occur after the onset of PD
D. Duration
The symptom(s) in criterion A are recurrent or continuous for 1 month
E. Exclusion of other causes
The symptoms in criterion A are not better accounted for by another cause of parkinsonism, such as dementia with Lewy bodies, psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, mood disorder with psychotic features, or a general medical condition including delirium
DSM-5: Psychotic Disorder Due to Another Medical Condition[b]
A. Prominent hallucinations or delusions
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition
C. The disturbance is not better explained by another mental disorder
D. The disturbance does not occur exclusively during the course of a delirium
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

[a] NIMH, National Institute of Mental Health; NINDS, National Institute of Neurological Disorders and Stroke; PD, Parkinson's disease.

[b] Reprinted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC, APA, 2013. Copyright © 2013, American Psychiatric Association. Used with permission.

HALLUCINATIONS

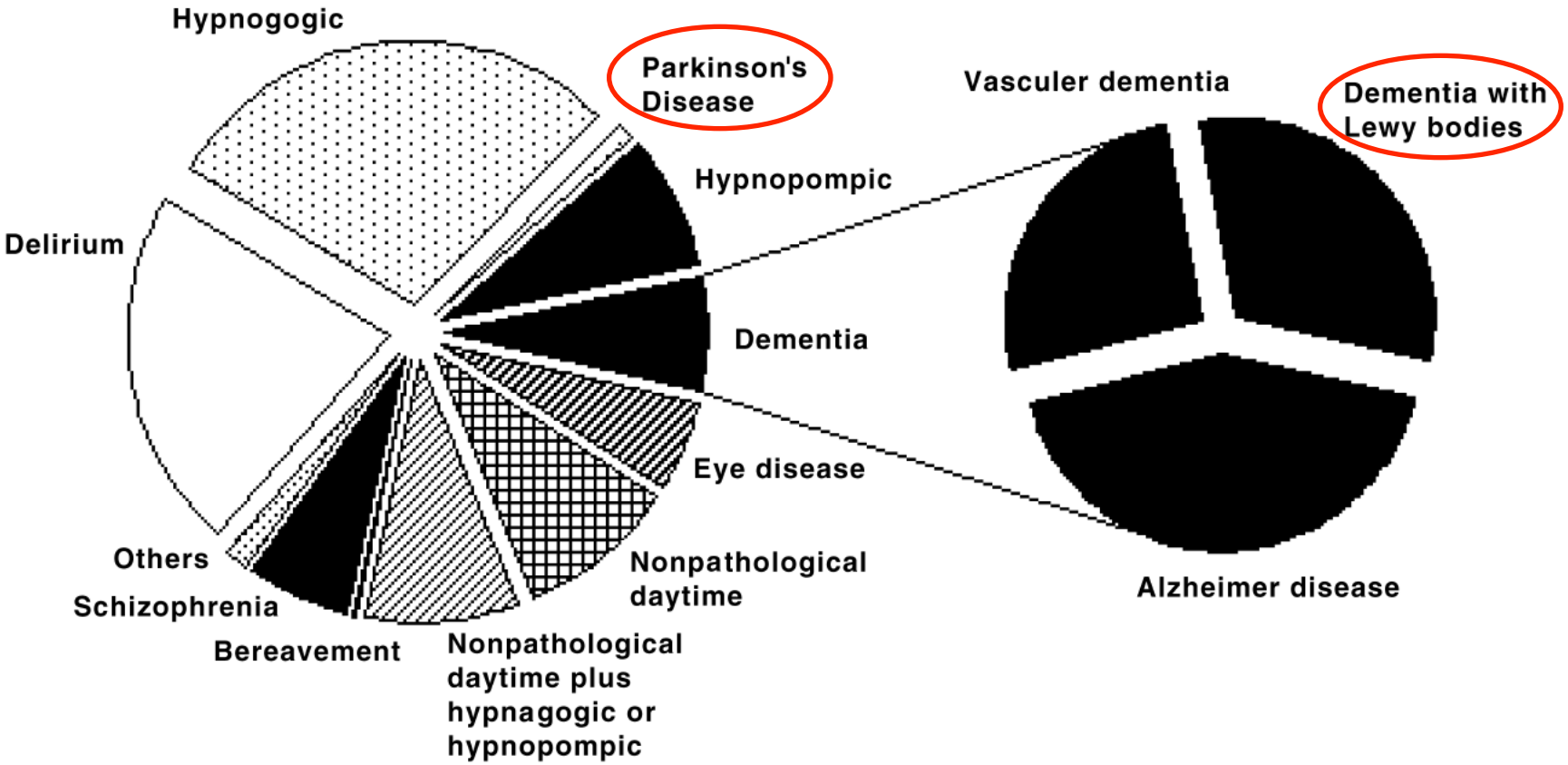
- The hallucinations are stereotypic:
- Typically visual and have no emotional content
- Usually involve people or pet animals,
- Typically ignore the patient

Friedman J. et al. EXP REV NEUROTHER, 2016

Lilliputian Figures

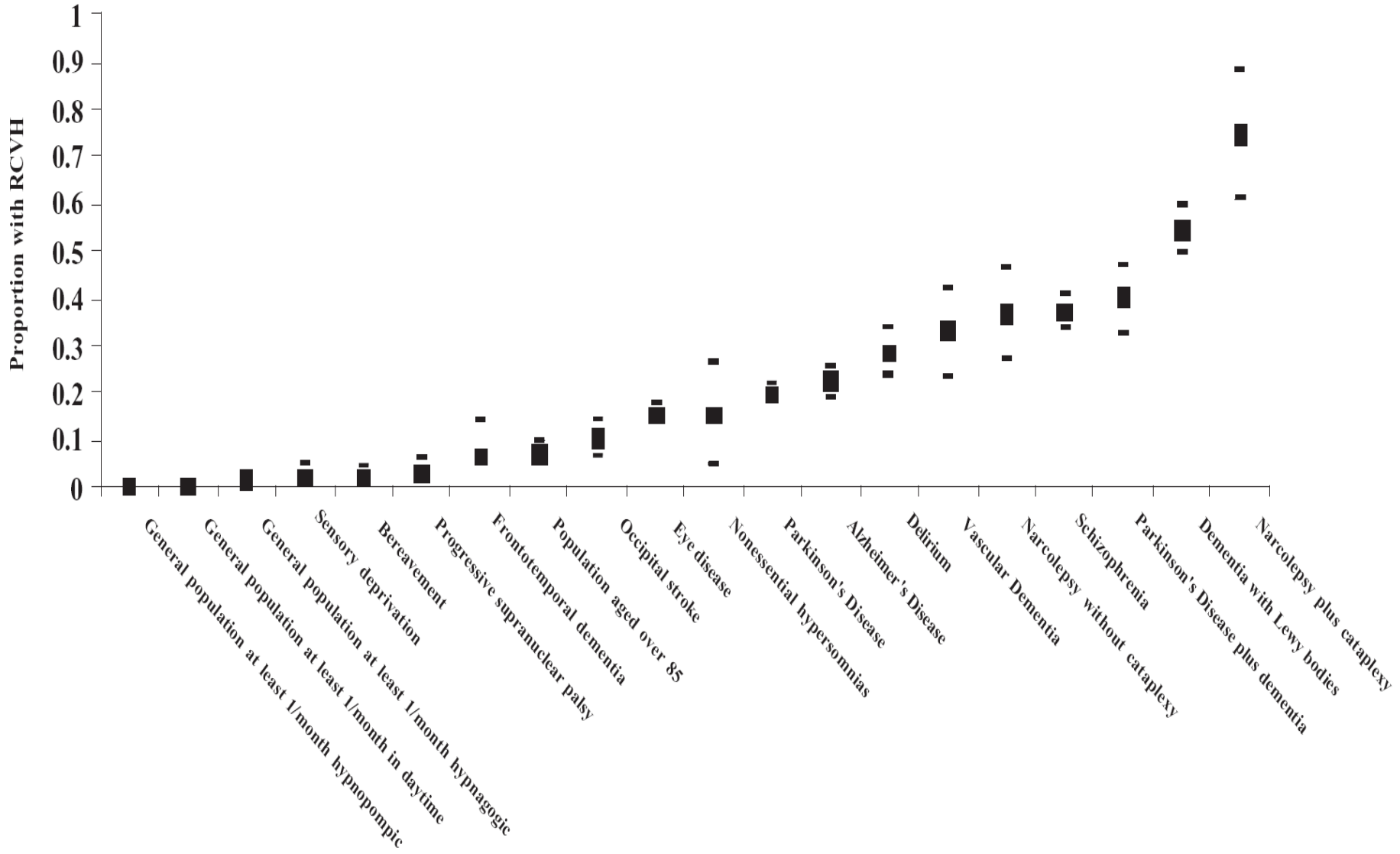
ffytche DH. Dialogues CNS 2007;9:173-189

RCVH's



Collerton D. Behav & Brain 2005;28:737-794.

Rates of Complex Visual Hallucinations



Collerton D. Behav & Brain 2005;28:737-794.

