Reversal learning in Parkinson's disease depends on medication status and outcome valence

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DA depletions in PD

- Mesocortical and nigrostriatal DA systems involved in cognitive and reward-related processing.
- In PD, there is DA depletion in the nigostriatal and some mesocorticolimbic areas.
- DA medication remedies the cognitive effects of dorsal striatum depletion, but overdoses the ventral striatum (Cools et al. 2001).
  - Inverted U

Frank et al. (2004) Study

- 'DA bursts' from unexpected rewards support 'GO' learning.
- 'DA dips' from unexpected punishment support 'NoGO' (avoidance) learning.
  - PD patients ON medication-> normal DA dips are blocked-> impaired avoidance learning-> better at learning to choose positive outcomes (reward) than negative outcomes (punishment).
  - PD patients OFF medication better than patients ON at learning to avoid negative outcomes (punishment)
- **Cools et al. HYPOTHESIS: mild PD patients on DA medication will have impairment in reversal shifting only in cases with an unexpected negative outcome (no impairment in positive outcome).**

Subjects

3 groups:

1) 10 mild PD ON, 2) 10 mild PD OFF, 3) 12 control subjects

Table 3
Background neuropsychology

	MoCA	FAS	Semflu	Str-words
OFF	27.1 (2.2)	41.7 (12.6)	34.7 (11.4)	92.5 (20.4)
ON	25.7 (1.5)	36.9 (8.8)	31.5 (8.4)	91.3 (14.3)
CS	26.7 (2.0)	43.8 (12.7)	36.3 (12.4)	92.8 (17.4)
P	0.3	0.4	0.6	0.9

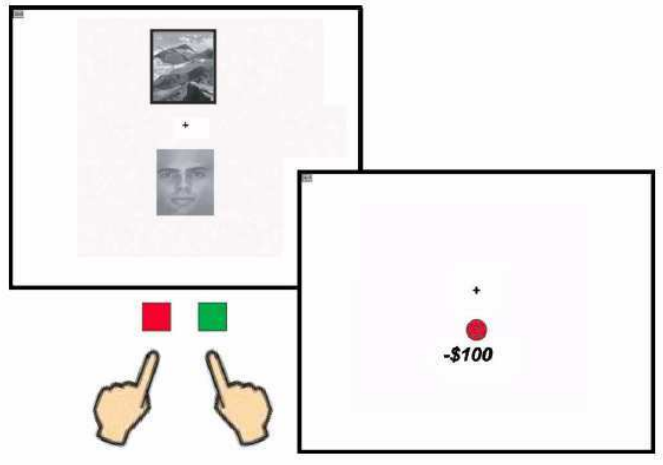
	Str-colors	Str-interf	Str-err-words	Str-err-colors	Str-err-interf
OFF	60.6 (11.3)	31.6 (8.5)	0.3 (0.7)	0.2 (0.4)	0.6 (0.8)
ON	53.1 (16.6)	30.1 (12.7)	0.8 (2.2)	1.8 (3.0)	1.7 (2.1)
CS	61.3 (9.0)	34.1 (10.7)	0.1 (0.3)	0.9 (2.3)	1.1 (1.6)
P	0.3	0.7	0.4	0.3	0.3

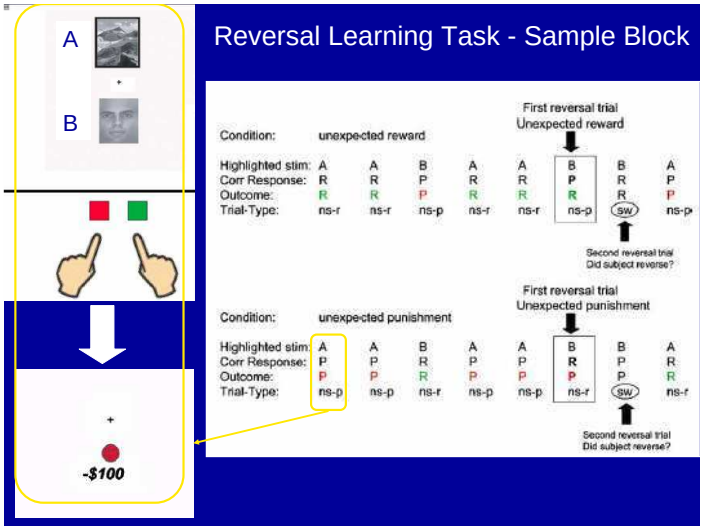
Table 2
Demographics and clinical characteristics

