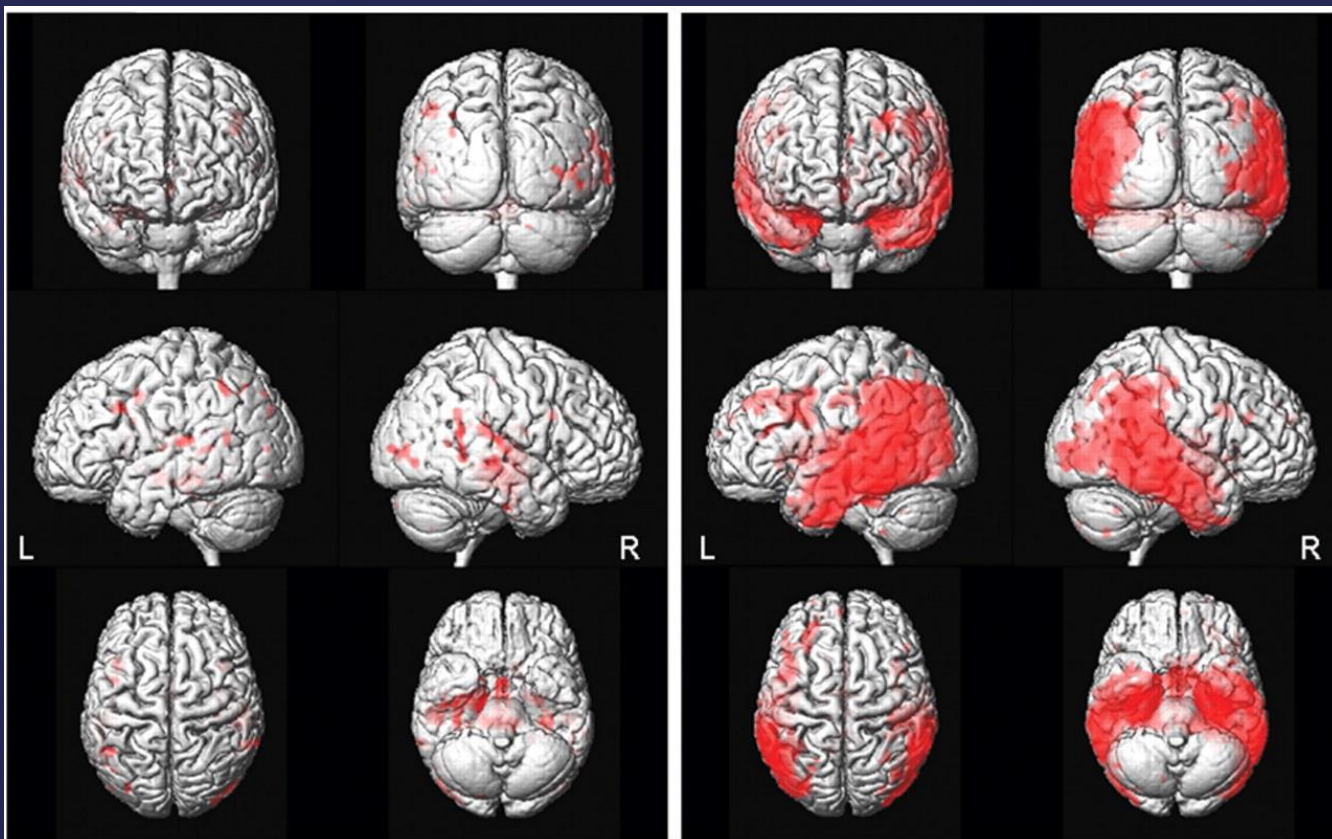


PARKINSON'S DEMENTIA AND RELATED CONDITIONS



Diagnosis and therapy

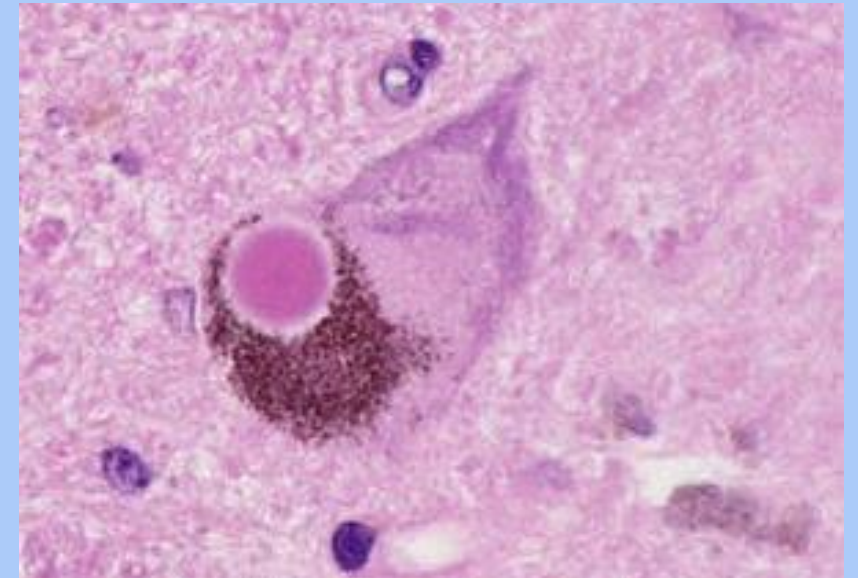
Sean Rogers, MD, PhD
Co-Director

 **INOVA**[®]
Movement Disorders Program

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LEWY BODIES AND THEIR LOCATIONS

