Parkinson's disease Dementia Clinical Features and Treatments

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JAN 22nd 2015

Objectives

- To review the clinical features of cognitive impairment in PD

- To review treatment options for cognitive problems.

Neuropsychiatric symptoms in PD

a) Mood:

Anxiety, Depression, irritability, panic attacks, apathy, fatigue

b) Psychotic symptoms;

Euphoria, agitation, hallucinations, delusions, paranoia

c) Cognitive dysfunction:

Dementia; Mild cognitive impairment (MCI)

Neuropsychiatric manifestations in Parkinson's Disease are a major cause of morbidity.

14,354 Medicare beneficiaries with YOPD……Compared to the general population of medically disabled Americans, those with **YOPD were more likely to receive medical care** for

- **depression** (OR: 1.89, 1.83-1.95),
- **dementia** (OR: 7.73, 7.38-8.09),
- substance abuse/dependence (OR: 3.00, 2.99-3.01)
- **psychosis** (OR: 3.36, 3.19-3.53),
- personality/impulse control disorders (OR: 4.56, 3.28-6.34)
- **psychosocial dysfunction** (OR: 3.85, 2.89-5.14).

Willis et al Parkinsonism and Related Disord 2013 Feb;19(2):202-6.

PD Dementia

- Dementia is common
- Affects 30- 80% of advanced PD.

Hely MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord 2008;23:837-844.

Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. J Neurol Sci 2010;289(1-2):18-22.

Dementia as Milestone marker of PD progression

- **Four 'milestones' in progression of PD**

1. Falls ……
2. Hallucinations
3. Dementia
4. Nursing home care

Once milestone is reached the average time to death is the same – about 5y regardless of age-of-disease onset

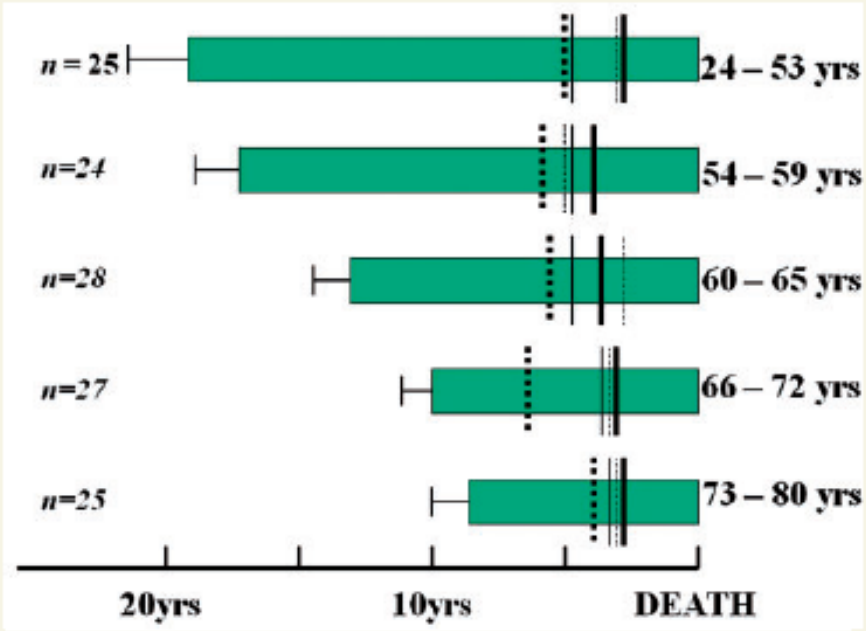


Figure 2 Disease course and disability milestones for five age-at-onset groups. Disease courses aligned for time of death. Same milestone legend as Fig. 1. Error bars show the standard error of the mean disease duration.

Kempster PA, et al Brain 2010;133:1755-1762.

What is Dementia in PD?

- **Gradual cognitive decline within the context of Parkinson Disease**
  - Decline in function
    - what was (premorbid) baseline?
  - Heterogeneous cognitive domains affected
    - Executive function; attention, learning and memory, verbal fluency, visuospatial abilities
    - > 1 domain affected
    - Severe enough to impact Activities of Daily Living

Diagnostic Criteria for PDD

TABLE 2. Criteria for PDD[4]

	Core Features	Associated Features	Exclusions
Probable PDD	1. PD diagnosis	1. Typical cognitive deficits in two of four domains (attention, executive function, visuospatial function, and free recall)	1. Vascular disease on imaging or other abnormality that may cause cognitive impairment, but not dementia
	2. Slowly progressive dementia syndrome	2. At least one behavioral symptom (apathy, depression/anxious mood, hallucinations, delusions, or excessive daytime sleepiness)	2. Unknown time interval between motor and cognitive symptoms
			3. Acute confusion resulting from systemic diseases or abnormalities or drug intoxication
			4. Features compatible with probable vascular dementia

Emre et al Mov Disord 2007;22:1689-1707

Mild Cognitive Impairment (MCI)

- Definition

1) A complaint of cognitive dysfunction

2) Scores of at least 1.5 standard deviations below the age-corrected mean on one or more core psychological tests

3) No significant *functional* impairment as a result of cognitive deficit

- Affects 15 - 30% of early PD patients

FEATURED ARTICLE CME

Diagnostic Criteria for Mild Cognitive Impairment in Parkinson's Disease: *Movement* Disorder Society Task Force Guidelines

Irene Litvan, MD,[1]* Jennifer G. Goldman, MD, MS,[2] Alexander I. Tröster, PhD,[3] Ben A. Schmand, PhD,[4] Daniel Weintraub, MD,[5] Ronald C. Petersen, MD, PhD,[6] Brit Mollenhauer, MD,[7] Charles H. Adler, MD, PhD,[8] Karen Marder, MD,[9] Caroline H. Williams-Gray, MRCP, PhD,[10] Dag Aarsland, MD, PhD,[11] Jaime Kulisevsky, MD, PhD,[12] Maria C. Rodriguez-Oroz, MD, PhD,[13] David J. Burn, MD, FRCP,[14] Roger A. Barker, BSc, MBBS, MRCP, PhD,[10] and Murat Emre, MD[15]

Litvan et al Mov Disord 2012;27:349-356

- Yarnall et el. Characterizing mild cognitive impairment in incident Parkinson disease; the ICICLE-PD Study : Neurology. 2014 28;82(4):308-16

How to assess cognitive function in PD

1. Cognitive Screening Tests

2. Neuropsychological Assessments

3. Research studies – Diagnostic Criteria/Imaging studies (Dr Monchi)

1. Cognitive Screening Tests

Scale name	Assessed cognitive domains	Approximate administration time
Mini-Mental State Examination (MMSE)	Orientation, verbal registration and recall, attention, naming and repetition, verbal comprehension, praxis, visuospatial	10 min
Montreal Cognitive Assessment (MoCA)	Orientation, attention, memory, naming, fluency, verbal repetition, visuospatial/executive	10 min
Addenbrooke Cognitive Examination (Revised) - ACE (R)	Attention/orientation, memory, fluency, language, visuospatial	20 min
Cambridge Cognitive Assessment (Revised) - CAMCOG (R)	Orientation, language, memory, attention, praxis, calculations, abstract reasoning, perception	25 min
Dementia Rating Scale (2nd edition)/Mattis Dementia Ratings Scale - DRS (2)	Attention, initiation/perseveration, construction, conceptualization, memory	30 min
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Attention, language, visuospatial/construction, Immediate memory, delayed memory	30 min
Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog)	Memory, language, praxis	30 min

Marras et al Mov Disor 2014;29:584-596

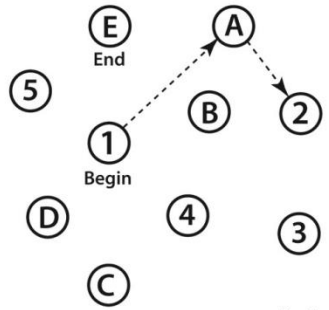
1. Cognitive Screening Tests

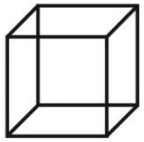
- MOCA is possibly better screen than MMSE
  - MoCA possibly better due to ability to detect executive dysfunction; a relative deficiency of the MMSE
- Quick screens?
  - ‘Incorrect hippo response’
  - ‘Pill questionnaire’
  - ‘Head-Turning Sign’

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE





Copy cube

[ ] [ ]

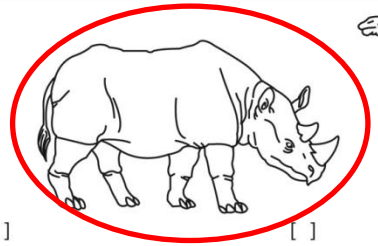
Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING

[ ]



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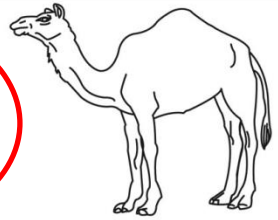


[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

www.mocatest.org
Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Incorrect response
= Hippo rather than Rhino

The incorrect ‘Hippo’ response can predict an abnormal MoCA

- 117 non-demented PD subjects
- 27 (23%) incorrectly responded “hippo” to the rhinoceros naming item on the MoCA
- “Hippo” responders scored significantly lower on the MoCA and MMSE.
- Poor scores on tasks requiring visuospatial and executive abilities across testing modalities.

Armstrong, Fox , Marras et al ParkRel Dis2013 The meaning of a "hippo" response on the Montreal Cognitive Assessment in Parkinson's disease.

The Pill Questionnaire in a Nondemented Parkinson's Disease Population

Movement Disorders, Vol. 27, No. 10, 2012

The physician rated each subject's ability to report medication on the Pill Questionnaire according to 1 of 5 categories:

1. The patient is able to spontaneously and clearly describe the drugs, doses, and timing of the treatment.
2a. The patient needs some help from the examiner but is successful without clinically pertinent errors, and the caregiver verifies that the patient can take the medications safely and reliably.
2b. The patient needs some help from the examiner, and the caregiver verifies that the patient cannot take medications safely and reliably.
2c. The patient needs some help from the examiner, and the caregiver does not know whether the patient can take medications safely and reliably.
3. The patient is unable to describe medications even with help from the examiner.

The Pill Questionnaire did **not show** sensitivity or specificity enough to be used as a single screen

However – inaccurate reporting is associated with deficits in many cognitive domains an should be an **'alerting factor'**

Head-Turning Sign

Head turning sign: pragmatic utility in clinical diagnosis of cognitive impairment

Table 1 Diagnostic parameters for head turning test (with 95% CIs)

	Whole cohort (N=207)	Cohort minus 'attended alone' (n=133)
Overall test accuracy	0.83 (0.77 to 0.88)	0.76 (0.69 to 0.83)
Sensitivity	0.60 (0.49 to 0.70)	0.63 (0.52 to 0.74)
Specificity	0.98 (0.95 to 1.00)	0.95 (0.89 to 1.00)
Positive predictive value	0.94 (0.88 to 1.00)	0.94 (0.88 to 1.00)
Negative predictive value	0.79 (0.72 to 0.85)	0.64 (0.54 to 0.75)
Diagnostic odds ratio	60.4 (19.5 to 187.3)	29.3 (9.62 to 89.2)
Positive likelihood ratio	24.9 (8.0 to 77.2)	11.5 (3.78 to 35.1)
Negative likelihood ratio	0.41 (0.13 to 1.28)	0.39 (0.13 to 1.20)
Clinical utility index +	0.56 (adequate)	0.59 (adequate)
Clinical utility index −	0.77 (good)	0.61 (adequate)

A J Larner *J Neurol Neurosurg Psychiatry* 2012;**83**:852–853.