	Age	Dis dur	NAART	Edu
OFF ($n=10$)	64.6 (8.5)	11.0 (8.8)	122.9 (11.9)	17.5 (2.9)
ON ($n=10$)	68.9 (8.7)	8.1 (5.8)	122.8 (5.8)	17.9 (2.4)
CS ($n=12$)	67.8 (8.2)	Na	122.6 (6.2)	17.2 (3.4)
P	0.4	0.4	0.9	0.8

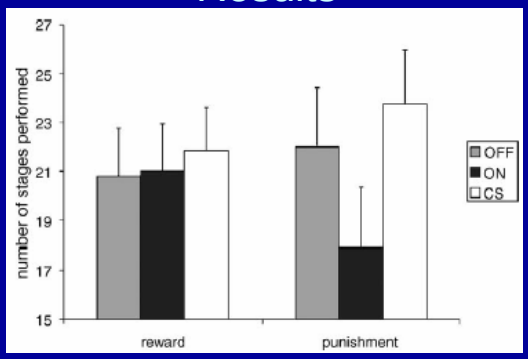
	BDI	L-Dopa	Updrs ON	Updrs at test	Hours since last dose
OFF ($n=10$)	8.4 (4.8)	640.0 (450.6)	22.4 (15.1)	32.1 (17.0)	19.2 (2.1)
ON ($n=10$)	7.7 (3.6)	835.8 (924.7)	25.4 (16.2)	25.4 (16.2)	1.85 (1.2)
CS ($n=12$)	5.7 (4.7)				
P	0.3	0.6	0.7	0.3	0.0001

Reversal Learning Task - Sample Trial

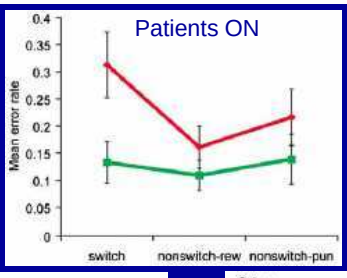


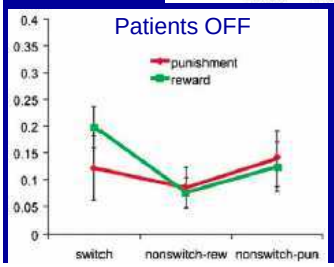


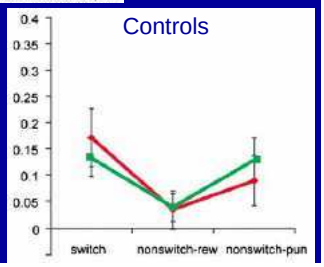
Results



- PD OFF and CS performed the same in both conditions.
- PD OFF performed better than PD ON in the punishment condition
- PD ON performed worst in the unexpected punishment condition.







Pramipexole

Table 1
Medications

	PD ON	PD OFF
Sinemet	9	9
Pramipexole (D3 agonist)	6	7
Pergolide (D1/D2 agonist)	1	0
Amantadine	2	3
Comtan (COMT inhibitor)	3	2
Methylphenidate	0	1
Modafinil	0	1
Namenda (NMDA antagonist)	0	1
Anti-depressants (SSRIs)	3	4

Table 4
Performance as a function of pramipexole use

	Switch	Nonswitch-reward	Nonswitch-punishment
Patients-not-on-pramipexole			
Punishment	0.12 (0.09)	0.04 (0.07)	0.03 (0.08)
Reward	0.11 (0.07)	0.05 (0.05)	0.06 (0.06)
Patients-on-pramipexole			
Punishment	0.44 (0.07)	0.24 (0.06)	0.34 (0.07)
Reward	0.15 (0.06)	0.15 (0.04)	0.19 (0.05)

Values represent means (standard errors of the mean).

