

Dementia in Parkinson's disease:

A 20 year Prospective Neuropsychological Study Sydney Multicentre Study

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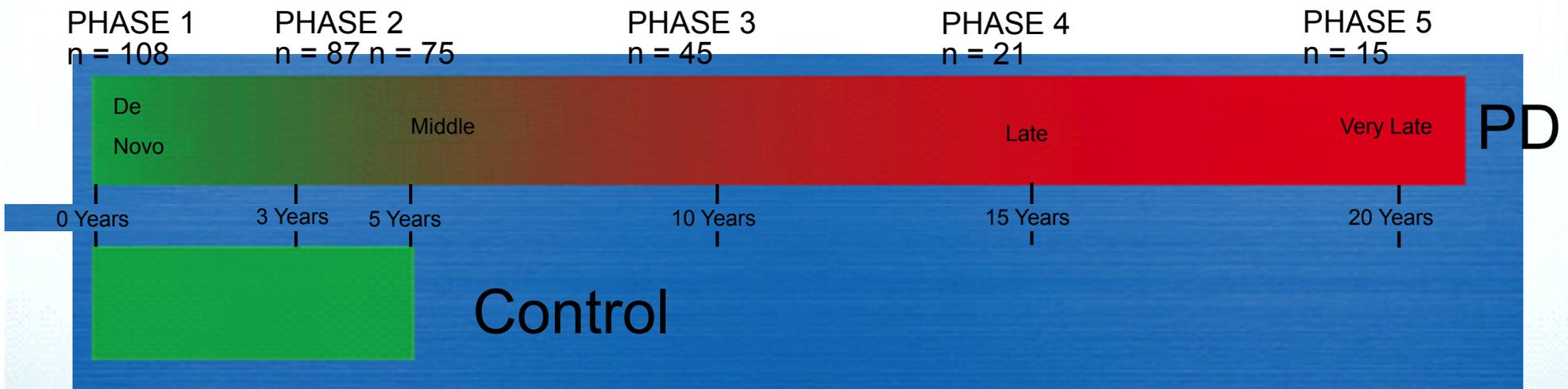
Method

- **149 newly–diagnosed community living Parkinson’s Disease cases**
- **108 received full neuropsychological assessment at baseline (untreated)**
- **41 excluded from neuropsychological assessment**

Non English-speaking	N = 22
Refusals	N = 6
Atypical	N = 13
- **50 Control (similar age and education)**
- **All assessed by same neurologist and neuropsychologist on same day of week at same time of day over 20 years – (baseline, 3yrs, 5yrs, 10yrs, 15yrs and 20 yrs)**

Sydney Multicentre Study -neuropsychological study in Parkinson's Disease (PD)

Phases studied in the course of PD



Areas of Interest

- **Age of Onset**
- **Cognitive Functioning**
- **Dementia**
- **The Relationship Between Motor and Cognitive Impairment**
- **Depression**
- **Psychological mechanisms associated with the development of Dyskinesia**
- **Treatment Response**

Neuropsychological Test Battery (Reid et al 1989)

- Vocabulary, Age scale score (WAIS-R)
- Ravens Coloured Progressive Matrices (RCPM)
- Rey Auditory Verbal Learning Test (RAVLT)
- Verbal Fluency (FAS)
- Animal Category Fluency
- Block Design, Raw scores (WAIS-R)
- Benton Visual Retention Test, Correct & error scores (BVRT)
- Simple Reaction Time
- Choice Reaction Time
- Object naming
- Auditory Verbal Comprehension
- Writing (Western Aphasia Battery - WAB)

Later Added Tests

- Boston Naming Test
- MMSE
- CDR
- Geriatric Depression Scale

Clinical and Neuropsychological Assessments

- Clinical:

Signs and symptoms of Parkinson's Disease –

- Modified Columbia Scale
- North Western Disability Scale

Cognitive Functioning (Reid et al 1989, 1992)

+ **Motor symptoms**

- Symmetrical symptoms
- Bradykinesia

+ **Treatment**

- Dyskinesia - patients with good cognitive functioning at onset
- Hallucinations- more likely to be associated with cognitive impairment

