The Selection of Patient Groups for Neuroprotective Trials

- W. Poewe
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TARGET POPULATIONS FOR NEUROPROTECTIVE TRIALS IN PD - SELECTION CRITERIA -

- PD subtype
  - * clinically defined
  - * genetically defined
  - * biomarker defined

- Disease stage

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SELECTING PD TRIAL POPULATIONS BY PD SUBTYPE

PRO's:

- homogeneous groups
- common underlying pathophysiology (e.g. LRKK2 mutations)
- molecular definition of drug targets

CON's:

- limited generalisibility of trial results
- narrow recruitment base

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CLINICAL PROGRESSION OF PARKINSON'S DISEASE

- Progression of cardinal motor features
- Evolution of treatment-related motor complications
- Progression of „non-dopaminergic" motor impairment
- Evolution of non-motor symptoms / signs
- Progression of global disability
- Mortality

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MODIFYING PD PROGRESSION
- Target Populations -

* At risk subjects

* Early disease
  - untreated, „de-novo“
  - treated stable disease

* Advanced disease
  - motor complications
  - „non-dopaminergic“ motor features
  - non-motor features

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DISEASE PROGRESSION IN EARLY UNTREATED PD
- Clinical Issues -

- slow / stop progression of cardinal motor features

- maintain symptomatic control

- prevent / delay motor complications

- prevent / delay disability

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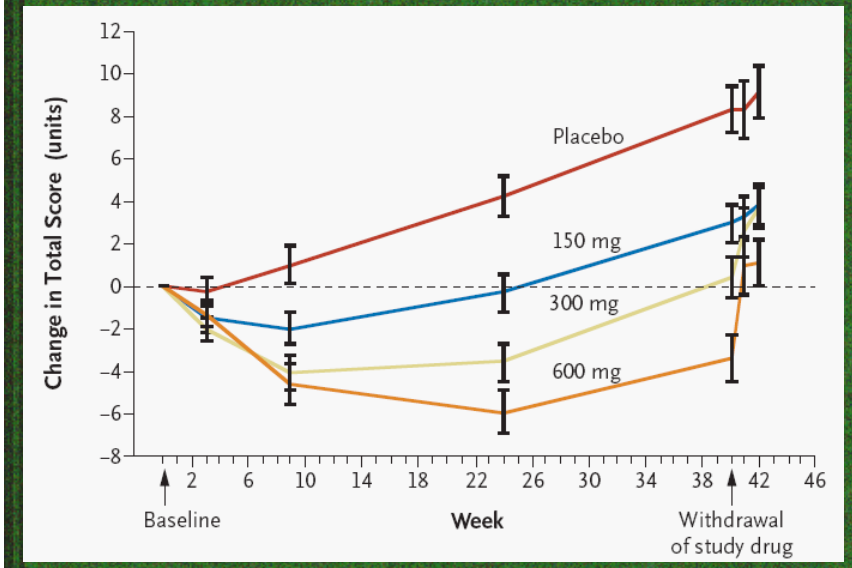
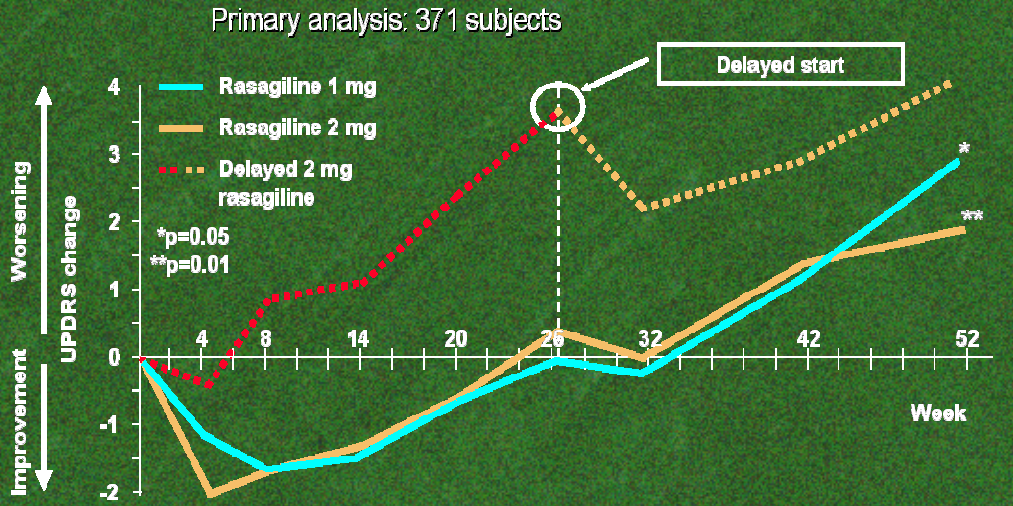
PROGRESSION OF MOTOR IMPAIRMENT IN EARLY PD