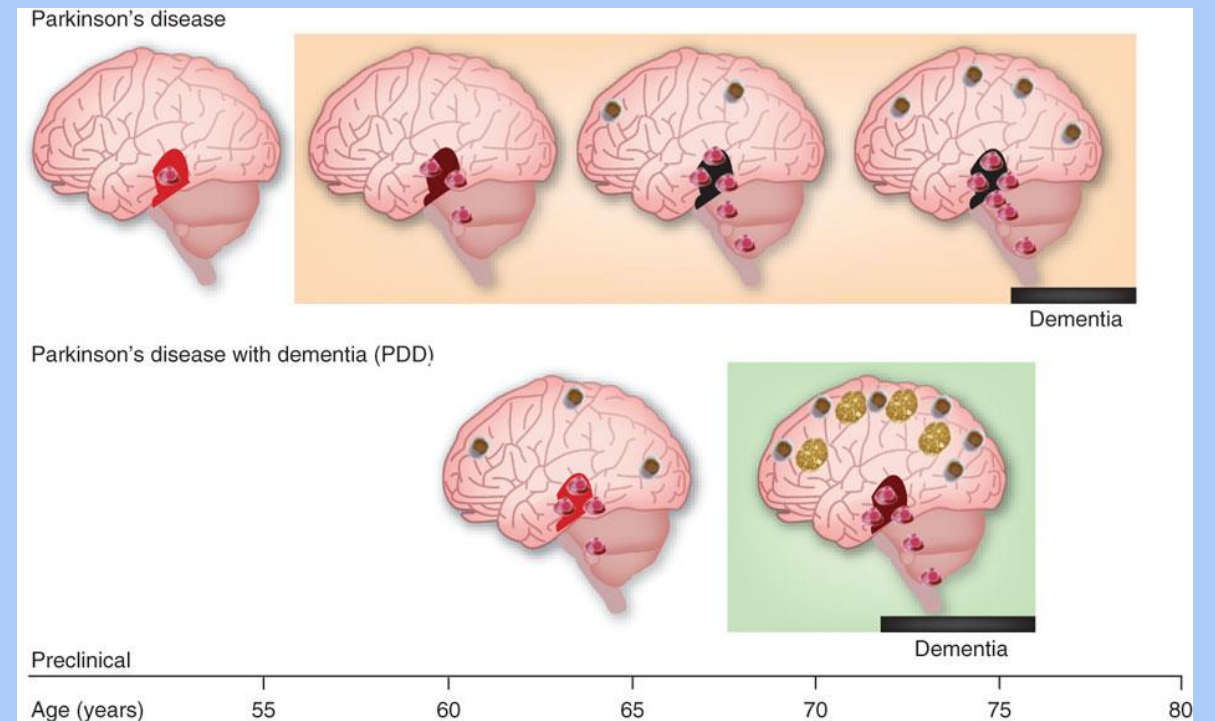
- **Abnormal Build-up of Protein in Cells:**
 - Alpha-synuclein – Abnormally Folded Protein
 - Garbage Disposal is overwhelmed
- **Classically found in “Synucleinopathies”**
 - Parkinson’s Disease
 - Lewy Body Dementia
 - Multisystem Atrophy



Ref 12 – Lewy body in the Substantia Nigra.

LEWY BODIES AND THEIR LOCATIONS

- Location, location, location
- Begins peripherally
 - GI
 - Skin
- Travels up the Vagus Nerve³
 - Transported by axons
- Dementia - expansion to bilateral fronto/parietal lobe projections and hippocampal circuit
 - Rapid vs slow
 - Timing can often determine Diagnosis and Prognosis



Ref 14 - Lewy body locations, and amyloid plaque/neurofibrillary tangle development