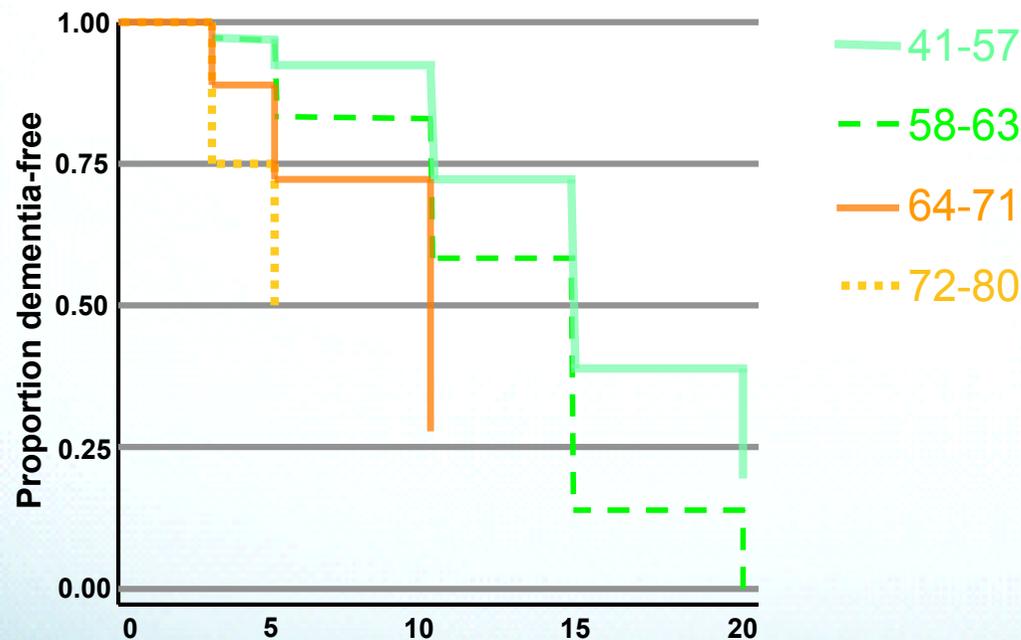
Survival

- Cox proportional hazards modeling, hazards ratio of 1.08 (95% confidence interval 1.03-1.13, $p=0.001$).
- Subject at 75 years is 4.82 times as likely as a subject with an onset age of 55 to develop dementia.

Age of Onset

(Reid et al, 1989, 1996)

Dementia-free survival time



> 70 years age of onset

- Cognitive impairment
- Greater disability – falls, automatic failure
- Shorter duration of disease
- Symmetrical disease
- More severe symptoms of PD
- Poorer response to treatment

Overall: Dementia onset within PD occurred at a similar age (70yrs) regardless of the timing of PD onset suggesting a separate dementia syndrome separate from PDD.

Dementia Prevalence in PD

- Average frequency across 27 studies = 40% (Cummings 1988)
- 8 year prevalence rate 78.2% (95% CI, 71%-84%) Aarsland et al 2003

Problems Studying Dementia in Parkinson's Disease

- Majority of studies cross-sectional - varying rates of progression affecting cognitive motor function, mood, behaviour
- Differing cognitive measures
- Definition of cognitive impairment and dementia
- Don't take into account relationship between dementia and survival
- NH patients often not included