The ELLDOPA Study (Fahn et al, NEJM 2004)



12-month results: Mean change in Total UPDRS



Comparison between rasagiline for 1 year and delayed-rasagiline
Effect size: comparing rasagiline 1 mg for one year with delayed rasagiline was -1.8 units (95% CI, -3.64 to 0.01, *p=0.05), and the effect size comparing rasagiline 2 mg for one year with delayed rasagiline was -2.3 units (95% CI, -4.11 to -0.48, **p=0.01)

Parkinson Study Group. Arch Neurol 2004; 61: 561–566

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Annual increase in total UPDRS Scores in placebo-controlled studies

Study	Duration (yrs)	Change in Mean total UPDRS for Placebo Group	Extrapolated Annual Increase, total UPDRS scores	Extrapolated Annual Increase UPDRS III
PSG. *N Engl J Med*. 2004 (placebo vs levodopa; ELLDOPA)	0.81	7.8	9.6	6.4
Shults et al. *Arch Neurol*. 2002 (placebo vs coenzyme Q10)	1.3	12.0	9.2	4.9
PSG. *Ann Neurol*. 1996 (placebo vs lazabemide)	1.0	8.1	8.1	5.3
PSG. *Arch Neurol*. 2002 (placebo vs rasagiline)	0.5	4.2	8.4	---

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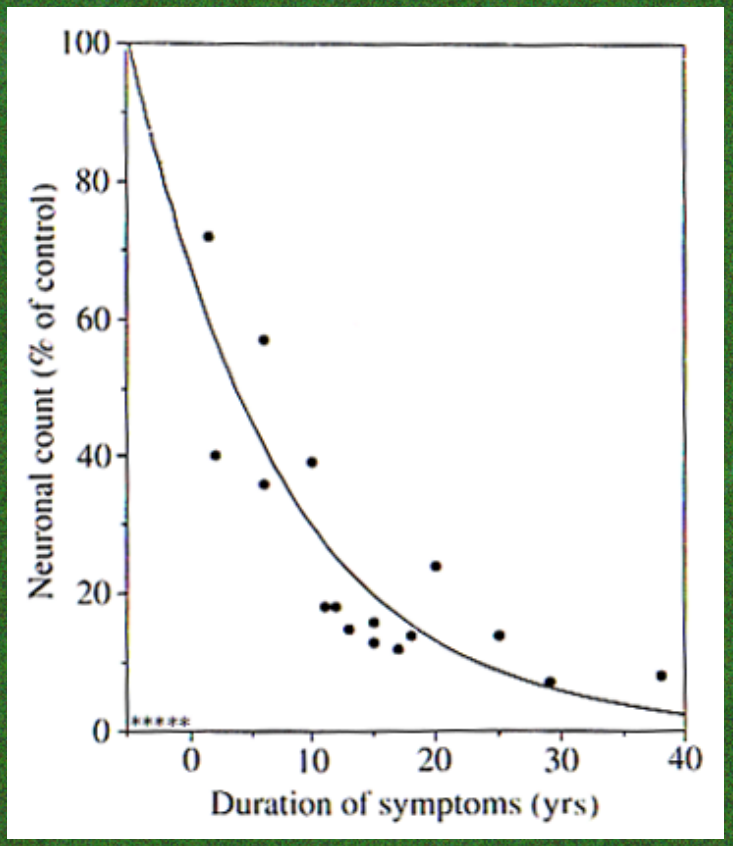
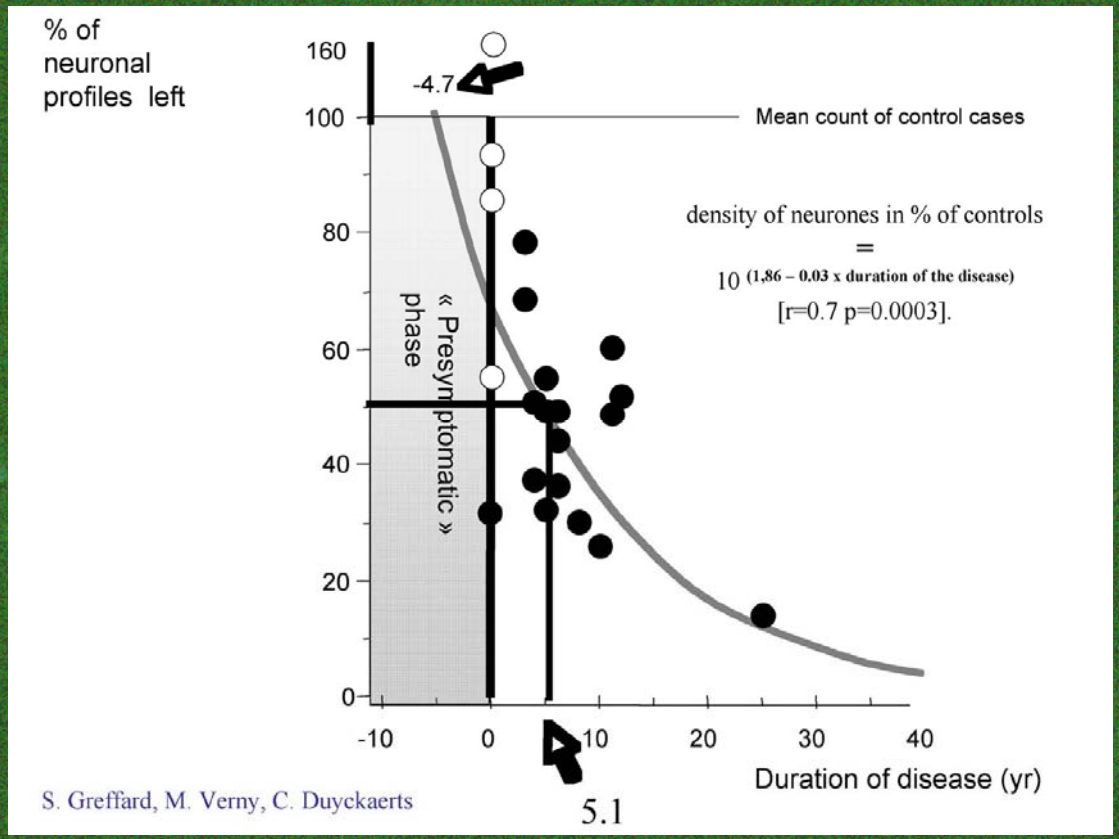
Total nigral age-adjusted count vs Symptom Duration (Fearnley and Lees Brain 1991)



