Current Parkinson's Developments

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Outline

1. ICICLE-PD
   - Overview
   - Results – Incidence, NMS and MRI
   - Learning points
2. Current UK Clinical trials for PD
3. PD research in Edinburgh - the future
4. Discussion

Section 1

ICICLE-PD

Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's Disease

ICICLE-PD

- £1.2M Parkinson's UK programme grant

- Additional funding
  - Lockhart PD Fund
  - Michael J Fox Foundation

- Newcastle and Cambridge

- CI David Burn

Aims

- Better understand the anatomical, biochemical and genotypic mechanisms determining the transition from PD to dementia associated with PD
- Determine clinical features associated with a high risk of incident dementia
- Establish putative biomarkers predictive of dementia

ICICLE-PD: Biomarkers

- Neuroimaging
  - MRI
  - FDG-PET
- Genetics
  - MAPT, COMT
- Homocysteine
- Telomere length
- CSF proteins
  - α-synuclein, amyloid ß, tau
- Short afferent latency inhibition
- Brain banking

ICICLE-PD Sub-studies

- Incidence of PD in Newcastle and Gateshead
  - Gordon Duncan and Tien Khoo
- Non-motor symptoms in early PD
  - Gordon Duncan and Tien Khoo
- Gait study
  - Lynn Rochester
- Sleep study
  - Kirsty Anderson

Participants

- Recruitment target was 175 per site: newly diagnosed PD

- Recruitment June 2009 - Dec 2011 (30 months)
  - All incident cases of parkinsonism
  - Movement disorder, neurology, elderly medicine, primary care and psychiatry

- Newcastle
  - 162 PD
  - 100 age-matched controls
- Cambridge
  - 101 PD

Assessments

- **Motor**
  - Hoehn and Yahr stage, MDS-UPDRS
- Cognitive
  - MMSE, MoCA, CANTAB, CDR
- Non-motor symptoms
- Mood
  - GDS-15
- Sleep
  - Epworth Sleep Scale, Pittsburgh Sleep Quality Index
- Quality of life
  - PDQ-39

Incidence of PD in Newcastle & Gateshead

- Determine the incidence of PD in Newcastle-Gateshead

- Newcastle = 283,393
- Gateshead = 205,183
  - total population: 488,576
- Recruitment period: 1st June 2009 – 31st May 2011

Age Group (years)	PD cases (n)	Denominator Population	Incidence 100 000 per year
30-34	1	34 212	1.5
35-39	1	32 825	1.5
40-44	1	34 168	1.5
45-49	4	34 813	5.8
50-54	0	31 069	0
55-59	8	26 905	14.9
60-64	14	26 770	26.2
65-69	21	19 796	53.1
70-74	41	18 042	113.6
75-79	44	15 134	145.4
80-84	27	10 932	123.5
85+	11	9 293	59.2
All ages	**173**	**488 576**	**17.7**

Location	Duration (Months)	PD cases (n)	Denominator Population	Crude rate per 100 000	Age-adjusted rate per 100 000
Navarra[1]	24	86	523 563	8	7.36
London[2]	18	-	100 230	-	19
Cambridge[3]	25	159	708 715	13.6	10.8
Aberdeen[4]	36	50	148 600	22.4	22.1
Norway[5]	22	265	1 052 075	13.7	12.6
Umea[6]	30	93	141 950	19.7	22.5
Newcastle	**24**	**173**	**488 576**	**17.7**	**13.2**

1 Vines JJ 1999
2 MacDonald BK 2000
3 Foltynie T 2004
4 Taylor KS 2006
5 Alves G 2009
6 Linder J 2010

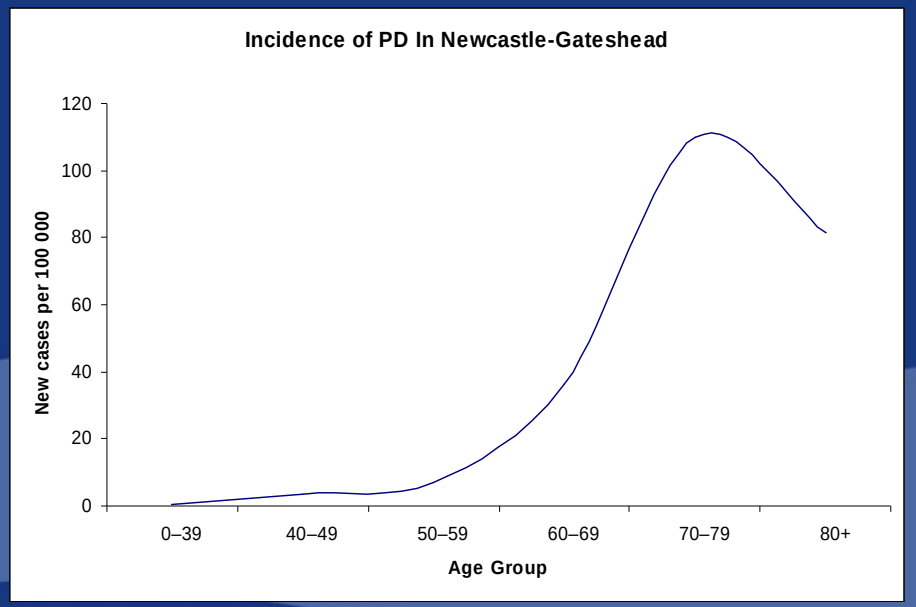
Core business…

Age at diagnosis:

Aberdeen: 74.8 years

Newcastle: 72.4 years

Cambridge: 72.0 years



Caslake R 2014
Duncan GW 2014
Foltynie T 2004

Non-motor symptoms in early PD

- Determine the prevalence of non-motor symptoms in patients with newly diagnosed PD

- Understand the impact of non-motor symptoms upon self reported quality of life in patients with newly diagnosed PD

Clinical characteristics

	PD n = 158	Controls n = 99	P-value
Male, n (%)	105 (66.0)	54 (54.5)	0.065
Age, years	66.6	67.9	0.451
Disease duration, months	6.3		
Hoehn and Yahr stage, n (%)			
1	**35 (22)**		
2	**92 (57.8)**		
3	31 (19.5)		
4	1 (0.6)		
Drug naïve, n (%)	20 (12.6)		
NMS per person (0 – 30)	**8.3**	**2.8**	**<0.001**