Definition and Assessment of Dementia

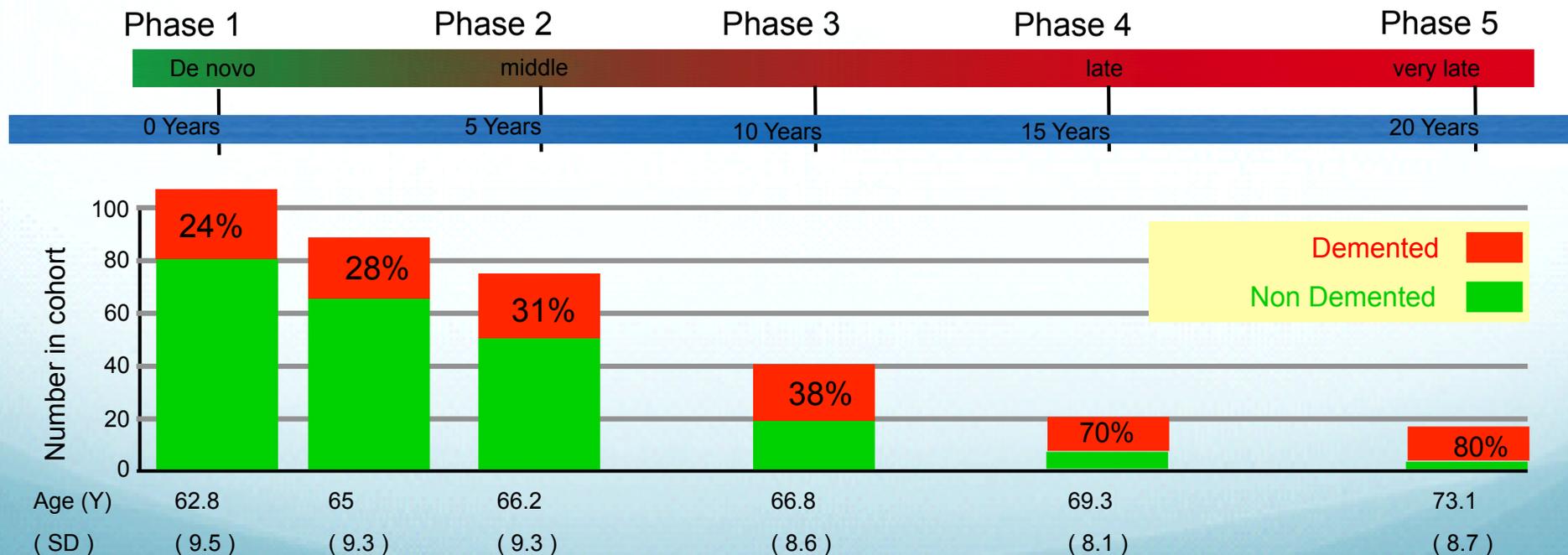
- Cognitive status quantified using z-score
- Cognitive impairment defined scores 2 SDs from mean score of controls
- Cognitive Domains
 - i. Memory (RAVLTS, Recall A, BVRT)
 - ii. Vocabulary
 - iii. Verbal Fluency (FAS, Animal Categories)
 - iv. Executive Function (a) Ravens Coloured Progressive Matrices
b) Block Design)
 - v. Simple Reaction Time
 - vi. Visuo Spatial (Block Design)

Dementia prevalence

Previous studies

- Average frequency across 27 studies = 40% (Cummings 1988)
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Sydney Multicare Study



Three dementia phenotypes – defined by their cognitive functioning

	EPDD	MPDD	LPDD
Age of PD onset	69.7 (6.5)	61.6 (6.3)	53.6 (6.2)
Dementia (from PD onset)	0-3 years	3-10 years	after 10 years
Dementia onset (years(SD))	70.4 (5.7)	70.6 (5.6)	69.1 (5.3)

0 years	5 years	10 years	15 years	20 years
De novo	middle		late	very late
PHASE 1	PHASE 2	PHASE 3	PHASE 4	PHASE 5

OVERALL: Cases with dementia at baseline (24%, dementia with Lewy bodies (DLB)) were significantly older and had a shorter life expectancy than those dementing after 3 years (PD+dementia).