Total nigral age-adjusted count vs Symptom Duration (Duyckaerts et al, 2005)



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NEUROPROTECTIVE TRIALS IN EARLY UNTREATED PD

- Challenges -

- slow progression of early PD
- trial duration
- large patient numbers
- clinical relevance of small effects
- diagnostic uncertainty
- heterogeneity of PD

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PROGRESSION OF DISABILITY IN IPD
- Percentages remaining in stage 1 or 2 for up to 10 yrs. -

Hoehn + Yahr, 1967	37 %
Marttila and Rinne, 1977	45 %
Hoehn, 1983	32 %
Hely, 1999	28 %

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DISEASE PROGRESSION IN EARLY TREATED (STABLE) PD
- Clinical Issues -

- prevent progression of cardinal motor features

- prevent / delay drug-related motor complications

- prevent / delay gait and balance problems

- prevent / delay evolution of non-motor disability

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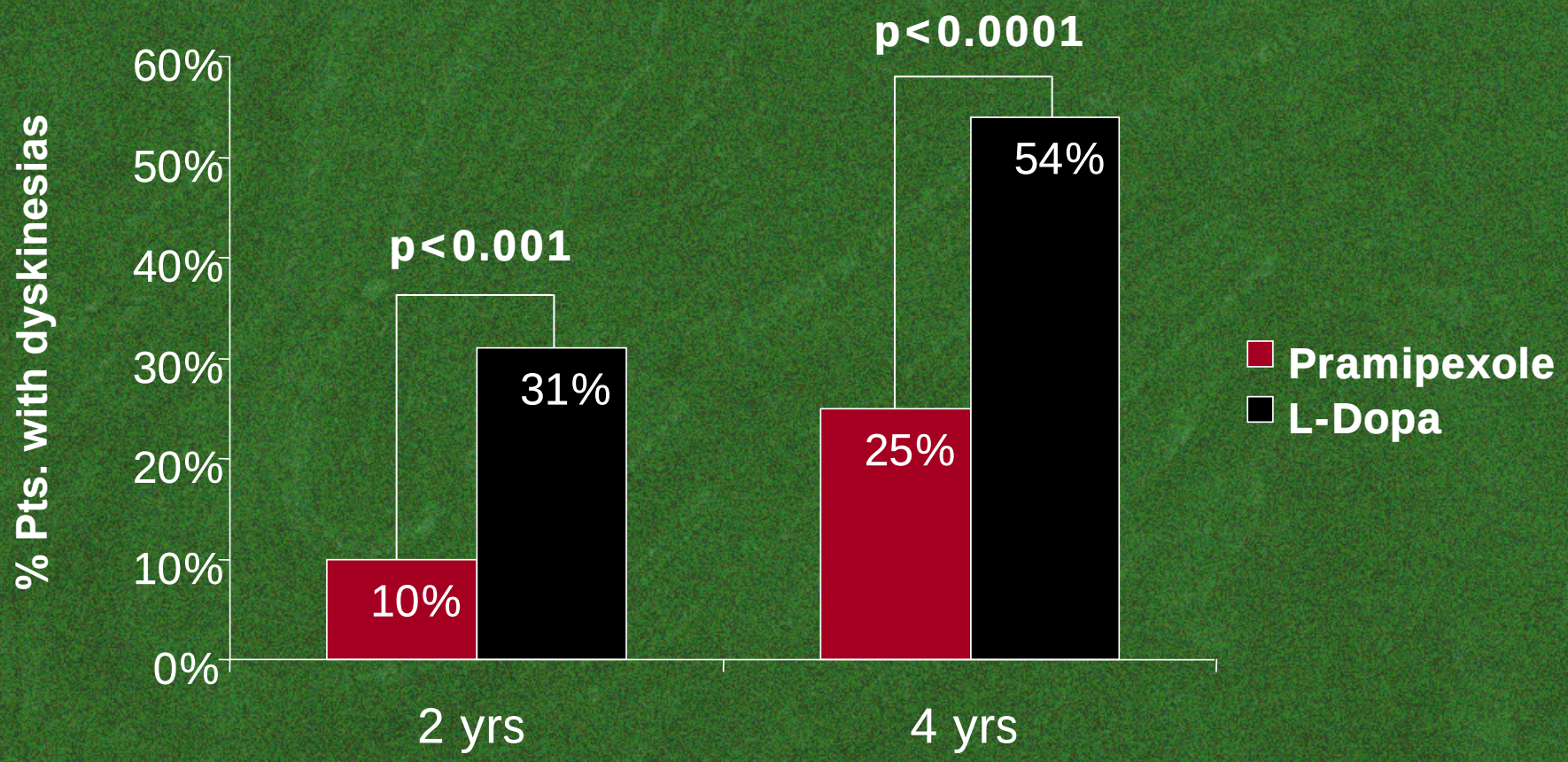
CALM-PD - Dyskinesia risk at 2 and 4 yrs.



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Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease

A 4-Year Randomized Controlled Trial

*The Parkinson Study Group**

Arch Neurol. 2004;61:1044-1053

	Pramipexole	L-Dopa
Dyskinesia rate	24.5 %	54 % *
Disabling dyskinesias	4.4 %	6.9 %
L-Dopa dose	434 mg/d	702 mg/d
Freezing	37.1 %	25.3 % **
∆ UPDRS	+2.0	-3.2 ***

* p < 0.001 ** p = 0.01 *** p = 0.003

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PROGRESSION OF PD COMPLICATIONS