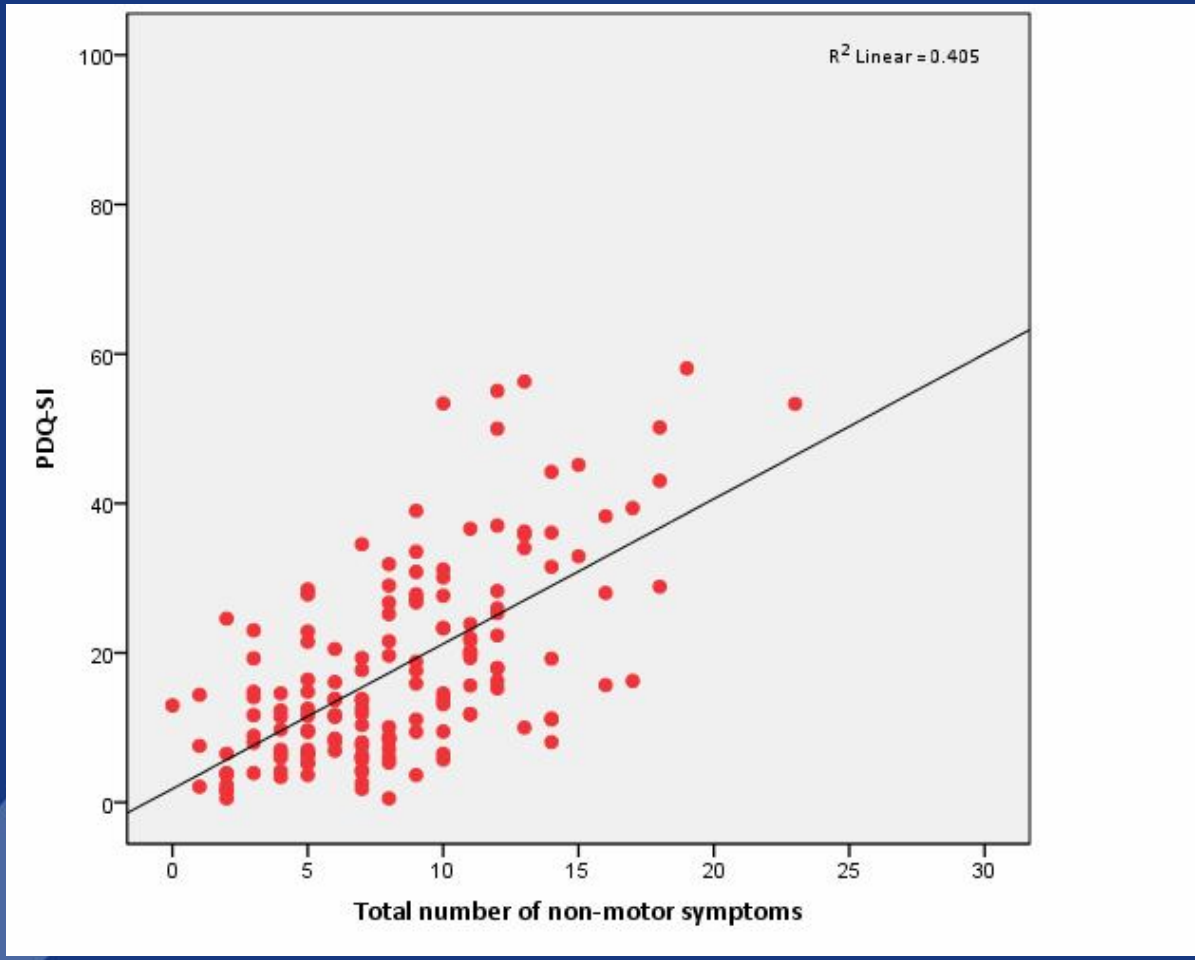
	PD (N = 158) %	Control (N = 99) %	P-value
Gastrointestinal			
Excess saliva and dribbling	56	6	<0.001
Hyposmia	45	10	<0.001
Constipation	42	7	<0.001
Incomplete bowel emptying	32	12	<0.001
Dysphagia	20	3	<0.001
Nausea	3	15	0.142
Bowel incontinence	6	5	1.000
Weight change (unexplained)	23	19	0.536
Urinary			
Urinary urgency	46	19	<0.001
Nocturia	26	17	0.095
Sexual function			
Sexual dysfunction	21	10	0.026
Impaired libido	18	7	0.016
Pain	38	3	<0.001

	PD N = 158 %	Control N = 99 %	P-Value
Cardiovascular			
Orthostatic symptoms	33	11	<0.001
Falls	23	4	<0.001
Lower limb swelling	18	11	0.157
Neuropsychiatric and Cognitive	43	10	<0.001
Anxiety	37	10	<0.001
Low mood	30	2	<0.001
Impaired concentration	28	3	<0.001
Loss of interest & apathy	22	0	<0.001
Visual hallucinations	55	41	0.040
Forgetfulness	1	0	1.000
Delusions			
Sleep			
Daytime somnolence	37	18	0.001
Dream re-enactment	35	8	<0.001
Vivid dreams	30	5	<0.001
Restless legs	28	11	0.002
Insomnia	18	13	0.385
Miscellaneous			
Diplopia	10	3	0.048
Hyperhydrosis	10	6	0.360