PD-specific Cognitive Screens

TABLE 6. Parkinson's disease specific cognitive screening measures

Scale name	Assessed cognitive domains	Approximate administration time
Parkinson's Disease Dementia - Short Screen (PDD-SC)	Immediate and delayed verbal recall, alternating verbal fluency, visuospatial	7 min
Parkinson NeuropsychometricDementiaAssessment (PANDA)	Attention/working memory, immediate and delayed recall, alternating verbal fluency, visuospatial	10 min
Mini-Mental Parkinson (MMP)	Orientation, attention, fluency, visual registration, visual memory, set-shifting, conceptualization	15 min
Parkinson's Disease Cognitive Rating Scale (PD - CRS)	Attention, working memory, fluency (alternating and action), naming, visuospatial, immediate and delayed memory	15 - 25[a] min
Scales for Outcomes of Parkinson's Disease - Cognition (SCOPA - Cog)	Attention, memory, executive function, delayed recall, visuospatial	15 min

[a]in demented patients

- Longer to administer
- Not fully evaluated for reliability in PD, as yet

Marras et al Mov Disord 2014;29:584-596

2. Neuropsychological Assessments

1. Estimate of premorbid function/Intelligence
2. Language
3. Attention
4. Processing speed
5. Executive function
6. Learning and Memory
7. Visuo-spatial

- **Gold Standard**
  - Neuropsychology/Trained administrator
  - Long Time = 2h
  - Affected by:
    - Time of day
    - Medications
    - Co-morbidities - depression etc.

Symptoms that are often associated or preludes to cognitive decline in PD

- Depression and Anxiety
- Apathy
- Psychosis- visual hallucinations

Psychosis

- **Features**
  - **Vivid dreams/nightmares**
  - **Illusions**
  - **Hallucinations**
  - **Paranoid delusions**

Hallucinations in PD

- Visual most common
- Can affect up to 50% of PD patients
- Typically are well-formed hallucinations of people, animals, insects; Veridical
- Usually occur on going to sleep and on awakening
- Frequently stable, and chronic
- Rarely auditory; tactile

Parkinson's disease Dementia vs Dementia with Lewy Bodies

Parkinson's disease Dementia (PDD)

- *Later onset* dementia
- Occurs after many years of typical levodopa-responsive PD

Dementia with Lewy Bodies (DLB)

- *Early onset* dementia, before or within one year of motor symptoms
- *Fluctuations* with pronounced variations in attention and alertness
- Visual hallucinations ++
- Older age
- Autonomic symptoms ++
- REM sleep behavior disorder
- Very sensitive to drugs esp any neuroleptics

- Pathological- alpha synuclein deposition

- Cortical Lewy Body Disease (CLBD) = pathological term for extensive alpha synuclein deposition in cortex

	DLB	Alzheimer Disease	PD	PD Dementia
Extrapyramidal symptoms	Often more symmetric	Rare, usually mild in late stages	Initially often asymmetric	Initially often asymmetric
PIGD subtype	69%	-	38%	88%
- **TD subtype**	31%	-	62%	12%
Hypomimia	48.5%	4.2%		
- **Hypophonia**	30.8%	3.4%		
- **Rigidity**	44.6%	9.8%		
- **Impaired posture/gait**	43.1%	14.2%		
- **Bradykinesia**	55.4%	19.3%		
- **Impaired chair rise**	28.9%	15.4%		
- **Postural instability**	26.2%	12.5%		
- **Resting tremor**	13.9%	3.2%		
- **Action/postural tremor**	12.3%	6.2%		
Cognitive impairment	Early disturbances in attention & visuoperceptive functions	Early impairment of declarative memory & attention	Impaired executive and visuoperceptive functions	Impaired executive and visuoperceptive functions
Fluctuations in cognition	Prominent, early second to hourly variations	Moderate day to day variations	Mild day to day variations	Mild day to day variations
Neuropsychiatric symptoms				
Visual hallucinations	Typical, early & persistent	Sometimes, late course	Often present – drugs trigger	Often present – drugs trigger
Delusions	Typical	Usually present	Present	Present
Depression	Usually present	Usually present	Usually present	Usually present

Treating Cognitive problems in PD

RESEARCH ARTICLE

The *Movement* Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease

Klaus Seppi, MD,[1*] Daniel Weintraub, MD,[2] Miguel Coelho, MD,[3] Santiago Perez-Lloret, MD, PhD,[4] Susan H. Fox, MRCP (UK), PhD,[5] Regina Katzenschlager, MD,[6] Eva-Maria Hametner, MD,[1] Werner Poewe, MD,[1] Olivier Rascol, MD, PhD,[4] Christopher G. Goetz, MD,[7] and Cristina Sampaio, MD, PhD[8*]

Movement Disorders, Vol. 26, No. S3, 2011

UPDATED: 2013:

Treatments for Non-Motor Symptoms of PD

http://www.movementdisorders.org/publications/ebm_reviews

Canadian Guidelines on Parkinson's Disease

Can J Neurol Sci. 2012;39: Suppl 4: S1-20;

Randomized Controlled Trials in PDD

Cholinesterase inhibitors (daily dose)	Outcome vs. placebo (n receiving active) (duration)	Refs
Donepezil (2.5 – 10mg)	**POSITIVE** MMSE, NEGATIVE CIBIC (n = 14) (10w) **POSITIVE** DRS (n = 16) ; (18w) NEGATIVE ADaSCog ; **POSITIVE** MMSE ((n = 22); (10w) NEGATIVE ADASCog /CGI ; **POSITIVE** MMSE ; (n = 550) (24 w)	Aarsland et al 2002 Leroi et al 2004 Ravina et al 2005 Dubois et al 2012
Rivastigmine (3 – 12mg)	**POSITIVE** (ADCS-CGI and ADASCog (n = 541) (24 w)	Emre et al 2004

Glutamate antagonists	Outcome vs. placebo (n receiving active) (duration)	References
Memantine (10 – 20 mg)	NEGATIVE DRS, MMSE (n = 25) **POSITIVE** CGI (n = 72) **POSITIVE** ADCS-CGIC in DLB not PDD (n = 195)	Lerois et al 2009 Aarsland et al 2009 Emre et al 2010

Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (Review)

Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD006504.

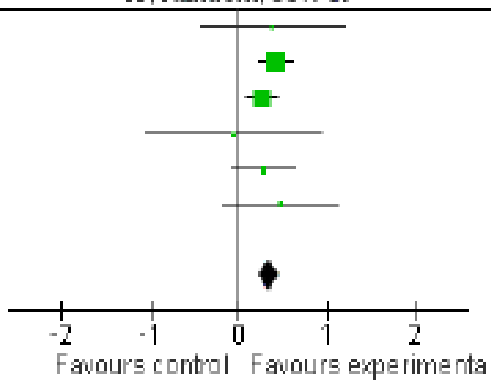
Rolinski M, Fox C, Maidment I, McShane R

- **6 Trials using Donepezil, Rivastigmine; n = 1236 subjects**

Figure 2. Forest plot of comparison: 2 Cognitive function, outcome: 2.3 Combined: MMSE or ADASCog.

Study or Subgroup	Cholinesterase Inhibitor Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Aarsland 2002a	22.8	3.7	12	21	5	12	2.1%	0.40 [-0.41, 1.20]
Dubois 2007	3.01	6.26	377	0.3	6.5	173	42.3%	0.43 [0.25, 0.61]
Emre 2004	0.8	3.8	335	-0.2	3.5	166	40.0%	0.27 [0.08, 0.46]
Leroi 2004	25.33	3.78	7	25.56	3.75	9	1.4%	-0.06 [-1.05, 0.93]
Mckeith 2000	0.67	4.26	59	-0.57	4.26	61	10.8%	0.29 [-0.07, 0.65]
Ravina 2005	24.5	3.2	19	22.5	4.7	19	3.3%	0.49 [-0.16, 1.13]
Total (95% CI)			**809**			**440**	**100.0%**	**0.34 [0.23, 0.46]**

Heterogeneity: Tau² = 0.00; Chi² = 2.34, df = 5 (P = 0.80); I² = 0%
Test for overall effect: Z = 5.70 (P < 0.00001)

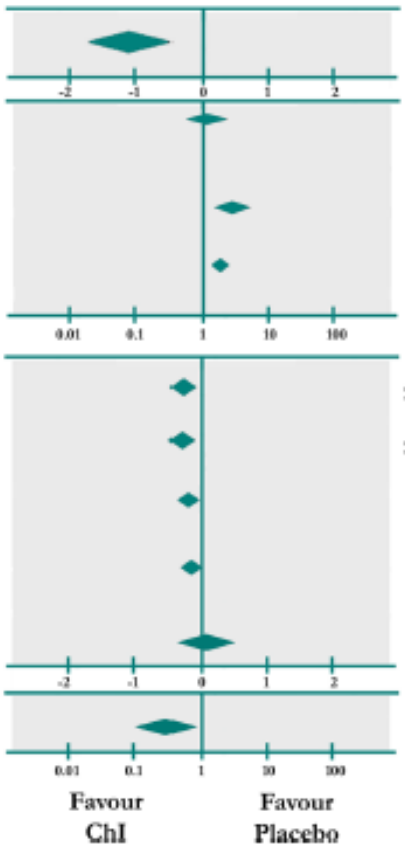


AEs more common in rivastigmine groups
= Nausea and vomiting

Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis

Gennaro Pagano,[1,2] Giuseppe Rengo,[3] Giuseppe Pasqualetti,[4] Grazia Daniela Femminella,[2] Fabio Monzani,[4] Nicola Ferrara,[2,3] Michele Tagliati[5]

	Participants ChI	Participants Placebo	Studies	Effect size (95% CI) random	p value	Heterogeneity I^2
A						
Primary end-points						
Efficacy						
MMSE decline	588	394	1, 2, 3, 4	MD -1.12 [-1.64 to -0.61]	0.001	44.6%
Falls	33/524	24/349	1, 3, 4	OR 1.13 [0.62 to 2.07]	0.681	0%
Safety						
Tremor	50/494	12/340	1, 4	OR 2.81 [1.513 to 5.578]	0.001	0%
B Adverse drug reactions	345/564	156/372	1, 2, 4	OR 1.860 [1.330 to 2.601]	<0.0001	0%
Secondary end-points						
Efficacy						
ADAScog	565	372	1, 2, 4	SMD -0.266 [-0.399 to -0.133]	<0.0001	0%
Global assessment	587	393	1, 2, 3, 4	SMD -0.287 [-0.423 to -0.151]	<0.0001	0%
Behavioural disturbances	565	372	1, 2, 4	SMD -0.152 [-0.285 to -0.019]	0.025	0%
Disability	544	352	1, 4	SMD -0.134 [-0.270 to -0.002]	0.053	38.5%
Safety						
UPDRS score part 3	43	41	2, 3	SMD 0.054 [-0.374 to 0.482]	0.805	0%
Deaths	5/560	12/360	1, 2, 4	OR 0.295 [0.108 to 0.806]	0.017	0%



Pagano G, *et al. J Neurol Neurosurg Psychiatry* 2014;**0**:1–7.

Safety and tolerability of cholinesterase inhibitors?

- **ECG before starting**
  - risk of prolonged QTc interval

- **Nausea** and **vomiting**
  - up to 30% of patients
  - Rivastigmine patch may be better tolerated

Safety and tolerability of cholinesterase inhibitors?