EXTRACAMPINE HALLUCINATIONS

- Previously quoted figure in literature was ~16% "sensed presence"
- Recent survey found **50% of respondents** had them

EH 3x > RCVH's

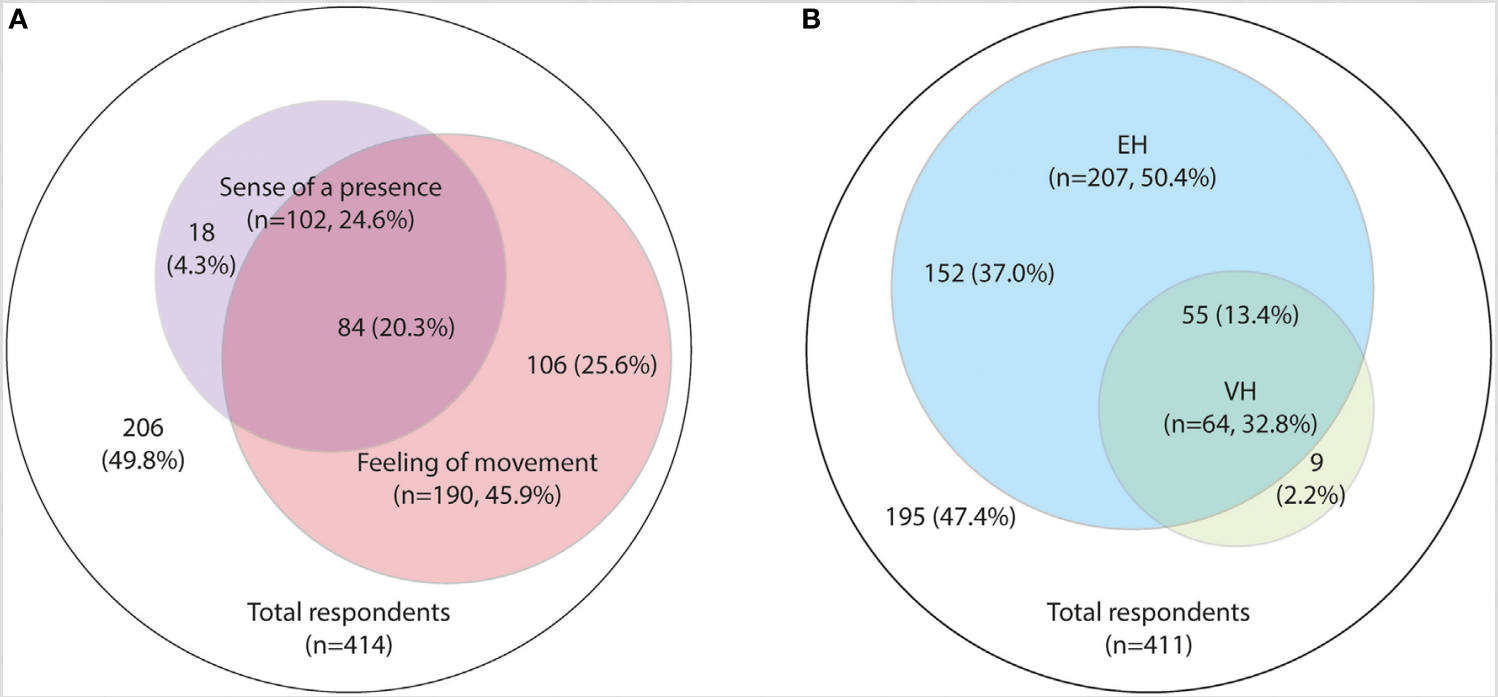


FIGURE 2 | Prevalence of hallucinations. **(A)** Extracampine hallucinations (EH), "feeling or imagining a presence" versus a "feeling of movement"; **(B)** Prevalence of EH and visual hallucinations (VH).

TABLE 1 | Questionnaire items as posed to participants.

Modified Hoehn and Yahr score	Parkinson's disease progresses through five stages, called "Hoehn and Yahr" stages. Please indicate which of the five statements below best describes your status at the moment 1. I have symptoms on one side of my body only 2. I have symptoms on both sides of my body but no problems with balance or walking 3. I'm having problems with my balance and walking 4. I can still stand and walk but with great difficulty 5. I cannot stand or walk independently; I need help or a wheelchair
Illusions	Q1. Have you ever looked at something and thought it was something else altogether? (*For example: spots on the wall looking like insects or a lampshade cover being mistaken for a person*.) *Yes/No*
EH: feeling of a *movement*	Q2. Have you ever experienced a feeling of movement past you when there was nothing there to account for this feeling? (*Some patients report a sensation that something has flashed past them, out of the corner of their eyes*.) *Yes/No* Q3. Where was the feeling of movement in relation to you? *Front/Behind/To the side* Q4. If to the side, do they occur more on the left or the right? *Mostly on the left/Mostly on the right/There is no pattern/I have not noticed a pattern/Does not apply* Q5. Are these experiences more common at a particular time of day? *Morning/Afternoon/Evening/Night/There is no pattern*

EH: feeling of a *presence*	Q6. Have you ever felt of imagined a presence either behind or alongside you when there was nothing there to account for this feeling? *Yes/No* Q7. Do you feel as though this presence is human, animal or other? *Human/Animal/Other* Q8. Is the presence familiar to you? *Yes/No* Q9. Does the presence ever speak to you or make another noise? *Yes/No* Q10. Does the presence ever touch you? *Yes/No* Q11. Are these experiences always the same? *Yes/No* Q12. Have any of your medications ever made these experiences better OR worse? *Yes/No* Q13. If you have ever taken any of the following medications* please indicate how they affected these experiences. *Improved symptoms/Worsened symptoms/No effect on my symptoms/I have never taken this medication* Q14. If you have ever taken any other medications for your Parkinson's disease, please indicate what these were and how they affected these experiences Q15. Do you have a reduced sense of smell? *Yes/No* Q16. Have you noticed a decline in your memory or thinking? *Yes/No* Q17. Have you noticed a change in your ability to walk or maintain balance? *Yes/No* Q18. Have you noticed that your sleeping has become more restless or disturbed? *Yes/No* **For questions 15–18, if the answer was yes participants were also asked** Q19. Did you notice this before or after you FIRST noticed the presence? *Before/After* Q20. Are you able to estimate how much time passed between noticing this and first becoming aware of a presence? *Yes, I can/No, I cannot* Q21. If yes, please estimate this period (in days, weeks, months, or years)

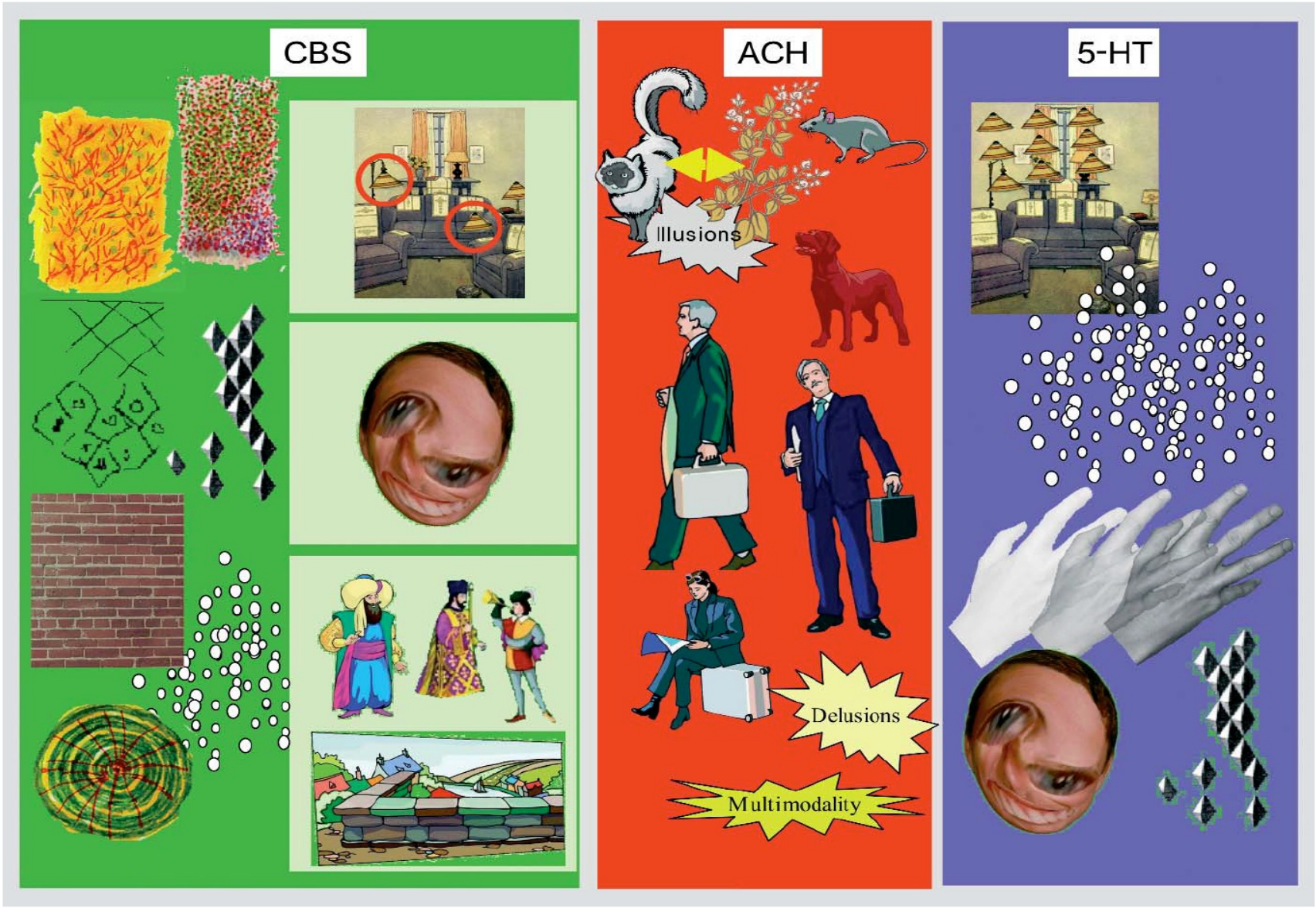


Figure 4. Caricatures of the deafferentation (CBS), cholinergic (Ach) and serotonergic (5-HT) visual perceptual syndromes. The deafferentation syndrome has three subsyndromic forms shown as light green regions. top = parietal; middle = superior temporal; bottom = ventral temporal)

ffytche DH. Dialogues CNS 2007;9:173-189.