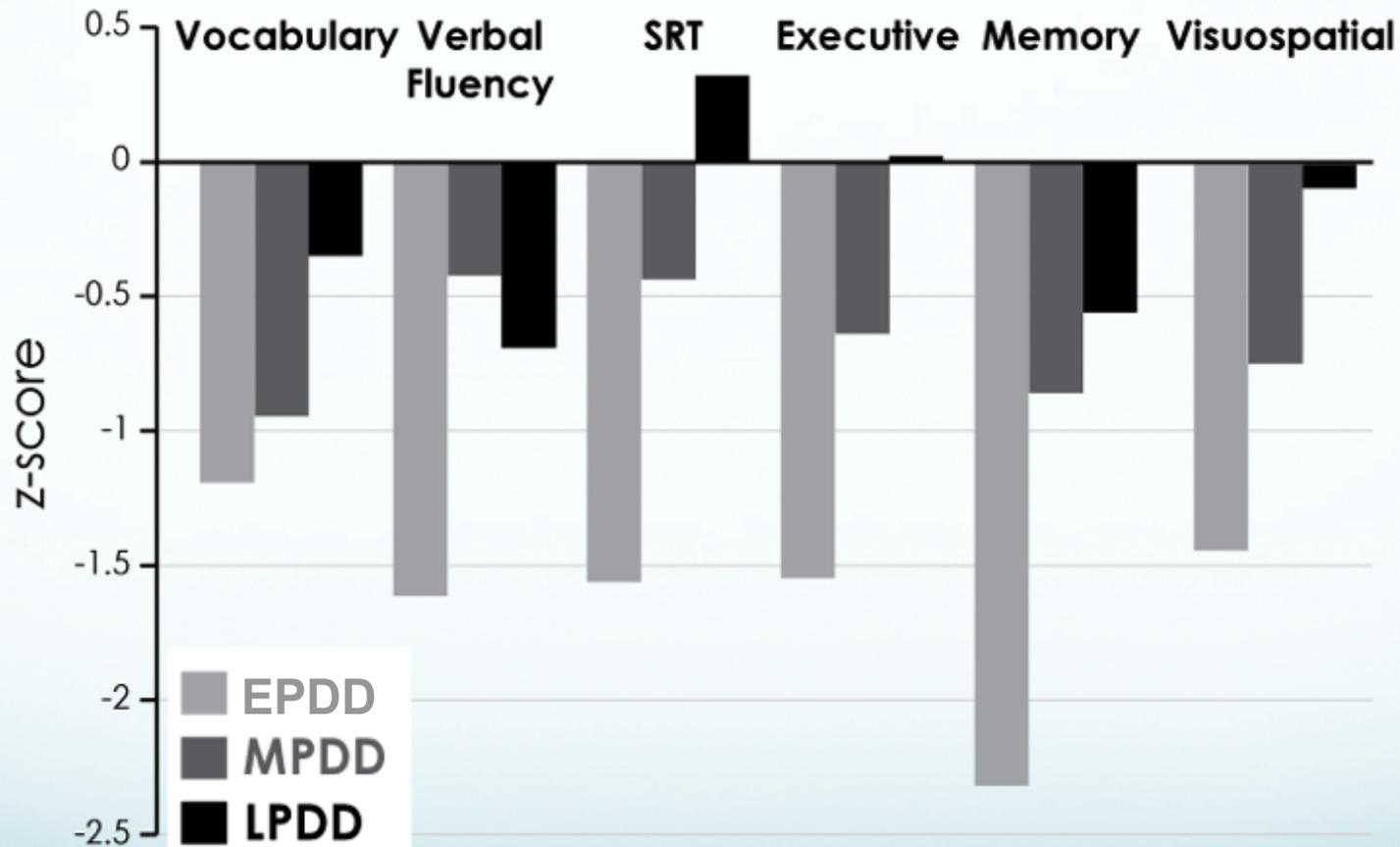
Early Dementia (EPDD)

Clinical and Neuropsychological characteristics

- Older at onset
- EPDD Fullfilled DLB criteria (McKeith et al 2005) and current criteria for PD with dementia (Emre et al 2007)
- All had more severe motor symptoms of PD
- Did not have prior diagnosis of dementia detected by referring Neurologist
- Widespread cognitive deficits

OVERALL: Compared with denovo untreated PD, DLB significantly impaired across all cognitive tests ($p < 0.000$)

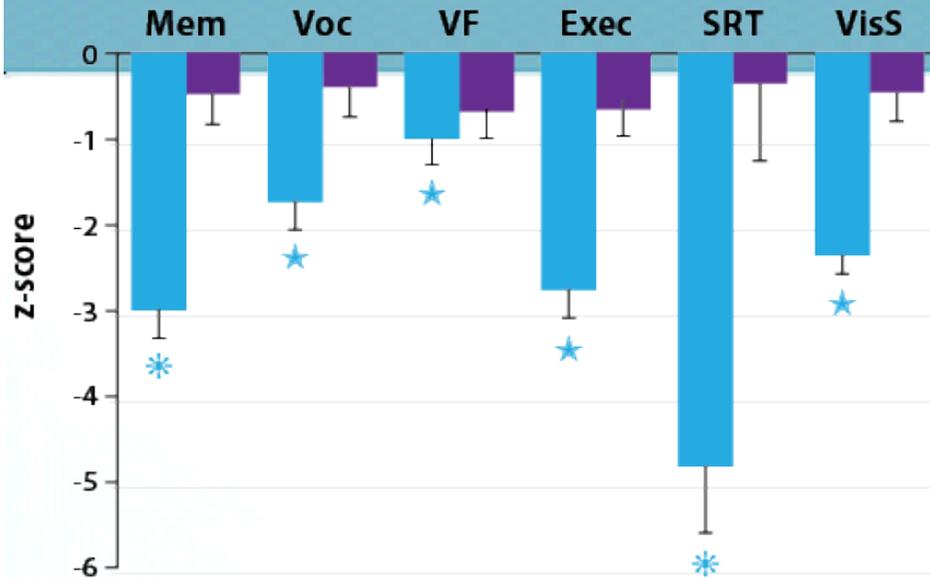
Cognitive functioning at baseline for all 3 groups