(Shoulson et al, 2002)

* N = 368 pts. from DATATOP treated with L-Dopa

* New onset of motor and non-motor complications over 2 year follow-up

	LD / Plac.	LD / Depr.
- wearing-off	52 %	42 %
- on-off	9 %	3 %
- dyskinesias	14 %	34 % *
- FOG	29 %	16 % **
- confusion	7 %	7 %
- dementia	3 %	4 %

* p = 0.006 ** p = 0.0003

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PROGRESSION OF DISABILITY IN IPD
- Latencies to reach successive H+Y stages -

STUDY	HY 1	HY 2	HY 3	HY 4	HY 5
Hoehn + Yahr, 1967	*3,0*	*6,0*	*7,0*	*9,0*	*14,0*
Marttila + Rinne, 1977	*---*	*2,9*	*5,5*	*7,5*	*9,7*
Hoehn, 1983	---	9,0	12,0	12,0	18,0
Hely et al, 1999	---	---	4,0	7,0	6,0
Müller et al, 2000	---	3,0	5,5	14,0	15,0
Lücking et al, 2000	---	11,0	19,0	26,0	40

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NEUROPROTECTIVE TRIALS IN EARLY TREATED (STABLE) PD
- Challenges -

- trial duration

- “soft” definitions of outcomes

- patient numbers

- exclusion of symptomatic effects

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DISEASE PROGRESSION IN ADVANCED PD
- Clinical Issues -

- motor complications
- falls
- dysphagia, dysarthria
- cognitive decline, psychosis
- autonomic failure
- sleep-wake-dysregulation
- nursing-home placement
- mortality

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LONG-TERM PROGNOSIS OF PD
- Sydney multicentre study (Hely et al, 2005) -

- 149 pts recruted into low-dose L-Dopa vs. bromocriptine trial

- 52 survivors after 15 – 18 yrs

- High prevalence of „L-Dopa resistant“ symptoms:

