CHOLINERGIC SYSTEMS DYSFUNCTION IN PARKINSON DISEASE

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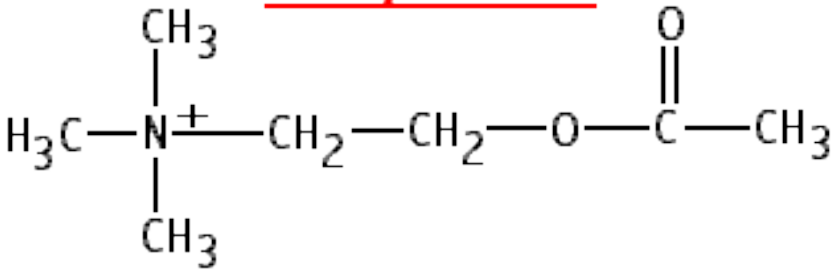
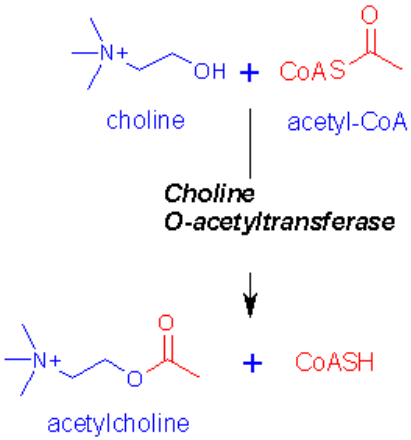
Acetylcholine



REVIEW

Acetylcholine identified in 1914 by Henry Dale as having action on heart tissue, confirmed as a neurotransmitter by Loewi "vagusstoff"

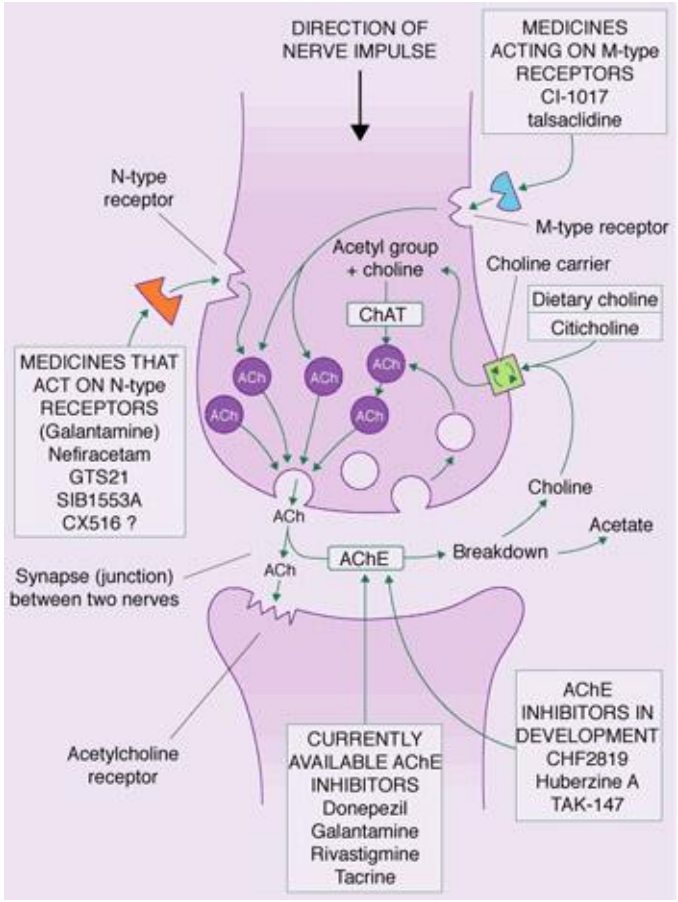


Unlike the catecholamines acetylcholine has a simple structure without aromatic rings.

Well described actions in Parasympathetic-sympathetic systems and NMJ

acetylcholinesterase converts acetylcholine into choline and acetate.

2 cholinergic receptor subtypes: nicotinic and muscarinic

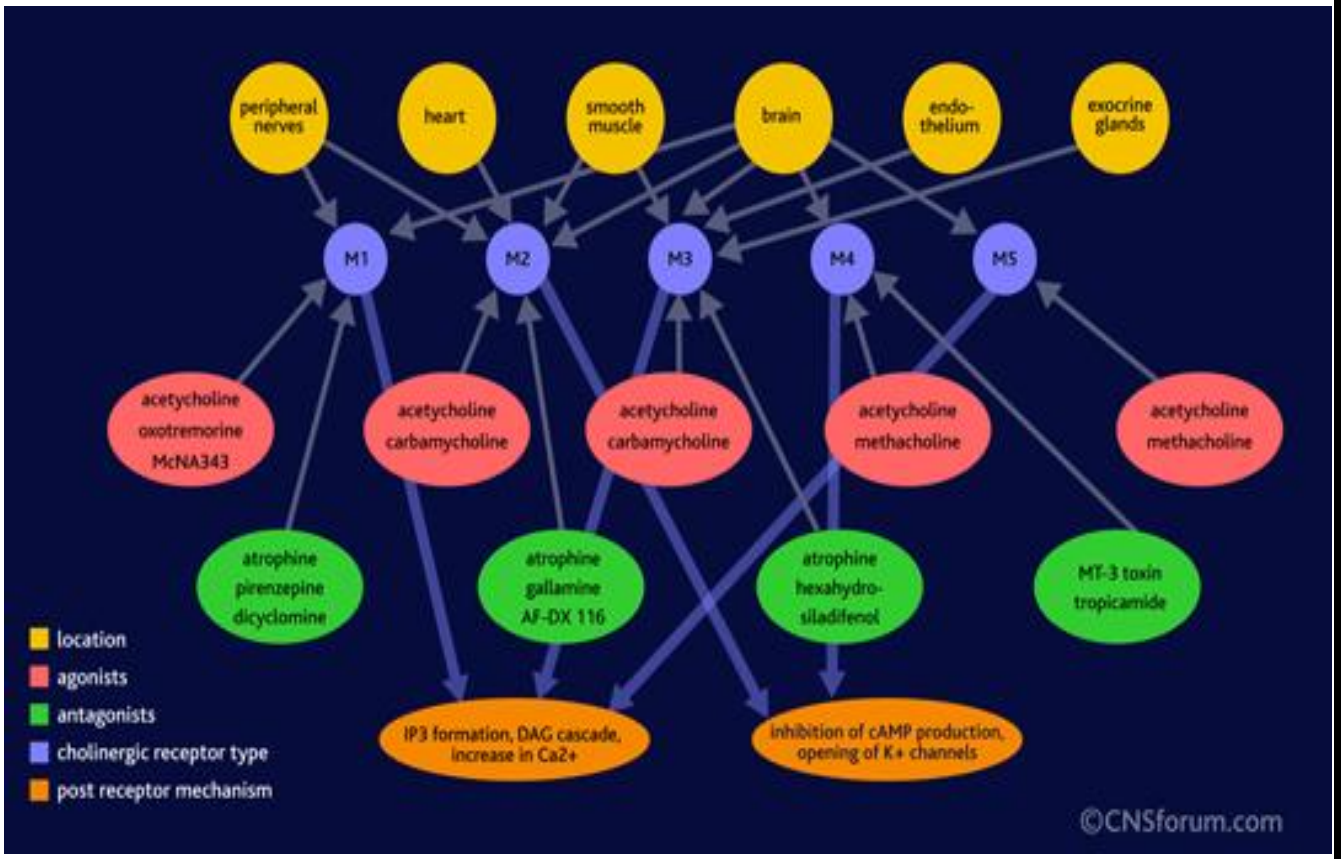


MUSCARINIC RECEPTORS

G-protein receptor superfamily

5 muscarinic subtypes (M1-5) cloned

The receptors are distinguished by location, post-receptor signalling pathway and agonist or antagonist interaction.

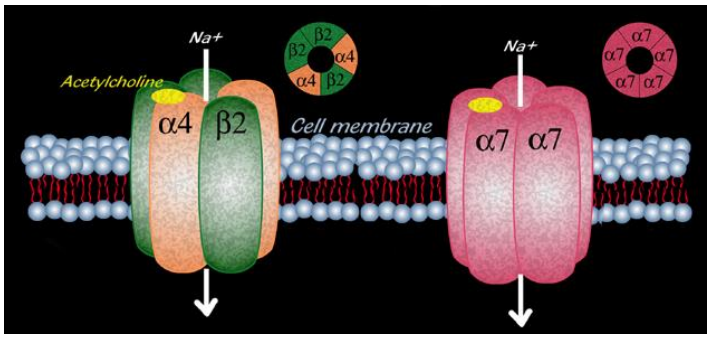


NICOTINIC RECEPTORS

ligand-gated ion channels, permeable to Na, K, Cl

Most peripheral AChr, inactivated by curare

Though low in number, widely distributed in brain



•composed of five protein subuits symmetrically arranged.

•The subunit composition is highly variable across different tissues. Homo or heteromeric

ACh binding site is at the border of α-subunits, thus 1 receptor can bind more than one ACh molecule

When 2 or more ACh are bound, there is conformation change to open a central pore.

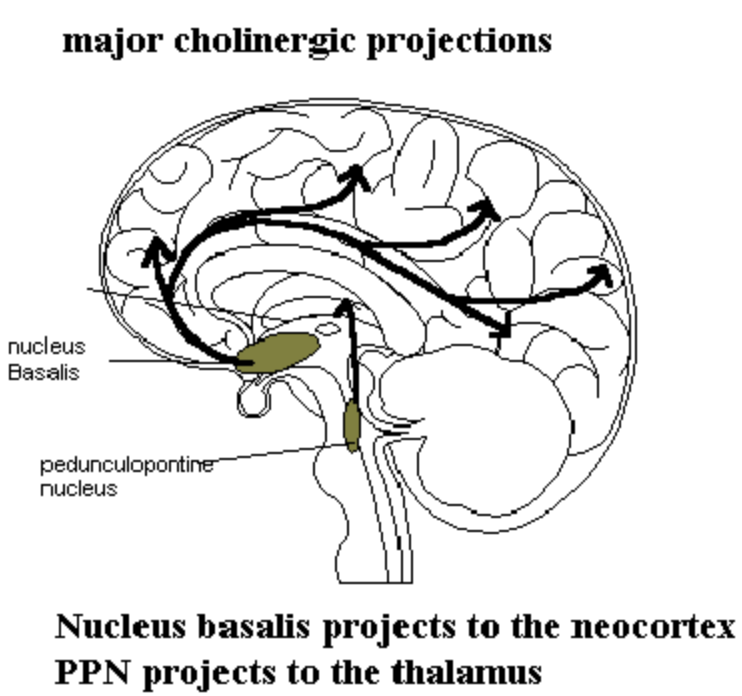
This pore allows cations (Na+ and Ca2+) to enter until the pore re-closes.

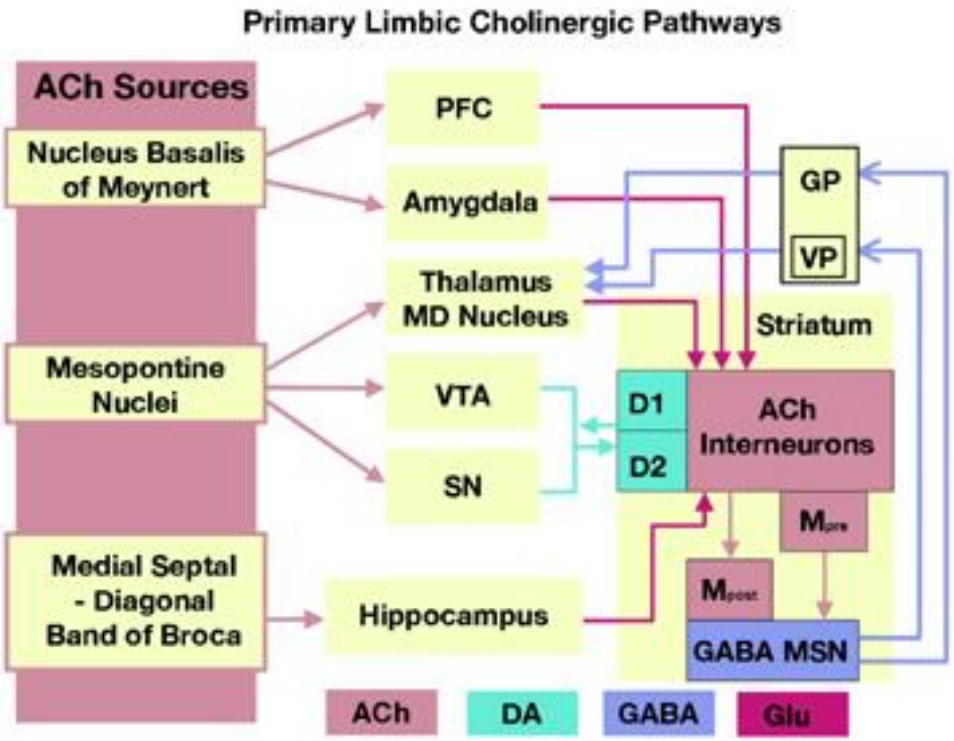
TABLE 1. *Putative subunit composition of nicotinic receptor subtypes in rodent, monkey, and human striatum*

Species	Nicotinic receptor subtypes
Rodents, monkeys, humans	α4β2, α6α4β2β3, α6β2β3, α7
Rodents only	α4α5β2, α6β2[a]
Monkeys only	α4α2β, α3β2[a]

[a]The possible presence of additional subunits in the receptor complex.