- **Worsening of Parkinsonism?**
  - More patients on rivastigmine vs. placebo reported **tremor** as an AE but **not UPDRS III**
    - » Rolinski et al Cochrane Review 2012

  - Open label safety study of rivastigmine oral vs patch for 76 w in PD dementia
    - Tremor = 24% oral vs 10% patch
    - No significant worsening of motor UPDRS in both
    - Discontinuation rate due to worse motor scores 2% in both
      - » Emre et al Clin Neuropharm 2014

Conclusions: PD Dementia Treatments

- Interventions assessed in MDS EBM Reviews -

Cholinesterase inhibitors	Practice implications
Donepezil	Possibly useful
Rivastigmine	Clinically useful
Galantamine	Possibly useful
Glutamate antagonists	**Practice implications**
Memantine	Possibly useful

CANADIAN NEUROLOGICAL SCIENCES FEDERATION
FÉDÉRATION DES SCIENCES NEUROLOGIQUES DU CANADA
The journal
Canadian Journal of Neurological Sciences
Volume 39 Number 4 (Supplement 4) July 2012

Canadian Guidelines on Parkinson's Disease

C71 Discontinue potential aggravators;

- Anticholinergics. EFNS level B
- Amantadine, tricyclic antidepressants, benzodiazepines, tolterodine and oxybutynin. EFNS Level C

C72 Donepezil should be considered for the treatment of dementia in PD. AAN Level B

C73 Rivastigmine should be considered for the treatment of dementia in PD or Dementia with Lewy Bodies. AAN Level B

Treatments for PD-MCI?

Therapy	Mechanism of action	Studies
Donepezil	**Cholinesterase inhibitor**	(MUSTARDD-PD (NCT01014858)- suspended due to low recruitment). DASH-PD in Japan; recruiting early PD subjects and following over 3y
Rivastigmine		Ongoing study using patch (NCT01519271)
Galantamine	**+ Allosteric modulator of nicotinic cholinergic receptors**	Negative DBRCT in non-demented PD (Grace et al 2009)
Rasagiline	**Mono amine oxidase B inhibitor (MAOB-I)**	Positive on attention and verbal fluency (Hanagasi et al 2011) NCT01723228 and NCT01497652 - ongoing
Safinamide	**MAOB-I/Glutamate release inhibition**	Ongoing study (NCT01211587)
Atomoxetine	**Noradrenaline and serotonin re-uptake inhibitor**	Ongoing study vs donepezil for attention in non-demented PD (NCT01340885) Ongoing vs placebo in PD MCI (NCT01738191)
Cognitive Speed Training		NCT01646333; NCT01393353; NCT02225314 - ongoing Positive outcomes in non-demented PD (Edwards et al 2013)

Management of PD Psychosis

Table 2: Evaluation of Acute PD Psychosis

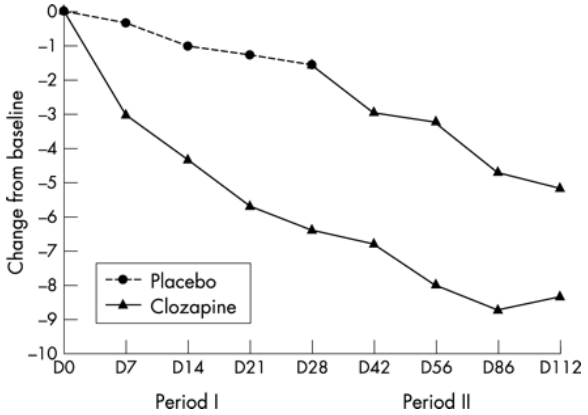
Differential Diagnosis

P -	Parkinson's disease medications
SY -	Systemic illness
C -	Centrally acting medication
H -	Hepatic, renal, or other metabolic dysfunction
O -	Overdose of medications or intoxication
S -	Sensory deprivation (hearing, visual impairment)
I -	Infection (urinary tract infection, pneumonia)
S -	Structural lesions (stroke, subdural hematoma, intracranial hemorrhage, trauma)

Vaughan and Goldman, ***Movement Disorder Emergencies: Diagnosis and Treatment,*** ed. S. Frucht

Specific treatments for psychosis in PD

- **Atypical antipsychotic agents**
  - **Quetiapine**
    - **25 - 150 mg** – start with half a tablet (25mg) at night and titrate according to response
  - **Clozapine**
    - **25 – 75 mg** - **Very effective** – start with half a tablet (25mg) at night and titrate according to response (average 50 mg)



Parkinson Study Group NEJM;1999 Mar 11;340(10):757-63

Pollack et al. J Neurol Neurosurg Psychiatry. 2004 May;75(5):689-95

Clozapine for PD

- **Safety issues:**
  - Side effects:
    - sedation, increased drooling, occasional Orthostatic hypotension
  - Leukopenia:
    - regular blood counts required (initially weekly – 2 weekly – 2 monthly)
    - 1 - 2% in the pre-CNR period vs. 382 / 99 502 (=0.38%) pts treated with CLZ with 12 leukopenia-related deaths (=0.00012%) *
    - 6 / 187 pts with psychosis in PD included into RCTs (transient)

*Honigfeld et al., J Clin Psychiatry; 1998 (CNR database 1990 - 1994) CNR = Clozaril National Registry

Safety issues with using atypical antipsychotics for psychosis in PD

- **general safety issues** to consider in elderly patients:
  - antipsychotics (including atypicals) are associated with a similarly increased risk for
    - all-cause mortality
    - cerebrovascular events
  - in elderly patients with dementia

Trifiro G et al. Use of antipsychotics in elderly patients with dementia: do atypical and conventional agents have a similar safety profile? Pharmacol Res. 2009;59:1–12.

Bullock R. Treatment of behavioural and psychiatric symptoms in dementia: implications of recent safety warnings. Curr Med Res Opin. 2005;21:1–10.

Avoid other ‘atypical neuroleptics”

- Olanzapine
- Risperdone
- Aripiprezole

- **All worsen PD**

Goetz et al Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology 2000 Sep 26;55(6):789-94

Friedmnan et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. Mov Disord 2006 Dec;21(12):2078-81

DLB

- **Treatment options**
  - Cholinesterase inhibitors – help Hallucinations and cognition
  - Quetiapine or Clozapine – Help sleep and Hallucinations
  - Minimise non-essential centrally acting drugs – very poorly tolerated

Clinical pearls for cognitive dysfunction in PD

- Simple in clinic screens – ‘head-turning’ sign; ‘Pill Questionnaire’
- Watch out for younger PD patient with work-related anxiety -‘multi-tasking’ jobs – a common reason for stopping work. Maybe a prelude to cognitive decline
- Depression /anxiety are often a prelude to dementia
- Subjects with MOCA < 25 should stop driving
- PD patients with dementia are extremely sensitive to medications *per se*; Reduce drug ‘load’ to minimum
- Social support networks and education of care givers are important for long term care of PD Dementia

Support

Alzheimer Society's website at **www.alzheimer.ca** or contact your local Alzheimer Society.

For more information on PD, please visit the **Parkinson Society Canada www.parkinson.ca.**

Additional Resources:

Alzheimer's Association: http://www.alz.org/dementia/parkinsons-disease-symptoms.asp

Alzheimer Europe: http://www.alzheimer-europe.org/Dementia/Other-forms-of-dementia/Neuro-Degenerative-Diseases/Dementia-in-Parkinson-s-disease-PDD?#fragment-1

Alzheimer's Society UK: ttp://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=135

HOTCHKISS BRAIN INSTITUTE
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CLINICAL NEURO SCIENCES
CALGARY CANADA

UNIVERSITY OF CALGARY

Parkinson's disease Dementia: Research and non-medication treatments exploration

Oury Monchi, PhD,

Tourmaline Oil Chair in Parkinson's disease,

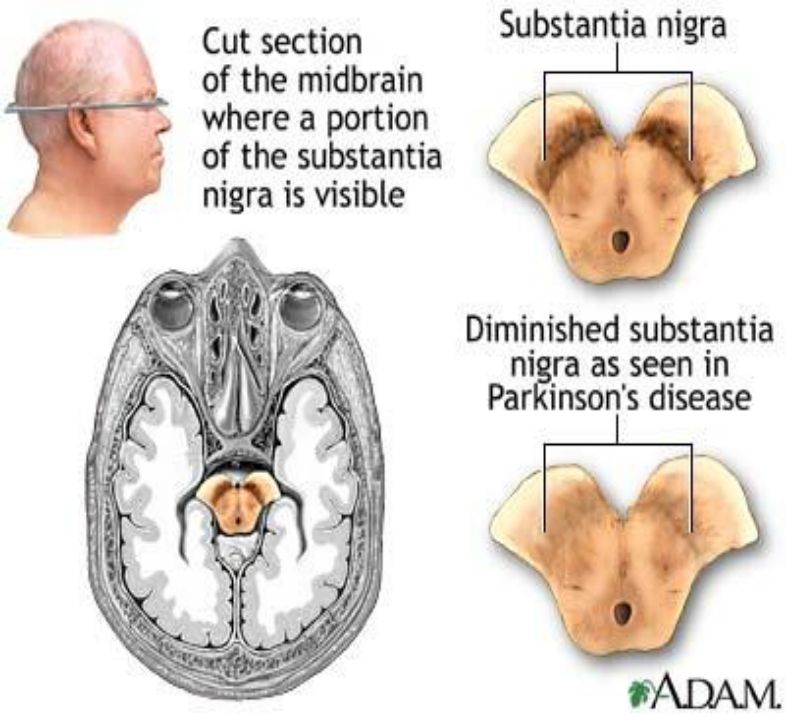
Movement Disorders Program,

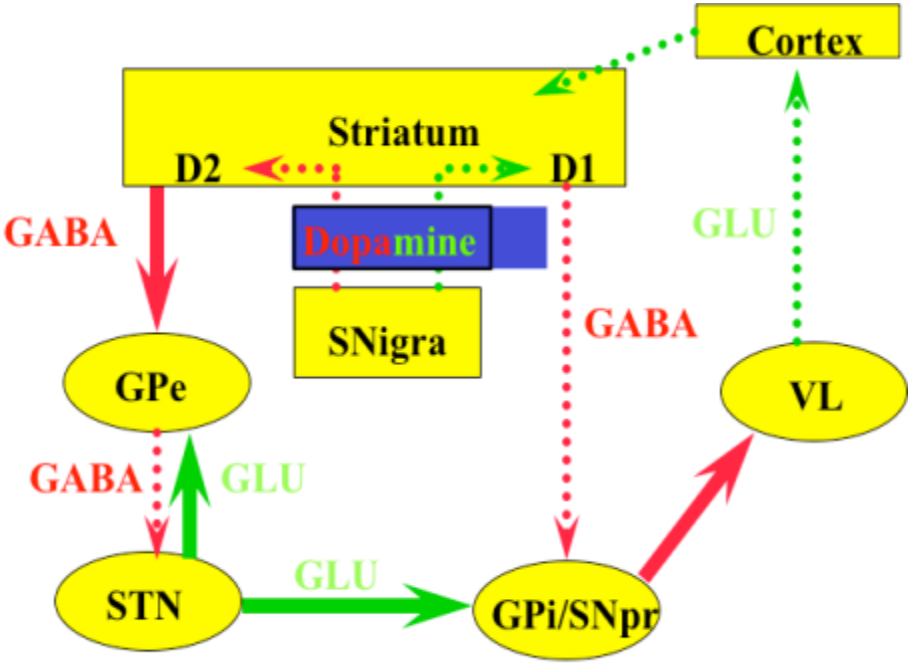
Departments of Clinical Neurosciences and Radiology,

Hotchkiss Brain Institute, Cumming School of Medecine,

University of Calgary.