Discussion

- DA medication in mild PD patients impaired reversal learning in tasks where reversals were signaled by unexpected punishment.
- DA medication blocks 'DA dips' that are critical to learning from punishment.
- In particular, Pramipexole targets D3 receptors predominantly localized in the ventral striatum, which mediates reversal learning.

Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease

Lewis, Cools, Robbins, Dove, Barker & Owen

Neuropsychologia 41 (2003)

Cognitive Control in PD; 26 July 2006

Introduction

- IPD: deficits in executive functions
- Spatial working memory deficits in even just mild to moderate PD
- Owen et al. (1993):
  - Patients with **mild to severe** PD impaired on **manipulation** of spatial information in WM
  - Patients with only **severe** PD impaired when only **maintenance & retrieval** of spatial information is required

Hypothesis

- Higher-level executive functions may be generally vulnerable to impairment
- Two experimental questions:
  - Determining whether impairments in verbal working memory in PD are selective to the **manipulation** of information
  - Testing two groups of PD patients, determined with respect to performance on the Tower of London task

Participants

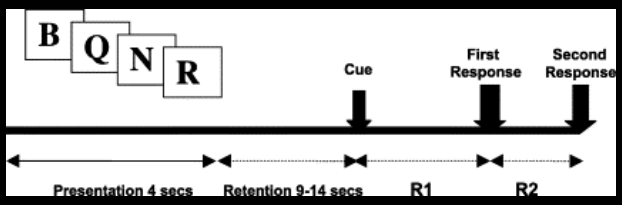
- 41 PD patients
  - All Hoehn & Yahr stages I-III
  - MMSE ≥ 26
  - No signs of dementia or depression
- Divided into 2 groups
  - TOL: average score of age-matched controls was 10.5/14
  - Unimpaired PD: TOL score ≥ 11/14
  - Impaired PD: TOL score ≤ 8/14

Group characteristics

Table 2
Group characteristics

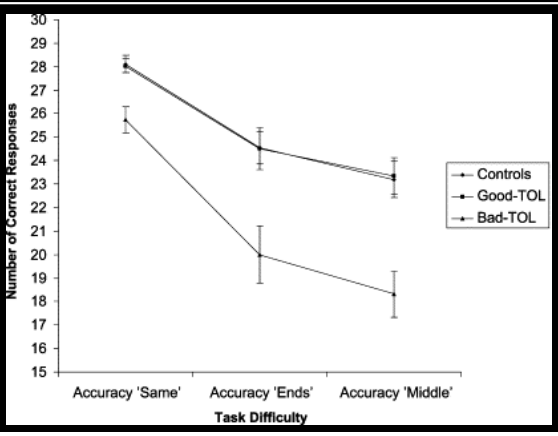
Group	Age (year)	Onset (year)	Dur. (year)	H&Y	UPDR	BDI	MMSE	NART	FAS	Anima	Pattern	Spatial	Latenc (ms)	L-dopa mg/da
Controls (n=24)														
Mean	65.3					5.4	29.5	115.1			20.7			
S.D.	8.2					3.7	0.7	6.9			1.3			
Unimpaired PD (n=22)														
Mean	63.7	56.2	7.5	2.0	38.4	9.6	29.2	116.5	41.2	22.7	19.3	15.4	1233	342.3
S.D.	8.4	8.0	4.9	0.6	14.9	7.0	0.9	5.7	9.9	5.8	3.0	2.0	430.5	289.5
Impaired PD (n=19)														
Mean	66.6	60.6	6.0	2.2	37.2	8.9	28.8	114.6	37.4	19.7	20.2	14.8	1301.0	431.6
S.D.	7.7	9.5	6.0	0.6	13.2	5.1	1.3	7.2	11.4	3.9	2.1	2.1	373.2	384.1