* Falls	81 %
* Cognitive decline	84 %
* Dementia	48 %
* Hallucinosis	50 %
* Depression	50 %
* Choking	50 %
* Symptomatic OH	35 %
* Urinary incontinence	41 %

- 40 % in nursing homes

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DEMENTIA AND THE PROGRESSION OF PD
- Epidemiology -

- Point prevalence: 31 % (Aarsland et al, 2005)
- Incidence rates: 10 % per year (Emre et al, 2006)
- Time to dementia: 10 years (Aarsland et al, 2003; Hughes et al, 2000)

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NEUROPROTECTIVE TRIALS IN ADVANCED PD
- Challenges -

- “natural” progression rates poorly defined

- fragile populations with abundant comorbidity

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MODIFYING PD PROGRESSION
- Target Populations -

* At risk subjects

* Early disease
  - untreated, „de-novo“
  - treated stable disease

* Advanced disease
  - motor complications
  - „non-dopaminergic“ motor features
  - non-motor features

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DEFINING POPULATIONS AT-RISK FOR PD
- Clinical Issues -

- primary prevention

  * delay onset
  * reduce incidence

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DEFINING POPULATIONS AT-RISK FOR PD
- Challenges -

- define risk markers / biomarkers
  - * genetic
  - * proteomic
  - * imaging
  - * neurophysiology

- define conversion rates in at-risk populations

- ethical issues

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The Genomic Age

	Inheritance	Locus	Onset	Lewy-bodies	Gene
PARK1	Autosomal-dominant	4q21	~ 40	+	Alpha-Synuclein
PARK2	Autosomal-recessive	6q25	20 - 50	- (?)	Parkin
PARK3	Autosomal-dominant	2p13	~ 60	+	?
PARK4	Autosomal-dominant	4p15	30 – 40	(+)	?
PARK5	Autosomal-dominant	4p15	~ 50	?	Ubiquitin hydrolase L1
PARK6	Autosomal-recessive	1p35	~ 30	?	PINK1
PARK7	Autosomal-recessive	1p36	~ 30	?	DJ-1
PARK8	Autosomal-dominant	12q	~40	variable	LRRK2
PARK9	Autosomal-recessive	1q36	~30	?	?
PARK10	Autosomal-dominant	1p32	late	?	?
PARK11	Autosomal-dominant	2q36-37	late	?	?

Phenotype: Parkinson Syndrome

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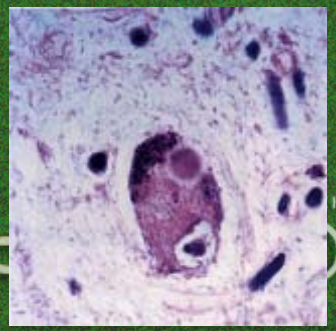
Courtesy Prof. Gasser, Tübingen



IMAGING MARKERS

SPECT

PET

MRI

Midbrain ultrasound

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NEUROPHYSIOLOGICAL MARKERS

- Hyposmia
- RBD
- Constipation
- Codon vision

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IDIOPATHIC HYPOSMIA AS A PRECLINICAL SIGN OF PD

(Ponsen et al, Ann. Neurol. 56, 2004)

* 361 asympt. first degree relatives of PD pts.

* 2 yr follow-up (smell-test, clinical, ß-CIT-SPECT)

* 40 „hyposmic“ vs. 38 „normosmic“ subjects
  - 4 vs. 0 clinical PD
  - significantly greater decline in DAT-SPECT indices (30 %- 45 %in 5 [12 %] subjects)