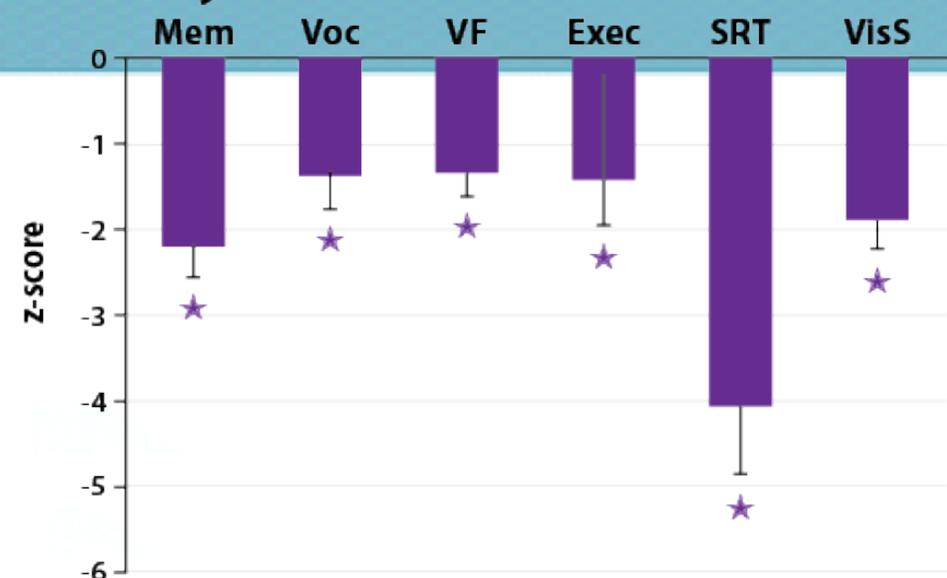
OVERALL: EPDD cases had greater impairment on memory ($p < 0.47$) and verbal fluency (VF) ($p < 0.004$) than PDD.

Cross-sectional assessments of neuropsychological functioning in MPDD compared with LPDD