Quality of life

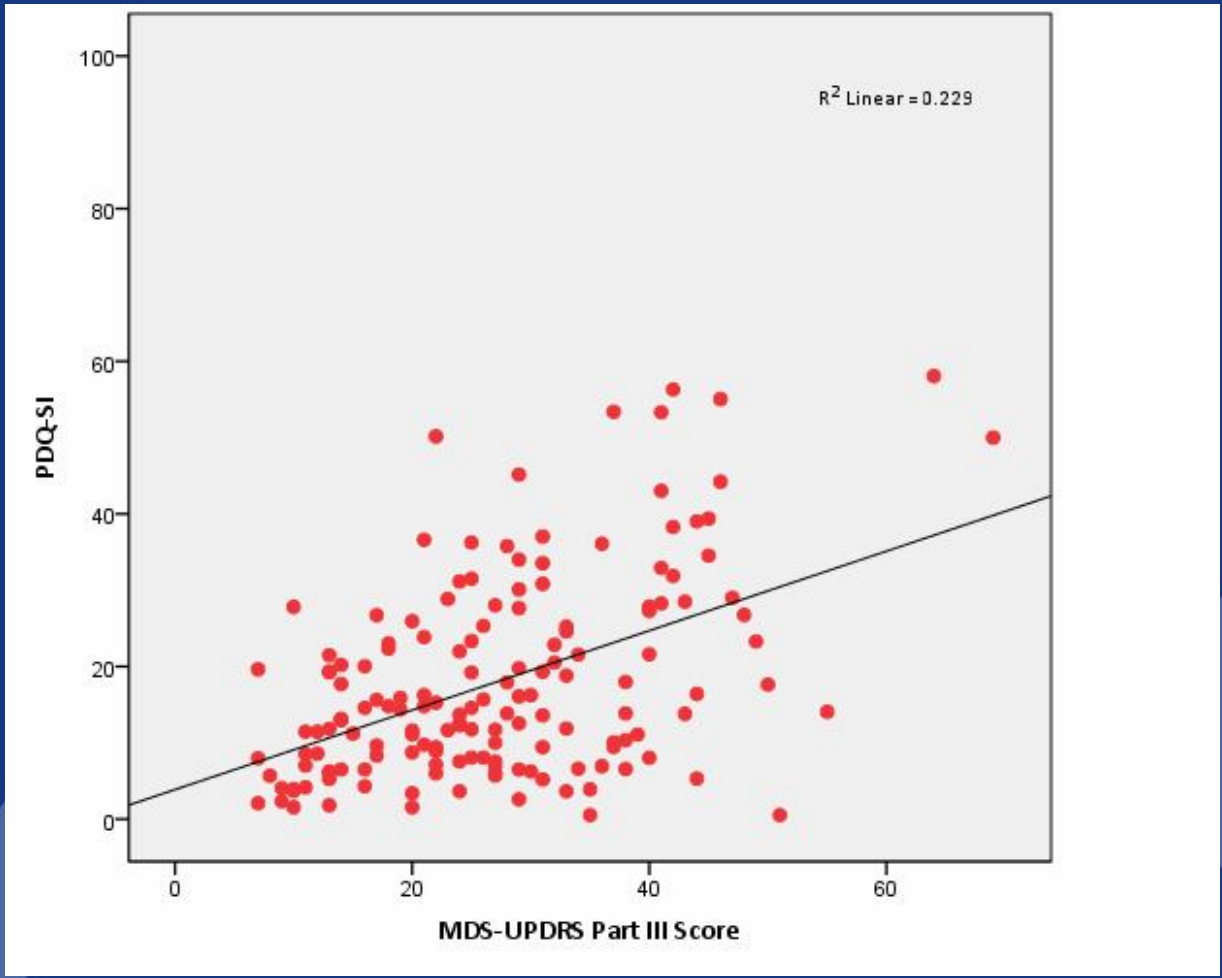
PDQ-39 Domain	Score (0 – 100)
Bodily discomfort (3)	29
Mobility (10)	24
Activities of daily living (6)	21
Cognition (4)	21
Emotional wellbeing (6)	20
Stigma (4)	15
Communication (3)	11
Social support (3)	4
PDQ-39 Summary Index Score	**18**

Non-motor symptoms and Quality of Life



Duncan GW 2013

Motor severity and Quality of Life

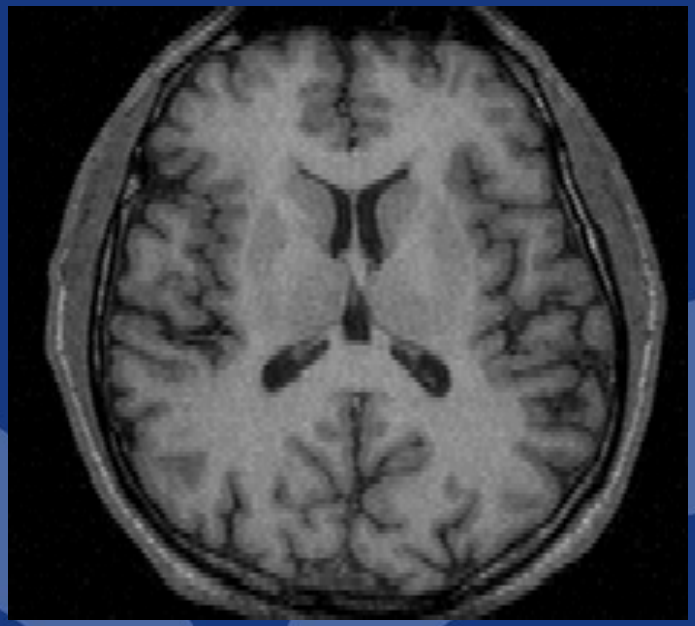


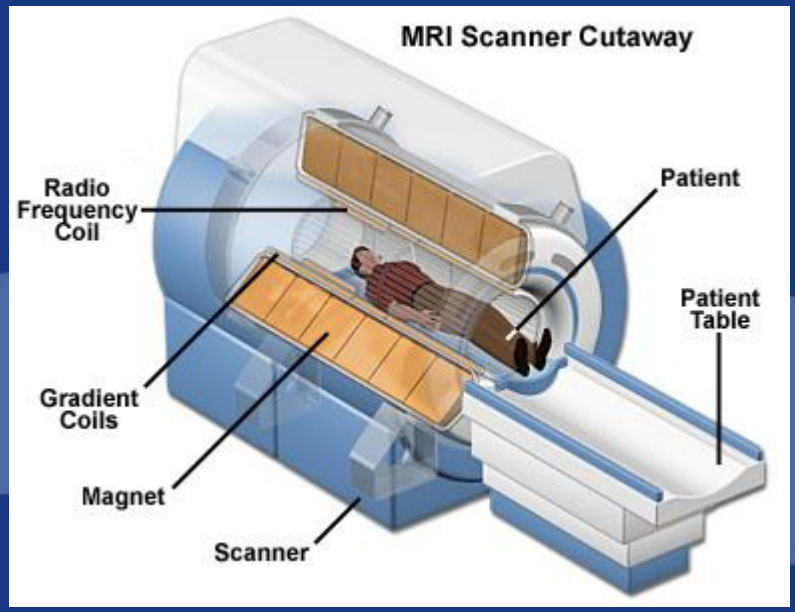
Duncan GW 2013

Non-motor symptoms

- NMS are common in newly diagnosed PD
- Reflect the underlying disease process?
- Reduced QoL scores are predicted by increasing number of NMS
- Neuropsychiatric symptoms have greatest negative impact upon QoL
- Dopaminergic and non-dopaminergic substrates
- Treatment options are available…

Imaging ICICLE: What can MRI tell us about cognitive function in early PD?





MRI as a biomarker?