CHOLINERGIC FACTORS

- An acetylcholine deficit appears to correlate with tendency to visually hallucinate
- VH's are associated with ↓'d muscarinic Ach activity in the temporal and frontal cortex
- These areas may be hypometabolic on neuroimaging

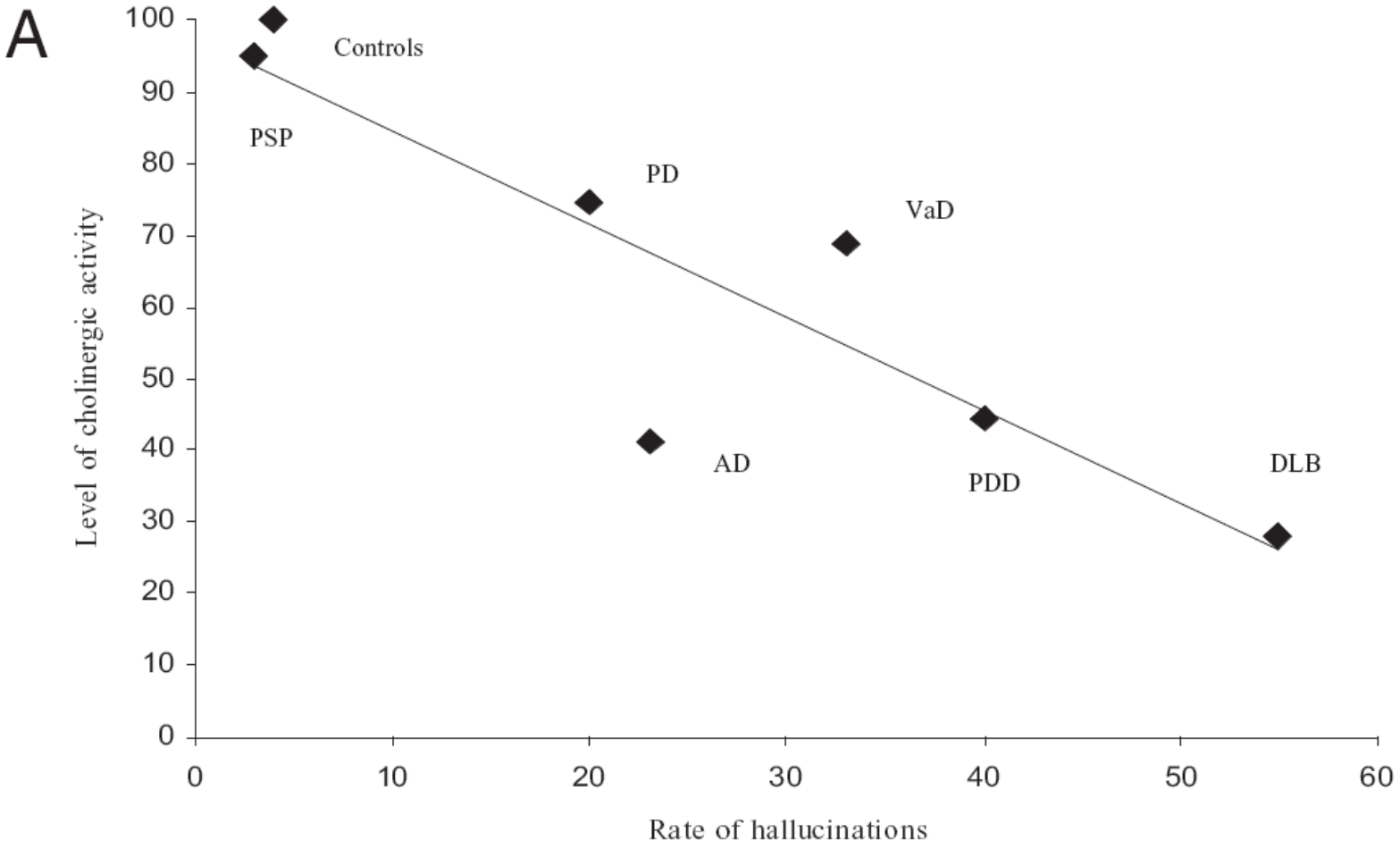
Friedman J. et al. EXP REV NEUROTHER, 2016

CHOLINERGIC FACTORS

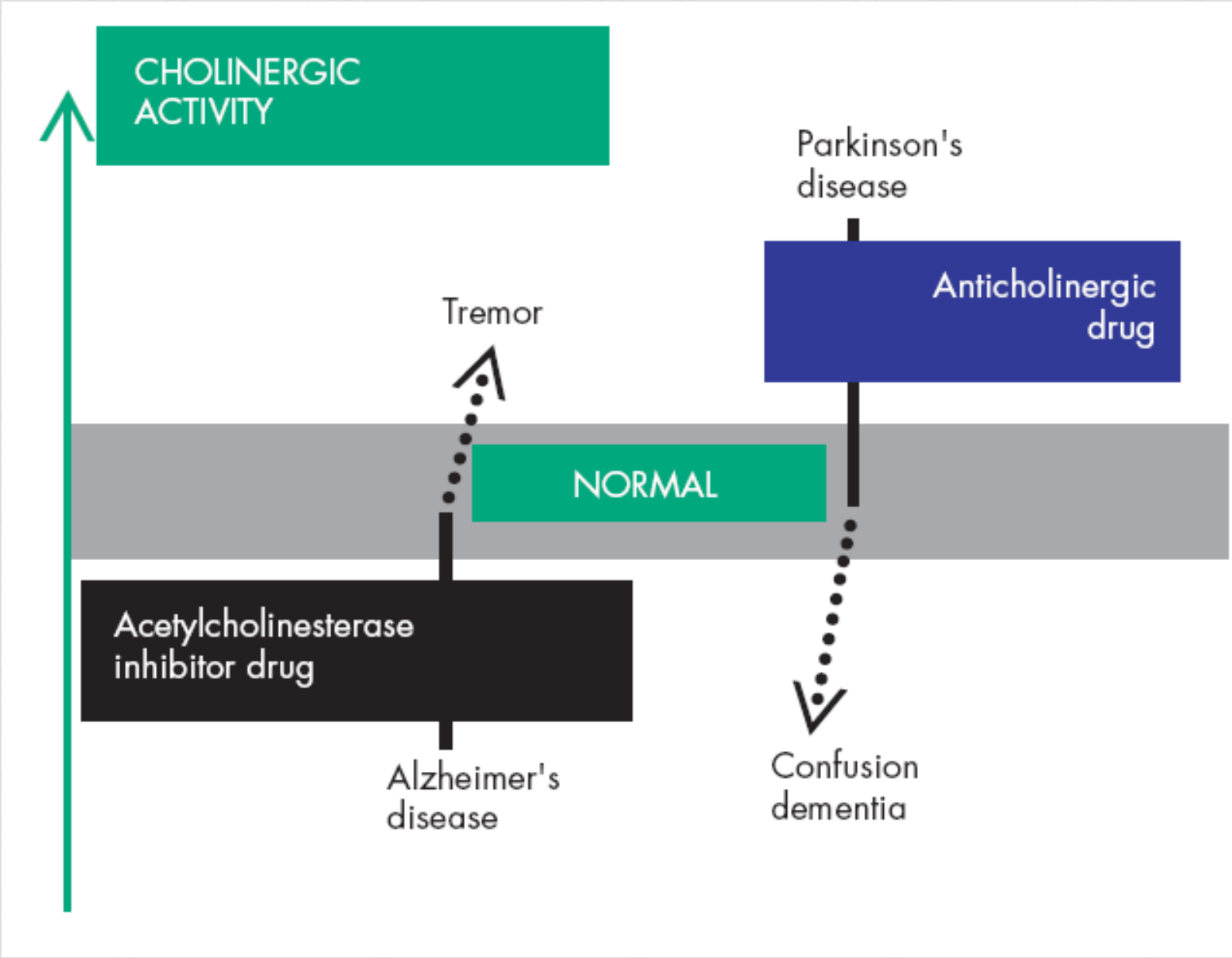
- Cortical AChase activities are significantly ⬇'d
- -27.8 % in DLB
- - 8.2 % in AD
- DLB patients showed more profound cholinergic decline in almost all cortical areas compared with AD.

Shimada H.Int J Geriatr Psychiatry 2015; 30: 1105–1113

VH's Correlate with ↓ AcH in Inferior Temporal Cortex



Collerton D. Behav & Brain 2005;28:737-794.


CHOLINERGIC ACTIVITY
Parkinson's disease
Anticholinergic drug
Tremor
NORMAL
Acetylcholinesterase inhibitor drug
Alzheimer's disease
Confusion dementia

CHOLINERGIC FACTORS

- Pts with acetylcholinergic deficits generally do not see simple VH's
- They usually c/o:
  - Complex, mundane figures
  - Illusions & fully formed VH's
  - Extracampine (sensed presence) hallucinations
  - Multimodal hallucinations
  - Delusional elaboration

ffytche DH. Dialogues CNS 2007;9:173-189.

Ffytche DH. Dialogues CNS 2007;9:173-189.

RCVH'S

- when a PD patient develops VH, plaques and/or neurofibrillary tangles may have developed.
- VH's may predict concomitant **AD/PD pathology** even when criteria are not met for a second diagnosis.

Jacobsen S.Parkinsonism Relat Disord. 2014 September ; 20(9): 1009–1014.