Experimental design

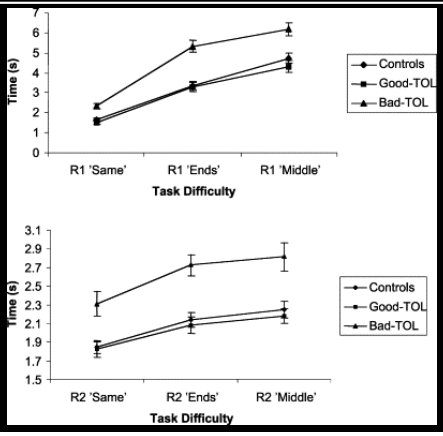


- Cue:
  - **same**: recall letters in same order
  - **ends**: recall letters in order 3 4 1 2
  - **middle**: recall letters in order 1 3 2 4

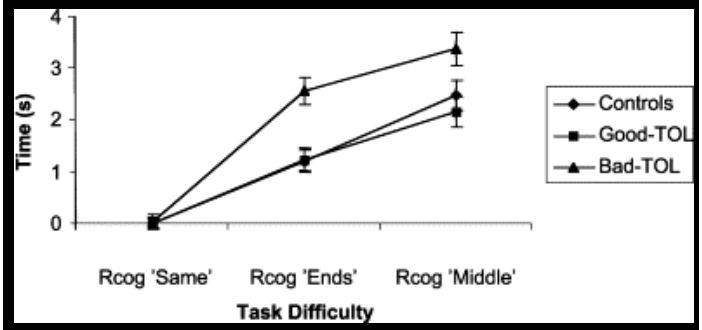
Accuracy



Response time



"Thinking" time



Discussion

- Differences in motor symptoms between groups?
  - Motor requirements for maintenance & manipulation conditions were identical
  - Rcog controls for motor effects
- Global difference in cognitive function between groups?
  - Indistinguishable wrt performance on other neuropsychological tasks

Discussion

- Results due to similarities between TOL and present task?
  - TOL: visuospatial task involving WM and planning resources
  - Present task: verbal WM task
  - Patients subdivided according to TOL accuracy
  - Primary dissociation on verbal task is response time

Conclusion

- Patients with executive dysfunction have selective deficits in verbal WM response time when manipulation of information is required
- May be consequence of differential DA depletion in the caudate nucleus

Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach

Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA, 2005

July 26, 2006

Heterogeneity of early PD

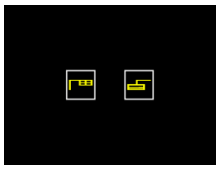
- Parkinson's disease is a clinically heterogeneous disorder, and difficult to accurately diagnose in some cases
- Advanced disease symptoms are often confounded by coexisting pathologies
- Classification of "matched groups" based on predetermined values tends to be an arbitrary division
- Prior data-driven approaches for delineating heterogeneity have included more clinically advanced (and therefore less clinically diverse) patients, and have not reserved subsets of patient data for post hoc comparison

Methods

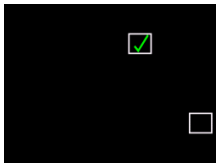
- 120 PD patients
  - 77 male, 43 female
  - mean age = 64.4 years (9.3)
  - Hoehn and Yahr between I and III
  - mean disease duration = 7.8 years (5.4)
- All patients satisfied UKPDS Brain Bank criteria
- 80 patients had recent brain imaging; no significant pathology
- Assessed at "best on" state; 1 two-hour session
- Recorded information on disease onset, disease duration, symptoms at onset, medications, motor fluctuations, L-dopa induced dyskinesias, family history