CHOLINERGIC PROJECTIONS





IMAGING THE CHOLINERGIC SYSTEM IN PD—PET AND SPECT

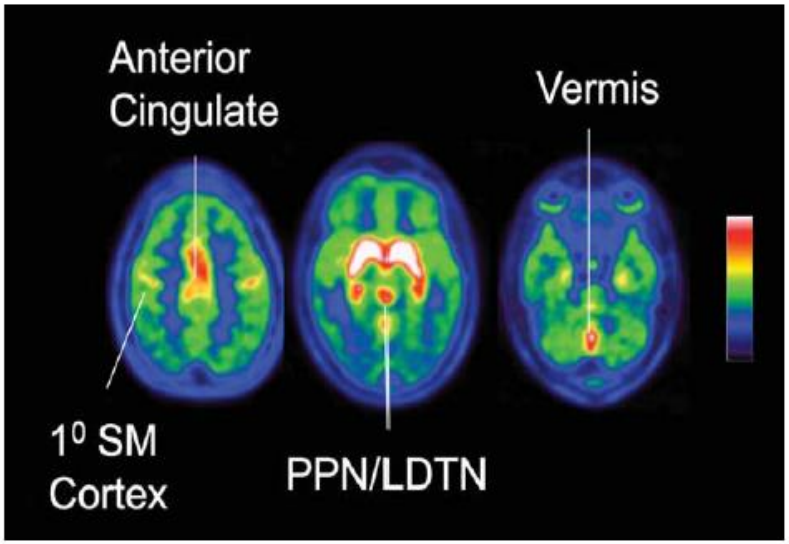


FIG. 2. Normal biodistribution of vesicular acetylcholine transporters using the [^{18}F]fluoroethoxybenzovesamicol ligand is illustrated. More prominent uptake is observed in areas important for attention and sensorimotor locomotor functions. 1° SM cortex indicates primary sensorimotor cortex; PPN/LDTN, pedunculopontine nucleus-laterodorsal tegmental complex.

Imaging: What Can it Tell Us About Parkinsonian Gait?
Nicolaas I. Bohnen, MD, PhD,[1,2,3*] and Klaus Jahn, MD[4,5]
Movement Disorders, Vol. 28, No. 11, 2013

PET : acetylcholine analogues (tracers) are metabolized and trapped by acetylcholinesterase (AChE)

AChE is a reliable marker of cholinergic pathways

AChE PET imaging

Highest activity

- BASAL GANGLIA and
- BASAL FOREBRAIN

Intermediate activity

- CEREBELLUM

Lowest activity

- CORTEX

VARIABILITY OF CHOLINERGIC DEGENERATION IN PD

Cholinergic denervation seen by molecular neuroimaging is similar to histopathology.

- **cholinergic PET shows deficits in PD with and without dementia, less severe but reductions in medial secondary occipital cortex.**
- **PDD c/w Alzheimer (AD) shows more severe cortical AChE loss with similar severity of dementia.**

- **Overall, the degree of cholinergic denervation appears to be variable across PD cases. In one study, cortical and thalamic AChE activity was within-normal-range for 65/101 PD (based on 5th percentile cutoff from normal)**

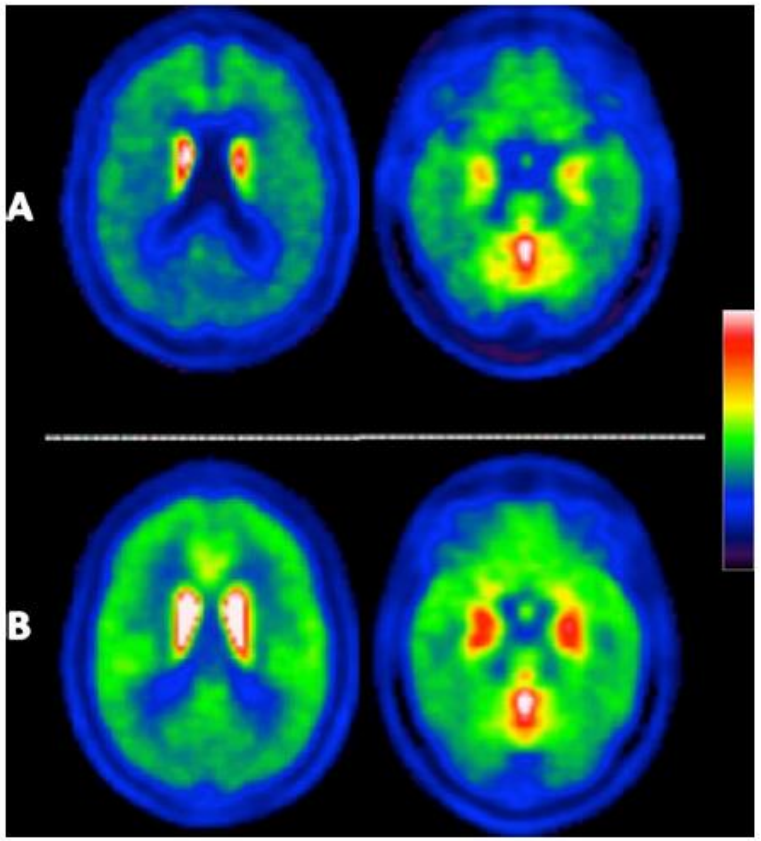


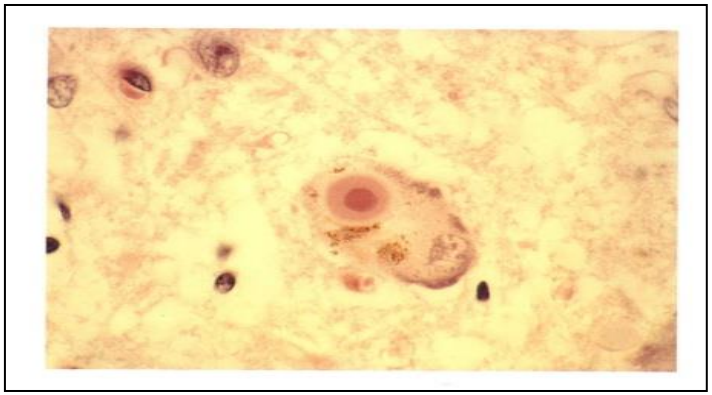
Fig. 1 Transaxial images of a vesicular acetylcholine transporter ([^{18}F]FEOBV) PET study shows widespread cholinergic denervation in a patient with parkinsonian dementia (A: top row) compared with a healthy control subject (B: bottom row)

COGNITION AND ACETYLCHOLINE

COGNITION

The Lewy body was first identified in the Nucleus Basalis of Meynert,

- *Lewy FH. Zur pathologischen Anatomie der Paralysis agitans. Dtsch Ztschr Nervenheilkunde 1913;50:50-55.*



Dementia prevalence at 8 years is 78.2% (Aarsland Prevalence and characteristics of dementia in PD: an 8 year prosp study. Archives of Neurology 2003.

***Table 3** Cortical Lewy body score in PD with and without dementia*

	Cortical Lewy body score				
Dementia	0	1	2	3	Total
Yes, n (%)	0 (0.0)	2 (9.1)	13 (59.1)	7 (31.8)	22 (100)
No, n (%)	1 (5.0)	17 (85.0)	2 (10.0)	0 (0.0)	20 (100)
Total	1	19	15	7	42

Greater Lewy bodies in the cortex correlate with PDD diagnosis. **Hurtig HI, Trojanowski JQ et al. Alpha-synuclein Cortical Lewy Bodies correlate with Dementia in PD. Neurology 2000**

What about the Nucleus Basalis?

FUNCTIONAL IMAGING OF CHOLINERGIC AND DOPAMINERGIC PATHWAYS IN PDD

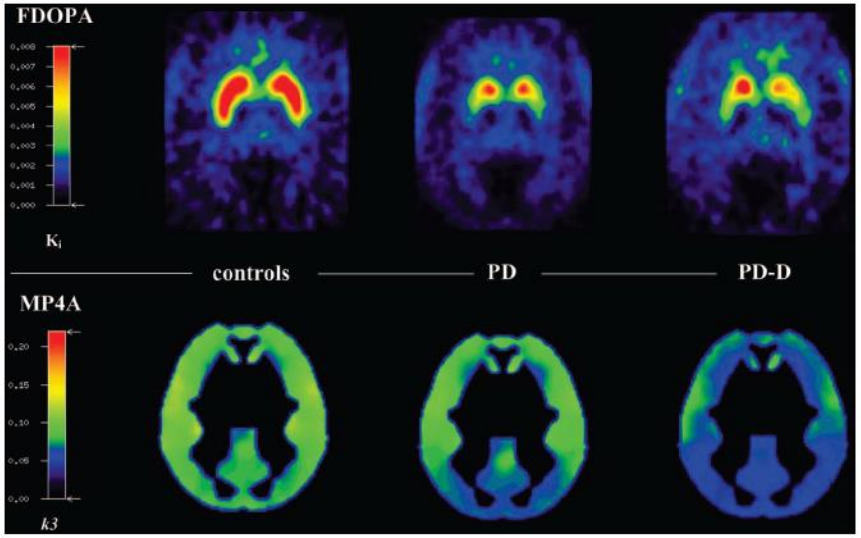
(HILKER R, THOMAS AV ET AL NEUROLOGY 2005).

[^{11}C] MP4A PET imaging along with FDOPA

17 PD, 10 PDD, 31 age matched controls

Results: FDOPA striatal uptake severely decreased in PD, no difference b/w PD, PDD

Global cortical MP4A binding severly reduced by 29.7% in PDD (p<0.001) and moderately in PD 10.7% (P<0.01) vs controls



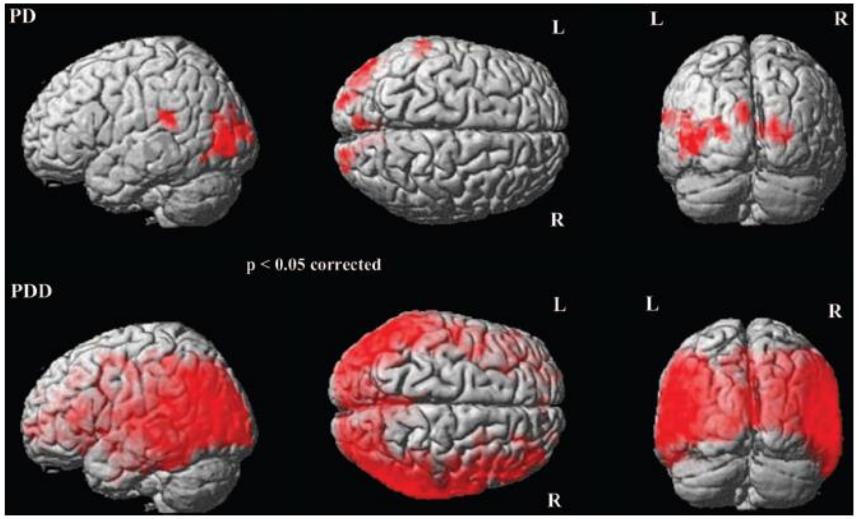


Figure 3. Regions with significantly decreased cortical MP4A binding vs controls in the Parkinson disease (first row) and the Parkinson disease with dementia group (second row).

HOW ABOUT CHOLINESTERASE INHIBITORS? A REVIEW OF CLINICAL TRIALS IN PD

Rivastigmine for Dementia Associated with Parkinson's Disease. Emre M, Aarsland D, et al N Engl J Med Dec 2004

Multicenter RCT of n=541 subjects with mild-moderate dementia (MMSE 10-24)

Rivastigmine vs placebo. Mean final dose 8.6 mg/d (3mg daily increasing as tolerated to maximum 12 mg)

Improved scores on 2 co-primary cognitive outcomes scales in PDD

- AD Cooperative Study-Clinicians GIC (7 point scale anchored at 4 →no change)
- AD Assessment Scale-cognitive subscale (ADAS-cog, 70 points max, higher scores = more impaired)

Other secondary outcomes

- MMSE
- Computerized attention tests
- ADL
- Clock drawing
- Delis-Kapal Executive Function system
- 10-item Neuropsychiatric inventory

Of 541 enrolled, 362 randomized to rivastigmine, 179 to placebo

- 131 discontinued , 27% from the active drug, 17.9% from placebo

C/W baseline, 24 week ADAS-cog scores improved by 8.8% in rivastigmine group and declined by 2.9% in placebo

- Absolute score reduction of 2.9 points
- ADCS-CGIC : 0.5 point improvement

An analysis of clinically meaningful changes results in loss of statistical significance. 19.8% vs 14.5% reached "clinically significant improvement" with a NNT of 19.

All secondary outcomes significantly beneficially affected.