Parkinson's Disease





Non-motor deficits

Benjamin Ball, France 1855

Visual hallucinations in PD

Intellectual perturbation is not Just a coincidence nor irritability linked to the diagnosis, but an Integral part of the disease

Largely forgotten until end of 20th century

End of 1980's

Brain (1986), **109**, 845–883

FRONTAL LOBE DYSFUNCTION IN PARKINSON'S DISEASE

THE CORTICAL FOCUS OF NEOSTRIATAL OUTFLOW

by ANN E. TAYLOR, J. A. SAINT-CYR *and* A. E. LANG

(*From the Departments of Psychology and Medicine, Division of Neurology and Playfair Neuroscience Unit, Toronto Western Hospital, and Departments of Anatomy and Medicine and the Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada*)

To investigate the influence of central cholinergic deficit on cognitive function in Parkinson's disease (PD), we compared the neuropsychological performance of a group of 20 patients who were treated with anticholinergic drugs (mean daily dose, 10.2 mg) with that of a group of 20 patients who received no anticholinergics. The two groups were matched for all the variables of parkinsonism and levodopa therapy. At the dose used, there was no significant difference between the two groups of patients for intellectual, visuospatial, instrumental, and memory function. In contrast, in the group that received anticholinergics severe impairment was observed on tests believed to assess frontal lobe function. These results suggest that the lesion of the ascending cholinergic neurons, which has been demonstrated post mortem in PD, may play a role in the subcorticofrontal behavioral impairment of this disease.

Dubois B, Pillon B, Lhermitte F, Agid Y. Cholinergic deficiency and frontal dysfunction in Parkinson's disease. Ann Neurol 1990;28:117–121

Cognitive deficits

- **Executive deficits:**

  'higher order processes' that are used when planning, problem-solving initiating a new task.

- **Attention difficulties:**

Problems in focusing or dividing attention in complex situations.

In real life, this may translate into difficulties in resisting to distraction

Cognitive Deficits

- **Visio-spatial problems:**

  Problems in estimating distances,

  Discriminating and acting on visual information.

  This can sometimes increase the risk of falls.

  In real life this may translate in difficulties in orientation in an environment with complex visual stimuli, such as finding a specific isle in a supermarket.

- At the later stages of the disease, illusions or little hallucinations are observed in some patients only.

Cognitive Deficits

- **Language dysfunction:** Word finding and naming deficits.
- **Memory:** Retrieving information that has already been learned.

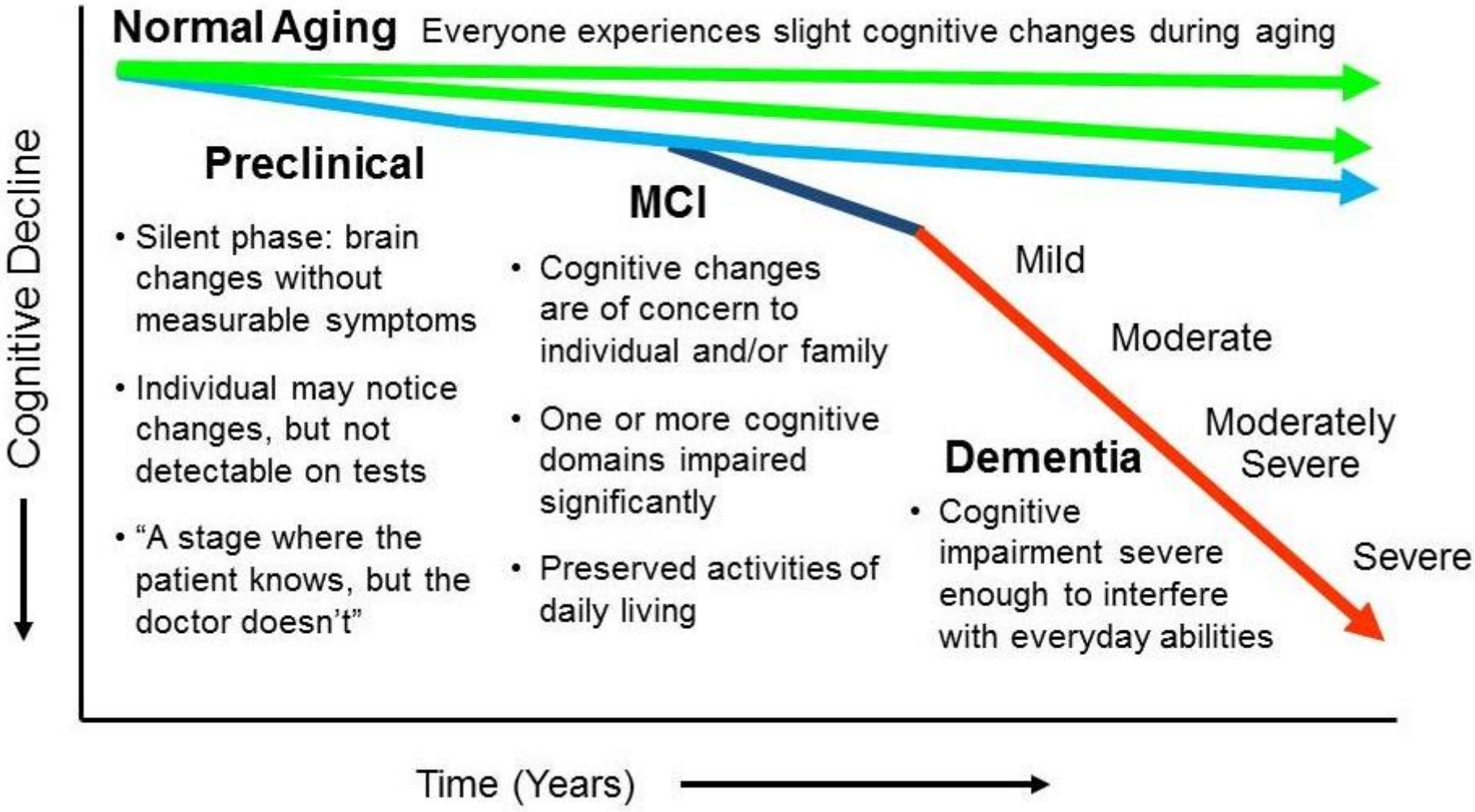
  In PD the problem is mostly with recall, and not with pure semantic or encoding like can occur in Alzheimer's disease.

  Using a notepad can help

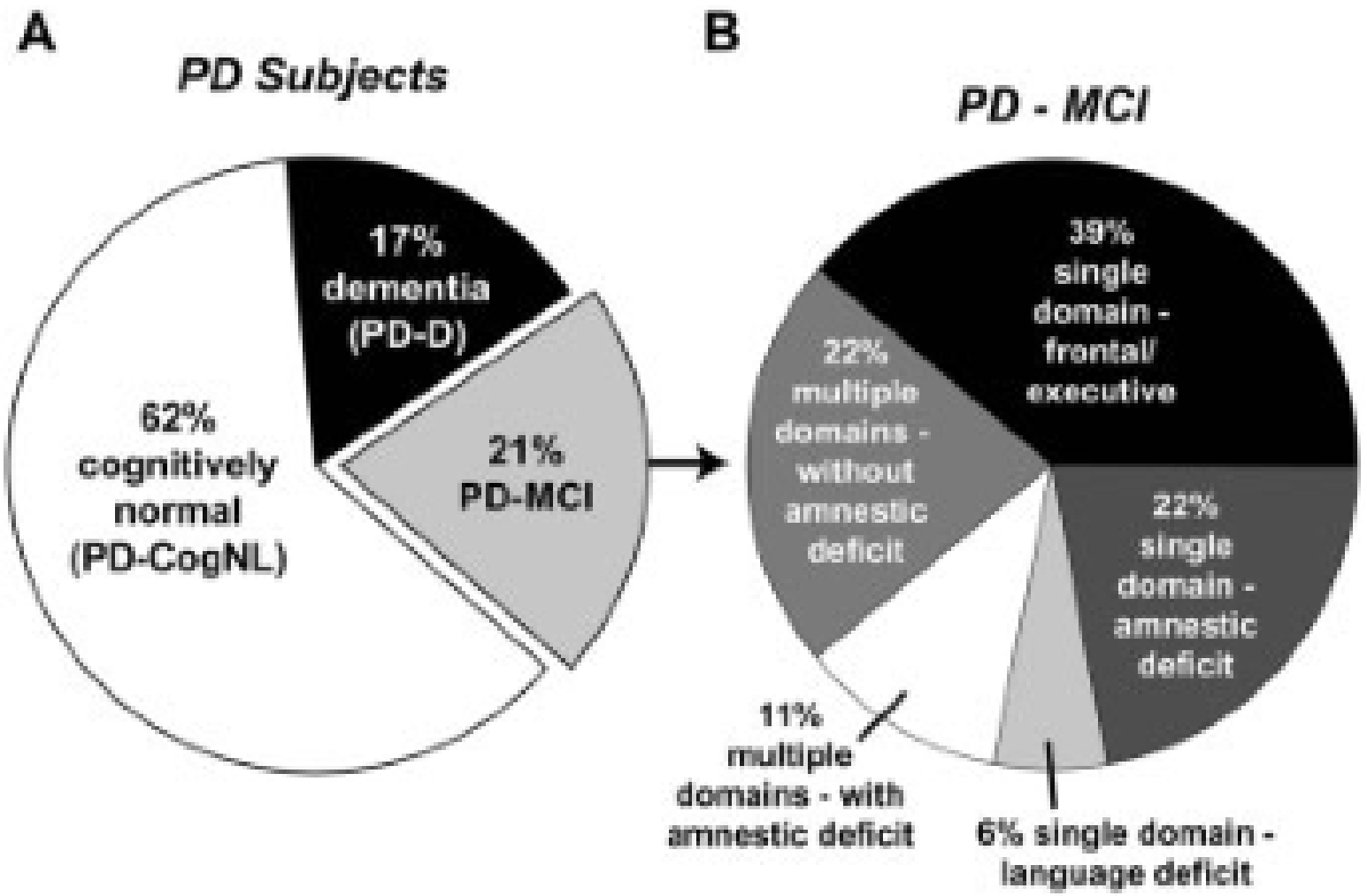
- **IMPORTANT:** Not all these symptoms are present in patients, and great differences exist between them.

Depression and Anxiety

- Depression is common in PD patients. A depressed person has trouble experimenting joy, may stop hobbies enjoyed before, and may not want to perform his daily routine. Diagnosis of Parkinson's disease can certainly cause stress and sadness, but depression can occur independently.
- Indeed a large number of patients with PD have experienced depression before they had the diagnosis
- Anxiety often occurs with depression in PD. They may have excessive worry about everyday things they can not control. Some people have outbreaks of anxiety called "panic attacks".