Advantages

- SAFE
- Detailed images
- No radiation
- Repeatable
- Cheap (ish)
- Examine both disease and normal structure and microstructure

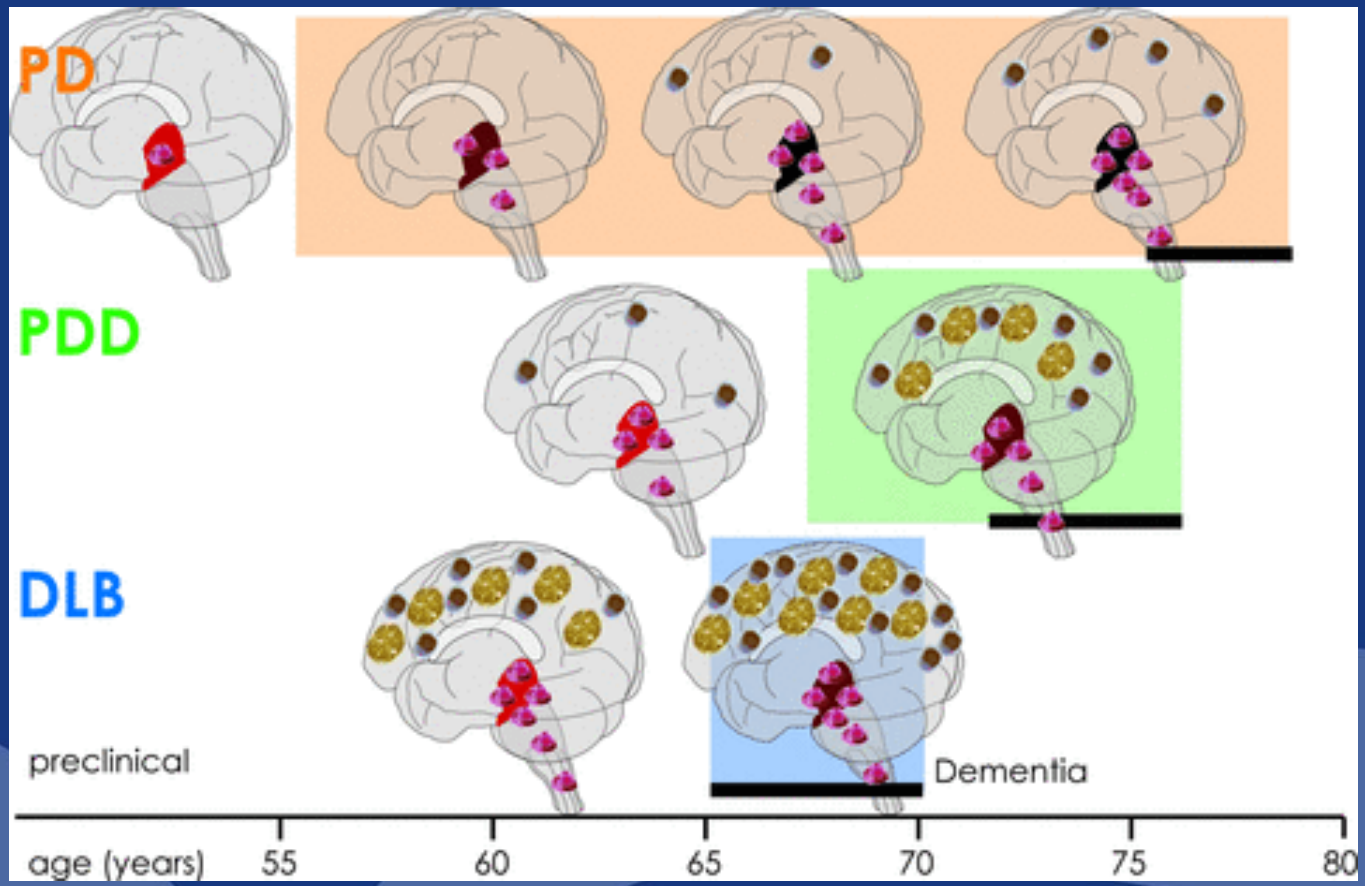
Disadvantages

- Noisy
- Time consuming
- Need to lie flat
- Claustrophobia
- Ferrous metals

MRI as a biomarker?

- Uses radiofrequency and magnetic fields to acquire detailed anatomical images
- Established in studies of AD and amnestic MCI
- Grey matter (GM) atrophy quantifiable PDD

Pathology in PD



Annals of the New York Academy of Sciences
Volume 1184, Issue 1, pages 188-195, 24 NOV 2009

MRI as a biomarker?

- Reflect the anatomical and patho-physiological changes in PD?
- Prognosis: can it identify “high risk” patients who will develop dementia?
- Longitudinal: outcome measure of response in (early) therapeutic trials?

ICICLE-PD

Aim:

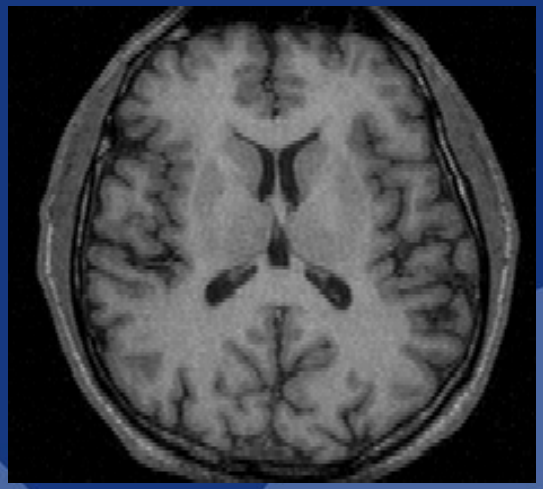
To determine the significance of early cerebral atrophy patterns seen on structural and diffusion-tensor MRI in patients with newly diagnosed PD

Objectives:

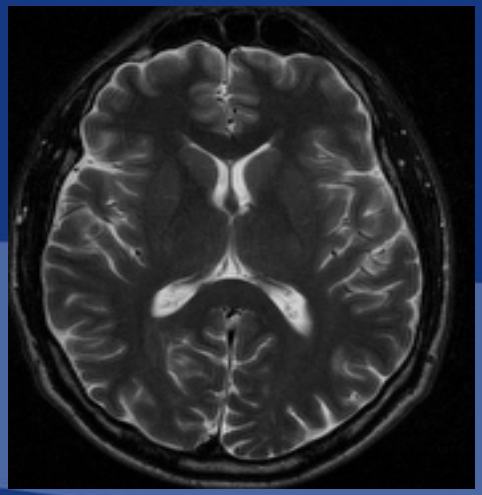
1. Accurate clinical and neuropsychological characterisation of a cohort of newly diagnosed Parkinson's disease patients
2. Perform structural MRI and diffusion tensor magnetic resonance imaging (DT-MRI) on all patients
3. Correlate MRI data analysis with the neurological and cognitive profiles of the patients according to our hypotheses
4. Perform the same clinical and imaging assessments with a healthy age and sex matched control group
5. Compare the patient and control groups