Table 2. Results of the Efficacy Analysis.*

Variable	No. of Patients	Baseline Score	Change at Week 24	Between-Group Difference at Week 24	
				Value	P Value
		mean ±SD			
Primary efficacy variables					
ADAS-cog score					
Rivastigmine	329	23.8±10.2	−2.1±8.2	2.90†	
Placebo	161	24.3±10.5	0.7±7.5		<0.001
ADCS-CGIC score					
Rivastigmine	329	—	3.8±1.4	0.5	
Placebo	165	—	4.3±1.5		0.007
Secondary efficacy variables					
ADCS-ADL score					
Rivastigmine	333	41.6±18.6	−1.1±12.6	2.50	0.02
Placebo	165	41.2±17.7	−3.6±10.3		
NPI-10 score					
Rivastigmine	334	12.7±11.7	−2.0±10.0	2.15†	0.02
Placebo	166	13.2±13.0	0.0±10.4		
MMSE score					
Rivastigmine	335	19.5±3.8	0.8±3.8	1.00	0.03
Placebo	166	19.2±4.0	−0.2±3.5		
CDR power of attention tests (msec)					
Rivastigmine	328	2197.0±1170.2	−31.0±989.8	294.84†	0.009
Placebo	158	2490.5±2314.8	142.7±1780.2		
D-KEFS Verbal Fluency Test (total no. of correct responses)					
Rivastigmine	258	13.9±9.5	1.7±6.8	2.80	<0.001‡
Placebo	144	14.5±9.4	−1.1±6.4		
Ten Point Clock-Drawing score					
Rivastigmine	49	3.4±3.7	0.5±2.5	1.10	0.02‡
Placebo	30	2.9±3.8	−0.6±2.4		

* Scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) can range from 0 to 70, with higher scores indicating more severe impairment; decreases in scores indicate improvement. Scores for the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC) can range from 1 to 7, with a score of 1 indicating marked improvement; a score of 2, moderate improvement; a score of 3, minimal improvement; a score of 4, no change; a score of 5, minimal worsening; a score of 6, moderate worsening; and a score of 7, marked worsening. There are no baseline scores for the ADCS-CGIC because this tool assesses change. Scores for the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) can range from 0 to 78, with higher scores indicating better functioning. Scores for the 10-item Neuropsychiatric Inventory (NPI-10) can range from 0 to 120, with higher scores indicating more frequent or more severe behavioral symptoms. Scores for the Mini–Mental State Examination (MMSE) can range from 0 to 30, with higher scores indicating better mental function. Higher scores for the Cognitive Drug Research (CDR) computerized assessment system power of attention tests indicate worse performance. Higher scores for the Delis–Kaplan Executive Function System (D-KEFS) Verbal Fluency test and the Ten Point Clock-Drawing test indicate better performance.

† The value is the modeled treatment difference (difference of least-square means).

‡ Because executive-function tests were not performed at all sites, analyses involving these tests included only patients who actually took these tests.

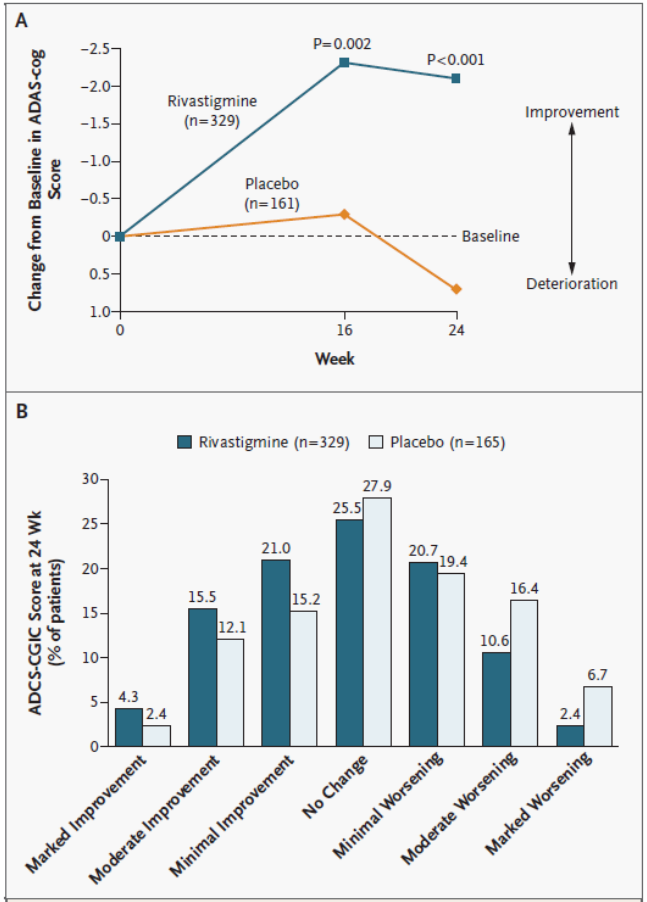


Figure 2. Results of the Primary Efficacy Analysis in the Efficacy Population.
Panel A shows the changes from baseline in the score for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). Scores can range from 0 to 70, with higher scores indicating more severe impairment and decreases in scores indicating improvement. Panel B shows the scores for the Alzheimer's Disease Cooperative Study–Clinician's Global Impression of Change (ADCS-CGIC) at 24 weeks. Minimal changes were predefined as those that were clinically detectable but that did not affect a patient's clinical status; moderate changes were defined as definite, detectable changes that had a corresponding effect on clinical status; and marked changes were defined as those that had a dramatic effect on clinical status. P=0.007 for the overall difference between groups at 24 weeks. A few patients in the efficacy analysis had missing data on either of the two primary end points at week 24.

Table 3. Most Frequently Reported Adverse Events.*

Adverse Event	Rivastigmine Group (N=362)	Placebo Group (N=179)	P Value
	no. (%)		
Any	303 (83.7)	127 (70.9)	<0.001
Nausea	105 (29.0)	20 (11.2)	<0.001
Vomiting	60 (16.6)	3 (1.7)	<0.001
Tremor	37 (10.2)	7 (3.9)	0.01
Diarrhea	26 (7.2)	8 (4.5)	0.26
Anorexia	22 (6.1)	5 (2.8)	0.14
Falls	21 (5.8)	11 (6.1)	0.85
Dizziness	21 (5.8)	2 (1.1)	0.01
Hypotension	19 (5.2)	14 (7.8)	0.25
Constipation	17 (4.7)	12 (6.7)	0.32
Hallucinations	17 (4.7)	17 (9.5)	0.04
Confusion	13 (3.6)	10 (5.6)	0.36
Orthostatic hypotension	6 (1.7)	9 (5.0)	0.05

* Adverse events occurring in at least 5 percent of the patients in either group are reported.

- Study discontinuation d/t side effects
  - 17% in the rivastigmine group
  - 7.8% in the placebo group.
  - Only 1.7% of rivstigmine treated patients discontinued d/t tremor worsening (tremor **was** 3rd most common reported se, but not reflected in overall UPDRS scores between groups).
  - Most of drop out was due to nausea or vomiting.

- Bottom Line Conclusions

  Rivastigmine mildly improves cognitive scale scores and a global impression of change

  Estimated NNT for achieving moderate or marked clinical improvement or avoiding mod/marked clinical worsening in cognition was 7

  NNH due to cholinergic side effects was 16 and from any side effect is ~11

  NNH for worsening of parkinsonism was 9 with tremor being most commonly affected NNH=16

OTHER CHOLINESTERASE INHIBITOR TRIALS

Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. **Aarsland D, Laake K, Larsen JP, Janvin C JNNP 2002.**

14 cognitively impaired PD subjects (16-26 MMSE) RC crossover T 10 weeks sequentially

Outomes:

- MMSE, clinician's interview based impression of change ,caregiver input (CIBIC+) score, Motor UPDRS

Results: 2 dropouts

- MMSE score +2.1(SD 2.7) on donepezil vs 0.3 (SD 3.2) points on placebo
- CIBIC+ score was 3.3 (SD 0.9) on donepezil and 4.1 (SD 0.8) on placebo.

Five (42%) patients on donepezil and two (17%) on placebo were rated as improved on the basis of the CIBIC+ score.

UPDRS not affected

CONCLUSIONS: Donepezil improves cognition, and seems to be well tolerated and not to worsen parkinsonism in patients with cognitive impairment.

Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study . **B Ravina, M Putt, A Siderowf, et al. J Neurol Neurosurg Psychiatry 2005;76:934–939**

22 subjects PDD, RC crossover T with 10 week periods and 6 week washout.

Primary outcome: ADAS-Cog

Results: Donepezil was well tolerated and most adverse events were mild. No UPDRS change.

- 1.9 point trend toward better scores on the ADAS cog compared with placebo

The secondary cognitive measures showed a statistically significant

- 2 point benefit on the MMSE and no change on the Mattis Dementia Rating Scale
- Clinical Global Impression of Change (CGI) showed a significant 0.37 point improvement on active tx.
- No improvement was observed on the MDRS or the Brief Psychiatric Rating Scale.

Conclusions: Donepezil was well tolerated and did not worsen PD. There may be a modest benefit on aspects of cognitive function.

A DOUBLE-BLIND COMPARISON OF GALANTAMINE HYDROBROMIDE ER AND PLACEBO IN PARKINSON DISEASE.

J NEUROL NEUROSURG PSYCHIATRY. 2009 JAN;80(1):18-23. EPUB 2008 OCT 17.

OBJECTIVE: To study the efficacy and safety of galantamine hydrobromide ER for the enhancement of cognition in non-demented Parkinson's patients (PD).

69 non-demented PD subjects

RCT of galantamine or placebo

- 16 weeks (8 mg/day for 4 weeks, a therapeutic dose of 16 mg/day for 6 weeks and a maximum dose of 24 mg/day for 6 weeks).

Outcome measures were neuropsychological (attention, verbal fluency, executive, memory, visuospatial), behavioural (Frontal Systems Behavior Scale, Neuropsychiatric Inventory-Questionnaire, PDQ-39) and motor (Unified Parkinson's Disease Rating Scale motor scale).

RESULTS: 26 individuals on active medication and 28 individuals on placebo were included in the outcome analyses.

No significant differences were found between the active and placebo groups on cognitive, behavioural or motor outcome measures. Most common adverse events were gastrointestinal and self-reported worsening of PD symptoms.

CONCLUSIONS: Galantamine treatment did not improve attention/executive, memory or visuospatial performance in non-demented PD patients.

EFFECTS OF RIVASTIGMINE IN PATIENTS WITH AND WITHOUT VISUAL HALLUCINATIONS IN DEMENTIA ASSOCIATED WITH PARKINSON'S DISEASE.

BURN D, EMRE M, MCKEITH ET AL. *MOVEMENT DISORDERS* VOL. 21, NO. 11, 2006, PP. 1899–1907

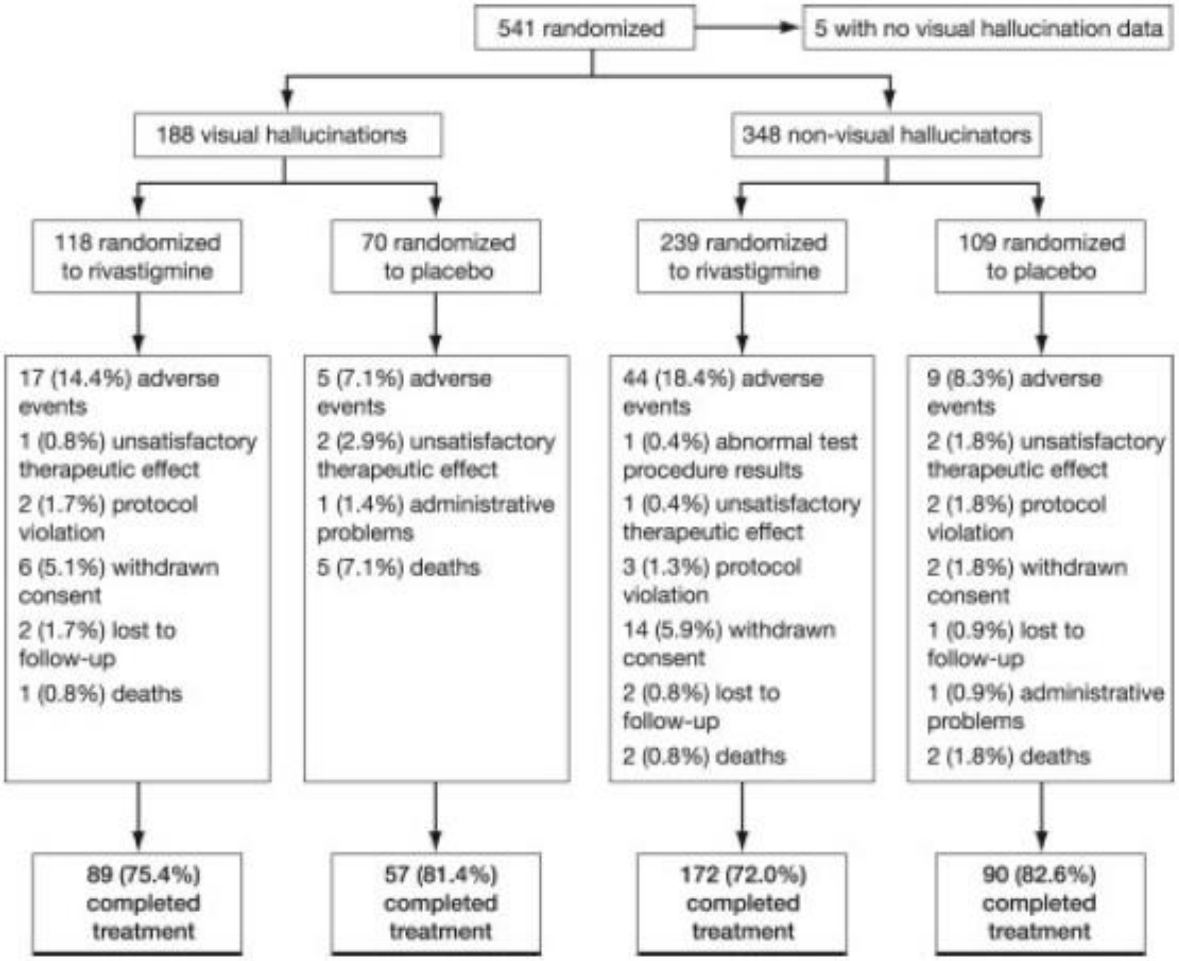


FIG. 1. Study profile.