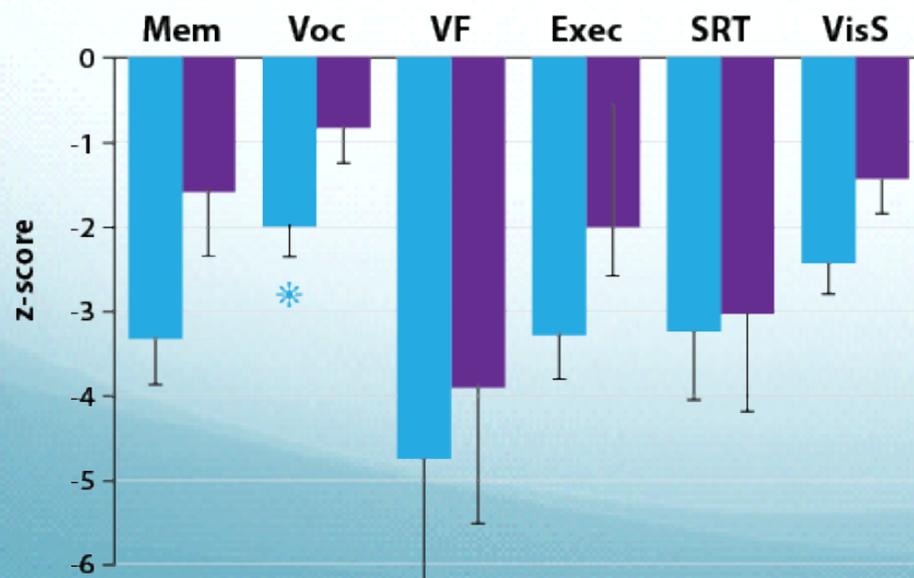
At 10 years



At 20 years

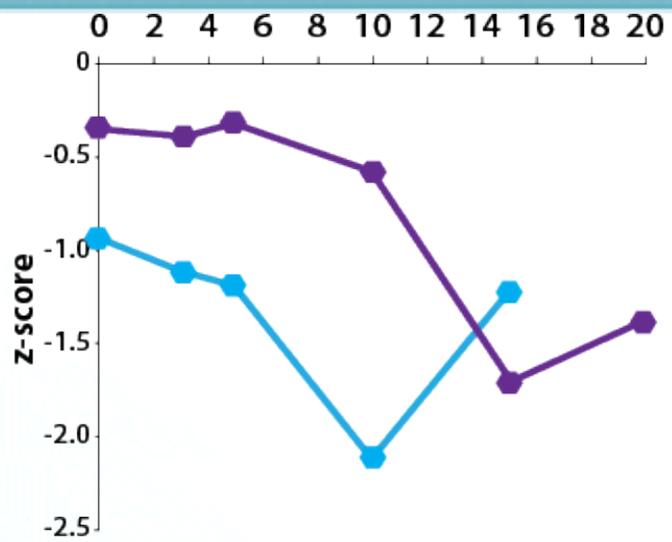


At Dementia Onset

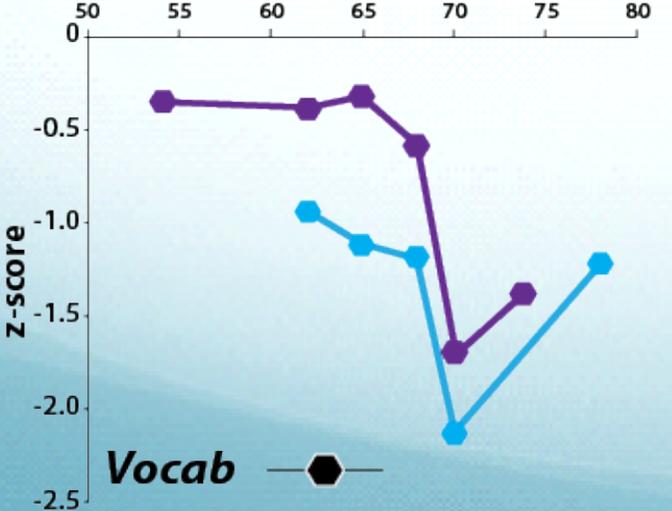