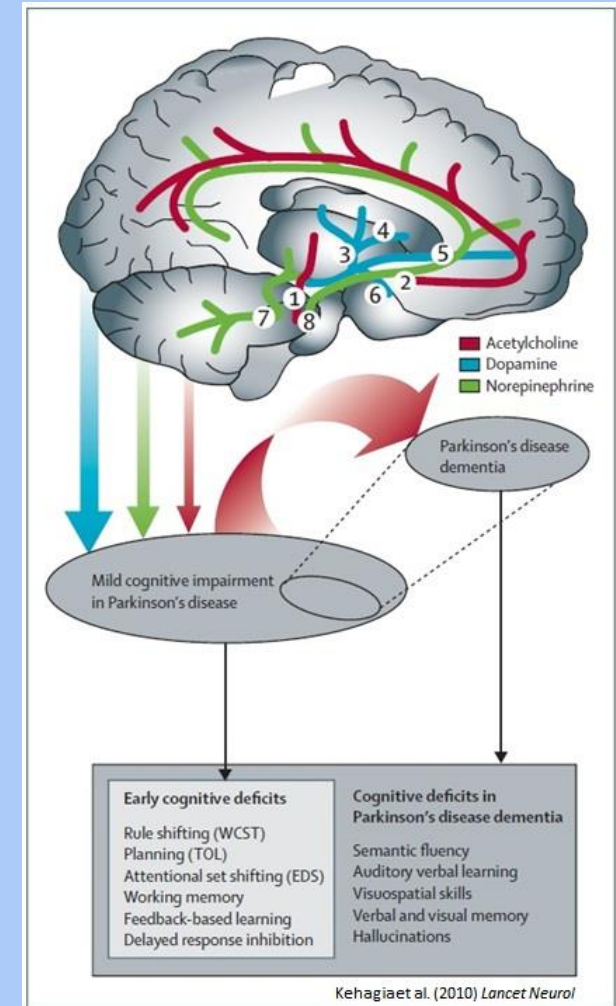
DEMENTIA IN PARKINSON'S DISEASE

■ Motor Symptoms:

- Basal ganglia – inputs of Dopamine, Acetylcholine, Norepinephrine
- Substantia Nigra pars compacta - ~400,000 dopamine neurons
- 70% loss with initial symptoms

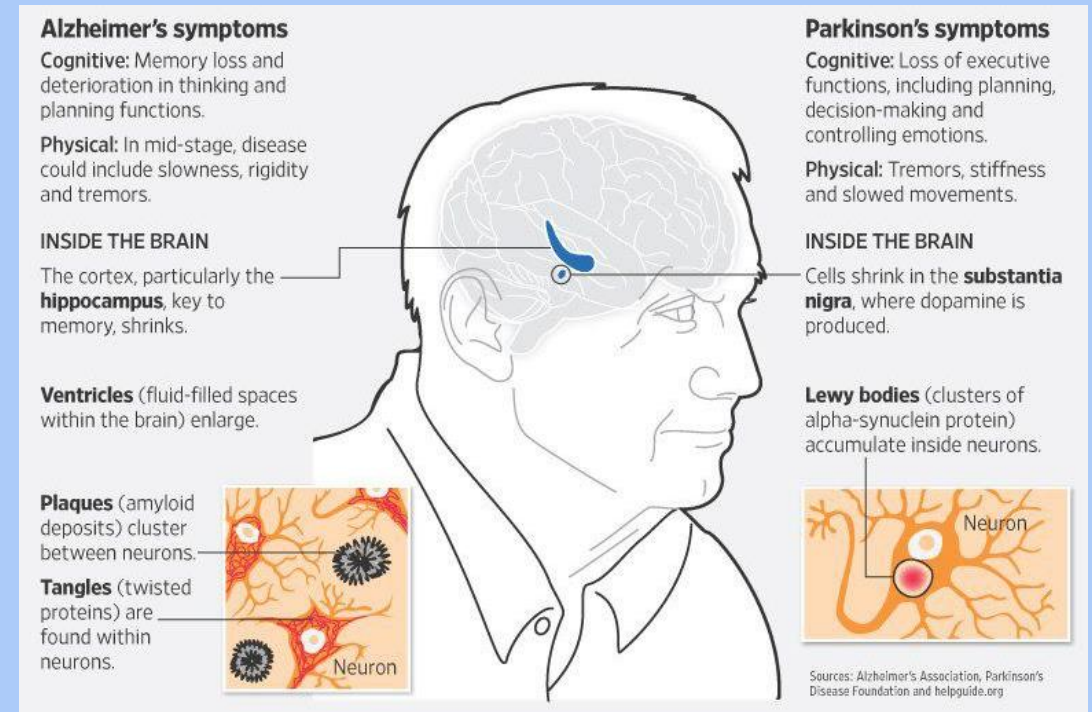
■ Memory/Cognitive Symptoms

- Eventual extension of pathology to hippocampal circuit and bi-frontal/parietal areas
- Early Mild Cognitive Impairment
- Later can have similarities with Alzheimer's
- Tau = neurofibrillary tangles in AD