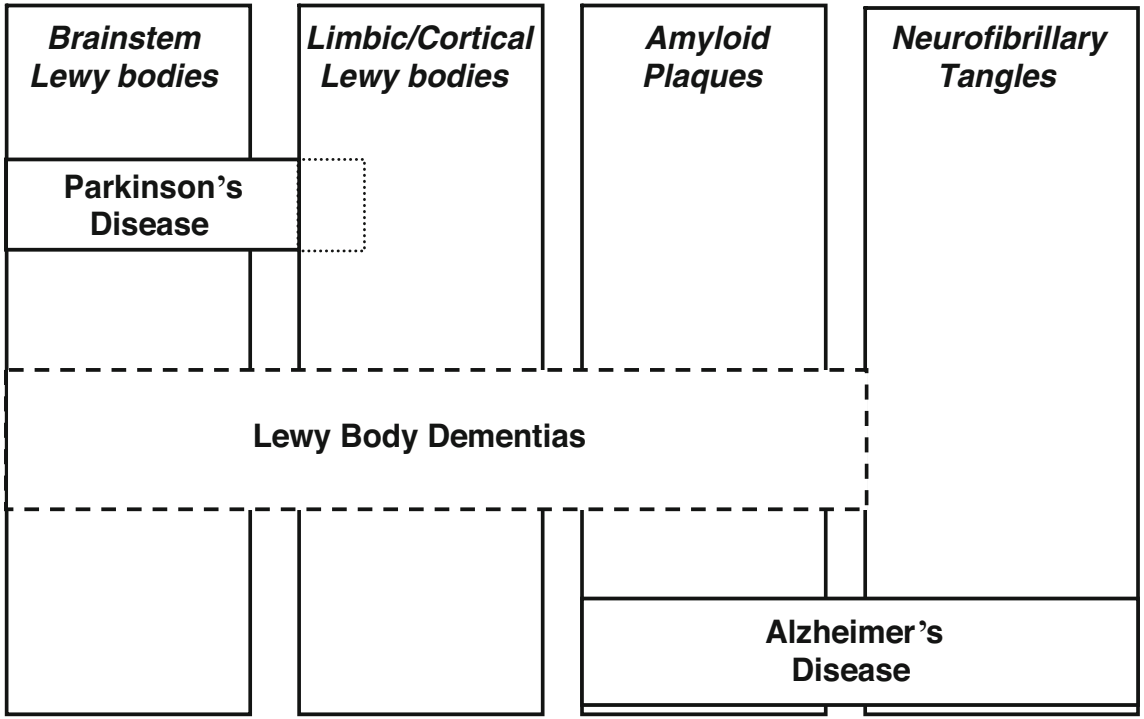


Fig. 1 Clinicopathologic relations among Alzheimer's disease and Lewy body disorders (Kaufer and Tröster 2008)

AMYLOID DEPOSITION

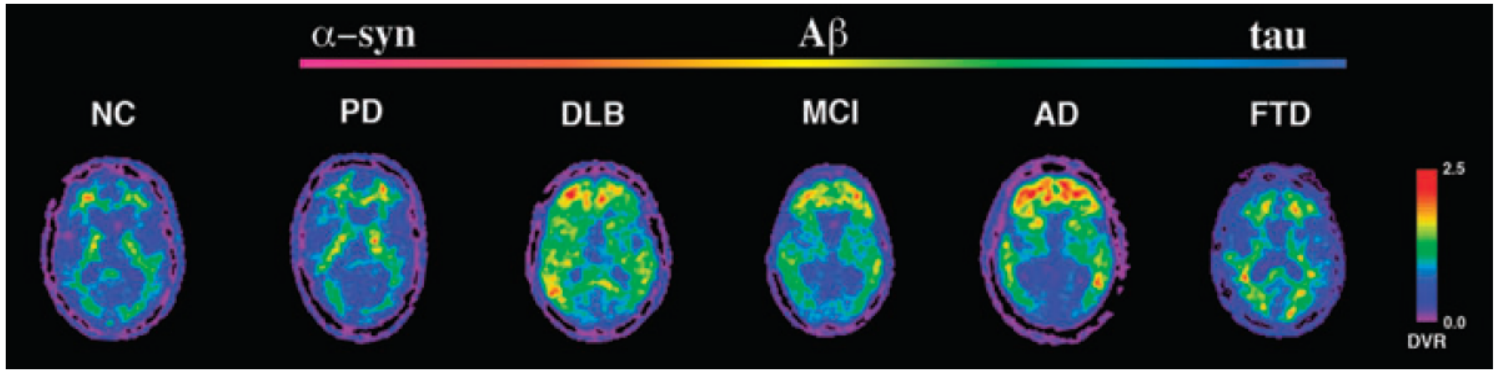


Fig. 3 Parametric PIB PET distribution volume ratio images (DVR) of a spectrum of neurodegenerative diseases secondary to misfolded proteins (α-syn, Aβ, tau). Representative PET images of a 73-year-old healthy control (NC) subject (MMSE 30), a 61-year-old Parkinson's disease (PD) patient (MMSE 27), a 78-year-old dementia with Lewy-body dementia (DLB) patient (MMSE 19), a 70-year-old mild cognitive impairment (MCI) patient (MMSE 26), an 82-year-old Alzheimer's disease (AD) patient (MMSE 22) and a 78-year-old frontotemporal dementia (FTD) patient (MMSE 26). DVR PET images show no cortical PIB retention in NC, PD or FTD with a clearly different pattern from DLB, MCI or AD patients, and significant PIB retention in the frontal and temporal cortices.

Masters C. J Neurochem 2006;97:1700-1725

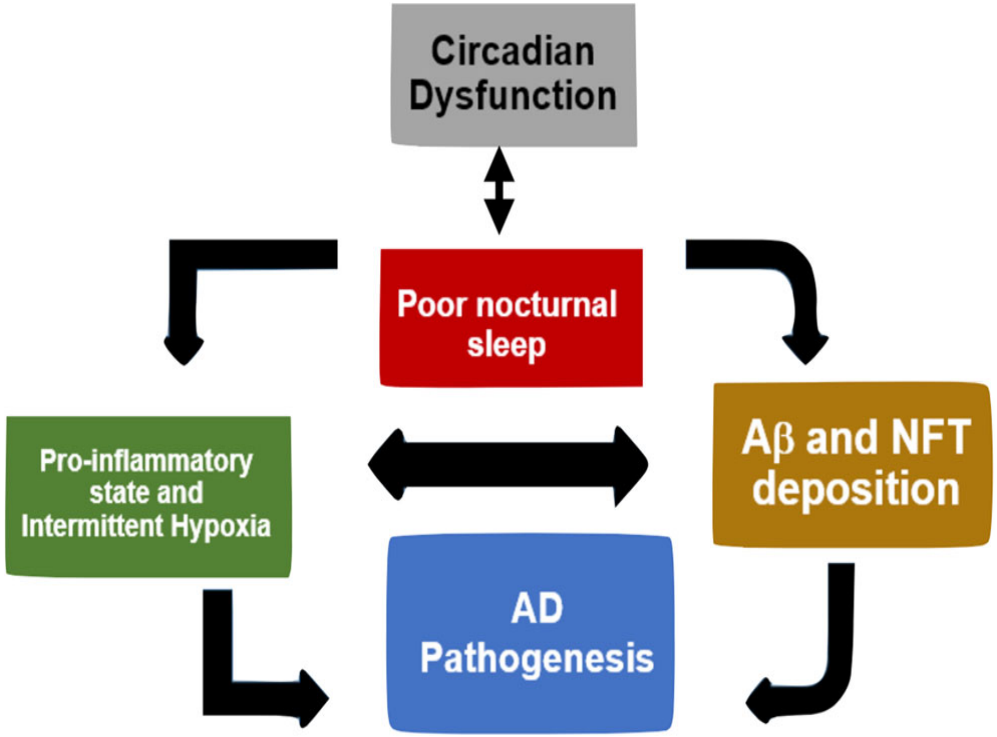


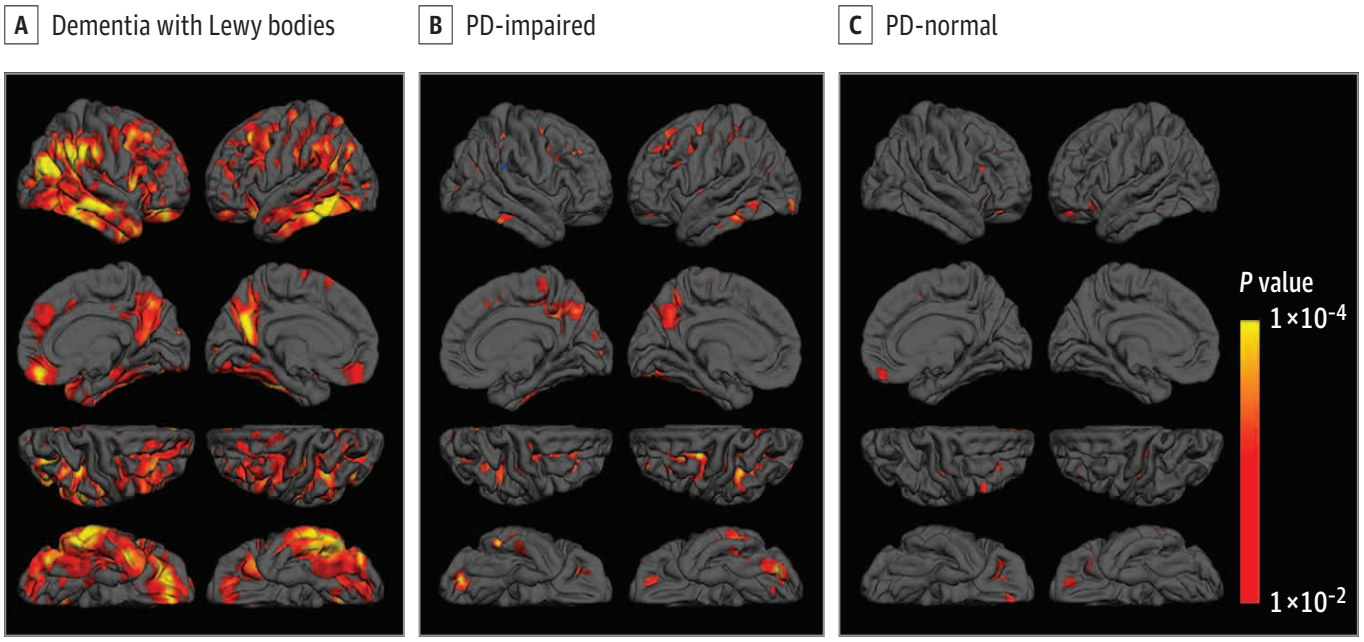
Fig. 1 AD pathophysiology as a product of circadian dysregulation and poor sleep: Recent data illustrates that the production of a soluble Aβ may be relatively accelerated during sleep due to the reduced NREM SWA in the context of aging and associated sleep disturbances (e.g., sleep apnea or insomnia). Disturbed sleep results in an increased time awake during the relative sleep period, and may link Aβ pathology with the hippocampal-dependent cognitive decline [15••]