* No clinical parkinsonism in remaining 283 relatives

HYPOSMIA IN FIRST DEGREE RELATIVES ASSOCIATED WITH 10 % TO 22 % RISK FOR PD

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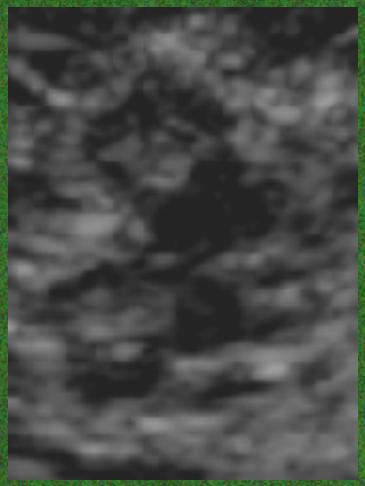
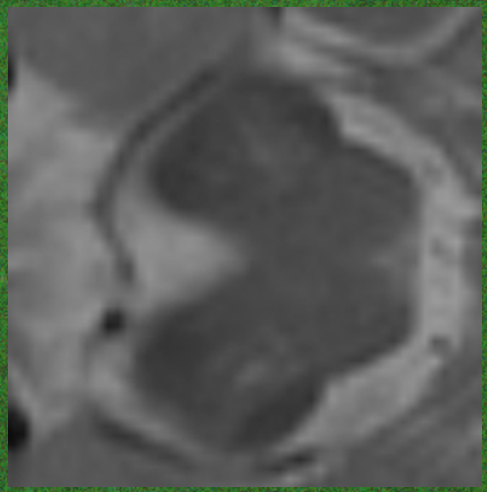
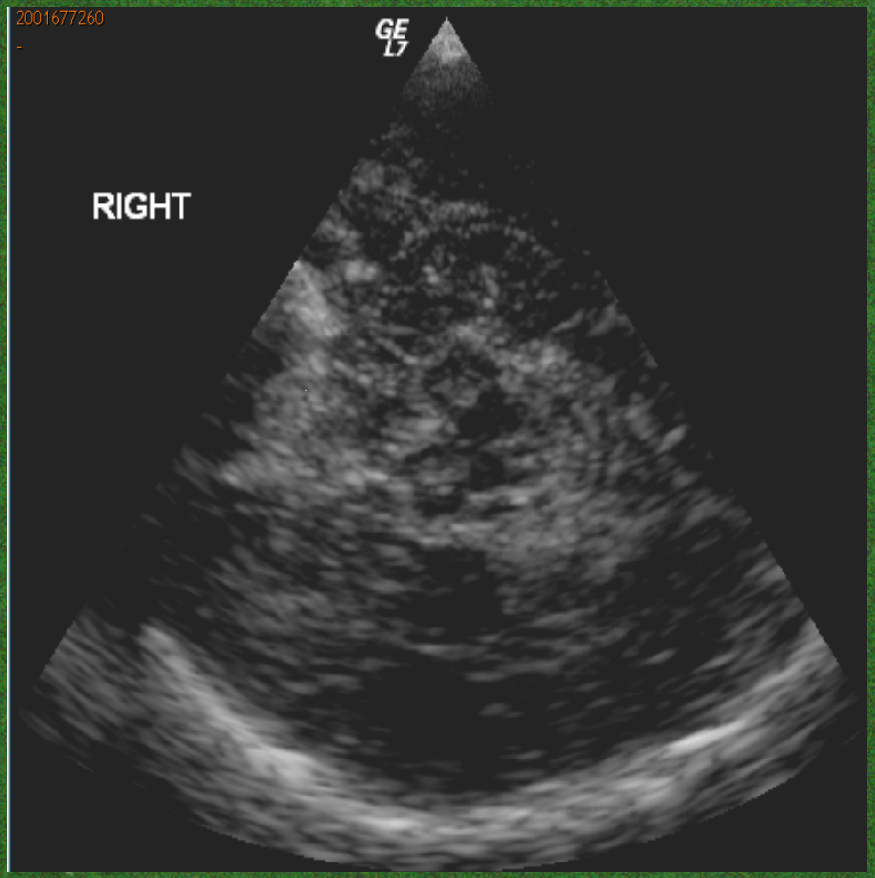
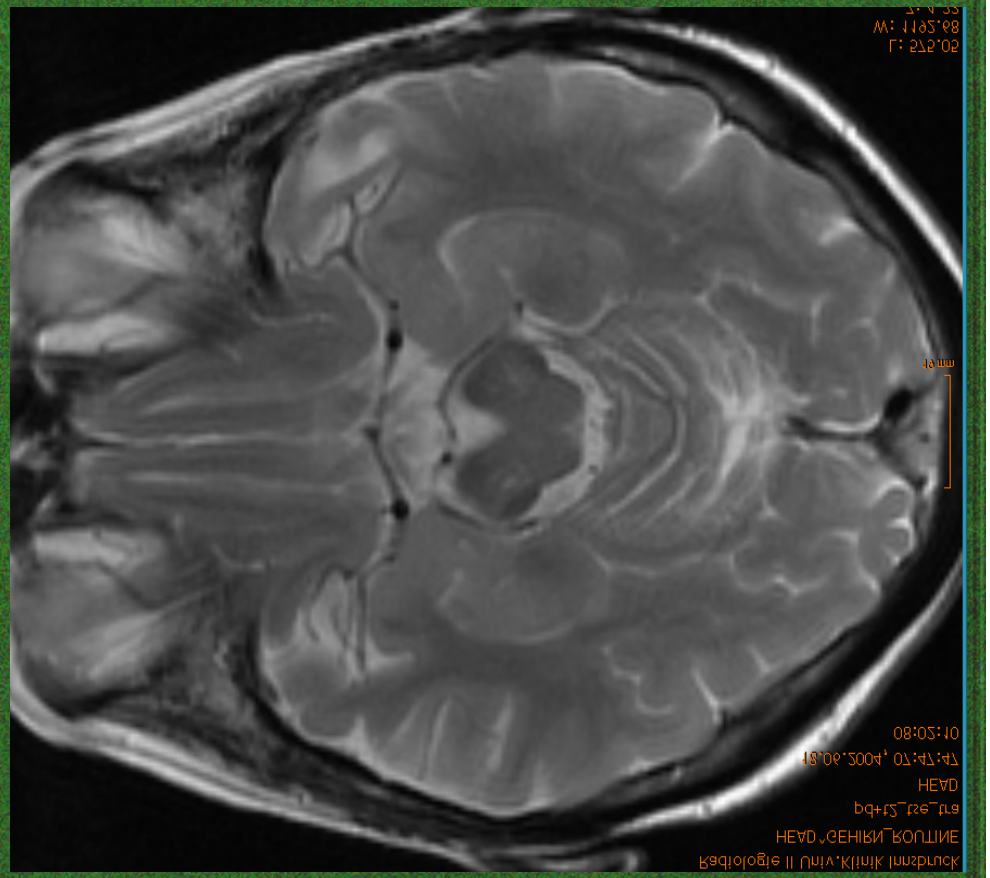
Mesencephalon
Subst. Nigra