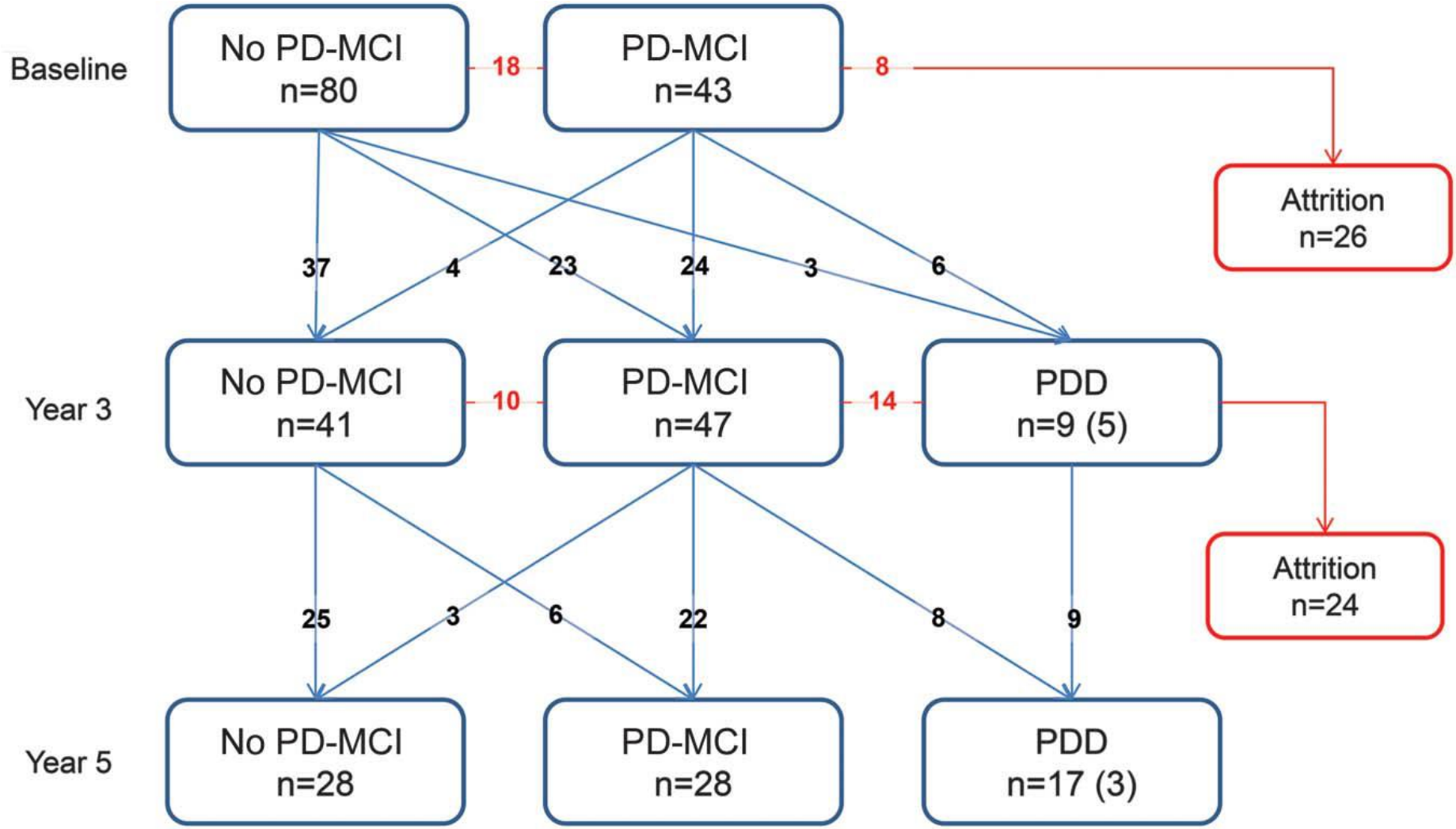

Normal Aging
Everyone experiences slight cognitive changes during aging
Preclinical
• Silent phase: brain changes without measurable symptoms
• Individual may notice changes, but not detectable on tests
• "A stage where the patient knows, but the doctor doesn't"
MCI
• Cognitive changes are of concern to individual and/or family
• One or more cognitive domains impaired significantly
• Preserved activities of daily living
Mild
Moderate
Moderately Severe
Severe
Dementia
• Cognitive impairment severe enough to interfere with everyday abilities
Cognitive Decline
Time (Years)

MCI very heterogeneous in Parkinson's Disease



Caviness et al. (2007)

Prevalence longitudinal studies



Broeders et al., Neurology, 2013

Neuroimaging anatomical MRI studies

The Pattern of Cortical Atrophy in Patients with Parkinson's Disease According to Cognitive Status

Sook K. Song, MD,[1] Ji E. Lee, MD,[2] Hae-Jeong Park, PhD,[3] Young H. Sohn, MD, PhD,[2] Jong Doo Lee, MD, PhD,[3] and Phil Hyu Lee, MD, PhD[1]*

[1]*Department of Neurology, Jeju University College of Medicine, Jeju, Korea*

[2]*Department of Neurology and Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea*

[3]*Department of Diagnostic Radiology, Nuclear Medicine and Research Institute of Radiological Science, Yonsei University College of Medicine, Seoul, Korea*

Movement Disorders, 2011

Method

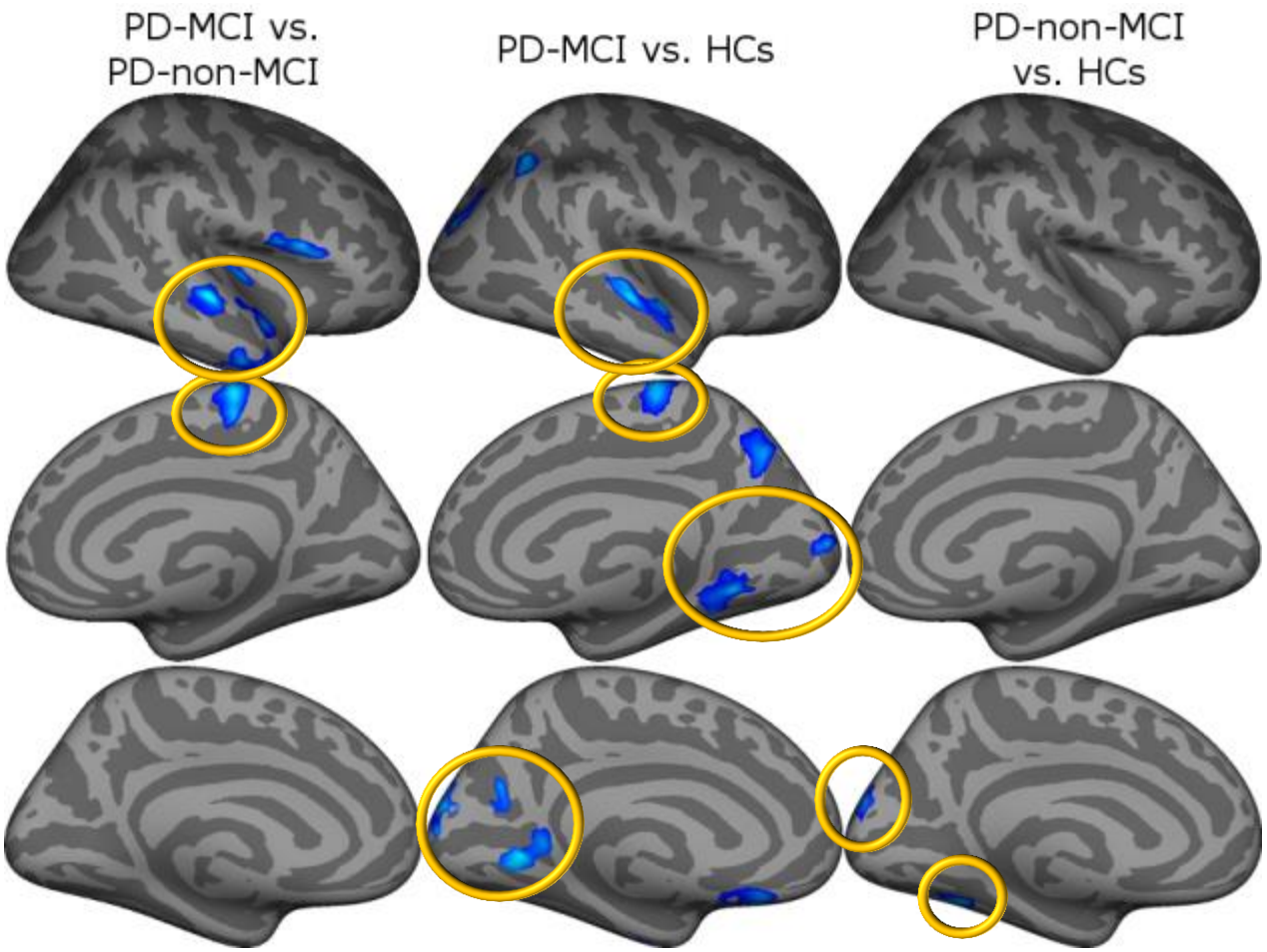
- 17 PD patients with MCI
- 15 PD patients without MCI
- 18 Healthy Controls

- MRI 3T
- FreeSurfer
  - Cortical thickness
  - Subcortical segmentation

MCI = Mild Cognitive Impairment
PD = Parkinson's disease

FreeSurfer

Results - thickness



PD-MCI	PD-non-MCI	HCs
-1.34%	-0.67%	-0.34%

Blue clusters
=
increased rate of
cortical thinning

Hanganu et al., Brain 2014

Results – subcortical

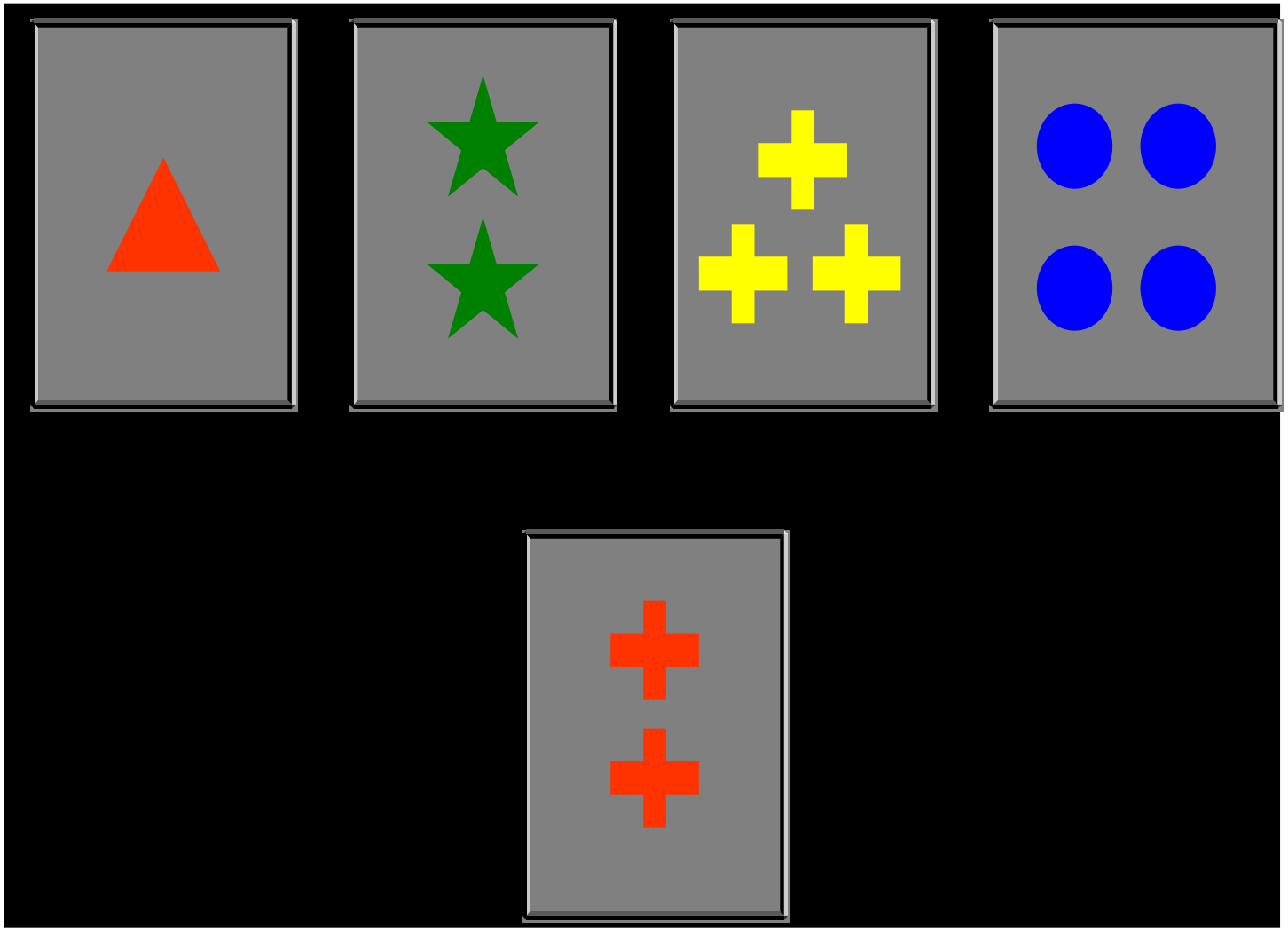
Mean percentage of change over time

	PD-MCI	PD-non-MCI	HCs
Thalamus	-1.51%	-1.80%	-3.71%
Caudate	-1.92%	-2.05	-0.99%
Putamen	-1.64%	-1.41	-0.40%
Hippocampus	-2.07%	-1.96	-3.08%
Amygdala	**-6.05%**	+0.58	+0.80%
N. Accumbens	**-5.98%**	-0.91	+2.19%