MOLECULAR CROSSTALK

- Impaired sleep increases β-amyloid
- Molecular crosstalk increases α-syn
- Tau, A-β & α-syn co-catalyze each other

TAU Deposition

Figure 2. Surface Renderings of Group Contrasts



General linear models comparing individuals with normal cognition with patients who had dementia with Lewy bodies (A), Parkinson disease associated with cognitive impairment (PD-impaired) (B), and PD without cognitive impairment (PD-normal) (C). Color bar shows significant binding at the $P = .01$ to $P = 1 \times 10^{-4}$ levels.

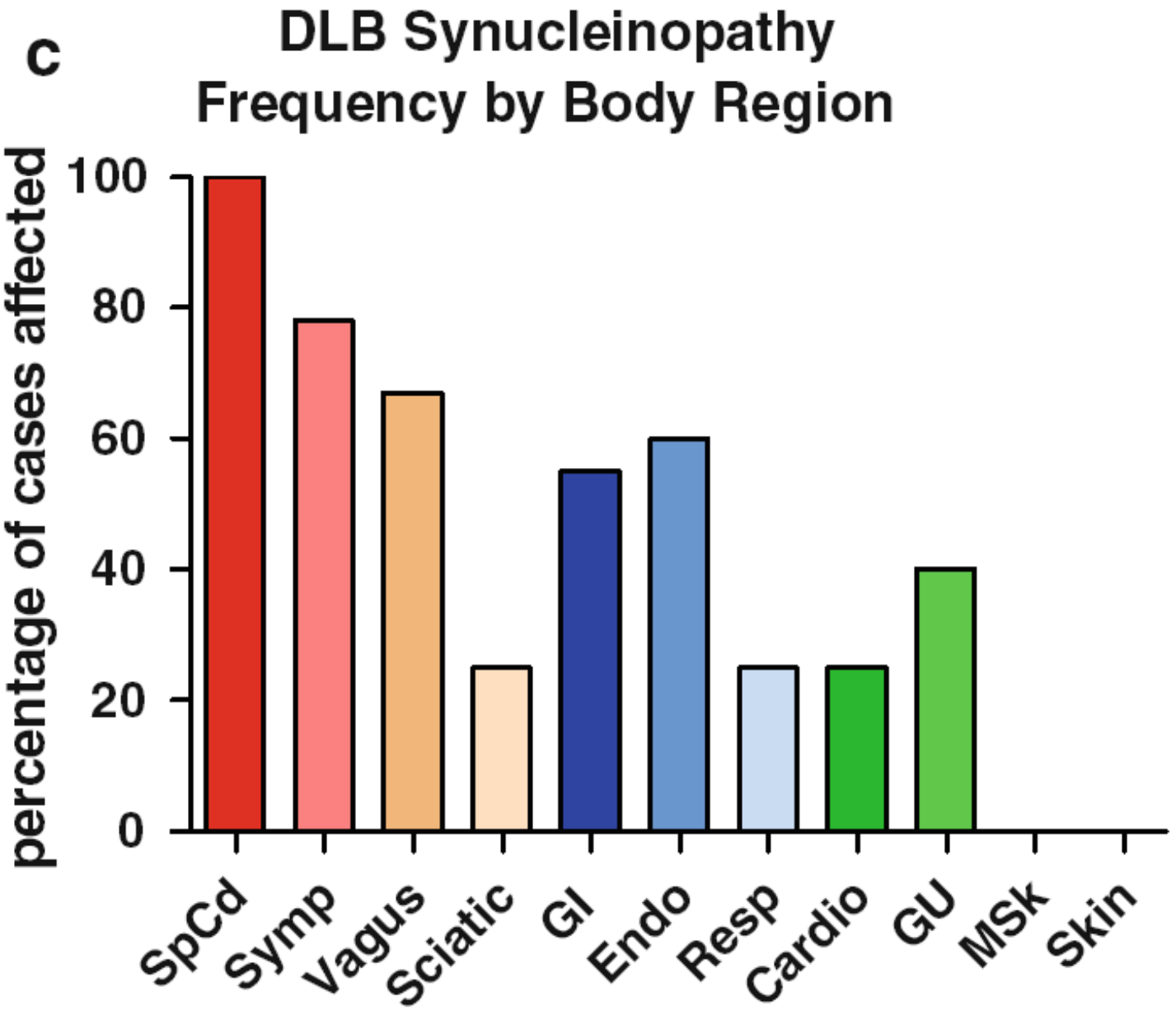
Gomperts SN. *JAMA Neurol.* doi:10.1001/jamaneurol.2016.3338

SYSTEMIC LEWY BODIES

LEWY BODIES ARE FOUND SYSTEMICALLY

- In addition to dopaminergic alterations, patients with α-synucleinopathy have involvement of:
- non-nigrostriatal brainstem nuclei,
- sympathetic,
- parasympathetic,
- enteric and pelvic plexuses,
- cardiac systems,
- submandibular gland,
- adrenal medulla, skin, &
- the **retina**

Price DL. Scientific Reports | 6:29523 | DOI: 10.1038/srep29523



Beach T. Acta Neuropathol 2010

TRANSGENIC MOUSE RETINAL DEPOSITS

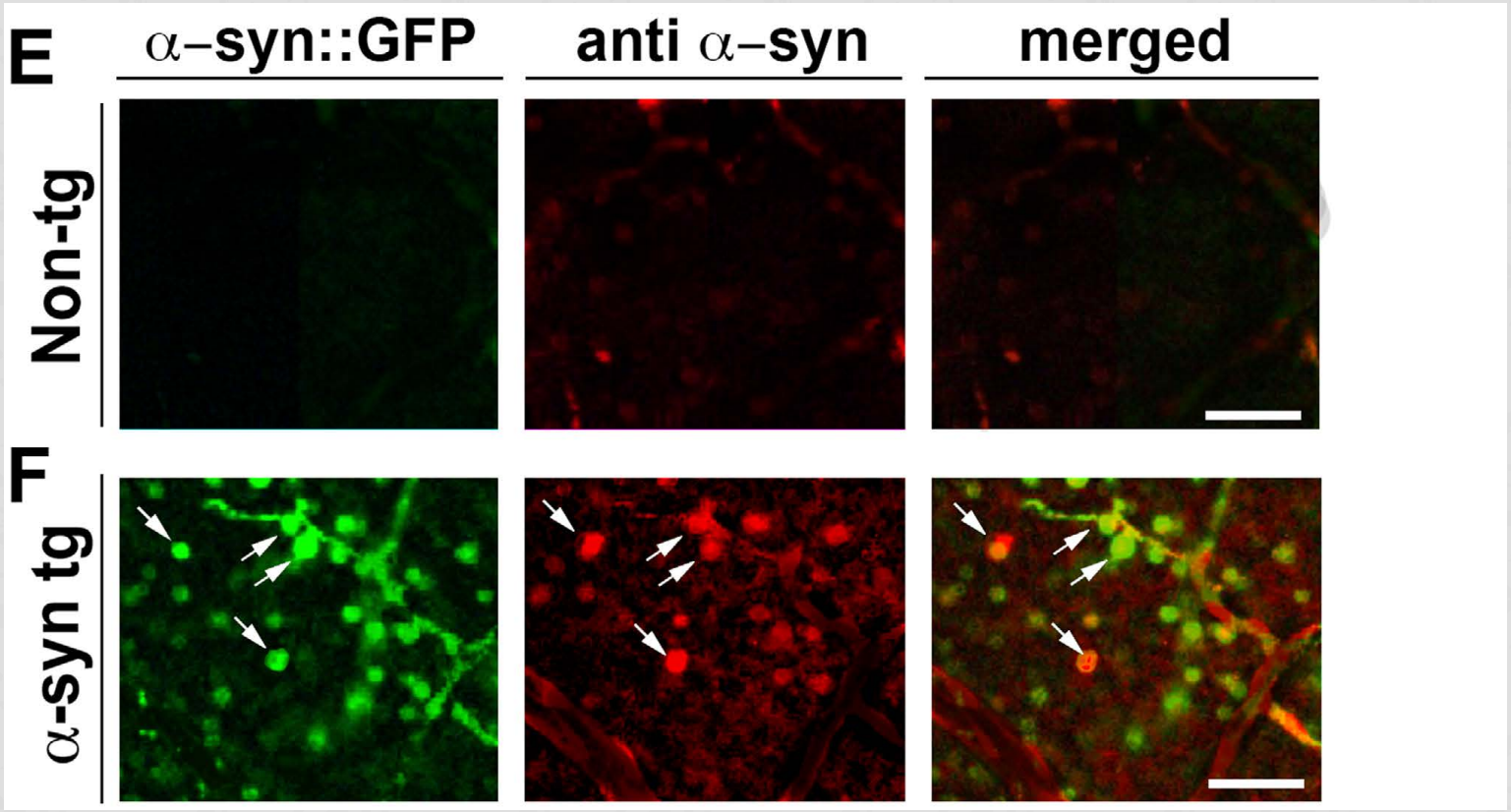


Figure 4. α-Syn::GFP dot-like structures detected in the retinoscopy are retinal ganglion cells.