Structural MRI

T1

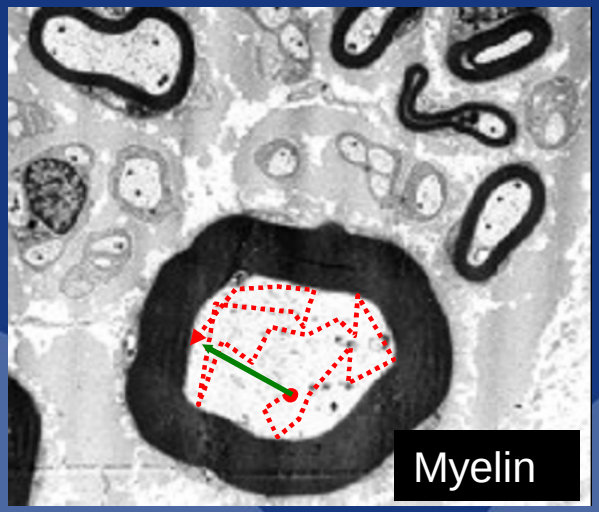


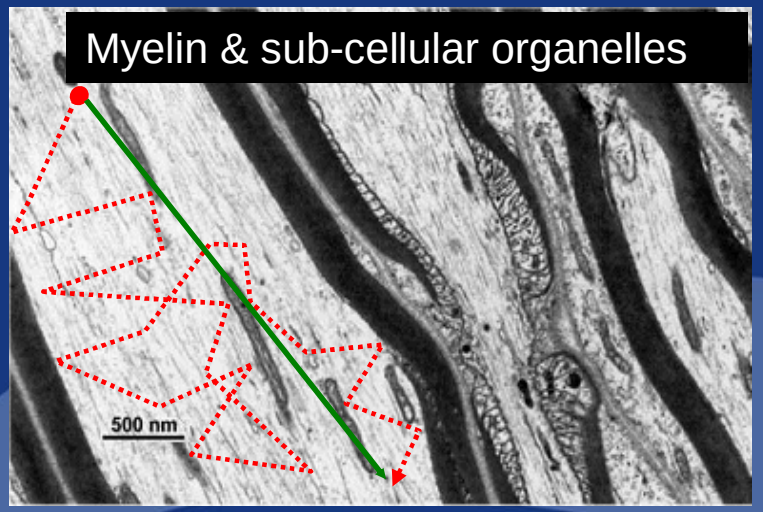
T2

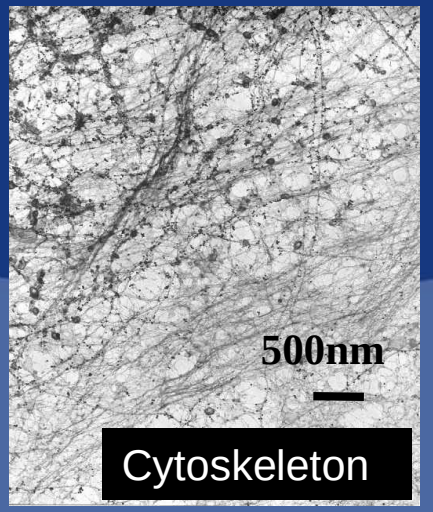


Diffusion Tensor Imaging

Water diffusion within the CNS is restricted by cellular and sub-cellular structures







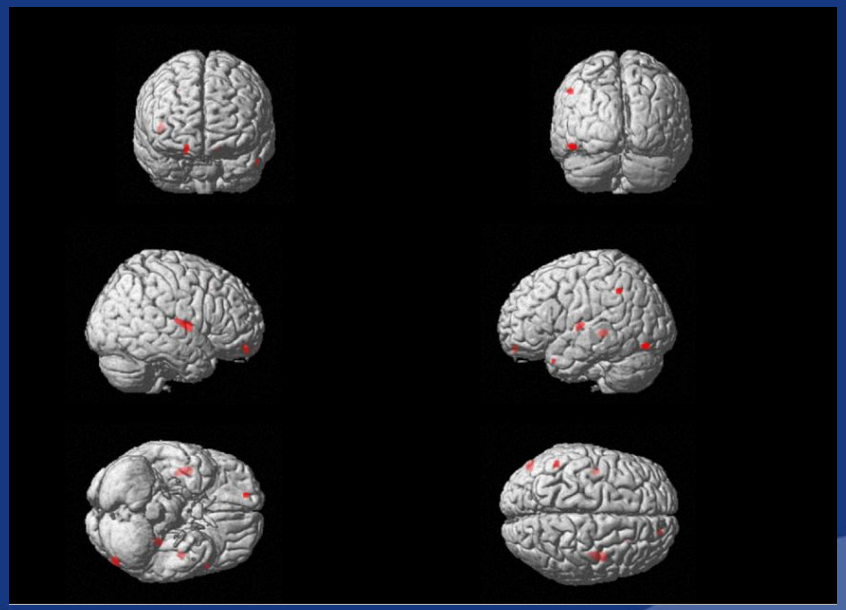
ICICLE-PD: MRI

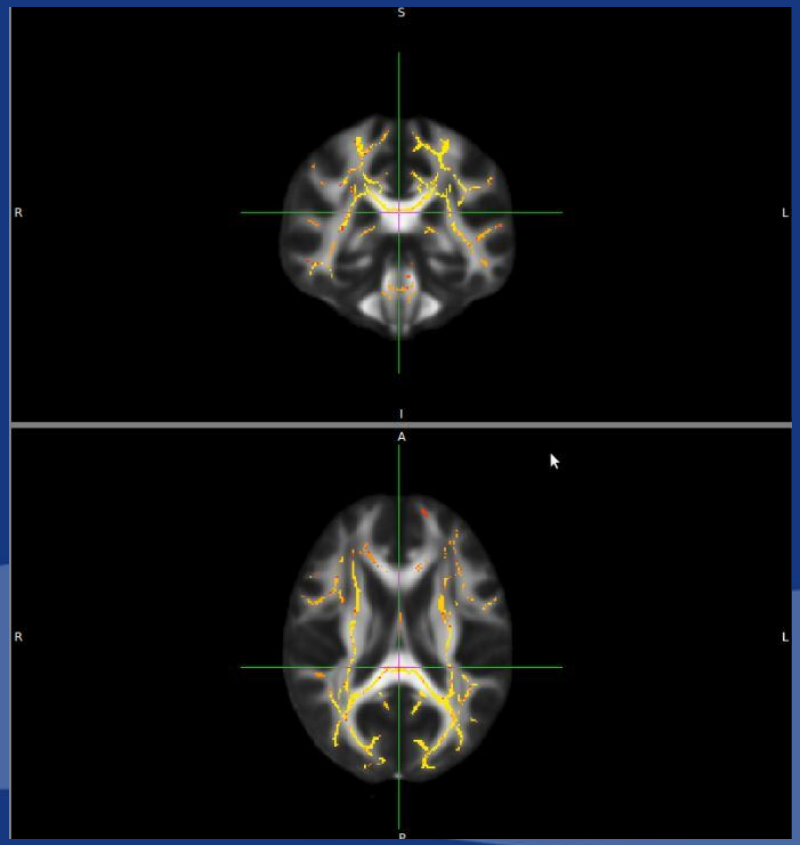
Characteristic	PD n = 125	Control n = 50	P Value
Age, years	66.0	65.8	0.881
Male, n (%)	85 (68)	29 (58)	0.210
Education, years	13.1	13.6	0.363
Duration of PD, months	6.15	-	-
Hoehn & Yahr I & II, n (%)	100 (80)	-	-
Hoehn & Yahr III, n (%)	25 (20.0)	-	-
GDS-15	2.7	0.96	< 0.001