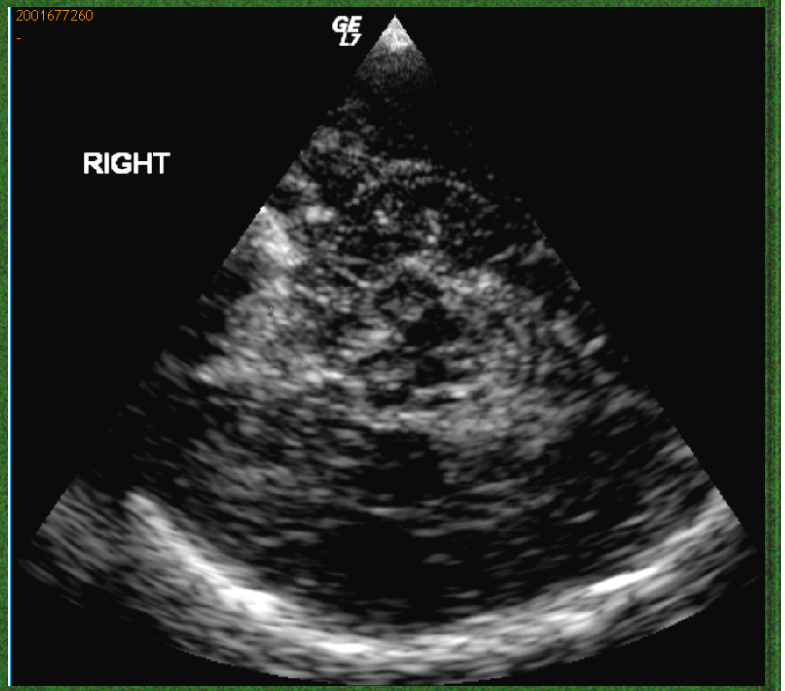






Population-based study
- TCS results -

- n=562, age 55-94, population-based
- 15% without temporal bone window → n=480 for analysis
- M. Parkinson: n=16
- SN-Hyperchogenicity in:
  - 16% of the population
  - 12% of „healthy“ population
  - 81% of patients with PD
- Diagnostic predictive value for PD:
  - PPV 17%
  - NPV 99%