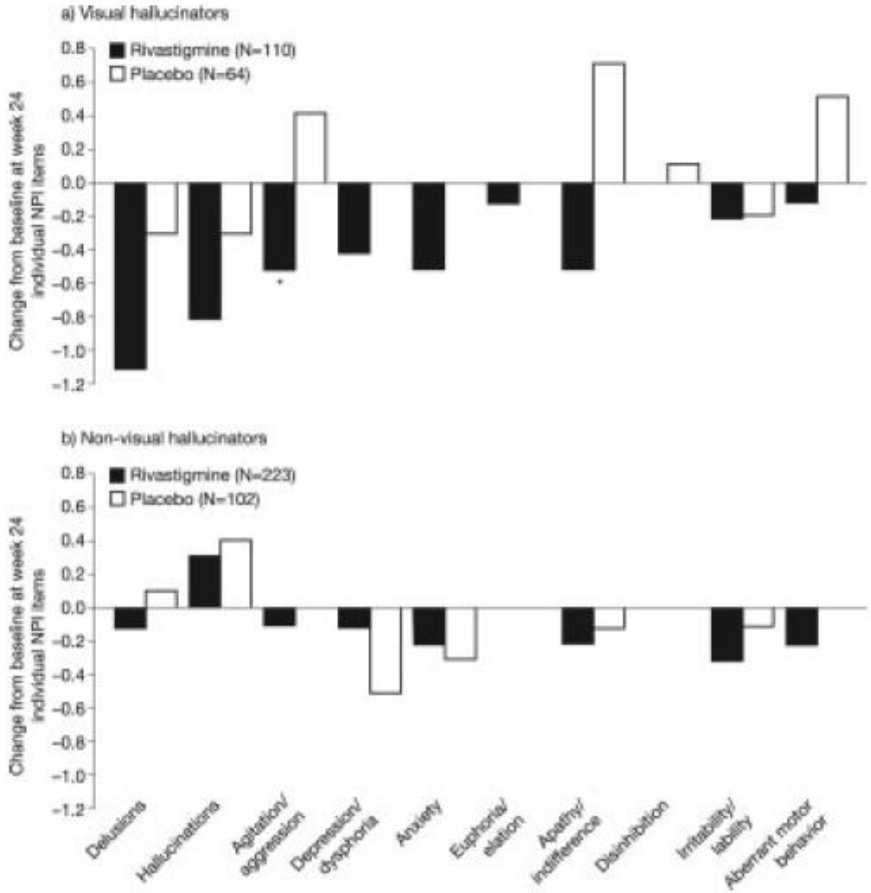


FIG. 4. Changes from baseline on individual items on the NPI-10 in visual hallucinators (**a**) and nonhallucinators (**b**) receiving rivastigmine or placebo (ITT + RDO). Negative scores indicate improvement. Asterisk, $P < 0.05$ versus placebo.

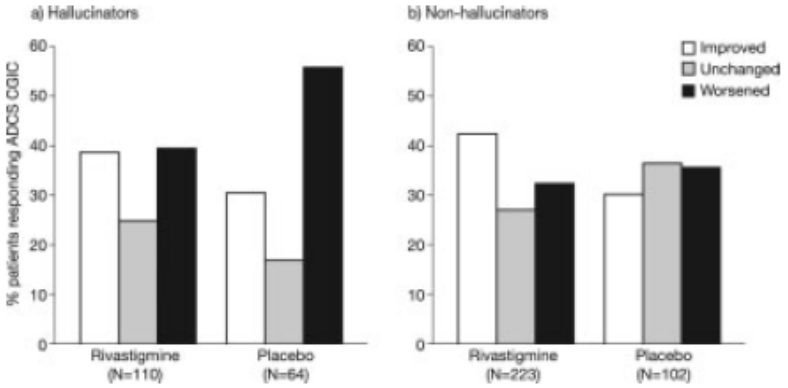


FIG. 3. Impressions of clinical change as assessed with the ADCS-CGIC in visual hallucinators (**a**) and nonhallucinators (**b**) receiving rivastigmine or placebo (ITT + RDO). Improved: combination of the categories markedly, moderately, and minimally improved. Worsened: combination of the categories markedly, moderately, and minimally worsened. Visual hallucinators: $P = 0.03$ for the between-group difference at 24 weeks (categorical analysis). Nonvisual hallucinators: $P = 0.11$ for the between-group difference at 24 weeks (categorical analysis).

SUMMARY: COGNITION

Cholinergic cell loss is substantial in PD, and cortical Lewy Body load correlates with dementia.

Acetylcholinesterase activity reductions are more common in parkinsonism with dementia

Cholinesterase inhibitors (rivastigmine best studied) can provide modest benefits in cognition and hallucinations in PDD

GAIT AND BALANCE

PHYSICAL AND COGNITIVE PERFORMANCE AND BURDEN OF ANTICHOLINERGICS, SEDATIVE AND ACE INHIBITORS IN OLDER WOMEN. CAO, MAGER, SIMONSICK, ABERNETHY ET AL. CLINICAL PHARMACOLOGY & THERAPEUTICS 2007

- **932 moderately to severely disabled community resident women >65yo who participated in the Women's Health and Aging Study I.**

- **"Drug Burden" score calculated and related to cognitive/physical function measures**

Results: <u>Anticholinergic</u> burden associated with greater difficulty in 4 physical function domains

- Adjusted OR **4.9** (95%CI 2-12) for balance difficulty
- **3.2** (1.5-6.9) for mobility difficulty
- **3.6** (1.6-8.0) for slow gait
- **4.2** (2-8.7) for chair stands difficulty

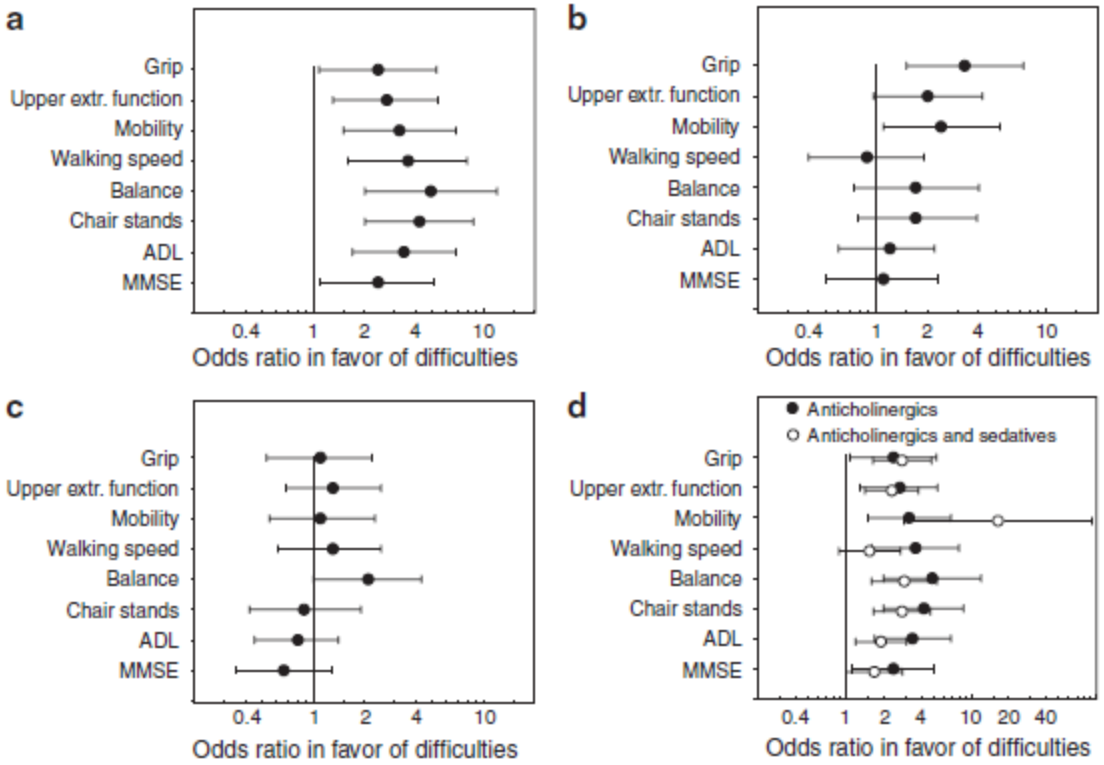


Figure 2 ORs for the association of physical and mental performance with burden of anticholinergics, sedatives, and ACE inhibitors. (**a**) Anticholinergics, (**b**) sedatives, (**c**) ACE inhibitors, (**d**) anticholinergics and sedatives. ORs were adjusted for age, race, education, depression, arthritis, visual and hearing impairment, hypertension, ischemic heart disease, congestive heart failure, pulmonary disease, osteoporosis, diabetes mellitus, cancer, disc disease, hip fracture, spinal stenosis, Parkinson's disease, and peripheral arterial disease. The following statistical interactions with ACE inhibitors were ignored: hypertension ($P = 0.032$), congestive heart failure ($P = 0.044$), and visual impairment ($P = 0.048$). The variance bars are for 95% CI. Upper extr. difficulty, upper extremity difficulty.

LOSS OF CHOLINERGIC NEURONS IN THE PPN IN PARKINSON DISEASE IS RELATED TO DISABILITY OF THE PATIENTS. RINNE, MA ET AL *PARKINSONISM AND RELATED DISORDERS* 14 (2008) 553-557.

40-57% of large PPN neurons lost in PD

Counted numbers of total neurons in PPN (Luxol fast blue), and cholinergic neurons (ChAT +) neurons in 11 PD, 9 controls

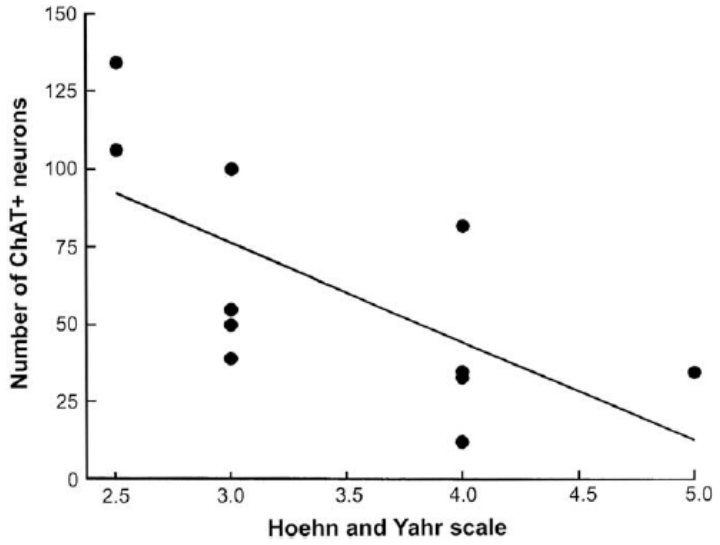
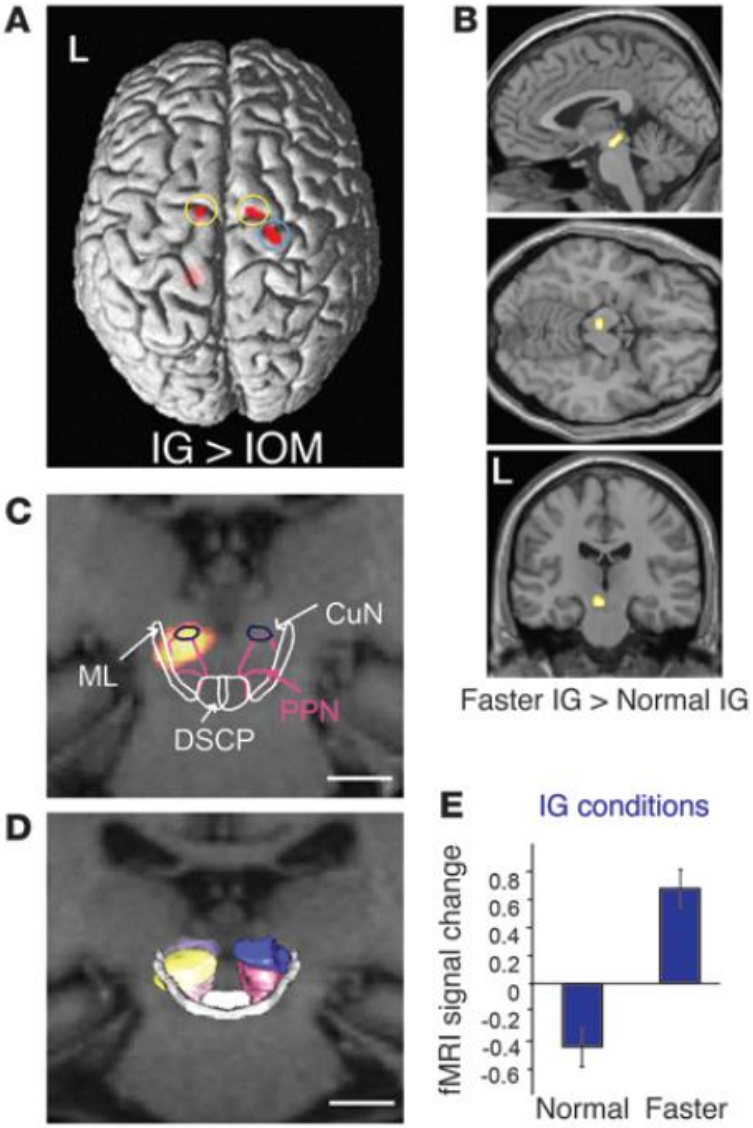