Price DL. Scientific Reports | 6:29523 | DOI: 10.1038/srep29523

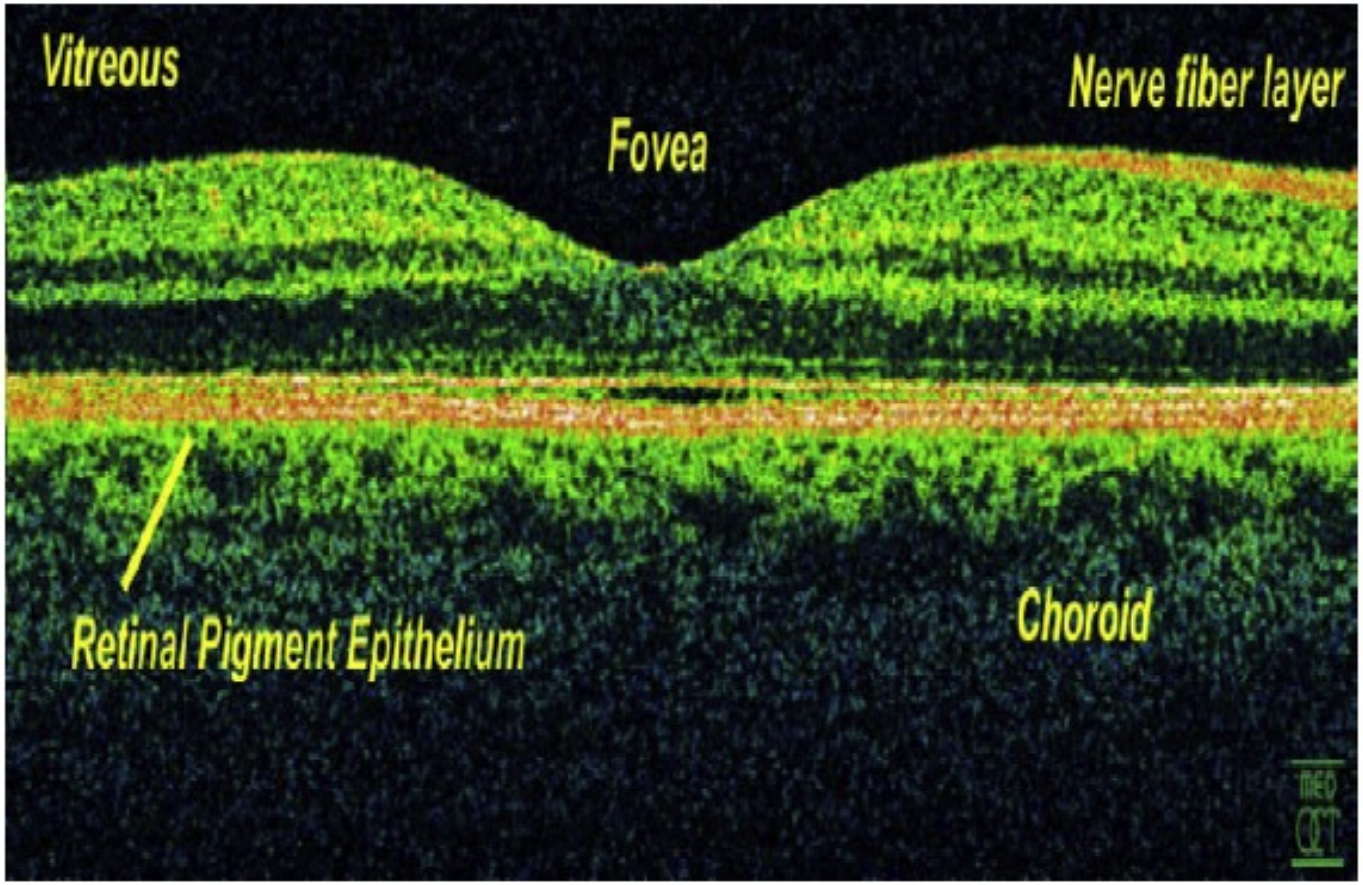
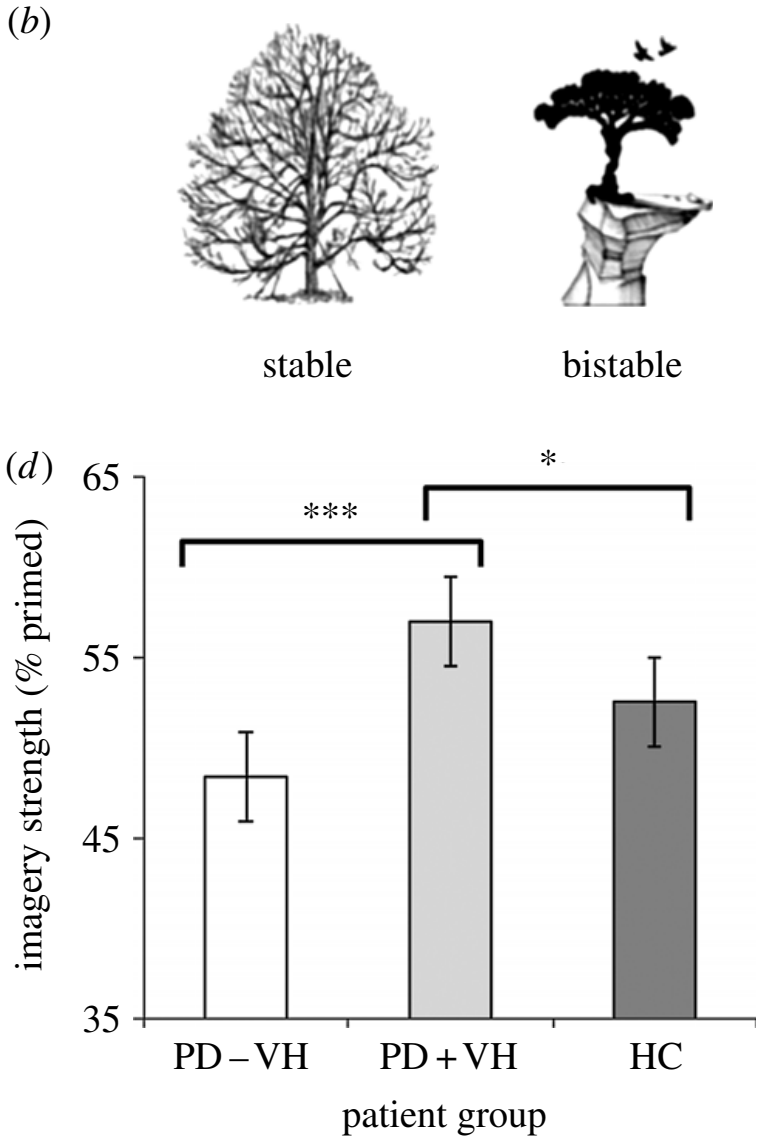


Fig. 1. The foveal region of the human retina. The colour coded illustration is an average, derived from a spectral domain optical coherence tomography (SD-OCT) study. Different retinal layers can be visually identified above the layer labelled retinal pigment epithelium. For further explanation and not averaged, but for single passage OCT-s see Fig. 10. (From an on-line Wikipedia entry).

Bodis-Wollner I. Parkinsonism and Related Disorders 19 (2013)



Shine JM. Proc. R. Soc. 2015 B 282: 20142047.