Testing

- Clinical:
  - UPDRS (I-III)
  - Hoehn and Yahr
  - BDI
- Cognitive function:
  - National Adult Reading Test (NART)
  - MMSE
  - TOL
  - FAS 60 seconds, animals 90 seconds
  - Cambridge Neuropsychological Test Automated Battery (CANTAB): PRM and SPM
- Quality of life:
  - PDQ-39



PRM (Pattern Recognition Memory)

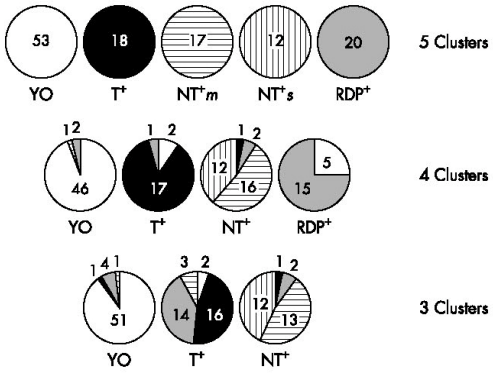


SRM (Spatial Recognition Memory)

Statistical analysis

- k-means (non-heirarchical) cluster analysis solved for 2 to 5 clusters
- variables used for cluster analysis: age at disease onset, rate of disease progression, dopaminergic therapy, motor phenotype score, MMSE, NART, PRM, TOL, BDI
- variables reserved: PDQ-39, SRM, FAS 60-s, animals 90-s, motor complications of disease, dopamine agonist use, presenting symptoms
- **rate of disease progression** = UPDRS / disease duration in years
- **dopaminergic therapy** score ranges from 0 to 2
  0 - No treatment with L-dopa or dopamine agonist
  1 - L-dopa dosage < 1000 mg/day with or without DA, or DA monotherapy
  2 - L-dopa dosage > 1000 mg/day
- **motor phenotype** score = tremor score / non-tremor score
  - tremor score = (Σ UPDRS questions 16, 20-26) / 8
  - non-tremor score = (Σ UPDRS questions 5, 7, 12-15, 18, 19, 27-44) / 26

Results



YO - younger onset
T+ - tremor dominant
NT+ - non-tremor dominant
NT+*m* - non-tremor dominant with mild cognitive impairment
NT+*s* - non-tremor dominant with severe cognitive impairment
RDP+ - rapid disease progression

Group trends

- **younger disease onset (YO; n = 49):** slow rate of disease progression, mild motor symptoms, no cognitive impairment, lower depression ratings
  - "on-off" phenomena (all cluster sizes)
  - dyskinesias (three clusters)
  - higher dopamine agonist use (three and four clusters)
- **tremor dominant (T+: n = 20):** slow rate of disease progression, modest motor symptoms, no significant cognitive impairment, absence of depression
  - associated with anticholinergic medication use (four and five clusters)
- **non-tremor dominant (NT+: n = 20)** executive dysfunction, significant depression scores, more rapid disease progression than YO/T+
  - higher mobility and cognitive impairment ratings on PDQ-39 (all cluster sizes)
- **rapid disease progression (RDP+: n = 31)** aggressive disease course, no severe motor disability or cognitive impairment, mild depression
  - less L-dopa usage than YO (four and five clusters) and NT+*s* (five clusters)
- **not significant between groups:** sex, motor symptom laterality, family history of PD, antidepressant use, benzodiazepines, COMT inhibitors, amantadine use