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Bruneck-Studie 2005

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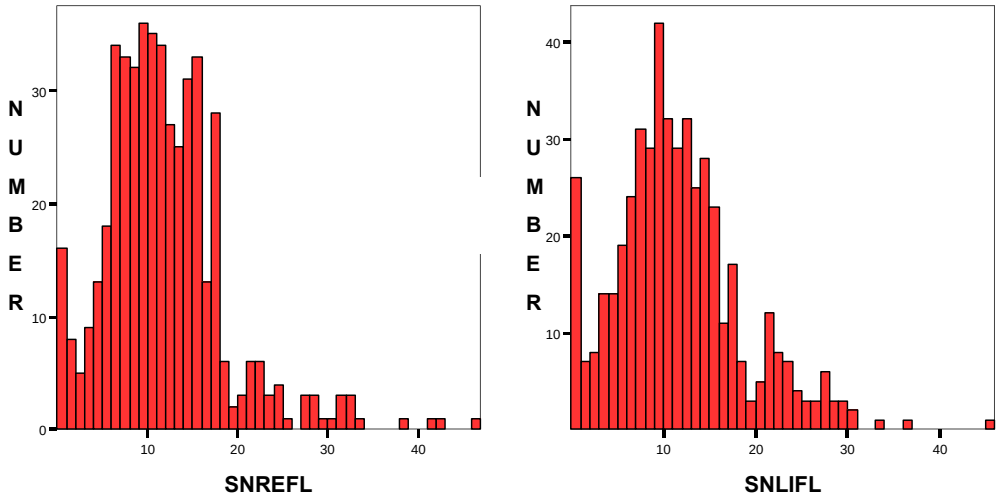
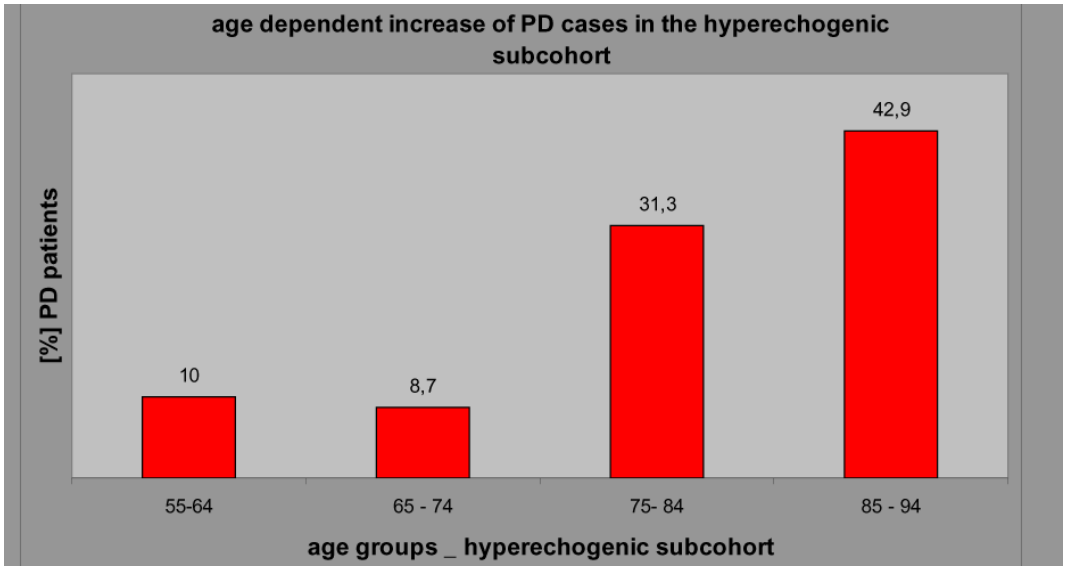
Midbrain transcranial sonography findings in a population - based study

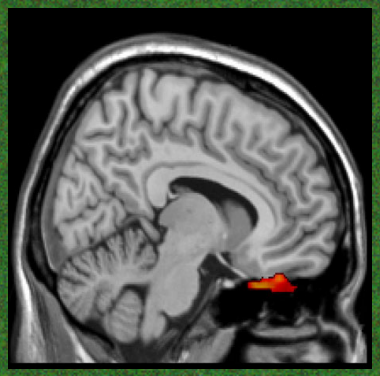
H Stockner, K Seppi, S Kiechl, C Schmidauer, M Sojer, J Schwaiger, M Sawires, J Willeit, W Poewe | Movement disorder congress Kyoto, 2006

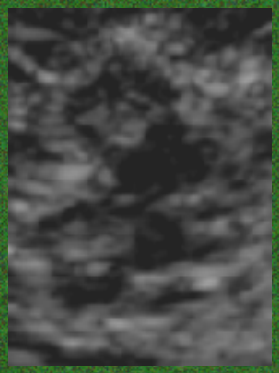


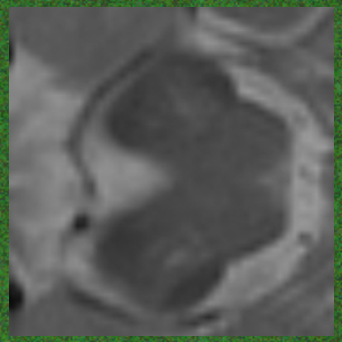


MODIFYING THE NATURAL HISTORY OF PD
- The Future -

* Define at-risk subjects
  - non-smokers, low caffeine consumers
  - subjects with introverted anancastic-rigid personality
  - subjects with hyposmia, RBD, constipation
  - 1st degree relatives or gene carriers (e.g. Park 2, 8)
  - subjects with abnormal midbrain ultrasound, DAT-SPECT, DW-MRI







* Define conversion rates
  - e.g. 10 % over 2 yrs in hyposmic 1st degree relatives (Ponsen et al, 2004)
* Test inverventions for risk reduction for clinical PD

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