Cognitive Function

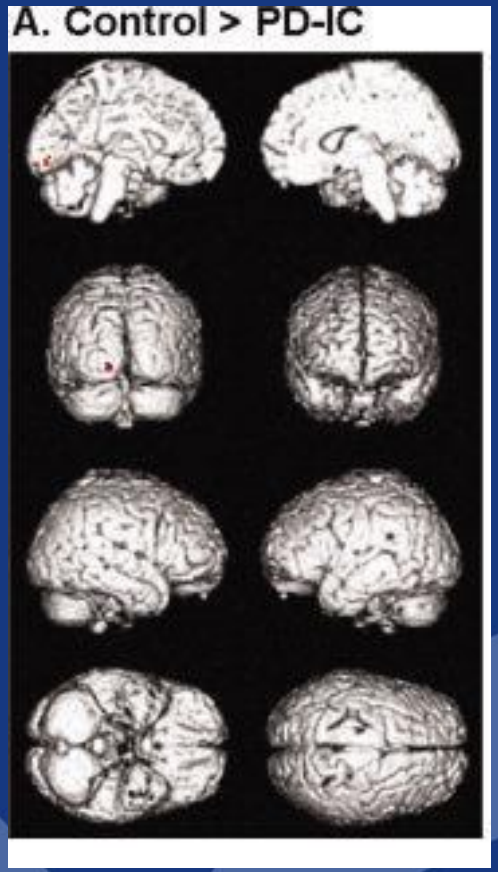
Cognitive Test	PD n = 125	Control n = 50	P Value
MMSE (30)	28.6	29.2	0.003
MoCA (30)	25.2	27.6	< 0.001
Phonemic fluency (FAS)	33	41	< 0.001
Semantic fluency (animals)	21	24	0.004
Power of attention (ms)	1363	1242	< 0.001
Spatial recognition memory	15.2	16.7	< 0.001
Pattern recognition memory	19.7	21.3	0.001
Language	4.5	4.7	0.247