Table 1: four cluster solution

Table 1 Group characteristics for the four cluster solution

	YO (n = 49)	T⁺ (n = 20)	RDP⁺ (n = 20)	NT⁺ (n = 31)
Age, years	60 (8)	66 (7)	66 (10)	69 (9)
Onset, years	50 (10)	59 (7)	62 (10)	62 (10)
Hoehn and Yahr	2 (1)	2 (1)	2 (1)	2 (1)
Unified Parkinson's Disease Rating Scale III	21 (10)	25 (12)	30 (11)	28 (13)
Duration, years	10 (6)	8 (4)	3 (1)	7 (5)
Disease progression score	4 (2)	5 (2)	13 (5)	8 (4)
L-dopa dose, mg	560 (468)	290 (264)	245 (229)	456 (580)
Motor phenotype score	1 (0.5)	2 (1)	1 (0.4)	0.6 (0.5)
Mini Mental State Examination	30 (1)	29 (1)	30 (1)	28 (1)
National Adult Reading Test	117 (6)	115 (8)	117 (6)	108 (10)
Verbal fluency (FAS)	46 (13)	40 (12)	44 (9)	33 (12)
Categorical fluency	24 (6)	21 (7)	22 (5)	17 (6)
Pattern recognition memory (max = 24)	21 (2)	18 (4)	21 (2)	17 (2)
Spatial recognition memory (max = 20)	16 (2)	14 (2)	15 (2)	14 (2)
Tower of London (max = 14)	10 (2)	10 (3)	11 (2)	5 (4)
Beck depression inventory	8 (6)	9 (5)	9 (5)	11 (6)

Values are mean (SD).
This clustering solution revealed four patient subgroups: younger onset (YO), tremor dominant (T⁺), non-tremor dominant (NT⁺), and rapid motor progression (RDP⁺). Group comparisons clearly demonstrated significant differences between numerous features of the disease. NT⁺ patients demonstrated cognitive deficits and had higher affective score ratings, while YO, T⁺, and RDP⁺ patients were distinguished by their age at onset, motor phenotype score, and rate of progression of motoric features, respectively. Similar distinctions were observed for other clustering solutions and notably the solution with five subgroups delineated the non-tremor dominant patients into those with moderate and those with severe cognitive impairment.

Table 2: subgroup characteristics

Table 2 Expected performance: subgroup characteristics

	Three clusters			Four clusters				Five clusters				
	YO	T⁺	NT⁺	YO	T⁺	RDP⁺	NT⁺	YO	T⁺	RDP⁺	NT⁺*m*	NT⁺*s*
PRM			†				†					††
SRM			†				†					†
TOL			††				††				†	††
BDI			*				*			*		*

*Mild depression
Only patients in the non-tremor dominant subgroup demonstrated any significant deficits (†one standard deviation below healthy controls) for pattern (PRM) and spatial recognition memory (SRM). These patients were also severely impaired on the Tower of London (TOL) task of executive function (††two standard deviations below healthy controls) and along with those patients with rapid motoric progression, also showed higher scores on the Beck depression inventory (BDI).
NT⁺, non-tremor dominant; NT⁺*m*, non-tremor dominant with moderate cognitive impairment; NT⁺*s*, non-tremor dominant with severe cognitive impairment; RDP⁺, rapid disease progression; T⁺, tremor dominant; YO, younger onset.

Discussion

- data-driven heterogeneity is not a definitive classification system; requires further clinicopathological study
- early cognitive impairment in PD may be largely localized to a subgroup of non-tremor dominant patients with more rapid disease progression
- subsequent specific working memory deficits seen in rapid disease progression groups (SJGL, unpublished data)
  - may represent a divergent parkinsonian syndrome from idiopathic PD
  - clusters were not taken beyond five due to low population numbers
- no significant familial role found in this study
- differing clinical subgroups likely points to differing neuropathologies, causes, and/or genetic backgrounds

Previous neuroimaging studies of executive function in PD have sometimes produced apparently conflicting results

- Dopaminergic neuronal loss represents the primary neuropathology in PD
- This loss occurs in the nigrostriatal tract and, to a lesser extent, in the mesocortical DA pathway
- Disruption of activation in nigrostriatal pathways (Owen et al., 1998a; Dagher et al., 2001)
- Disruption of activation in mesocortical pathways (Cools et al., 2002; Mattay et al., 2002)
- Although not mutually exclusive, the potentially confllicting results of these cognitive neuroimaging studies in PD may reflect the heterogeneity within the PD population