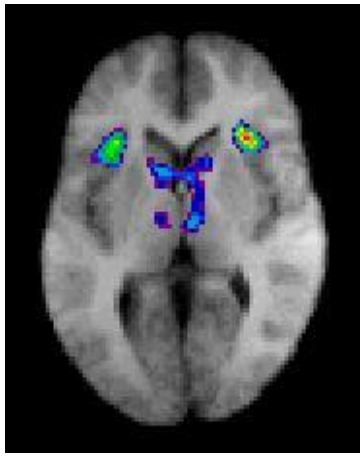
Ventral striatum has an increased degradation

Hanganu et al., Brain 2014

Neuroimaging studies fMRI



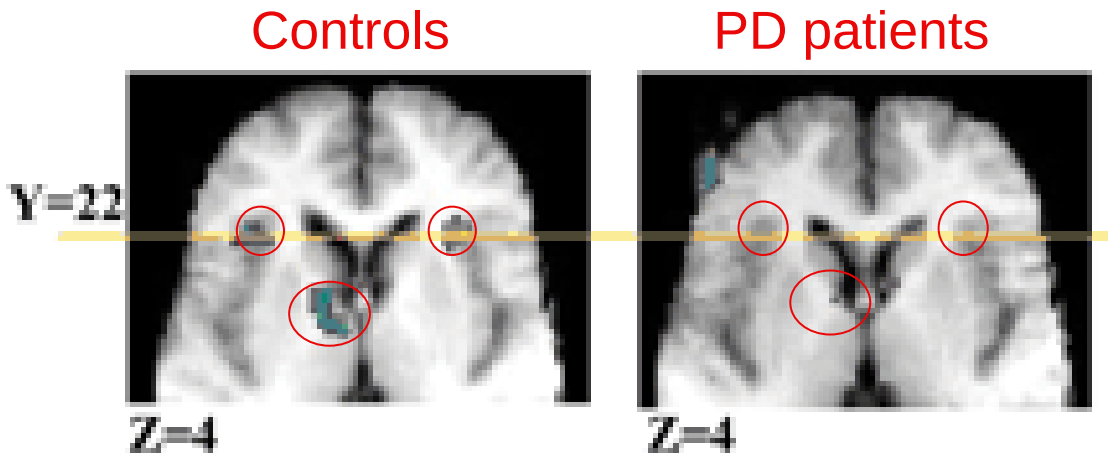
fMRI WCST Results in Young Controls: Shift-planning



Isolation of a cognitive cortico-striatal loop
including the ventrolateral PFC in the planning of a set-shift

Monchi et al., 2001: *Journal of Neuroscience*, editor's choice *Science* and *Nature Reviews Neuroscience*

fMRI WCST Results in PD-OFF and matched Controls: Shift-planning



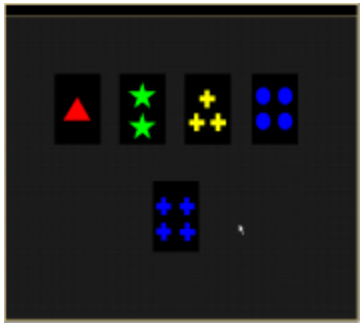
Decreased activity in PD in the‘cognitive’ cortico-striatal loop during planning the set-shift

Monchi et al., Journal of Neuroscience 2004
Highlighted in ‘This Week in the Journal’

fMRI WCST MCI vs. NON MCI OFF

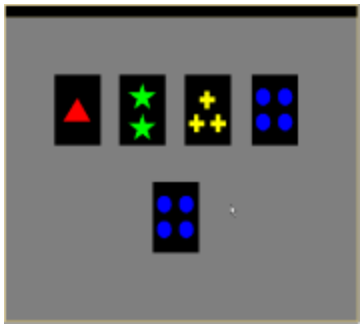
Shift Planning

Negative Feedback

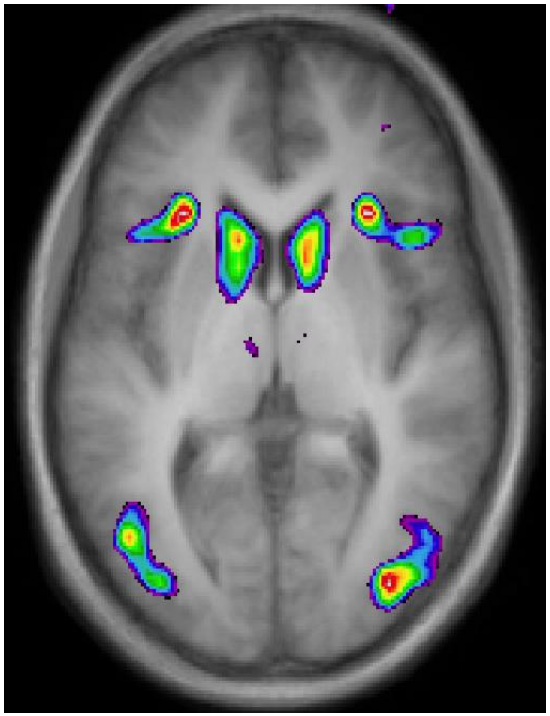


vs.

Control Feedback

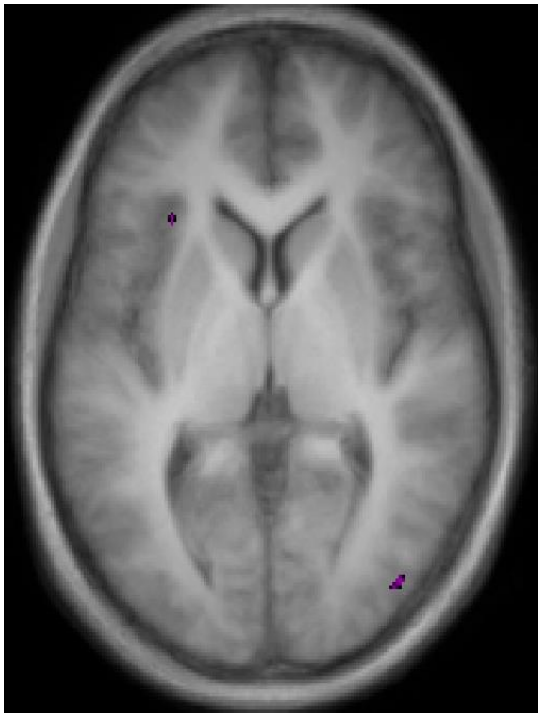


PD NON MCI



Z = +4

PD MCI

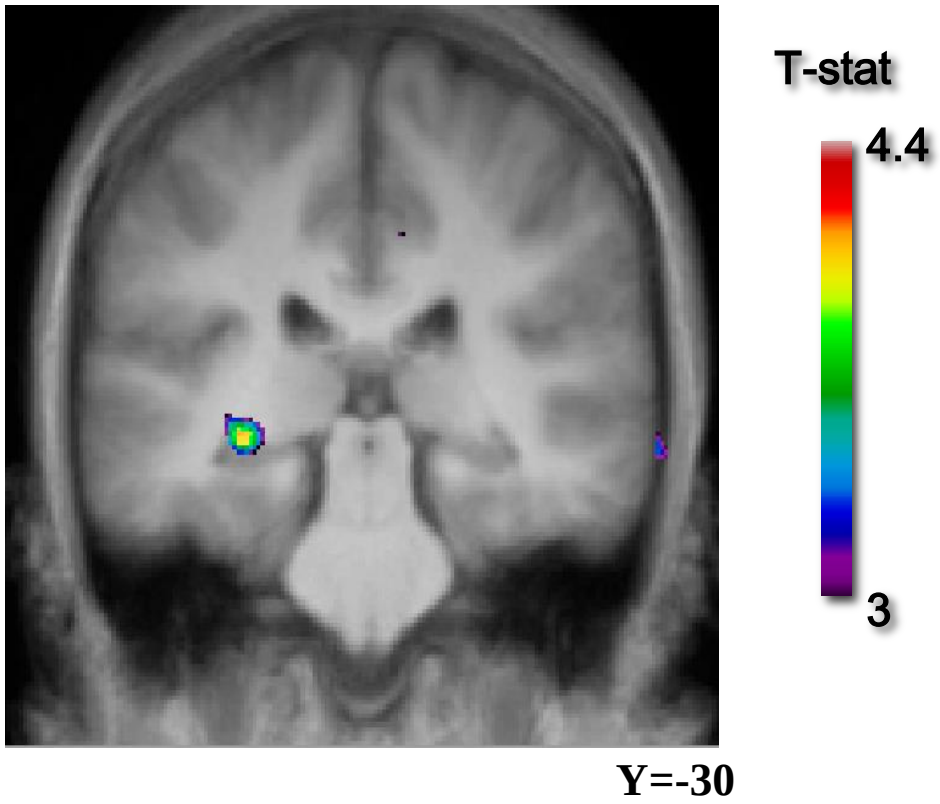


Z = +4

Effect more pronounced in patients with MCI

Correlation with retrieval list of RAVLT

Shift Execution



Patients with better scores (memory) use more the MTL eventhough it is not required for the task

Nagano-Saito et al.,2014, Neurobiology of Aging

Hippocampal compensation hypothesis

Published in final edited form as:
Neurobiol Dis. 2010 February ; 37(2): 455. doi:10.1016/j.nbd.2009.10.025.