DEFAULT MODE NETWORK

DEFAULT MODE NETWORK

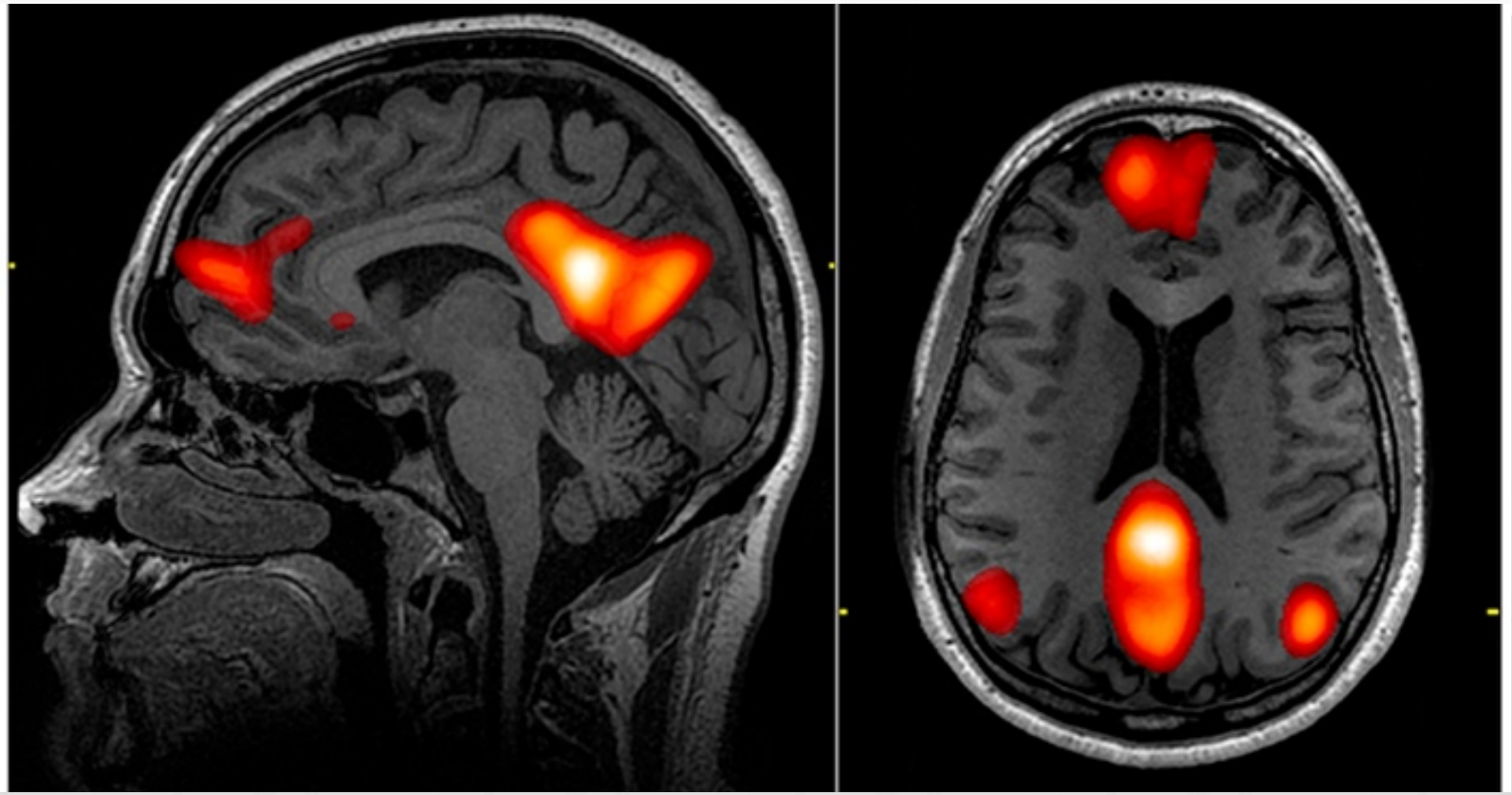
- The Default Mode Network (DMN) is a "task-negative" network which is active when individuals are **at rest**
- It is active in self-referential thoughts and **visual memory retrieval**
- In psychotic conditions, *hallucinations are linked with dysfunction of the DMN*

Yao N. Human Brain Mapping 2014; 35:5658–5666 (2014)

DMN

- This network is associated with high metabolic demands
- Parts of it appear to use similar sugar metabolism as cancer cells
- This is also where β amyloid deposits first occur
  - These are normally cleared in young healthy individuals especially during sleep
- If sleep is inadequate, more "debris" accumulates

Default Mode Network (DMN)



Source: Wikipedia

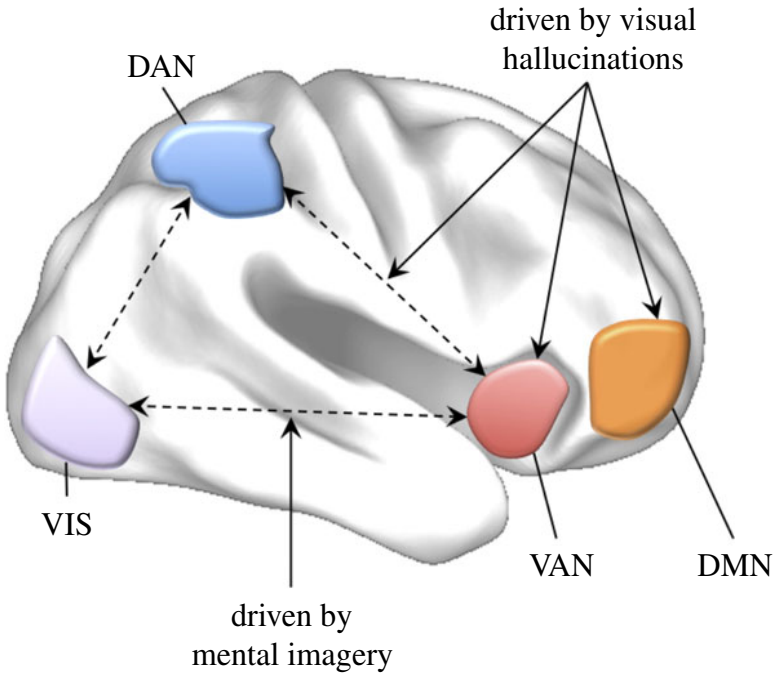
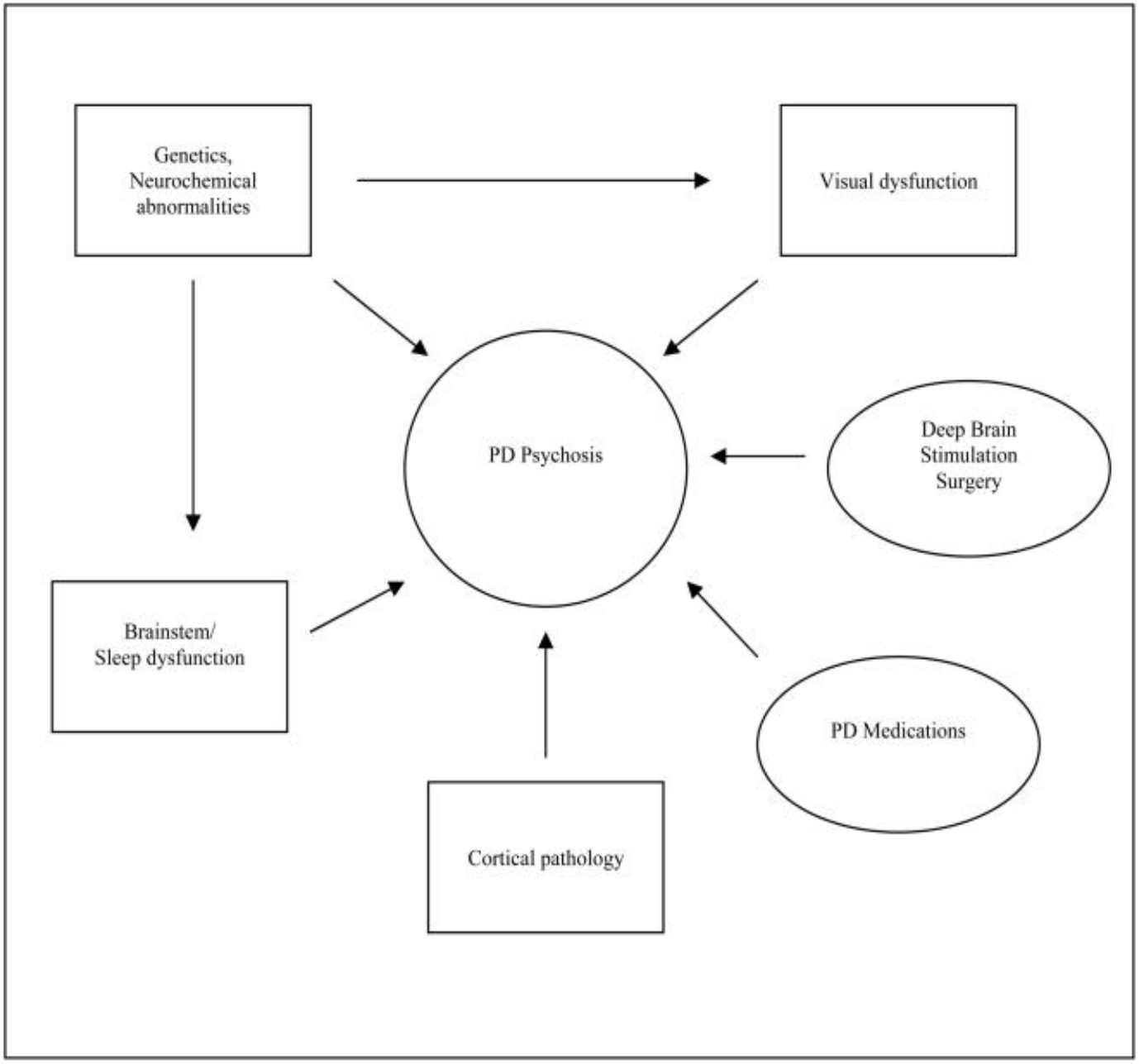


Figure 3. Putative neurological mechanism for visual hallucinations [2]. Abnormal connectivity between exogenous (dorsal attention network; DAN—blue), endogenous (ventral attention network; VAN—red) and primary visual (VIS—purple) networks, along with increased connectivity in ventral attention and default mode network (DMN—orange) predisposes individuals with PD to hallucinate visual images. Although these connectivity changes are strongly related to both imagery and visual hallucinations ($R > 0.45$, $p < 0.05$), individual connectivity scores are dissociable and strongly driven by one or the other mechanism (dotted lines represent impaired pathways of neural communication). (Online version in colour.)

Shine JM. 2015 Proc. R. Soc. B 282: 20142047.



Zahodne LB. Drugs Aging. 2008 ; 25(8): 665–682.