Longitudinal analysis of neuropsychological functioning in PD

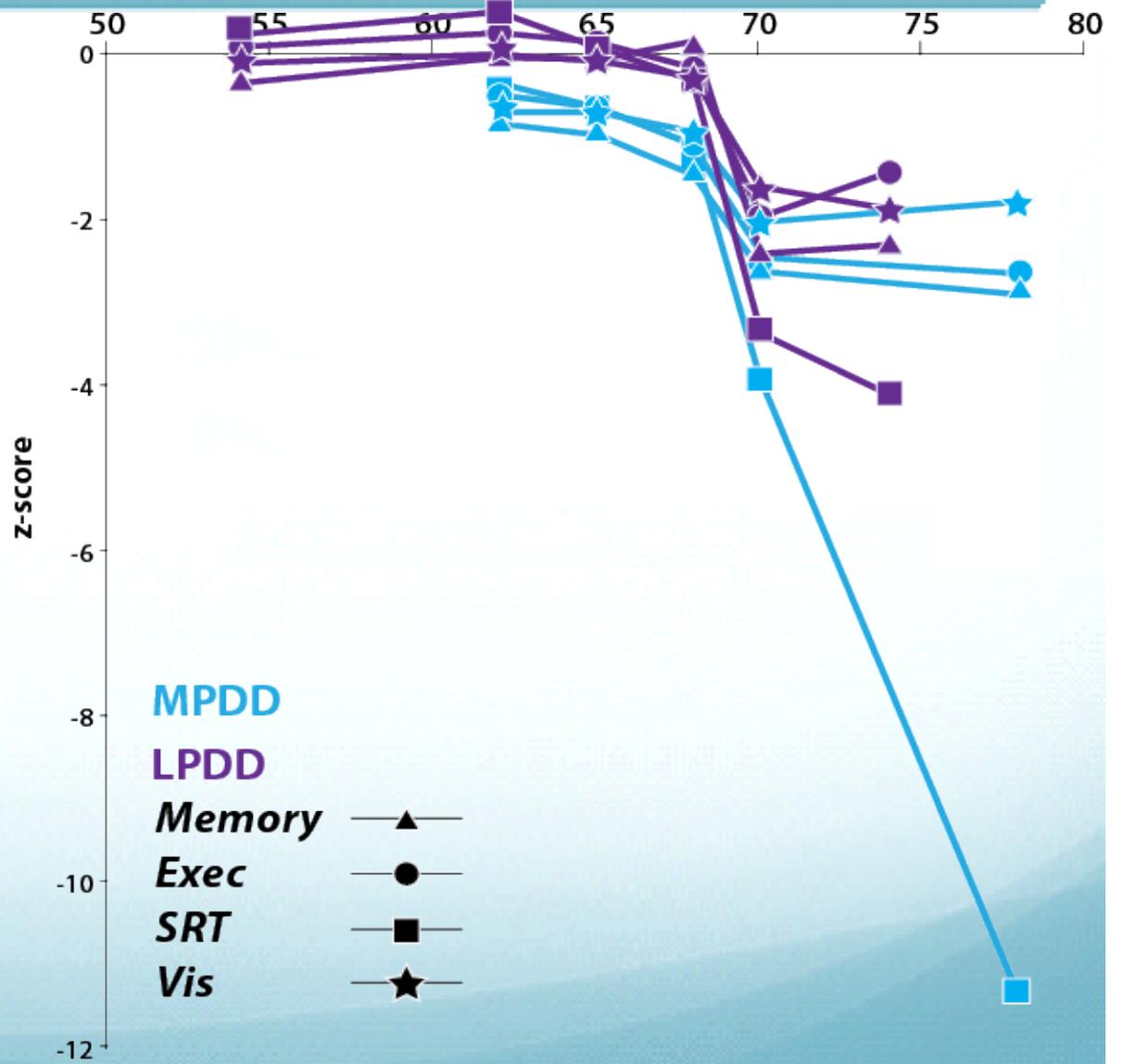
time (years)



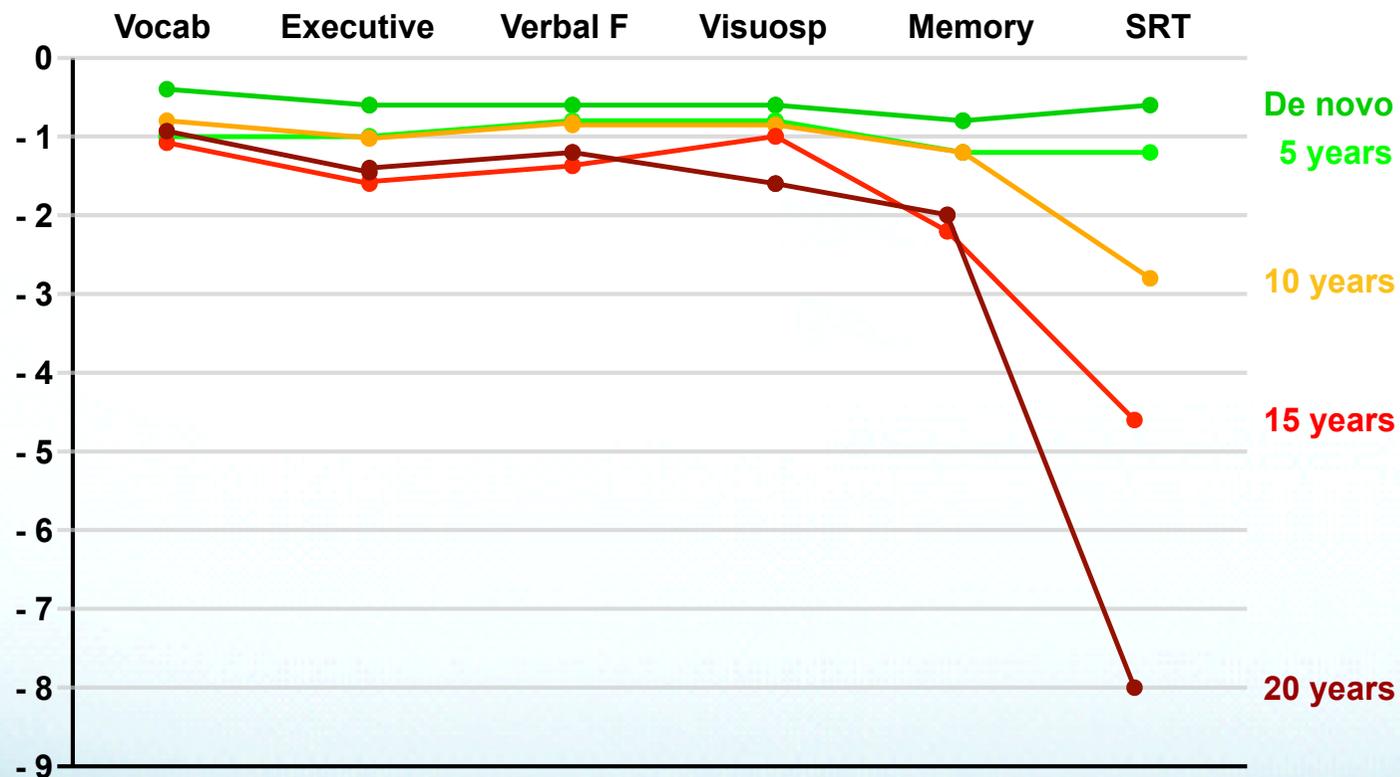
age (years)