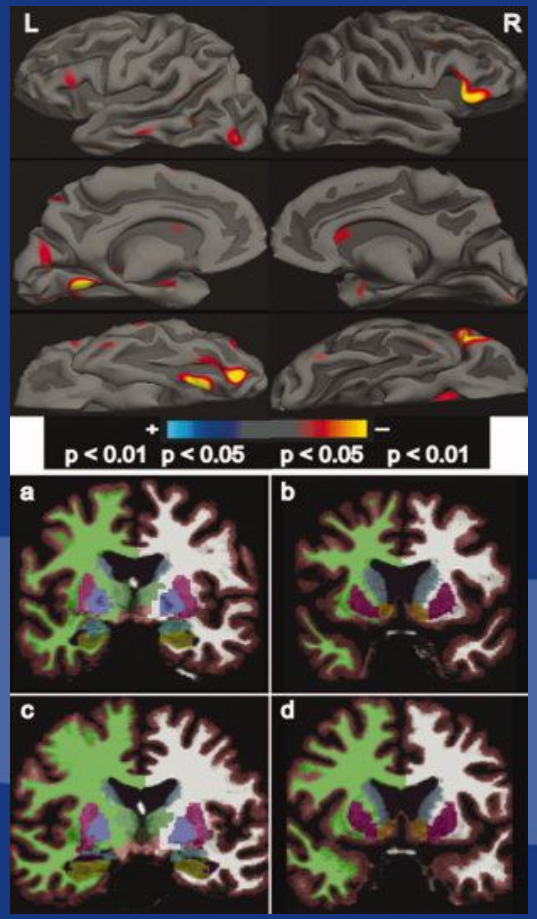
Early PD *vs.* controls: VBM and MD





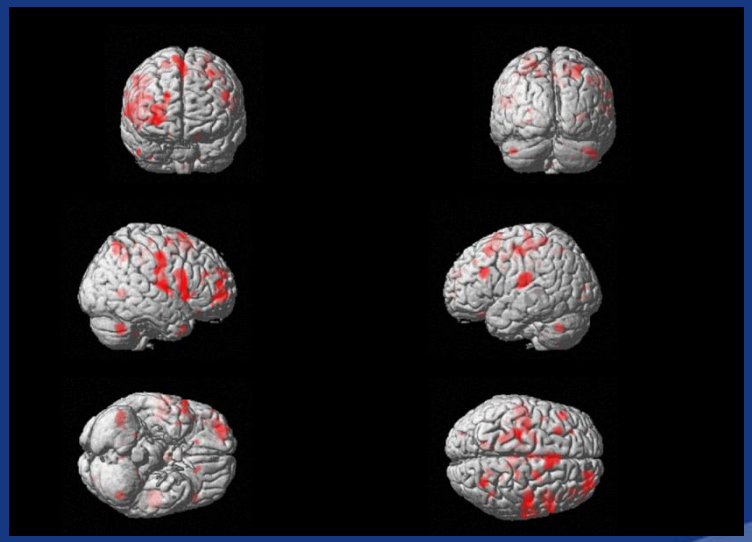
Early PD

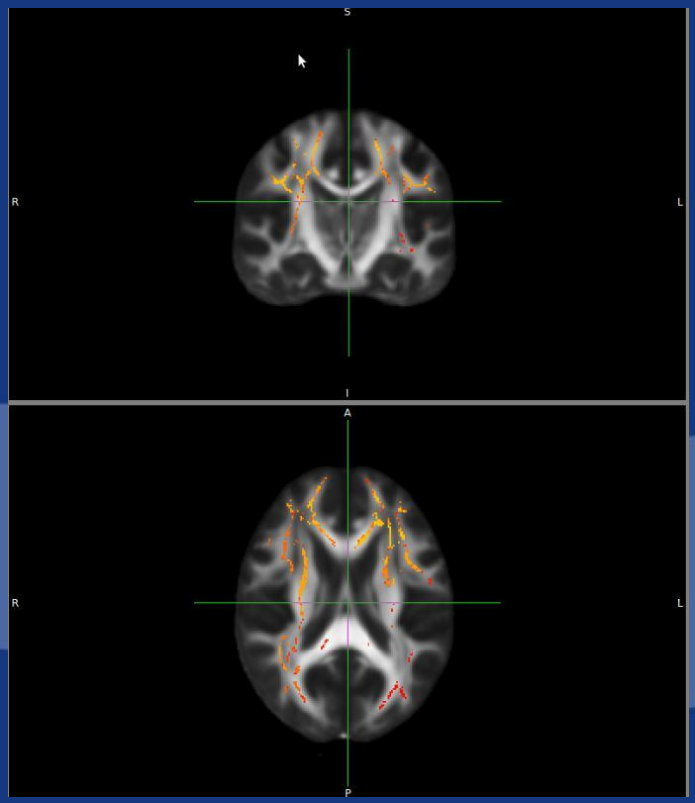




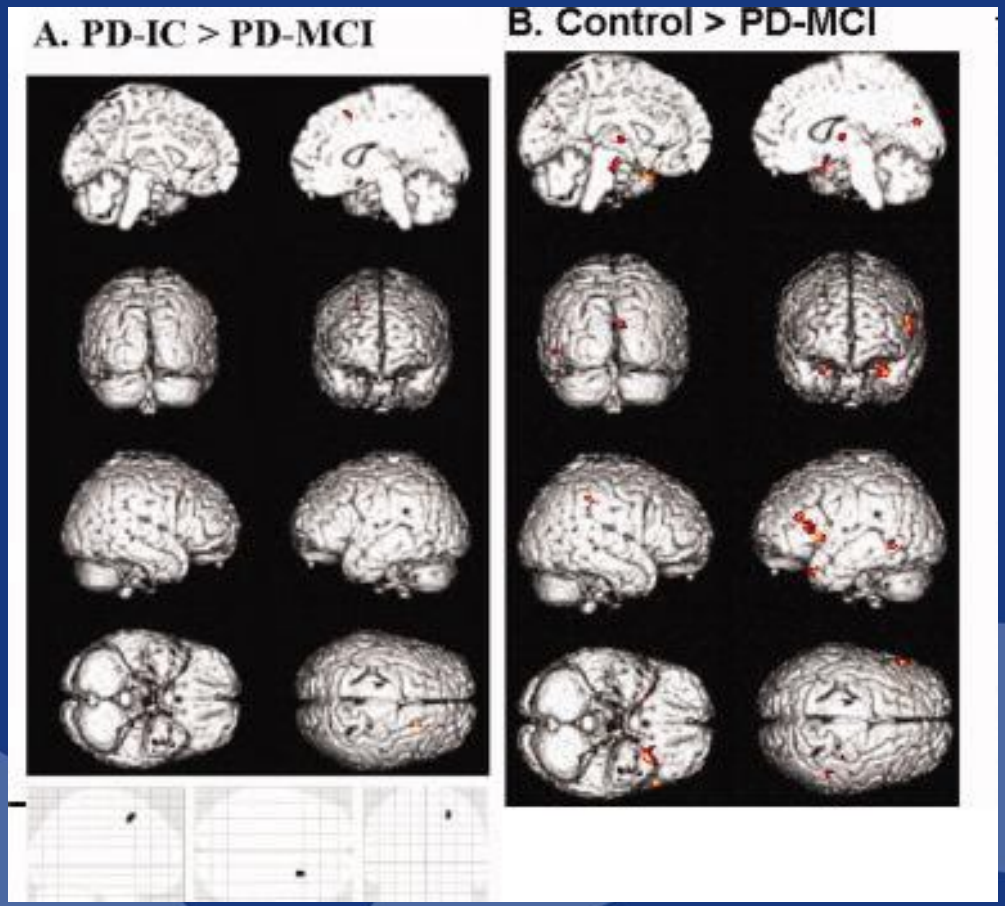
Song SK et al. Movement Disorders 2011:26;289-296.
Tinaz S et al. Movement Disorders 2011;26:436-41.

Semantic Fluency





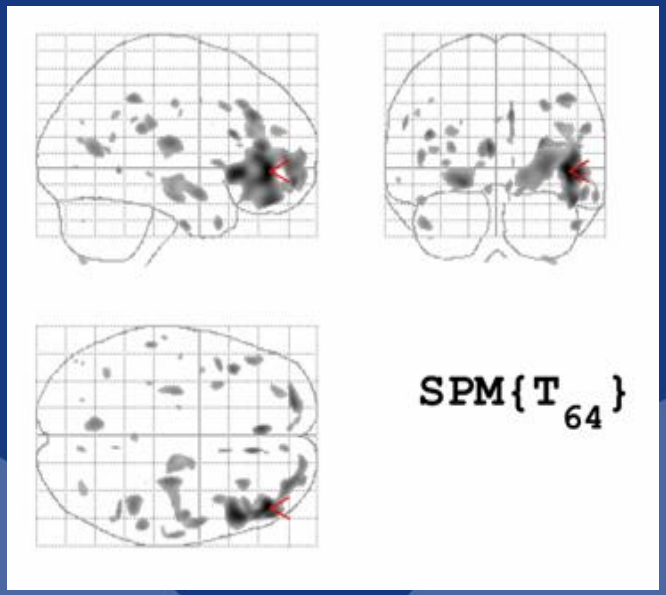
MCI and MRI



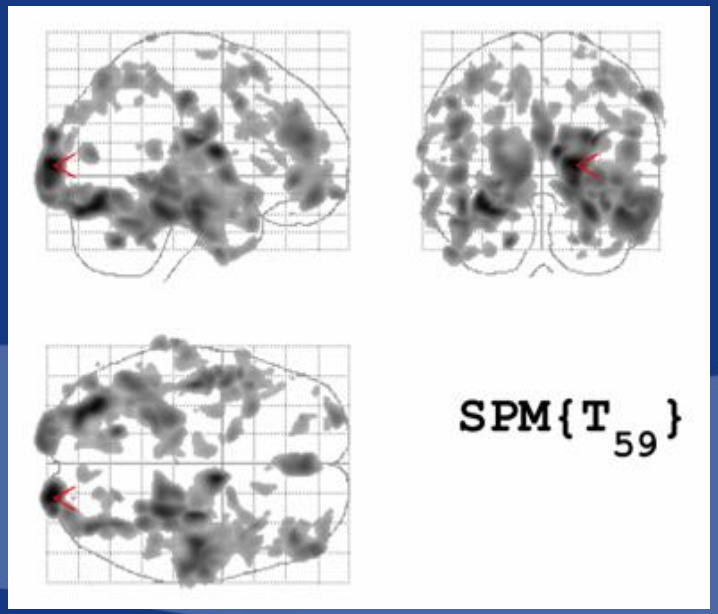
Song SK et al. Movement Disorders 2011:26;289-296.