Fig. 2. Correlation between the number of neuron profiles staining with an antibody against choline acetyltransferase in the PPN and the modified Hoehn and Yahr stage of PD patients. Each dot denotes an individual subject. $r = -0.66$, and $p = 0.03$.

More severe ChAT + loss correlates with higher H&Y (r=-0.66, p=0.03) LFB loss did not.

Braak staging not related with H&Y, nor ChAT positivity

***Conclusion*: Cholinergic cell loss and loss of volume in the PPN in PD is correlated with higher H&Y stage.**



Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease

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The PPN region is activated during fast imagined walking in healthy humans.

Cholinergic neurons in the PPN degenerate in faller PD patients

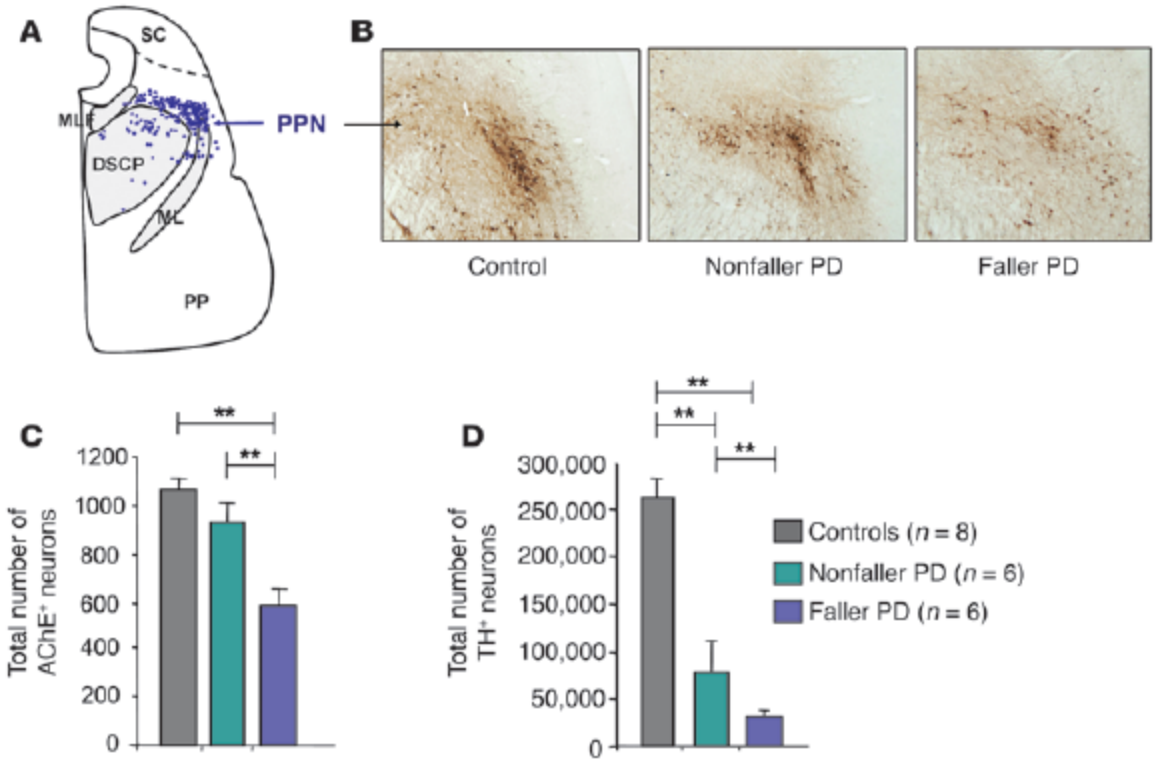
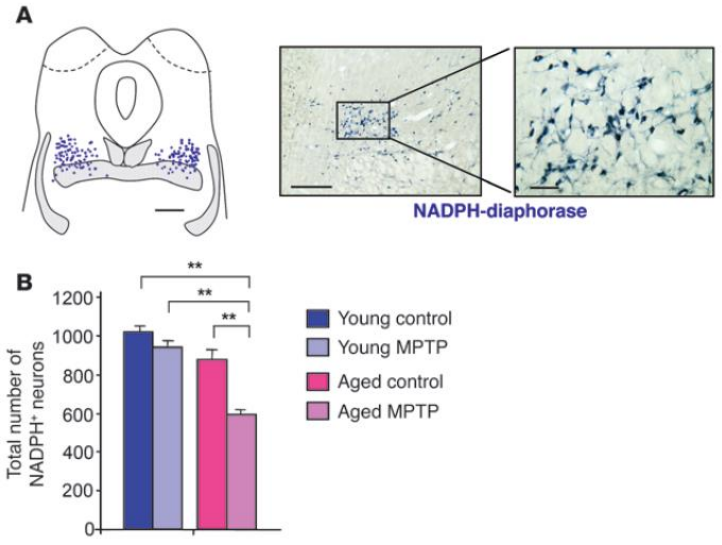


Figure 2

Relationship between loss of PPN cholinergic neurons and balance deficits in human PD patients. (**A**) Computer-generated map of AChE+ neurons in the PPN of a control brain. Blue dots represent individual neurons. (**B**) Transverse sections at PPN level illustrating that the loss of AChE+ neurons of a faller PD patient was more severe than in a nonfaller PD patient. (**C**) Total number of AChE+ neurons in the PPN of controls ($n = 8$), nonfaller PD patients ($n = 6$), and faller PD patients ($n = 6$). The mean value for the faller PD patients was significantly different from the mean for the control group and from the mean for the nonfaller PD patients. (**D**) Total number of TH+ neurons in the substantia nigra pars compacta of the same groups of control and PD patients. The mean values for the 2 PD groups were significantly different from the mean for the control group. MLF, medial longitudinal fasciculus; PP, pes pedunculi; SC, superior colliculus. $^{**}P < 0.01$, Mann-Whitney *U* test. Scale bar: 1 mm.

A loss of cholinergic neurons is detected in the PPN of aged parkinsonian monkeys displaying balance deficits.

- aged but not young monkeys develop balance and postural deficits after intoxication with MPTP
- current monkey models of MPTP-PD produces dopamine depletion but no loss of PPN cholinergic neurons in young adult monkeys
- Tested if balance/postural symptoms are associated with a loss of cholinergic neurons in the PPN
- MPTP resulted in nigrostriatal dopamine losses similar b/w old and young, but additional cholinergic PPN loss was only seen on the old (~30%)
- While both young and old manifested parkinsonism, only postural deficits were seen in the older monkeys



Cholinergic lesion within the PPN induces gait and postural disorders.

- **Selective lesion of cholinergic PPN in a different group of monkeys**
- **isolated cholinergic lesioning caused prominent deficits in gait and posture (< knee angle, > back curvature and abnormal tail posture (axial rigidity)**
- **No reversal of these gait and posture abn with apomorphine, in contrast to reversal of parkinsonian symptoms in MPTP lesioning**

History of falls in Parkinson disease is associated with reduced cholinergic activity

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44 PD subjects (H& Y I-III) and 15 controls

Clinical Assessment

PET scanning with

- [^{11}C] (PMP) acetylcholinesterase (AChE)
- [^{11}C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) brain PET

Table 2 Mean ± SD age, duration of disease, MMSE scores, UPDRS motor scores, and average daily "off" time (in hours) in the PD fallers and nonfallers groups

	PD fallers (n = 17)	PD nonfallers (n = 27)	Statistical significance
Age, y	72.5 ± 9.3	66.6 ± 9.1	$t = 2.07$; $p = 0.047$
Duration of disease, y	8.8 ± 4.3	6.0 ± 3.9	$t = 2.19$; $p = 0.034$
MMSE	28.8 ± 1.5	29.2 ± 1.4	$t = 0.86$; $p = 0.40$
UPDRS motor	30.4 ± 6.5	22.6 ± 7.8	$t = 3.44$; $p = 0.001$
UPDRS axial motor	6.6 ± 2.3	4.2 ± 1.9	$t = 3.93$; $p = 0.0003$
Daily "off" time	3.9 ± 4.3	3.3 ± 3.9	$t = 0.47$; $p = 0.63$

MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale; PD = Parkinson disease.

Table 1 Mean ± SD thalamic and cortical AChE hydrolysis rates (k_3; min^{-1}) and striatal VMAT2 (BP_{ND}) activity in the patients with PD and control subjects

	PD (n = 44)	Control subjects (n = 15)	Statistical significance
Cortical AChE k_3	0.0273 ± 0.0031	0.0304 ± 0.0032	$t = 3.24$; $p = 0.002$
Thalamic AChE k_3	0.0599 ± 0.0071	0.0640 ± 0.0040	$t = 3.37$; $p = 0.002$
Putamen DTBZ BP_{ND}	0.71 ± 0.18	1.85 ± 0.29	$t = 14.41$; $p < 0.0001$
Caudate nucleus DTBZ BP_{ND}	0.89 ± 0.33	1.53 ± 0.32	$t = 6.51$; $p < 0.0001$

AChE = acetylcholinesterase; PD = Parkinson disease.

CHOLINESTERASE AND STRIATAL VMAT2 ACTIVITY

Table 3 Mean ± SD cortical and thalamic AChE hydrolysis rates (k_3; min^{-1}) and striatal VMAT2 BP_{ND} activity in the PD fallers, PD nonfallers, and control subjects

	PD fallers (n = 17)*	PD nonfallers* (n = 27)	Control subjects* (n = 15)	Age effect	Group effect	Overall model
Cortical AChE k	0.0264 ± 0.0029 A	0.0281 ± 0.0030 B	0.0301 ± 0.0032 C	$F = 3.84$, $p = 0.055$	$F = 5.77$, $p = 0.005$	$F = 7.22$, $p = 0.0004$
Thalamic AChE k_3	0.0572 ± 0.0057 A	0.0617 ± 0.0074 B	0.0648 ± 0.0040 B	$F = 0.18$, $p = 0.68$	$F = 5.31$, $p = 0.008$	$F = 4.36$, $p = 0.008$
Putamen DTBZ BP_{ND}	0.69 ± 0.12 A	0.72 ± 0.21 A	1.84 ± 0.29 B	$F = 0.4$, $p = 0.52$	$F = 150.87$, $p < 0.0001$	$F = 106.55$, $p < 0.0001$
Caudate nucleus DTBZ BP_{ND}	0.91 ± 0.18 A	0.91 ± 0.27 A	1.29 ± 0.19 B	$F = 4.73$, $p = 0.034$	$F = 15.53$, $p < 0.0001$	$F = 14.26$, $p < 0.0001$

Analysis of covariance F values (with levels of significance) are listed for the age covariate and overall group effect with Duncan' Multiple Range post hoc testing between subgroups: subgroup means with the same letter are not significantly different. The group means are adjusted for the age covariate.
*The group means are age-adjusted.
AChE = acetylcholinesterase; PD = Parkinson disease.