age (years)



Patterns of deficits over years



OVER TIME: PD patients have most significant deficits in reaction time, memory and executive function compared to aged matched controls.

Conclusions: Neuropsychological Syndromes in PD

- **Baseline: MPDD & LPDD did not differ from controls in any cognitive domain**
- **10 years- (Linear Regression)- MPDD differed from baseline on all cognitive domains:
SRT>Memory>Executive>Visuospatial>Vocabulary>Verbal Fluency**
- **MPDD > LPDD on SRT & Memory**
- **20 years LPDD compared with B/L :
SRT>Memory>Visuospatial>Executive (decline in Vocabulary and VF very late)**

The Impact of Age on Dementia

- **Late age of onset PD - more rapid decline and poorer prognosis**
- **Earlier age onset- longer survival with very late effects on SRT and memory**
- **Evolution of dementia occurs at similar age, around 70 years regardless of timing of PD onset.**
- **Younger age of onset- significantly longer dementia free survival. Onset over 75 yrs 4.8 times greater dementia risk than age 55yrs.**

Neuropsychological Functioning in PD Delineates Three Separate Clinical Phenotypes

- **Current study supports separate groups - differ clinically, by time to dementia and severity of cognitive impairment.**
- **Does not support EPDD (DLB) vs PDD (part of spectrum (Emre et al 2007, McKeith et al 2005)**
- **MPDD (3-10yrs) have more severe impairment in Vocabulary at dementia onset than LPDD (>10yrs).**
- **Vocabulary impairment ? Reflects high level communication impairment associated with dysexecutive disorder (Ref Hochstadt et al 2006)**
- **? Reflects reduced brain reserve capacity (Brayne et al 2010)**

New LPDD

- **Younger age of onset of PD**
- **Minimal cognitive decline until 10 years**
- **After 10 years: >Memory>RT>Executive>Visuospatial**
- **More benign PD**
- **Memory impairment = loss of cholinergic neurons**
- **Clinicopathological studies- slow infiltration of LB's in the limbic system may underlie neurocognitive deficits (Ref Halliday et al 2008)**
- **Greater hope of developing drug interventions augmenting acetylcholine in combination with dopaminergic treatment- provide longer dementia free survival & better quality of life**

Proposed Mechanisms of Dementia in PD

- **Nigro-striatal pathology**
- **Co-existent disease**
- **Progressive damage to DA innervation of thalamic limbic nuclei**
- **Loss of cholinergic, dopaminergic, noradrenergic and serotonergic innervation (Emre 2003), particularly cholinergic cell loss and limbic pathology with disease progression.**
- **The progressive memory impairment is in keeping with recent reports of age-associated hippocampal and amygdala atrophy in PD (Bouchard et al 2007)**

Contributors to The Sydney Multicentre Study of Parkinson's Disease

Dr Mariese Hely

Prof John Morris

Dr Clement Loy

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