MRI in advanced PD

Grey matter loss in PD (n = 31)



Grey matter loss in PDD (n = 26)



Burton EJ 2004

MRI as a biomarker?

- No significant grey matter loss in early PD
  - Consistent with neuropathology
- Mild changes appear with subtle cognitive impairments
- White matter tract changes may be more sensitive
- Longitudinal research is vital

ICICLE-PD: Where next?

- Parkinson's UK renewal funding awarded
  - £350k until June 2017
- Increasing conversion to end-points
  - dementia & death
- Linkage to other studies
  - e.g. Tracking-PD, Monument-PD
- Clinico-pathological studies
  - brain tissue donations to NBTR

ICICLE-PD: Learning Points

- Research into early stages of PD is vital
- Supply and demand are unmet
- Strong links between clinic and university
- Collaboration between research disciplines - synergy

Learning Points: clinical practice

- Mean age of diagnosis is in early 70s
  - Applying research to patients
- NMS common across all stages of PD
  - Impact on QoL
  - Many therapeutic options available
- MRI is a promising biomarker
  - Multi-modal panel of clinical, imaging, genetic and biochemical tests

Acknowledgements

Newcastle

David Burn, Alison Yarnall, Rachael Lawson, Leanne Thompson, Kirstie Anderson, Sharon Reading, Tricia McGee, Una Brechany, Jane Noble, Barbara Wilson and Sarah Marrinan

NIHR

Dementia and Neurodegenerative Disease Research Network

Primary Care Research Network

Gateshead

David Beaumont, Richard Athey, Helen O'Connell and Imogen Forbes

Cambridge

John O'Brien and Roger Barker

Funding

Parkinson's UK

Lockhart Parkinson's Disease Research Fund

Section 2

Current UK Clinical trials for PD

Clinical trials: surgery

- Nucleus basalis deep brain stimulation for thinking and memory problems in Parkinson's
- Long term safety and efficacy study of ProSavin in Parkinson's disease

Clinical trials: medical

- Evaluating the effectiveness of Neupro (Rotigotine) and L-dopa combination therapy in patients with Parkinson's disease
- A trial of Exenatide for the treatment of moderate severity Parkinson’s disease
- A pilot clinical trial with the iron chelator deferiprone in Parkinson's disease
- The effects of an exercise intervention on pulmonary function, respiratory muscle strength, aerobic capacity and perception of breathlessness in a representative population of patients with idiopathic Parkinson's disease

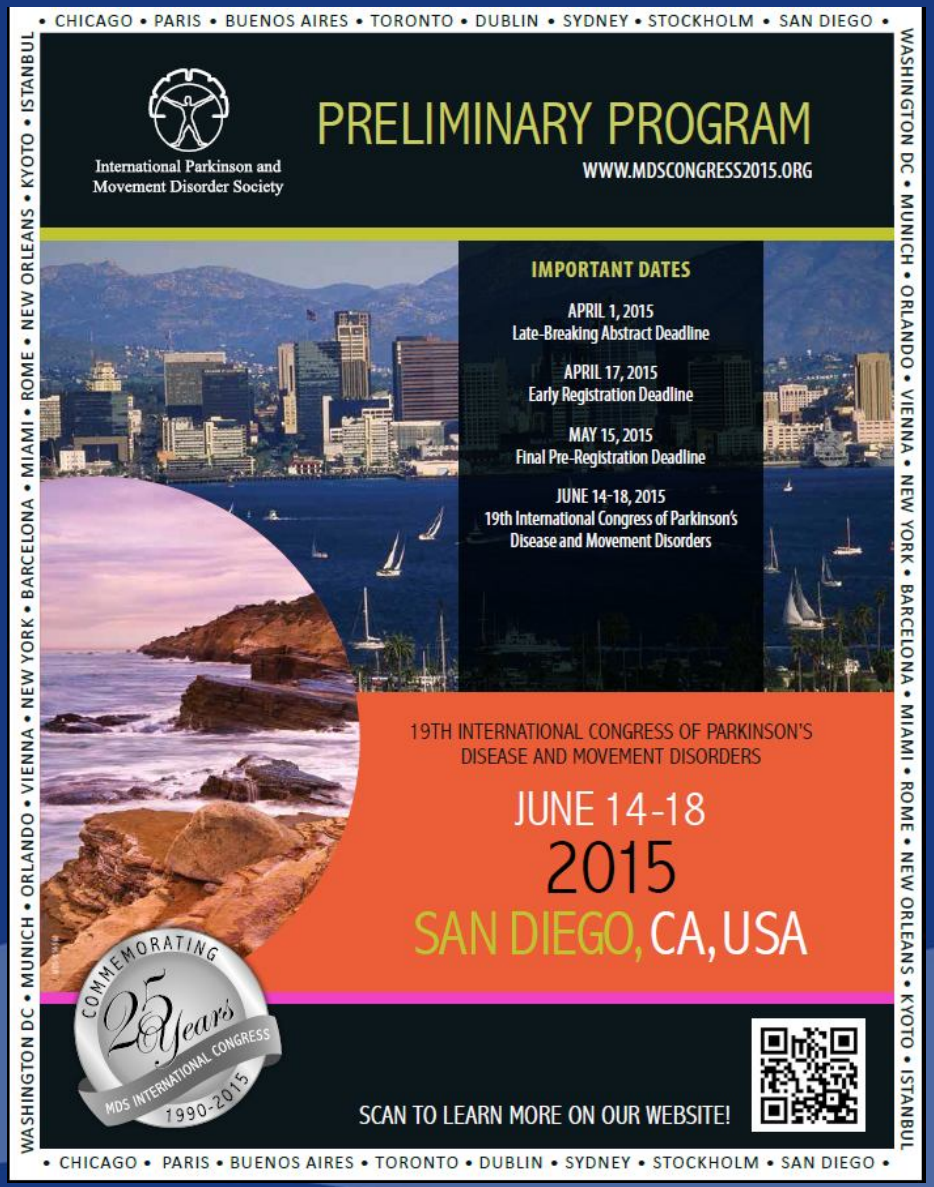
Section 3

Edinburgh PD Research - the future

Edinburgh PD Research - the future

- Health informatics / data linkage
- Scottish Health Research Register (SHARE)
- Hub for clinical trials in Scotland
- Participate in multi-centre observational studies

Discussion
and
Questions



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