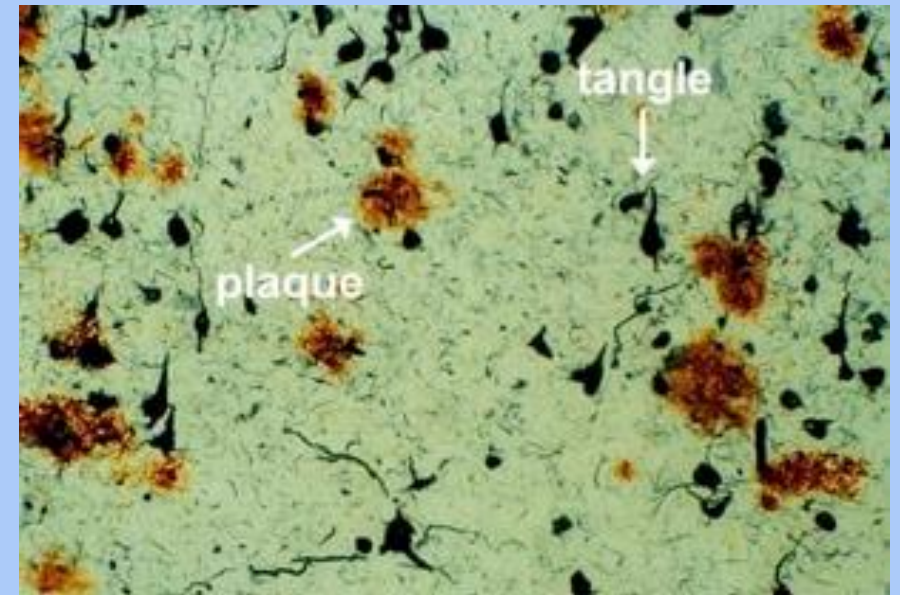
LEWY BODY DEMENTIA

- Dementia with Lewy Bodies, Diffuse Lewy Body Disease
- 30% of all dementias⁴, second to Alzheimer's.
 - 1.4 million people⁶
- Classically associated with:
 - EARLY cognitive change (within 1 yr of PD symptoms)
 - Relatively rapid onset
 - Fluctuating cognitive impairment
 - Visual hallucinations
 - Parkinsonism
 - Sensitivity to
 - Dopamine replacement – hallucinations, side-effects
 - Neuroleptics – catatonia, rigidity
- REM Behavioral Sleep Disorder now part of diagnostic criteria⁵



LEWY BODY DEMENTIA

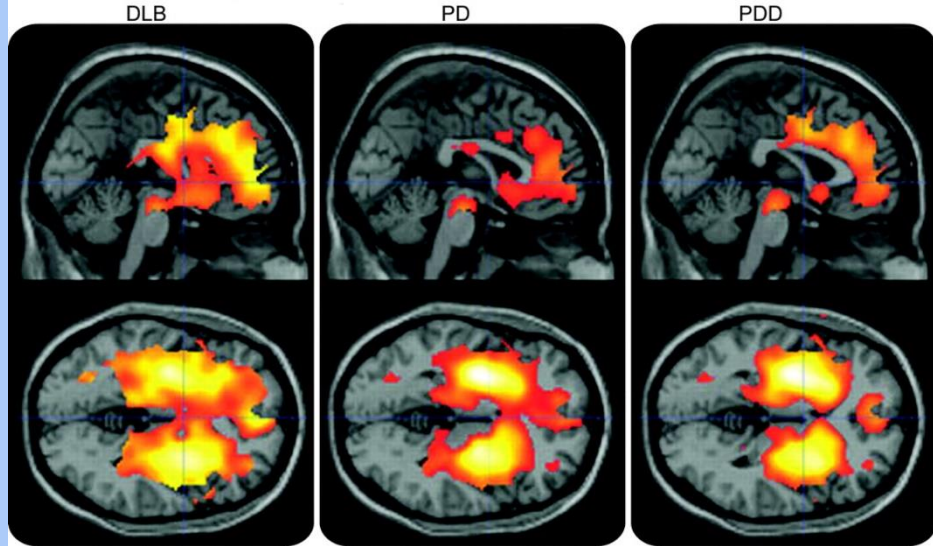
- Pathology:
 - Alzheimer's pathology usually present on autopsy (neurofibrillary tangles/tau)
 - Significant loss of:
 - Cholinergic neurons – cognitive change similar to AD
 - Dopaminergic neurons – Parkinsonian symptoms
- Eventually, Parkinson's Disease Dementia and Lewy Body Dementia are pathologically indistinguishable
- Location versus Timing