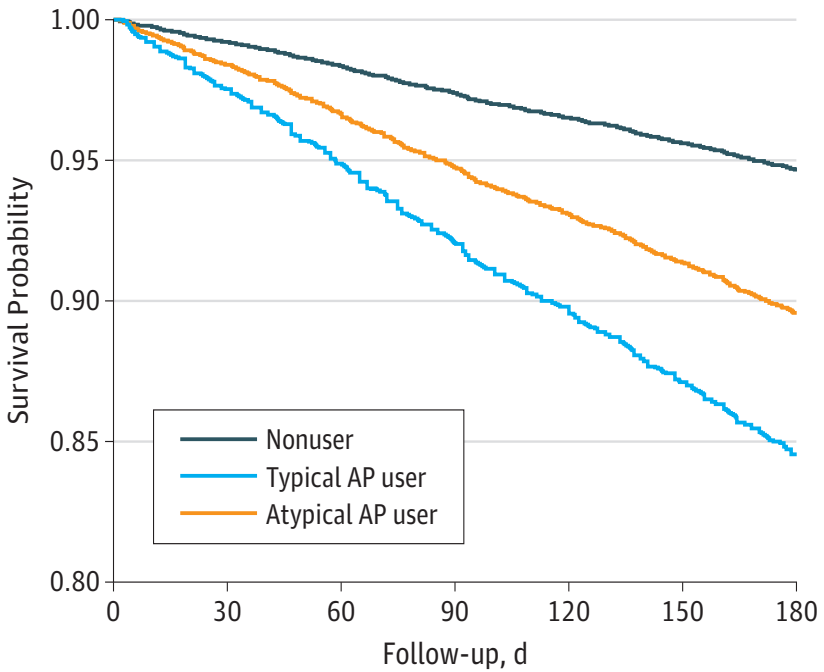
TREATMENT

2011 TX GUIDELINES FOR NMS

- The treatments that are **efficacious** for the management of non-motor symptoms are as follows:
- **pramipexole** for the treatment of depressive symptoms,
- **clozapine** for the treatment of psychosis,
- **rivastigmine** for the treatment of dementia,

Seppi K. Mov Disord. 2011 October ; 26(0 3): S42–S80

Figure. Mortality Rates in Antipsychotic (AP)-Exposed vs Non–AP-Exposed Patients



No. at risk							
Nonuser	7877	7819	7746	7670	7600	7529	7451
Typical AP user	7455	7349	7226	7089	6963	6834	6710
Atypical AP user	422	400	391	378	366	456	342

Covariate-adjusted 180-day survival estimates by baseline AP treatment status (intention-to-treat analysis) are shown. Graph is based on Cox proportional hazards regression modeling without pairing.

2011 TX GUIDELINES FOR NMS

- The treatments that are ***likely efficacious*** for the management of non-motor symptoms are as follows:
- the tricyclic antidepressants nortriptyline and desipramine for the treatment of depression or depressive symptoms and
- these treatments are ***possibly useful***.

Seppi K. Mov Disord. 2011 October ; 26(0 3): S42–S80

PIMAVANSERIN

- Pimavanserin is a selective serotonin 5-HT2A inverse agonist without DA, NE, H, or ACH affinity,
- is now approved as a treatment for PDP
- In PD, the binding of 5-HT2A receptors is increased in the neocortex,

Cummings J. Lancet 2014; 383: 533–40

PIMAVANSERIN

- With its receptor selectivity, pimavanserin was developed to provide antipsychotic benefit without the adverse effects of current antipsychotics.

Cummings J. Lancet 2014; 383: 533–40

PREVENTION

- Avoid risk factors
  - pesticides,
  - well water,
  - ?amyloidogenic factors such as milk, foie gras
- Sleep
- Exercise
- Non diabetogenic diet
- ?meditation
- ?Vagotomy

PROTECTIVE FACTORS

- Cigarette smoking
  - Nicotine may have neuroprotective action
  - A-7 nicotinic agonists, for symptomatic treatment and neuroprotection are being investigated

D.T. Dexter, P. Jenner / Free Radical Biology and Medicine 62 (2013) 132–144

PREVENTION

- Caffeine intake also appears protective against the development of PD
  - Men > women and
  - exerts neuroprotective effects via adenosine A2a receptors (?)
- antihypertensives (notably calcium antagonists),
- NSAIDs
- Antilipidemics, (HMGCOA reductase inhibitors etc)
- exercise and controlling metabolic factors

D.T. Dexter, P. Jenner / Free Radical Biology and Medicine 62 (2013) 132–144

OTHER TREATMENTS

- Mianserin and mirtazapine are antidepressants with 5-HT2A receptor antagonism similar to pimavanserin have reportedly improved psychosis symptoms in PD patients
- 5-HT2A receptor antagonists may also benefit PDP.

Meco G. Progress in Neuro-Psychopharmacology & Biological Psychiatry 31 (2007) 311–313

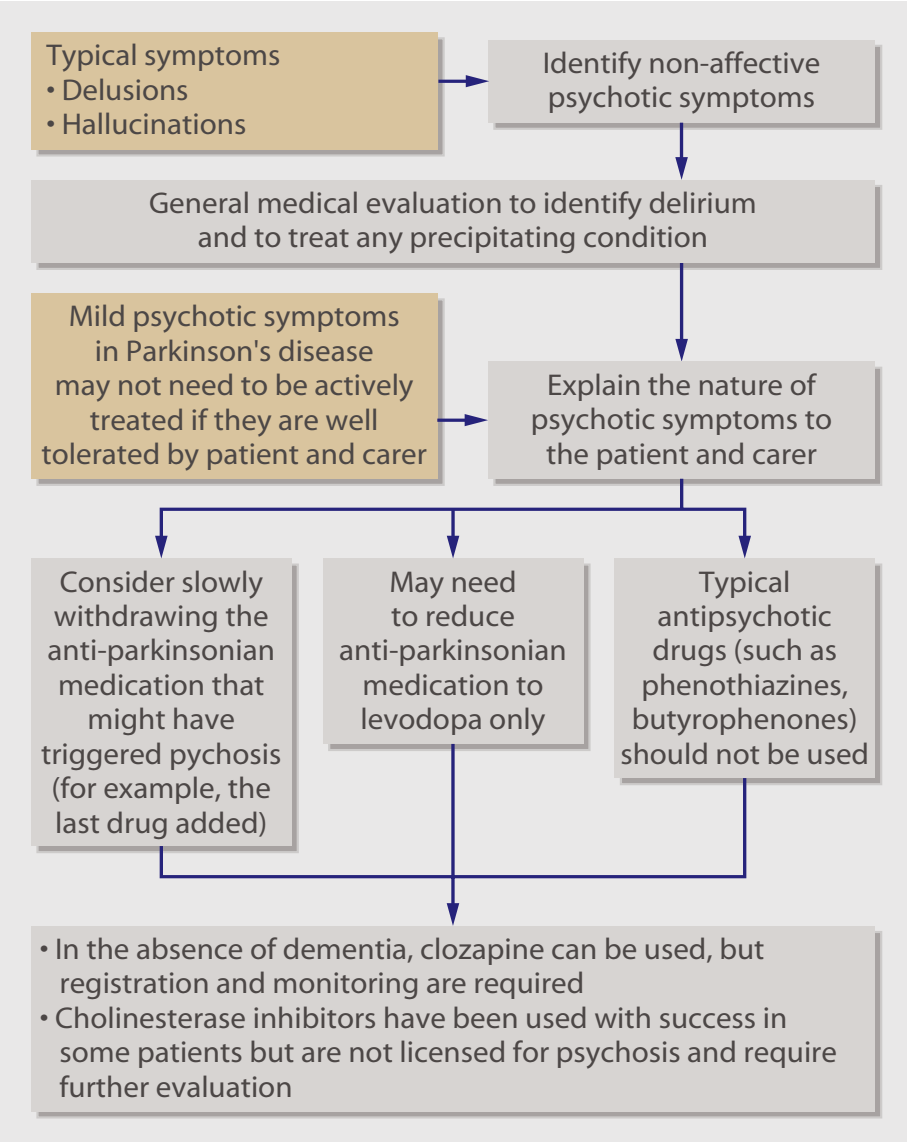


Fig 2 | **Management of psychosis in Parkinson's disease. Adapted with permission from NICE[3]**

BMJ 2007;335:441-5

TX SUMMARY

	Evidence in dementia with Lewy bodies	Evidence in Parkinson's disease dementia	Comments
Cognition			
Acetylcholinesterase inhibitors	Efficacious	Efficacious	Rivastigmine and donepezil class 1 efficacy in dementia with Lewy bodies; Cochrane review of dementia with Lewy bodies, Parkinson's disease dementia, and MCI-PD showed overall positive effect
Memantine	Insufficient evidence	Insufficient evidence	Small significant improvement in overall clinical impression
Parkinsonism			
Levodopa	Insufficient evidence	Insufficient evidence	Levodopa replacement less effective in dementia with Lewy bodies than in Parkinson's disease; probable increased risk of psychosis in patients with dementia with Lewy bodies
Hallucinations			
Acetylcholinesterase inhibitors	Insufficient evidence	Insufficient evidence	No randomised controlled trials have assessed hallucinations; other evidence is positive
Antipsychotic drugs	Unlikely to be efficacious	Mixed	In treatment of psychosis associated with Parkinson's disease and Parkinson's disease dementia, clozapine is effective and olanzapine ineffective; the evidence for quetiapine is mixed

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WHAT I DO

- Quetiapine
- Donepezil
- Trazodone
- Mirtazapine
- Citalopram
- ECT

TAKE HOME POINTS

- Cognitive impairment occurs in nearly all patients with PD
- Visual hallucinations and sensed presence hallucinations are common
- Cholinergic deficits are implicated
- Tau & beta-amyloid co-pathologies contribute
- Network degeneration likely plays a role
- Clozapine and pimavanserin are the only proven treatment for PDP
- ACHEI's are likely useful in DLB & PDD