Early Parkinson's Disease: Longitudinal Changes in Brain Activity during Sequence Learning

Maren Carbon, MD[a,b,1], Kathrin Reetz, MD[a,c,1], M. Felice Ghilardi, MD[d], Vijay Dhawan, PhD[a,b], and David Eidelberg, MD[a,b]

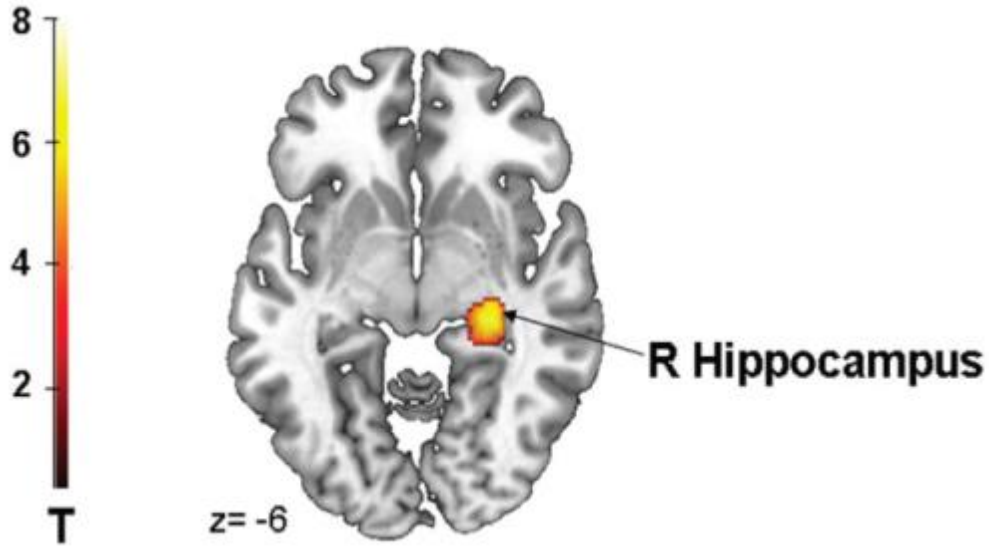
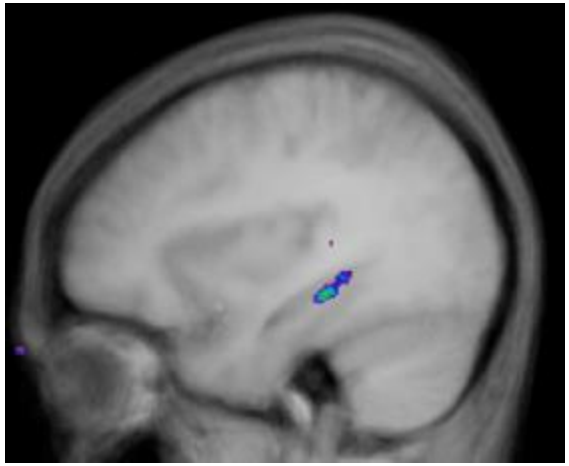


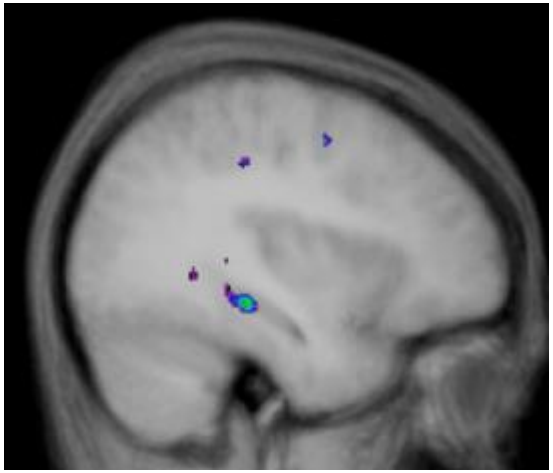
Figure 2. Increased hippocampal activation in PD patients with sustained learning performance over time

Could the lack of MTL compensation be a marker of dementia in PD?

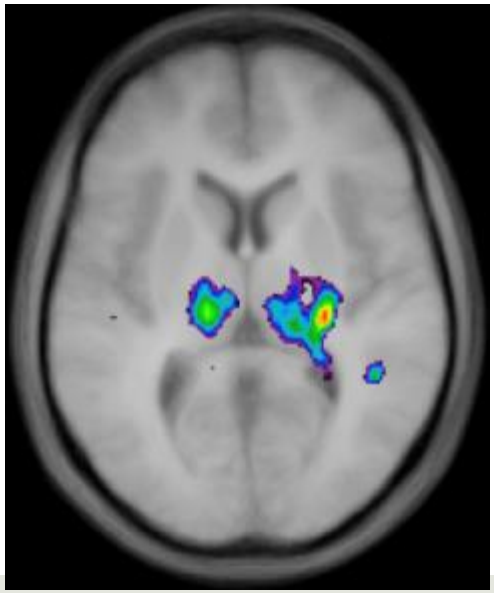
Longitudinal study fMRI WCST All PD T1 correlated with MOCA evolution, Planning set-shift



X=-34



X=+36



Z=+8

Genotypes and cognitive deficits

JAMA Neurol. 2014 Nov;71(11):1405-12. doi: 10.1001/jamaneurol.2014.1455.

APOE, MAPT, and SNCA genes and cognitive performance in Parkinson disease.

Mata IF[1], Leverenz JB[2], Weintraub D[3], Trojanowski JQ[4], Hurtig HI[5], Van Deerlin VM[6], Ritz B[7], Rausch R[8], Rhodes SL[9], Factor SA[10], Wood-Siverio C[10], Quinn JF[11], Chung KA[11], Peterson AL[11], Espay AJ[12], Revilla FJ[13], Devoto J[12], Hu SC[2], Cholerton BA[14], Wan JY[15], Montine TJ[16], Edwards KL[15], Zabetian CP[2].

⊕ **Author information**

Abstract

Mov Disord. 2010 Nov 15;25(15):2550-4. doi: 10.1002/mds.23319.

Catechol-O-methyltransferase val158met and cognitive function in Parkinson's disease.

Hoogland J[1], de Bie RM, Williams-Gray CH, Muslimović D, Schmand B, Post B.

Brain. 2014 Nov;137(Pt 11):3025-35. doi: 10.1093/brain/awu251. Epub 2014 Sep 10.

Dopamine transporter SLC6A3 genotype affects cortico-striatal activity of set-shifts in Parkinson's disease.

Habak C[1], Noreau A[2], Nagano-Saito A[1], Mejía-Constaín B[1], Degroot C[1], Strafella AP[3], Chouinard S[4], Lafontaine AL[5], Rouleau GA[2], Monchi O[6].

Neurol Neurochir Pol. 2014;48(4):258-61. doi: 10.1016/j.pjnns.2014.07.005. Epub 2014 Jul 29.

Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients.

Malec-Litwinowicz M[1], Rudzińska M[2], Szubiga M[3], Michalski M[4], Tomaszewski T[4], Szczudlik A[4].

Conclusion part I

- **Cognitive decline is very heterogeneous in PD**
- **PD dementia may occur from mixed pathologies, including some associated with AD.**
- **Studies currently taking place to find out longitudinally the differences between PD-MCI and nonPD-MCI**
- **Other factors such as age, neuropsychiatric symptoms and genetics also play a role in the occurrence of dementia in PD**

Cognitive training in PD

Eur J Neurol. 2014 Dec 22. doi: 10.1111/ene.12621. [Epub ahead of print]

Cognitive training in Parkinson's disease reduces cognitive decline in the long term.

Petrelli A[1], Kaesberg S, Barbe MT, Timmermann L, Rosen JB, Fink GR, Kessler J, Kalbe E.

Parkinsonism Relat Disord. 2014 Nov 20. pii: S1353-8020(14)00434-9. doi: 10.1016/j.parkreldis.2014.11.014. [Epub ahead of print]

Task force WANTED: Many reasons to promote research on cognitive rehabilitation to prevent, delay, and treat cognitive dysfunctions in patients with Parkinson's disease.

Kalbe E[1], Kessler J[2].

Exercise programs in PD

J Neurol Phys Ther. 2013 Jun;37(2):58-64. doi: 10.1097/NPT.0b013e31829219bc.

Aerobic exercise to improve executive function in Parkinson disease: a case series.

Tabak R[1], Aquije G, Fisher BE.

J Clin Neurol. 2013 Oct;9(4):237-43. doi: 10.3988/jcn.2013.9.4.237. Epub 2013 Oct 31.

The Efficacy of Exercise Programs for Parkinson's Disease: Tai Chi versus Combined Exercise.

Cheon SM[1], Chae BK, Sung HR, Lee GC, Kim JW.

DANCING PARKINSON'S

A PARTNERSHIP BETWEEN DECIDEDLY JAZZ DANCEWORKS & UNIVERSITY OF CALGARY DIVISION OF DANCE
WITH SUPPORT FROM THE ROZSA FOUNDATION & THE SOCIAL SCIENCES AND HUMANITIES RESEARCH COUNCIL

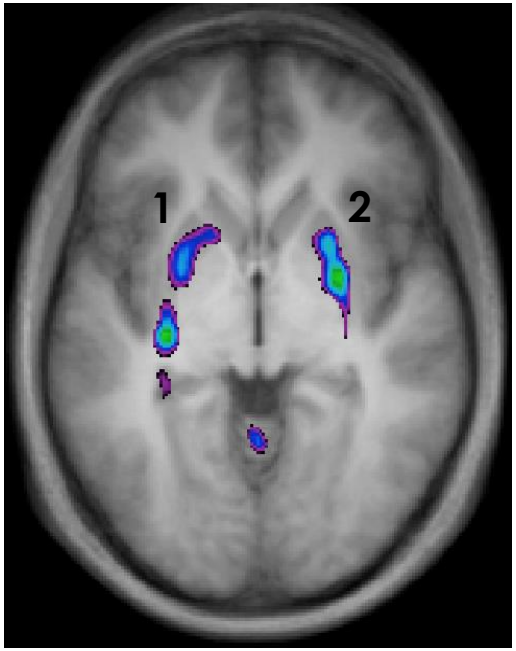
New possible treatments Transcranial Magnetic Stimulation (TMS)

Fronto-striatal connectivity during ‘rest’

TBS of PFC and ‘resting-state fMRI’

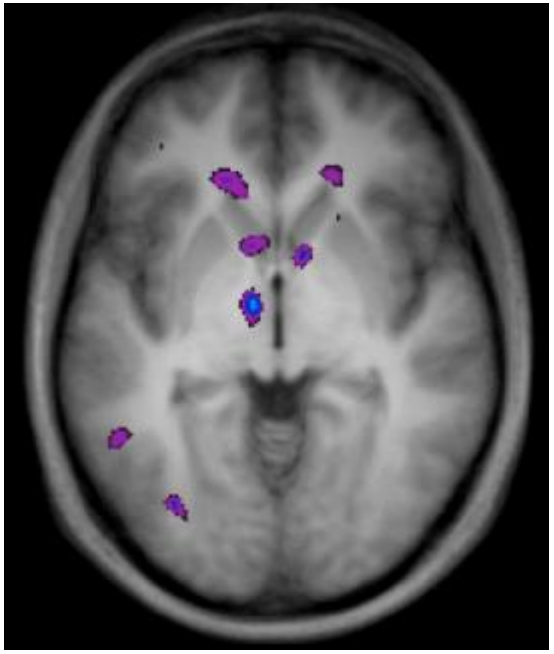
iTBS and rsfMRI correlation analysis
L caudate nucleus seed