Ref 16 – Silver stain identifying tangles and plaques

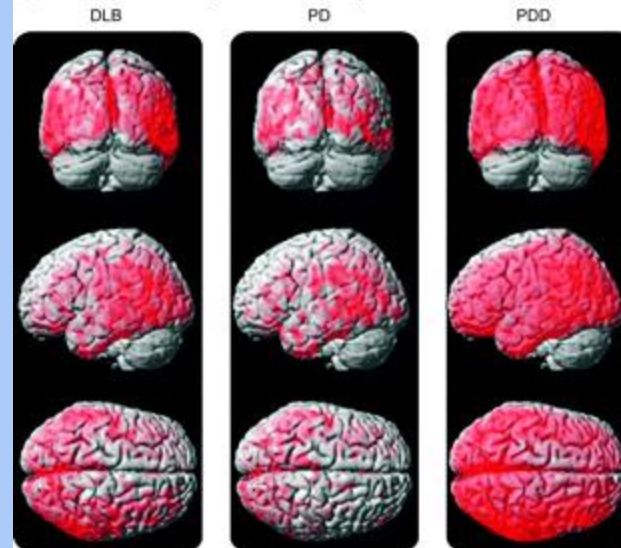
PET SCAN DATA COMPARING DLB, PD, PDD

Reduction of dopaminergic transmission compared to controls in



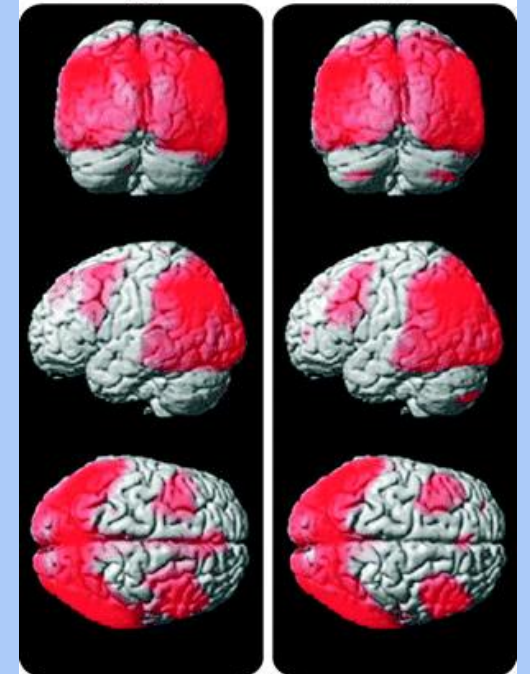
¹⁸flourodopa uptake
Dopaminergic system

A Reduction of cholinergic transmission compared to controls in



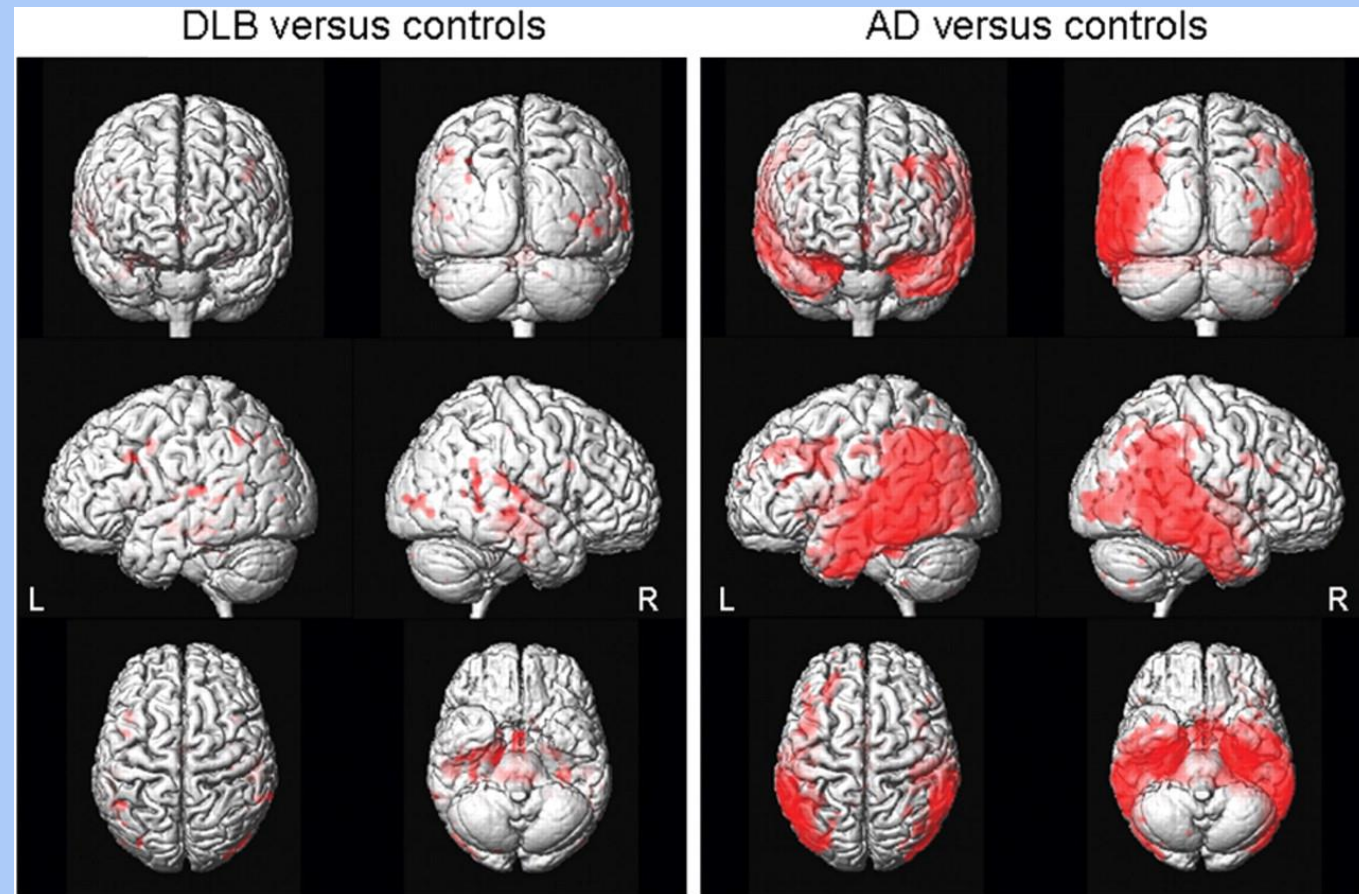
MP4A uptake
Cholinergic uptake

Impaired CMRGlC in



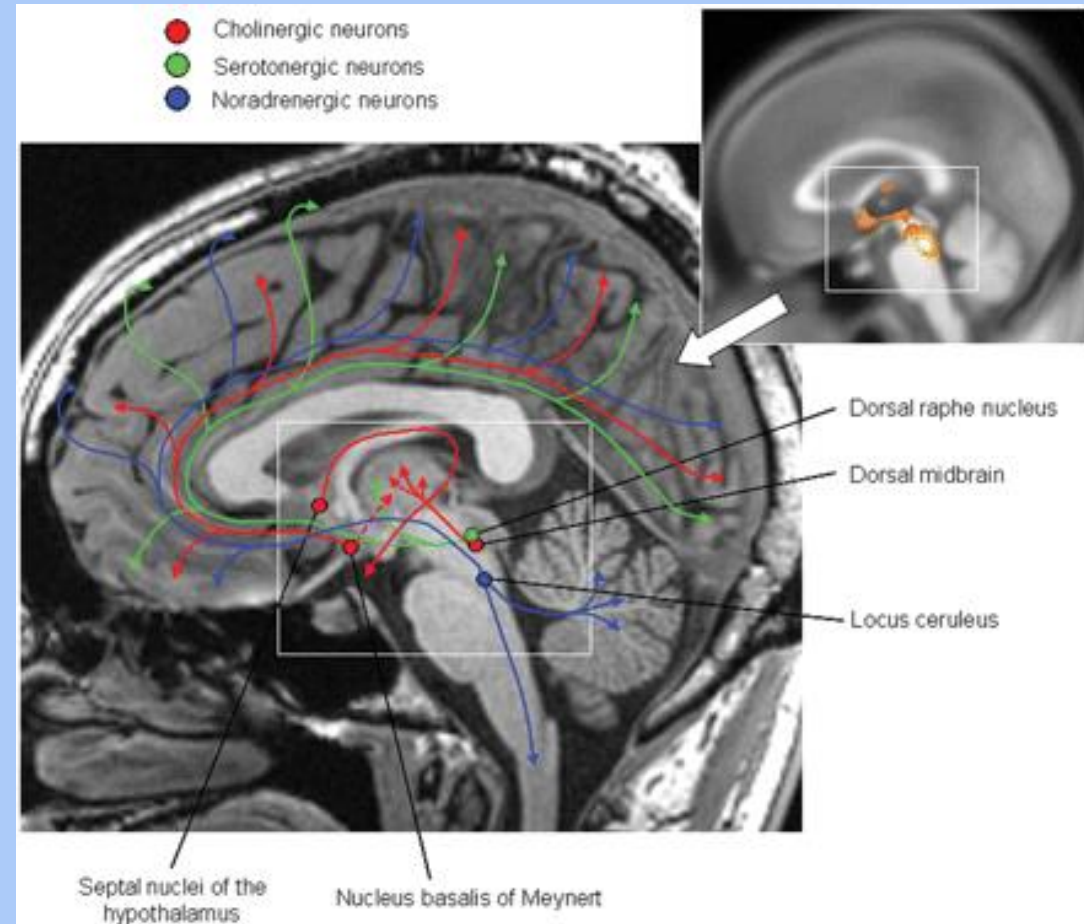
FDG uptake
Glucose metabolism

GREY MATTER LOSS: LBD VS ALZHEIMER'S



Cortical grey matter loss

IMPACT ON NEUROTRANSMITTER NUCLEI



Ref 15 – Location of Grey Matter loss in Lewy Body Dementia

OTHER PARKINSONIAN SYNDROMES

- **Multisystem Atrophy (MSA)**
- **Progressive Supranuclear Palsy (PSP)**
- **Corticobasal degeneration (CBD)**

TREATMENT

- Cognitive impairment from a number of reasons, including:
 - Initial reduction in Acetylcholine
 - Later overexpression of glutamate damages cells