Table 4 Mean ± SD cortical and thalamic AChE hydrolysis rates (k_3; min^{-1}) activity in the PD fallers, PD nonfallers, and control subjects

	PD fallers (n = 17)*	PD nonfallers* (n = 27)	Control subjects* (n = 15)	Age effect	Striatal DTBZ effect	Group effect	Overall model
Cortical AChE k_3	0.0265 ± 0.0034 n/a	0.0279 ± 0.0035 n/a	0.0299 ± 0.0050 n/a	$F = 5.29$, $p = 0.025$	$F = 0.04$, $p = 0.85$	$F = 2.11$, $p = 0.13$	$F = 6.16$, $p = 0.0004$
Thalamic AChE k_3	0.0567 ± 0.0074 A	0.0609 ± 0.0076 B	0.0663 ± 0.0110 B	$F = 0.44$, $p = 0.51$	$F = 0.49$, $p = 0.48$	$F = 3.78$, $p = 0.029$	$F = 3.33$, $p = 0.017$

Analysis of covariance F values (with levels of significance) are listed for the age and striatal DTBZ binding covariates and overall group effect with Duncan Multiple Range post hoc testing between subgroups: subgroup means with the same letter are not significantly different.
*The group means are age-adjusted.
AChE = acetylcholinesterase; PD = Parkinson disease.

Main point is that when controlling for age and degree of nigrostriatal denervation, thalamic differences in cholinesterase activity remained significant, even though the cortical fell below statistical significance.

Gait speed in Parkinson disease correlates with cholinergic degeneration

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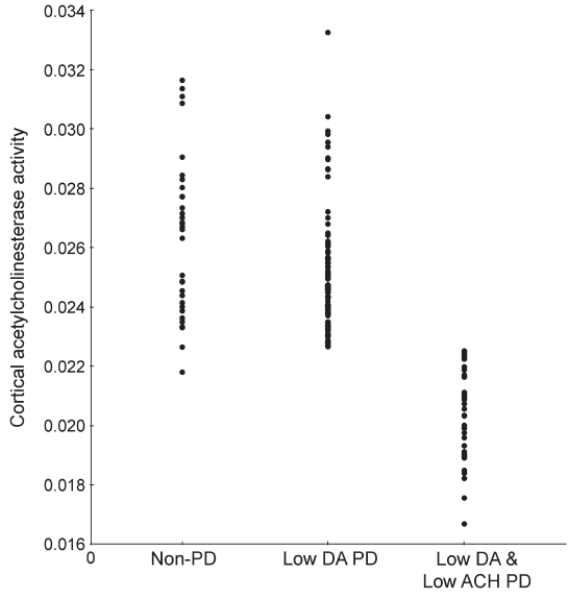
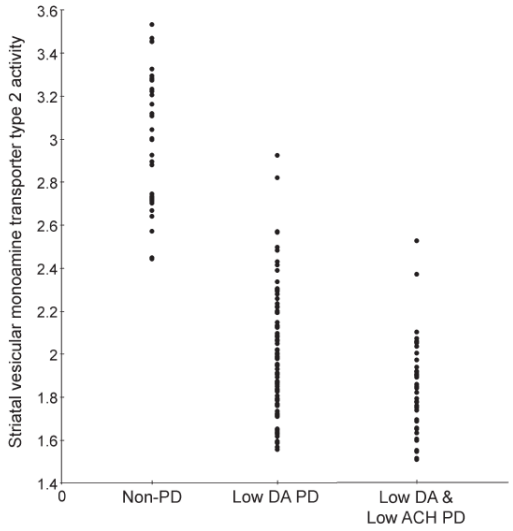
Figure 1 Distribution of cortical cholinergic innervation in the different groups



Group scatter plot of distribution of cortical acetylcholinesterase activity (k_3 hydrolysis rate, min^{-1}) in non-Parkinson disease control (Non-PD), relatively isolated dopamine (Low DA PD), and combined DA and acetylcholine (Low DA & Low ACH PD) degeneration PD groups.

Figure 2 Distribution of nigrostriatal dopaminergic innervation in the different groups



Group scatter plot of distribution of striatal vesicular monoamine type 2 distribution volume ratio in non-Parkinson disease control (Non-PD), relatively isolated dopamine (Low DA PD), and combined DA and acetylcholine (Low DA & Low ACH PD) degeneration PD groups. Although 7 subjects with PD had average striatal binding values in the low normal range, these subjects had evidence of more posterior putaminal dopaminergic denervation patterns consistent with the diagnosis of PD.

Table 2 Mean absolute gait speed (±SD) in the non-PD control, relatively isolated DA, and combined DA and ACh degeneration PD groups

Outcome variable	Non-PD control group (n = 32)	Relatively isolated DA degeneration but normal-range ACh activity PD group (n = 87)	Combined DA and ACh degeneration PD group (n = 38)
Gait speed, m/s	1.17 ± 0.18 (1.09)[a]	1.12 ± 0.20 (1.11)[a]	0.97 ± 0.2 (1.00)

Abbreviations: ACh = acetylcholine; DA = dopamine; PD = Parkinson disease.
Mean gait speed values adjusted for covariate effects of nigrostriatal denervation, sex, age, and global cognition are shown in parentheses.
[a] These subgroup means are not significantly different. Duncan post hoc testing was performed to assess for differences among subgroups.

- Comorbid cortical cholinergic denervation is a more robust marker of slowing of gait in PD than nigrostriatal denervation alone.
- Gait speed is not significantly slower than normal in subjects with PD with relatively isolated nigrostriatal denervation

Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease

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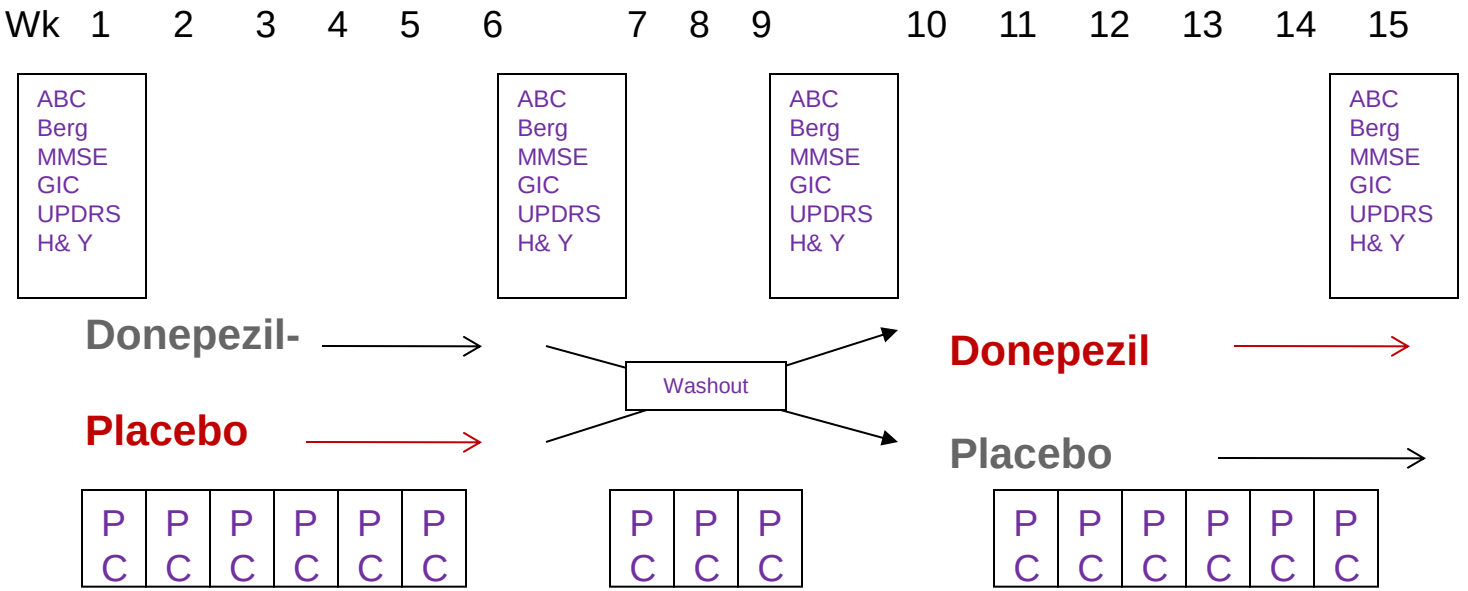
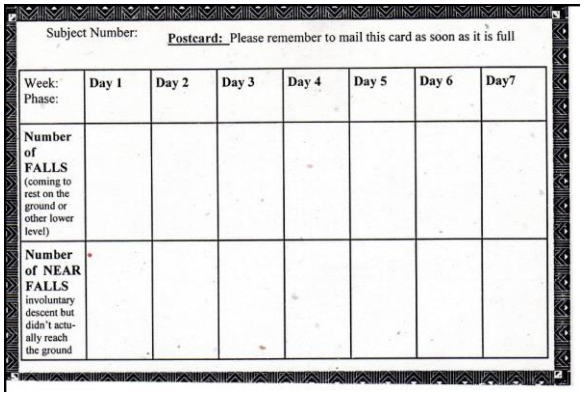
Neurology 75 October 5, 2010

•5 mg qam weeks 1-3, 10 mg qam weeks 3-6.
• 3 week washout between phases
•Primary Outcome: Fall frequency recorded daily on postcards, mailed weekly





Subject Number: **Postcard:** Please remember to mail this card as soon as it is full

Week: Phase:	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day7
Number of FALLS (coming to rest on the ground or other lower level)							
Number of NEAR FALLS involuntary descent but didn't actually reach the ground							

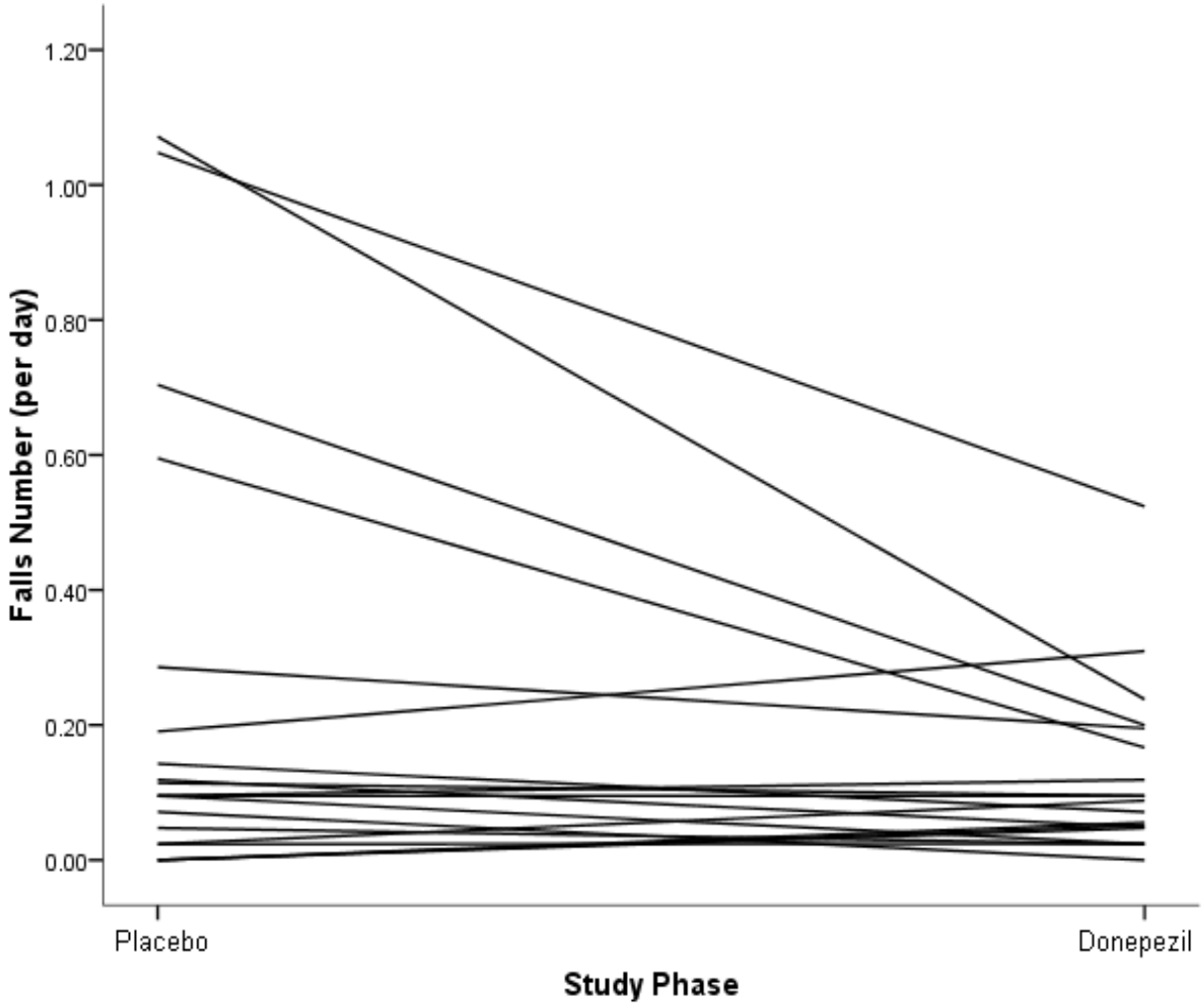
Study Procedures. PC = Postcard, ABC=Activities of Balance Confidence Scale, Berg=Berg Balance Scale, MMSE=Folstein Mini-Mental Status Examination, GIC= Global Impression of Change , UPDRS=motor Unified Parkinson Disease Rating Scale, H&Y= Hoehn and Yahr