Pre-iTBS



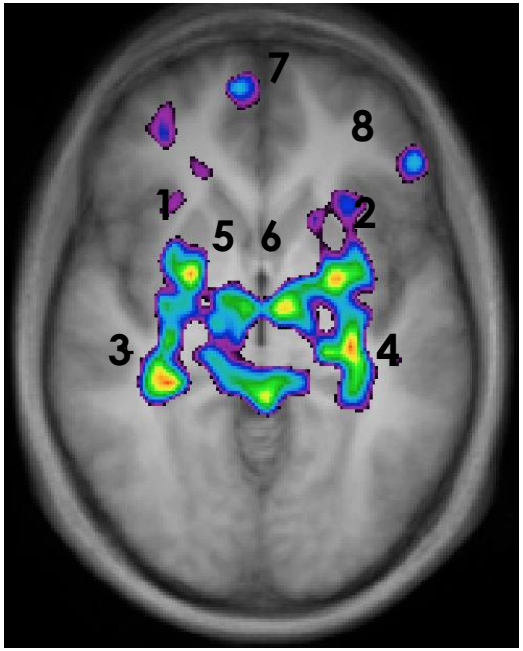
Z = -2

Sham TBC

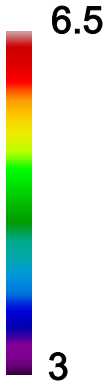


Y = -4

Post-iTBS

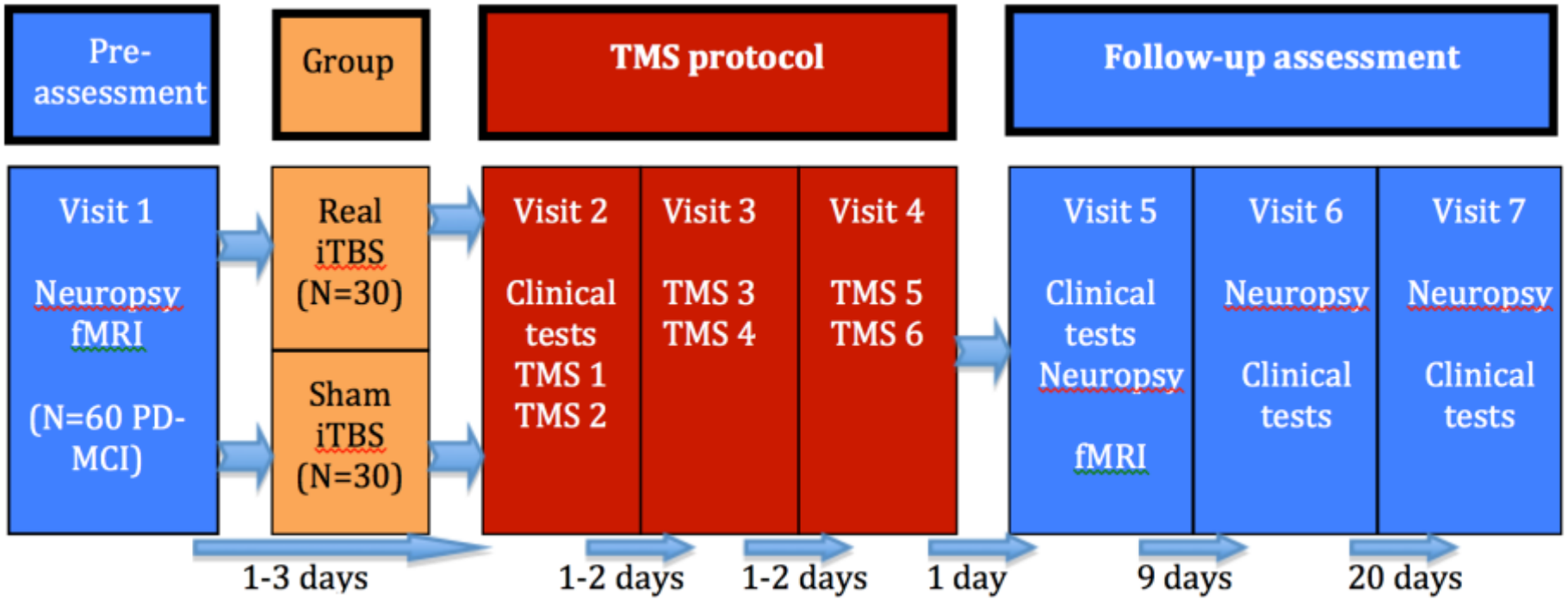


Z = -2

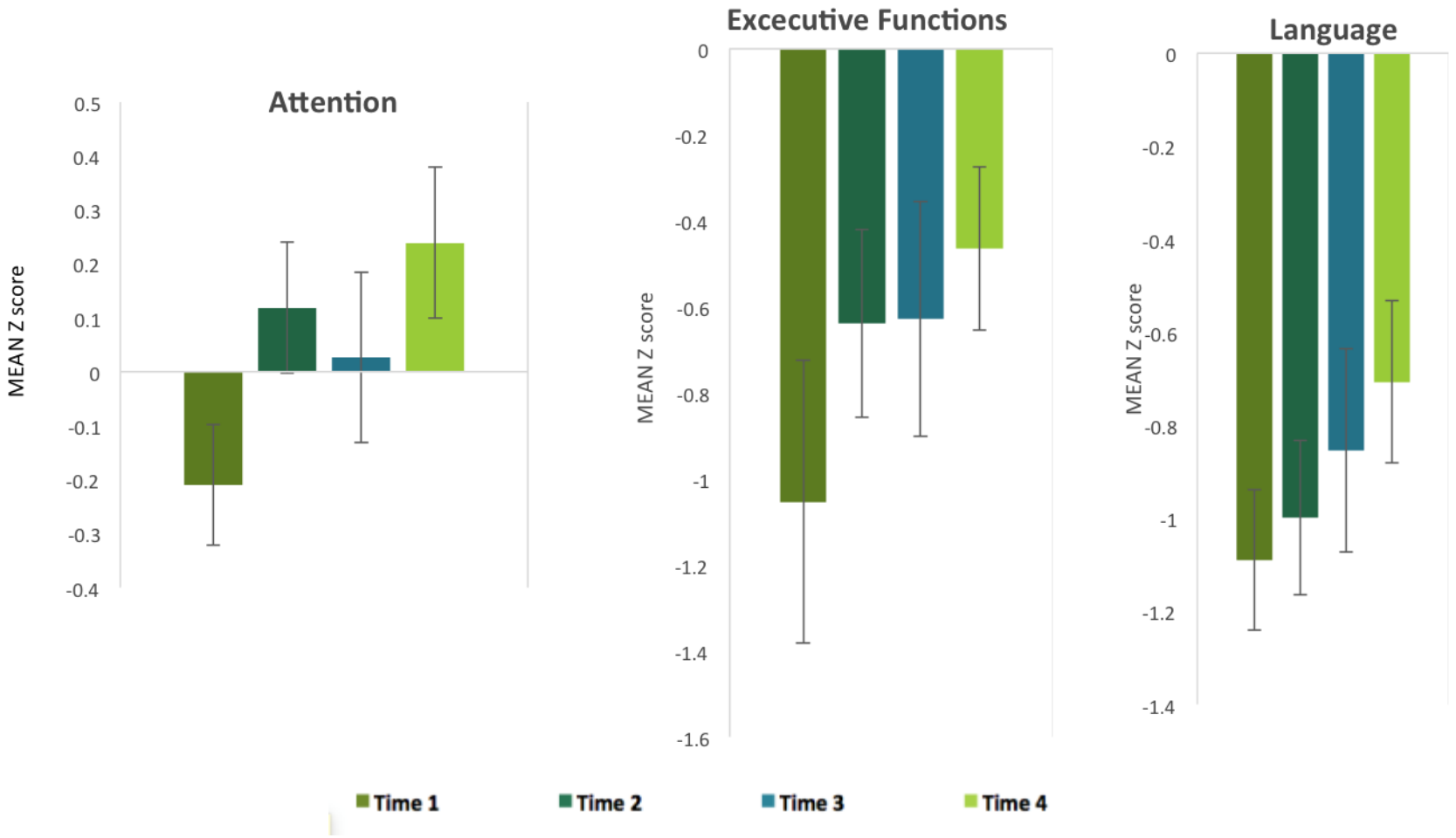


Loop affected in PD-MCI

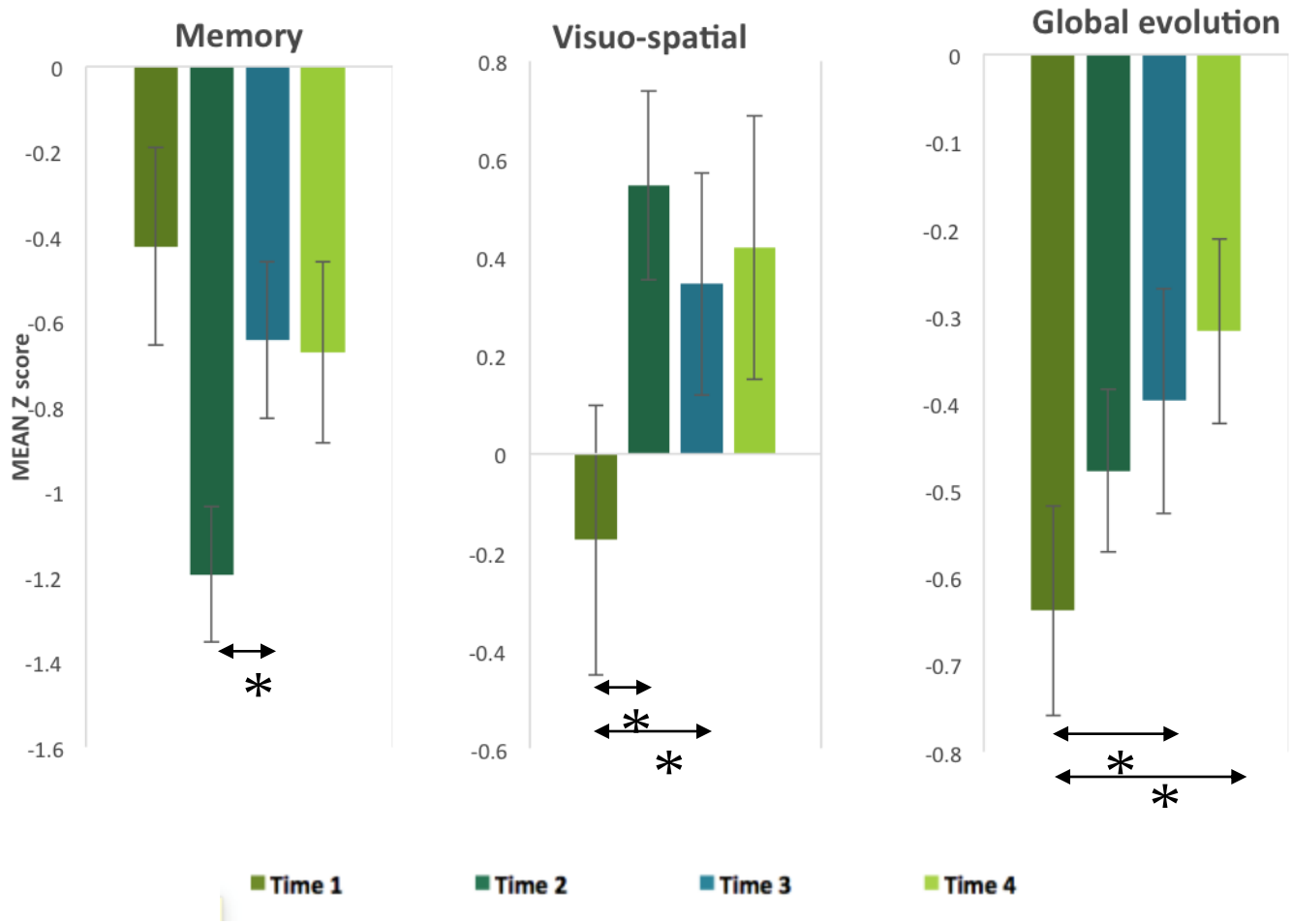
Therapeutical TMS trial in PD-MCI



Preliminary results 10 patients active iTBS neuropsychological tests



Preliminary results 10 patients active iTBS neuropsychological tests



$p<0.05$

Conclusion Part II

- Data on non-medication treatment is not yet conclusive
- Not enough studies
- Lack of guidelines
- Which is more beneficial?
- Confounding factor, 'being taken care of', placebo effect, social effect…..
- In need of proper large-scale clinical trials like for medication
- Nevertheless, get involved always some benefits and keep active mentally and physically as much as possible
- Regularity more important than intensity