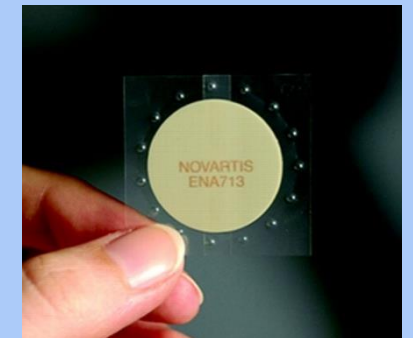
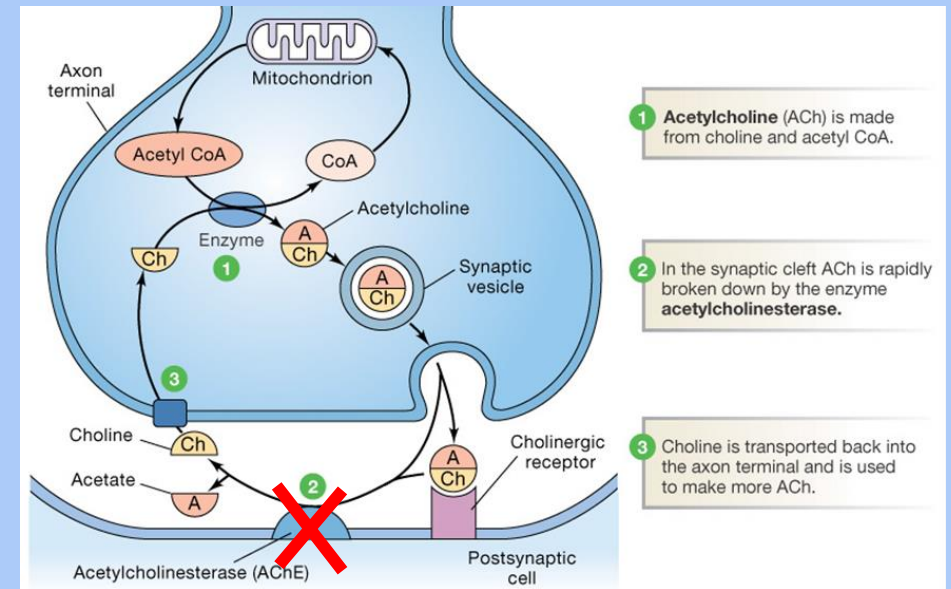
↑↑↑ Acetylcholine, ↓↓↓ glutamate (through NMDA)



Enhanced cognition AND reduction in hallucinations

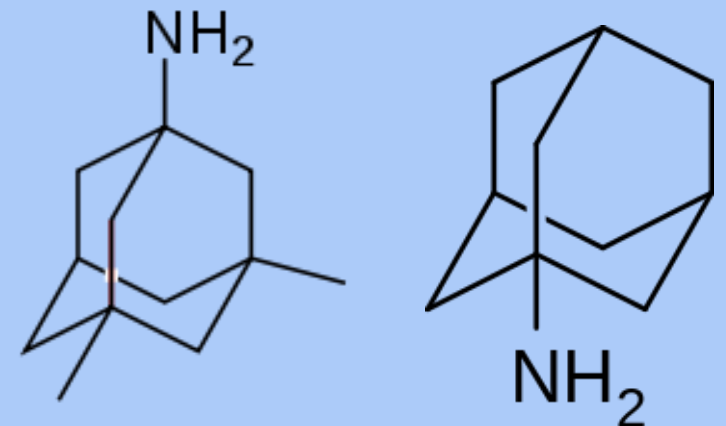
ACETYLCHOLINESTERASE INHIBITORS

- Block breakdown of Acetylcholine → Stays around cell longer → Improves function
 - Donepezil (Aricept®) - inhibits acetylcholinesterase
 - Rivastigmine (Exelon®) - inhibits butyrylcholinesterase and acetylcholinesterase
- Exelon is only of the two FDA approved for Parkinson's Dementia
 - Patch form, reduces risk of nausea/vomiting
- Because nucleus problem and not receptor problem, patients respond better than those with Alzheimer's⁸



NMDA BLOCKADE

- With LBD and PDD, acetylcholine is reduced
 - Triggers an increase in glutamate to compensate for the impaired functioning.
 - Overstimulation with glutamate causes neuronal hyper excitability and death.
- Memantine (Namenda®)
 - Blocks glutaminergic NMDA receptors
 - Reduces glutamate activity
- Corrects overexpression of glutamate
- No benefit in early dementia⁹
- Structurally similar to **Amantadine** → reduction in dyskinesias and other PD side-effects.