BASELINE CHARACTERISTICS

	Mean (+/- SD)
Age (y)	68.3 (10.8)
Gender	15 M, 4 F
PD Duration (y)	10 (5.6)
UPDRS III	24.7 (8.6)
Hoehn & Yahr	3.2 (0.4)
Berg Balance	41.6 (7.4)
ABC Scale	51% (0.2)
Folstein MMSE	27.6 (4.5)

Four dropped out before the 2nd phase (2 on active drug, 1 on placebo, and 1 in washout) and were excluded from the analysis. Two additional subjects withdrew before the end of the second crossover period, but were included in the analysis, leaving 19 subjects in whom the primary outcomes were measured

CHANGE IN FALL FREQUENCY



DONEPEZIL IMPROVES FALLING FREQUENCY

	Treatment Phase		
Outcome Measurement (Means and SEM)	Donepezil	Placebo	*P**
Fall Frequency (Falls/day) ‡	0.13 (0.13)	0.25 (0.34)	0.049
Near-Fall Frequency (Near falls/day) ‡	2.50 (4.1)	2.04 (2.08)	0.27
Global Impression of Change	3.07 (0.32)	4.07 (0.32)	0.06€
Change in ABC Scale	3.6 % (0.04)	0.1 % (0.03)	0.58€
Change in Berg Balance	1.65(1.37)	1.91(1.67)	0.85€
Change in Motor UPDRS	1.06 (0.96)	0.5 (1.07)	0.57
Change in MMSE	0.17 (0.86)	0.92 (0.5)	0.36
DBS Group (Fall Frequency) (n=6)	0.10 (0.03)	0.20 (0.21)	0.17€

Mean (SEM)
* *Paired T-test unless otherwise noted*
€ *Wilcoxon Signed Ranks Test*

•Of the 4 subjects who dropped out early before phase II, 2 did so because of side effects of the study medication (1 while on active drug due to intractable insomnia, 1 on placebo).
•Side effects such as nausea, abnormal sweating, insomnia, headache, poor appetite or weight loss were noted in 35% on donepezil, but were mild or transient in most.
•One subject dropped out early because of perceived benefit during the first phase, subsequent worsening during the washout and refusal to submit to the second phase. This subject was on active drug during the first phase.
•Interestingly, no fractures or other serious adverse events occurred during the course of this study despite nearly 200 falls.

CONCLUSIONS

Subjects with PD fall about half as often when administered a cholinesterase inhibitor. The benefit appears to occur in a proportion of subjects who are "responders". The mechanism of this benefit is unknown, but warrants further study.

UNILATERAL PEDUNCULOPONTINE STIMULATION IMPROVES FALLS IN PARKINSON'S DISEASE. ELENA MORO, CLEMENT HAMANI, YU-YAN POON, ET AL. BRAIN (2010) 133; 215–224

Table 2 Comparison between data obtained in off stimulation and on stimulation condition (and off and on medication) during the double-blind assessment in six patients after 3 and 12 months of continuous PPN stimulation

	Medication OFF						Medication ON					
	Stim off		Stim on		P-value		Stim off		Stim on		P-value	
	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo
UPDRS-II Total	16.7 ± 3.7	21.3 ± 5.4	15.6 ± 5.9	19.9 ± 6.0	0.59	0.10	9.2 ± 3.3	9.7 ± 2.5	7.8 ± 2.8	9.5 ± 2.5	0.17	0.98
Falling (item 13)	1.3 ± 0.8	1.2 ± 1.0	1.0 ± 0.9	0.8 ± 0.9	0.56	0.31	0.8 ± 0.7	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.5	0.17	0.98
Freezing (item 14)	2.0 ± 1.0	2.5 ± 0.5	1.0 ± 0.9	2.0 ± 1.0	0.10	0.17	1.0 ± 1.0	1.0 ± 1.0	0.7 ± 0.8	0.3 ± 0.5	0.89	0.78
UPDRS-III Total	33.8 ± 7.4	34.5 ± 4.4	32.1 ± 8.6	34.1 ± 8.5	0.58	0.91	17.9 ± 6.8	13.5 ± 17.6	19.7 ± 10.5	16.4 ± 8.0	0.71	0.46
Gait (item 29)	1.8 ± 0.7	2.0 ± 0.7	1.4 ± 0.7	2.0 ± 0.6	0.46	0.98	0.6 ± 0.5	0.9 ± 0.9	0.8 ± 0.7	0.3 ± 0.5	0.17	0.10
Balance (item 30)	1.5 ± 0.4	1.7 ± 1.0	1.2 ± 0.8	1.3 ± 1.0	0.34	0.27	1.0 ± 0.8	0.7 ± 0.8	1.2 ± 0.7	0.7 ± 0.8	0.15	0.65
Walking test time	23.25 ± 23.0	39.0 ± 34.8	14.8 ± 4.5	34.9 ± 29.1	0.50	0.83	10.8 ± 1.5	28.6 ± 43.4	11.7 ± 2.3	10.1 ± 1.4	0.31	0.14
Walking test steps	18.8 ± 13.3	21.9 ± 13.6	12.9 ± 3.9	17.4 ± 7.5	0.78	0.50	9.4 ± 1.4	9.7 ± 9.6	9.8 ± 1.5	9.1 ± 1.2	0.26	0.20
Contralateral tapping test	98.7 ± 18.6	90.3 ± 21.5	95.3 ± 17.5	90.2 ± 12.8	0.34	0.91	106.2 ± 17.1	101.0 ± 16.9	98.2 ± 12.9	106.7 ± 14.9	0.02	0.34

Scores are presented as mean (SD). Walking time is measured in seconds.

Table 3 Effects of unilateral PPN stimulation on UPDRS part II and subscores at baseline (before surgery), and after at 3 and 12 months of stimulation OFF medication

Patient no.	UPDRS-II total score				UPDRS-II item 13 (falling)				UPDRS-II item 14 (freezing when walking)			
	Preoperative	3 months	12 months	P-value	Preoperative	3 months	12 months	P-value	Preoperative	3 months	12 months	P-value
1	24.5	16	15		4	0	0		3	0	1	
2	22	5	27		2	0	1		3	0	3	
3	20	16	20		3	2	2		2	2	2	
4	25	15	25		3	1	2		2	1	2	
5	28	23	23		3	1	0		3	1	2	
6	22	19	13		2	2	0		3	2	2	
	23.6 (2.8)	15.6 (5.9)	19.9 (6.0)	0.02* 0.2**	2.8 (0.7)	0.9 (0.8)	0.8 (0.9)	0.04* 0.02**	3.0 (1.0)	1.0 (0.9)	2.0 (1.0)	0.04* 0.10**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline.

*****There was no significant difference in the double-blinded on versus off stimulation UPDRS scores after 3 or 12 months of continuous stimulation and no improvements compared to baseline. Subjects reported a significant reduction in falls in the ON and OFF med states both at 3 and 12 months after PPN-DBS as captured in the UPDRS part II (ADL) scores.**

Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial

Emily J Henderson, Stephen R Lord, Matthew A Brodie, Daisy M Gaunt, Andrew D Lawrence, Jacqueline C T Close, A L Whone, Y Ben-Shlomo**

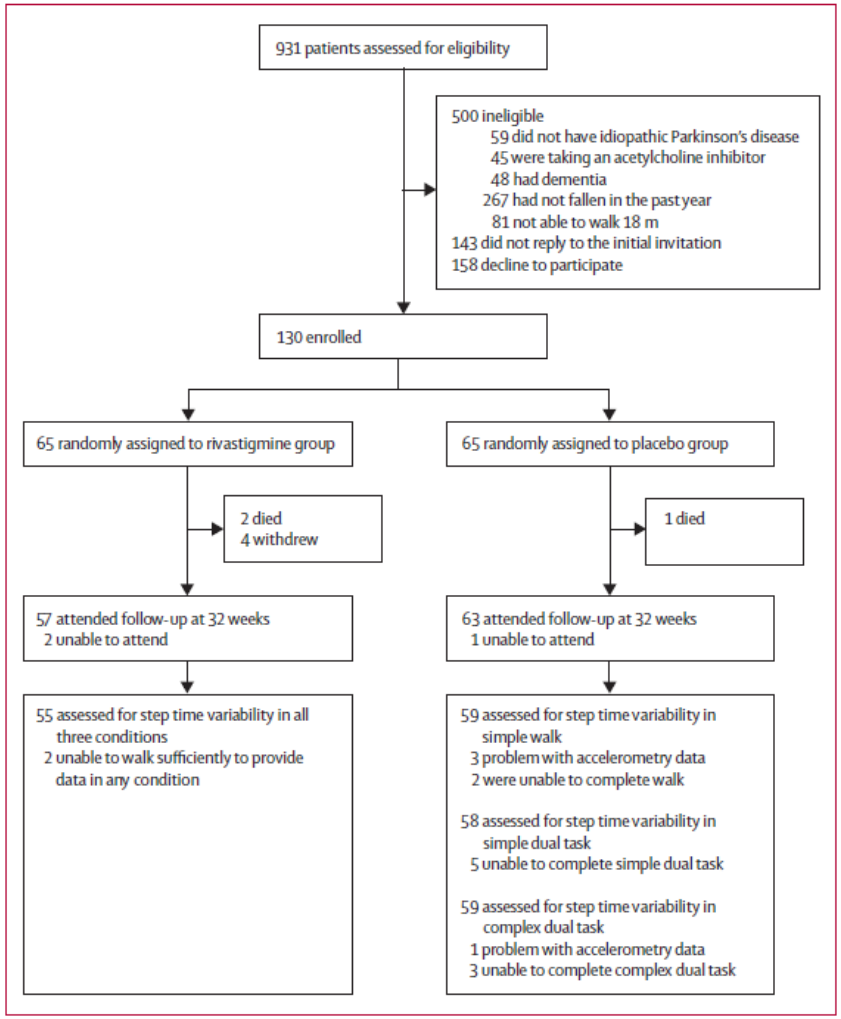


Figure 1: **Trial profile**

	Placebo group (n=59)	Rivastigmine group (n=55)	Unadjusted GMR (95% CI)	Adjusted* GMR (95% CI)	SE	p value	Reduction (%)
Normal walk†	0·064 s (0·114); 0·027 s (0·019–0·054)	0·043 s (0·044); 0·023 s (0·016–0·049)	0·83 (0·60–1·15)	0·72 (0·58–0·89)	0·076	p=0·002	28%
Simple cognitive task plus walk†	0·122 s (0·231); 0·060 s (0·034–0·114)	0·111 s (0·199); 0·042 s (0·025–0·145)	0·85 (0·59–1·23)	0·79 (0·62–0·99)	0·093	p=0·045	21%
Complex cognitive task plus walk	0·161 s (0·238); 0·078 s (0·040–0·162)	0·145 s (0·221); 0·065 s (0·031–0·167)	0·86 (0·58–1·27)	0·81 (0·60–1·09)	0·122	p=0·17	19%

Data for step time variability given in seconds (s) and are mean (SD); median (IQR). *Adjusted for centred age, centred baseline cognition (MoCA score), centred log baseline step time variability of condition, and previous falls categorised as (1, 2–3, 4–6, 7–19, ≥20). †n=58 for placebo group. GMR=Geometric mean ratio.

Table 2: **Step time variability at 32 weeks (primary outcome)**

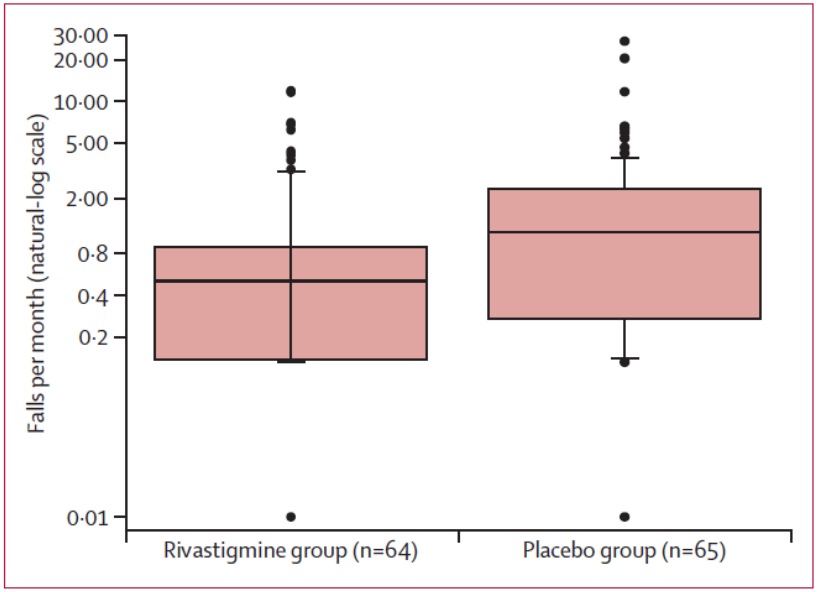


Figure 2: **Crude fall rate by treatment group**
Box and whisker plot shows median (line) and IQR (box); upper and lower whiskers represent the 15th to 85th centiles. Values above and below whiskers plotted separately (dots), but we excluded one extreme outlier. 18 participants (nine in each group) had a fall rate of zero and were assigned an arbitrary value of 0·01 on the log scale; dots for these participants are superimposed.