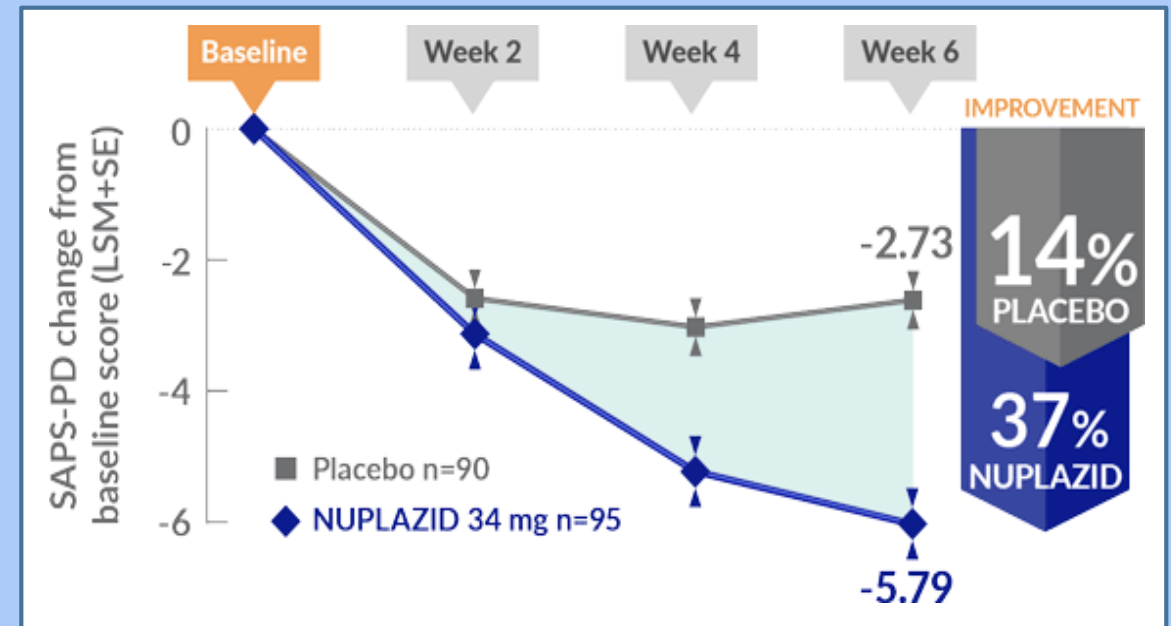


HALLUCINATIONS AND PSYCHOSIS

Nuplazid (Pimavanserin)TM

- First antipsychotic medication specifically designed for hallucinations and 'psychosis' associated with Parkinson's Dementia and Lewy Body Dementia.
- Serotonin Agonist with no impact on dopamine receptors
- + SAPS-PD improvement with no change in UPDRS

NUPLAZIDTM
(pimavanserin) tablets



AVOID

- **Avoid medications that block dopamine or acetylcholine**
 - Neuroleptics
 - Cold medication
 - Anti-emetics
 - Older Parkinson's medications such as Artane

DEPRESSION AND ANXIETY'S ROLE

- 60% of Parkinson's patients have clinical depression¹⁰
 - Equal numbers with Anxiety
- Serotonin, Norepinephrine and Dopamine all significantly reduced in Parkinson's
 - Sleep, focus, mood, attention, etc.
- Depression, Anxiety and Fatigue missed by Neurologists up to 50% of the time¹¹
- Treatment with SNRI or SSRI can significantly improve cognitive function in some patients

Depression masquerading as Dementia in the Parkinson's community.

WHAT ELSE CAN I DO?

- **Activity!!**
 - Physical and Mental
- **Healthy Diet**
 - Heart health is similar to Brain health
 - Cholesterol, blood pressure, diabetes
- **No strong evidence for any particular diet or supplements**

CONCLUSIONS

- Memory, cognitive functioning and mood are directly linked to Acetylcholine and Dopamine.
 - Treatment is complicated d/t balance of treating motor and non-motor symptoms, incorporating different neurotransmitter circuits to give benefit without side-effects
- Proper diagnosis is key, as treatment is different
 - Parkinson's vs
 - Lewy Body dementia vs
 - Parkinson's dementia vs
 - Parkinson's plus syndromes
 - +/- Depression
- Integrating a Movement Disorders Specialist into your treatment team

THANK YOU



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REFERENCES

- 1) <http://brain.oxfordjournals.org/content/130/3/708>
- 2) Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo, *Neurology* March 16, 2010 vol. 74 no. 11 885-892
- 3) Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. *Acta Neuropathol.* 2014 Dec;128(6):805-20. doi: 10.1007/s00401-014-1343-6. Epub 2014 Oct 9.
- 4) Zaccai et al, A systematic review of prevalence and incidence studies of dementia with Lewy bodies, *Age Ageing.* 2005 Nov.
- 5) Boeve and Sapier, 2006
- 6) Lewy body disease association
- 7) Klein, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology* March 16, 2010 vol. 74 no. 11 885-892
- 8) Neef, Doug; Walling, Anne D (2006-04-01), "Dementia with Lewy Bodies: an Emerging Disease", *American Family Physician* 73 (7): 1223-1229, PMID 16623209, retrieved 2010-01-29.
- 9) Schneider, LS; Dagerman, KS; Higgins, JP; McShane, R (August 2011). "Lack of evidence for the efficacy of memantine in mild Alzheimer disease.". *Archives of neurology* 68 (8): 991-8. doi:10.1001/archneurol.2011.69.PMID 21482915.
- 10) pdf.org
- 11) Shulman et al, Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism & related disorders.* January 2002 Volume 8, Issue 3, Pages 193-197
- 12) <http://www.mayo.edu/research/~media/kcms/gbs/research/images/2013/03/07/14/55/de12-2-parkinsons-lewy-body.jpg>
- 13) Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. *Lancet Neurol.* 2010 Dec;9(12):1200-13. doi: 10.1016/S1474-4422(10)70212-X. Epub 2010 Sep 27.
- 14) Obeso et al, Missing pieces in the Parkinson's disease puzzle, *Nature Medicine* 16, 653-661 (2010) doi:10.1038/nm.2165
- 15) Whitwell et al. Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease. <http://dx.doi.org/10.1093/brain/awl388> 708-719 First published online: 31 January 2007
- 16) http://www.mind.uci.edu/wp-content/uploads/2013/11/Winter2011_01.jpg
- 17) Hacksell, Uli et al. "On the Discovery and Development of Pimavanserin: A Novel Drug Candidate for Parkinson's Psychosis." *Neurochemical Research* 39.10 (2014): 2008-2017. PMC. Web. 4 June 2015.