	Placebo group	n	Rivastigmine group	n	Unadjusted difference between groups (95% CI)	Adjusted difference* between groups (95% CI)	p value
Falls							
Falls per month	2·4 (4·40)	65	1·4 (2·47)	65	0·60† (0·37–0·96)	0·55† (0·38 to 0·81)	0·002
PPA falls risk score	2·2 (2·0)	63	2·2 (1·1)	57	0·95‡ (0·65 to 1·38)	0·97‡ (0·67 to 1·39)	0·85
Fear of falling (ICON-FES)	24·9 (5·6)	63	23·8 (7·9)	58	−1·10‡ (−3·55 to 1·36)	−0·25‡ (−2·03 to 1·53)	0·78
Gait speed (m/s)							
Normal walk	0·99 (0·33)	58	1·08 (0·29)	55	0·08§ (−0·03 to 0·20)	0·11§ (0·04 to 0·18)	0·003
Walk plus simple cognitive task	0·74 (0·30)	58	0·79 (0·33)	55	0·05§ (−0·07 to 0·17)	0·08§ (0·00 to 0·16)	0·037
Walk plus complex cognitive task	0·66 (0·29)	59	0·71 (0·32)	55	0·05§ (−0·06 to 0·17)	0·08§ (0·00 to 0·16)	0·048
Controlled leaning balance score							
Low (good performance)	7 (12%)	58	18 (36%)	50	Ref	Ref	..
Medium	17 (29%)	58	12 (24%)	50	0·27¶ (0·09 to 0·86)	0·11¶ (0·02 to 0·57)	0·008
High	19 (33%)	58	8 (16%)	50	0·16¶ (0·05 to 0·54)	0·08¶ (0·01 to 0·53)	0·009
Very high (poor performance)	15 (26%)	58	12 (24%)	50	0·31¶ (0·10 to 1·00)	0·19¶ (0·03 to 1·26)	0·085
Freezing							
FOG episode in past month	48 (76%)	63	36 (63%)	57	0·54‖ (0·24 to 1·18)	0·46‖ (0·13 to 1·60)	0·22
New freezing of gait score if history of freezing	16·1 (4·4)	48	15·8 (4·4)	34	−0·29‡ (−2·25 to 1·67)	0·34‡ (−1·11 to 1·79)	0·64
Cognitive and mood measures							
Cognition (MoCA score)	24·3 (3·8)	63	24·1 (3·9)	57	1·01‡ (0·93 to 1·09)	0·99‡ (0·93 to 1·06)	0·78
Executive function (Frontal Assessment Battery score)	14·2 (3·3)	63	14·6 (2·7)	57	0·95‡ (0·78 to 1·15)	0·95‡ (0·81 to 1·12)	0·57
Mood (Geriatric Depression Scale score)	4·7 (3·0)	63	5·0 (3·7)	58	1·00‡ (0·80 to 1·24)	0·98‡ (0·80 to 1·19)	0·83
Cognitive failures questionnaire score	38·9 (14·6)	63	40·3 (14·2)	58	1·40§ (−3·79 to 6·59)	1·90§ (−1·28 to 5·09)	0·24
Disease measures							
MDS-UPDRS	95·5 (28·2)	63	87·2 (29·7)	57	−8·28§ (−18·76 to 2·20)	−3·29§ (−9·59 to 3·02)	0·30
Levodopa requirement							
Very low (<550 mg per day)	10 (17%)	59	18 (33%)	55	Ref	Ref	..
Low (551–889 mg per day)	16 (27%)	59	12 (22%)	55	0·42¶ (0·14 to 1·22)	1·42¶ (0·26 to 7·79)	0·68
Moderate (900–1244 mg per day)	14 (24%)	59	15 (27%)	55	0·60¶ (0·21 to 1·72)	5·20¶ (0·63 to 42·81)	0·13
High (≥1245mg per day)	19 (32%)	59	10 (18%)	55	0·29¶ (0·10 to 0·87)	2·22¶ (0·19 to 26·06)	0·53
Quality of life							
Quality of life (EQ-5D-5L) Index score	0·663 (0·19)	63	0·657 (0·21)	58	−0·006§ (−0·078 to 0·066)	0·007§ (−0·051 to 0·066)	0·82
Quality of life (EQ-5D-5L) VAS score	63 (18)	63	66 (16)	58	3·7§ (−2·5 to 10·0)	5·5§ (−0·2 to 11·2)	0·058

Outcome data are mean (SD) or n (%). MoCA=Montreal Cognitive Assessment. VAS=visual analogue score. PPA=Physiological Profile Assessment. MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale. ICON-FES=Iconographical Falls Efficacy Scale. FOG=freezing of gait. * Adjusted for baseline outcome, centred age, centred baseline cognition (MoCA score), centred baseline log step time variability during normal walking, and previous falls (categorised as 1, 2–3, 4–6, 7–19, ≥20). †Incidence rate ratio (negative binomial regression model). ‡Geometric mean ratio. §Mean difference. ¶Relative risk ratio. ‖Odds ratio.

Table 3: **Secondary outcomes**

IMPACT OF RIVASTIGMINE ON COGNITIVE DYSFUNCTION AND FALLING IN PARKINSON'S DISEASE PATIENTS

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The purpose of this study was to observe the incidence of falls in Parkinson's disease (PD) patients with different cognitive levels and to investigate the effect of the cholinesterase inhibitor Rivastigmine on cognitive dysfunction and falling in Parkinson's disease patients.

N=176

MoCA

NCI, MCI PDD

MCI /PDD randomized to placebo or rivast

Change in cognition and fall incidence = outcomes

Table 2 Comparison of the incidence of falls of patients in PD-NCI and PD-CI groups

Group	*n*	Number of falls per person（year）	Incidence of falls	OR	95% CI	*P*
PD-NCI group	87	1.66±1.55	19（24.1%）			
PD-MCI group	54	$3.22\pm1.43^{\Delta}$	21（43.8%）$^{\alpha}$	2.46	1.14-5.30	<0.01
PDD group	35	$4.58\pm2.09^{*\gamma}$	21（63.6%）$^{\beta\delta}$	5.53	2.30-13.28	<0.01

Compared to the PD-NCI group $^{\Delta}P$ <0.01, $^{*}P$ <0.001, $^{\alpha}P$ <0.01, $^{\beta}P$ <0.01; compared to the PD-MCI group $^{\gamma}P$ <0.01, $^{\delta}P$ <0.01;

Table 5 Comparison of the incidence of falls of patients in the Rivastigmine treatment and placebo groups

Compared to the placebo group $^{\Delta}P < 0.01$

Group	*N*	Number of falls per person （year）	Incidence of falls	OR	95% CI	*P*
Treatment group	41	1.82±1.99$^{\Delta}$	13（31.7%）	0.310	0.12-0.77	<0.01
Placebo group	40	4.26±1.63	24（60.0%）			

OLFACTION

Simple odor detection→ peripheral olfactory system

Identification and discrimination→central olfactory structures and requires higher-order cognitive control

The pathophysiology of olfactory dysfunction in PD is poorly understood.

- odor identification changes suggest in part impairment in odor memory, possibly due to hippocampal dysfunction.

Olfactory dysfunction occurs also in Alzheimer's disease (AD) and increases with severity of dementia.

Bohnen et al (2013) : multi-tracer PET scans

odor identification deficits (ie worse UPSIT) are best predicted by cholinergic denervation *and to a lesser extent by dopaminergic denervation (hippocampus).

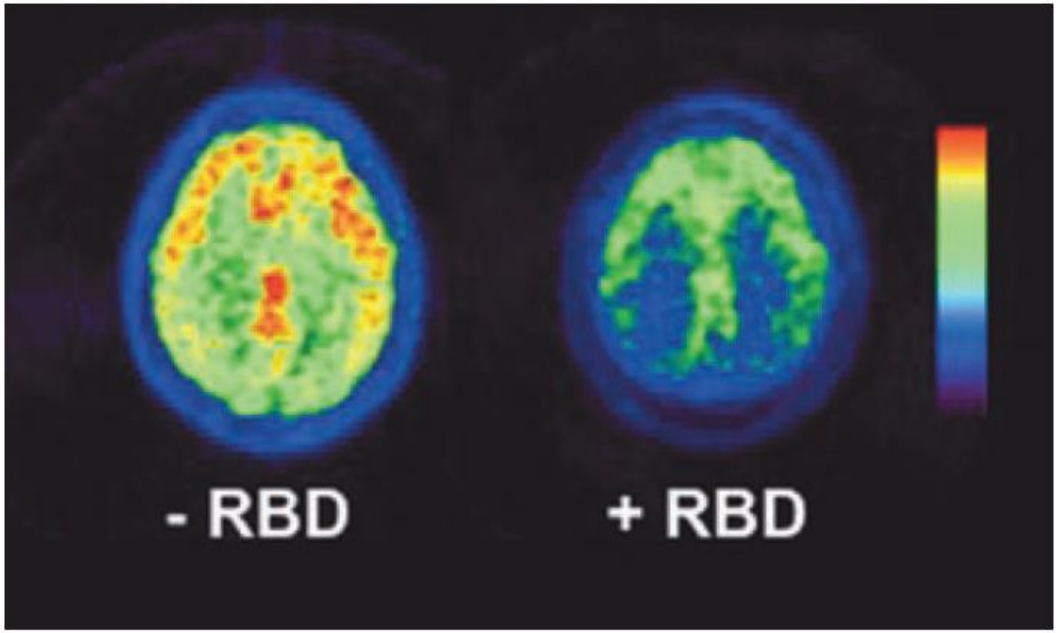
*** Lower limbic and cortical AChE activity, with limbic cholinergic denervation being the most significant predictor of hyposmia**

REM SLEEP BEHAVIOR DISORDER

Loss of normal atonia during sleep (“acting out of dreams”) is common in PD

A common cholinergic mechanism may exist between RBC and increased risk of dementia in PD.

34% of 80 nondemented PD subjects had RBD symptoms underwent dual AChE and dopaminergic PET studies. Those with RBD had decreased cholinergic innervation in the neocortex, limbic cortex, and thalamus



- This imaging study of 80 nondemented PD subjects indicates that RBD symptoms are associated preferentially with degeneration of brain cholinergic systems

TABLE 3: Mean ± SD Neocortical, Limbic Cortical, and Thalamic AChE Hydrolysis Rates (k3; min^{-1}), and Striatal VMAT2 DVR in Patients with and without Symptoms of RBD

PET Methods	PD with RBD sx, n = 29	PD without RBD sx, n = 55	Statistical Significance
Neocortical AChE k3	0.0213 ± 0.0018	0.0236 ± 0.0022	$t = 4.55$, $p < 0.0001$[a]
Limbic cortical AChE k3	0.0388 ± 0.0029	0.0423 ± 0.0058	$t_{approx} = 2.85$, $p = 0.0056$[a]
Thalamic AChE k3	0.0388 ± 0.0025	0.0427 ± 0.0042	$t_{approx} = 4.49$, $p < 0.0001$[a]
Putamen DTBZ DVR	1.7793 ± 0.2266	1.8206 ± 0.2981	$t = 0.63$, $p = 0.53$
Caudate DTBZ DVR	1.9689 ± 0.3216	2.0189 ± 0.3911	$t = 0.57$, $p = 0.57$
Raphe nucleus DASB DVR	2.8361 ± 0.3081 (n = 11)	2.8002 ± 0.3623 (n = 24)	$t = -0.28$, $p = 0.77$
Striatal DASB DVR	2.2771 ± 0.1522 (n = 11)	2.3014 ± 0.2061 (n = 24)	$t = 0.35$, $p = 0.72$

Mean ± SD raphe and striatal SERT DVR in the subset of patients who underwent [^{11}C]DASB SERT positron emission tomography imaging (n = 35). Student t values are presented with levels of significance. Satterthwaite's method of approximate t tests (t_{approx}) was used for comparison of groups with unequal variances.

[a]Statistically significant.

AChE = acetylcholinesterase; DASB = benzonitrile; DTBZ = [^{11}C]dihydrotetrabenazine; DVR = distribution volume ratio; PD = Parkinson disease; RBD = rapid eye movement sleep behavior disorder; SD = standard deviation; SERT = serotonin transporter; sx = symptoms; PET = positron emission tomography.

From Kotagal et al 2012 Annals of Neurology *Symptoms of Rapid Eye Movement Sleep Behavior Disorder are Associated with Cholinergic Denervation in Parkinson Disease*

SUMMARY

- **Increasing interest in clinical effects of cholinergic dysfunction in PD**
  - Basal forebrain
  - tegmental pedunculopontine projections
- **Cognition**
- **Olfaction**
- **REM behavior disorder**
- **Gait and balance**
  - Frequent falling is associated with impaired PPN integrity
  - In primates, cholinergic lesioning confirms role of PPN in posture and mobility impairment
  - Basal forebrain cholinergic projection degeneration correlates with decreased walking speed