Lewis et al., 2003c

Participant characteristics: PDs and CON

Not impaired Impaired

Demographic data	■ PD ($n = 10$)	● PD ($n = 11$)	Controls ($n = 10$)	p value
Age (years)	57.7 ± 2.4	60.9 ± 2.2	62.4 ± 2.0	NS
Duration of disease (years)	4.7 ± 1.1	5.9 ± 1.0		NS
Motor phenotype	0.9 ± 0.7	0.8 ± 0.8		NS
Onset side	Right, 5; left, 5	Right, 5; left, 6		NS
Hoehn & Yahr stage	2.0 ± 0.0	2.0 ± 0.0		NS
UPDRS	33.2 ± 3.5	39.2 ± 4.3		NS
Mini-mental state examination	29.6 ± 0.2	29.6 ± 0.2		NS
FAS fluency	47.1 ± 2.7	40.5 ± 4.9		NS
Categorical fluency	26.2 ± 1.6	21.5 ± 1.6		NS
Motor latency (msec)	1113.4 ± 189.7	1065.7 ± 50.7		NS
Pattern recognition (maximum score = 24)	21.9 ± 0.6	20.1 ± 0.7		NS
Spatial recognition (maximum score = 20)	15.4 ± 0.8	14.9 ± 0.7		NS
Beck Depression Inventory	5.4 ± 1.3	9.8 ± 1.8		NS
L-dopa dose (mg)	545.0 ± 122.2	409.1 ± 124.5		NS
Dopamine agonist use	7	8		NS
Tower of London (maximum = 14)	12.5 ± 0.3	6.8 ± 0.6		<0.001

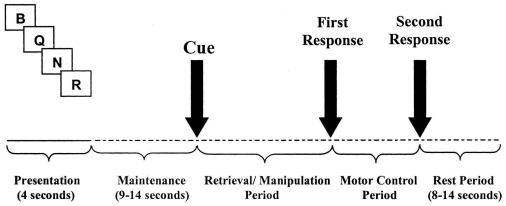
Demographic data (mean ± SEM) showing no significant differences among the patient subgroups ($p > 0.05$). Performance accuracy on the Tower of London planning task was used to separate those patients with a selective executive impairment (● PD) from those with no cognitive deficit (■ PD) before fMRI testing.

Patient subgroups were divided on the basis of their performance accuracy on the TOL task

All PDs were taking their regular meds

Lewis et al., 2003c

Working memory paradigm



After presentation of 4 letters, and a retention interval of 9-14 sec, a cue signaled one of 3 prelearned conditions: retrieval, simple manipulation, or complex manipulation. Ss responded with a key press (1st response) once the correct solution had been generated in mind, and with a second key press (2nd response) to select from two alternatives.

Lewis et al., 2003c

Pattern of fMRI activity during the working memory paradigm (*N*=31)

Retrieval and/or manipulation vs. maintenance

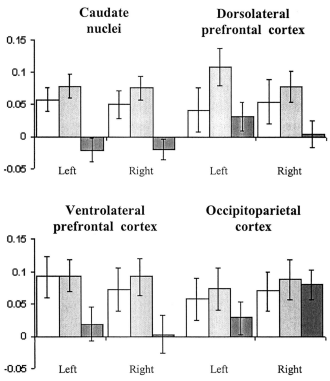
Top & middle: dorsolateral & ventrolateral PFC

Bottom: striatum bilaterally

Middle left: posterior association cortices bilaterally

Lewis et al., 2003c

Regional mean fMRI signal during manipulation



Open bars=CON

Light bars=unimpaired PDs

Dark bars=impaired PDs

The subgroup of PDs with "executive" impairments showed significant underactivation compared with the unimpaired PDs in the frontostriatal ROIs, but not in the posterior association cortex

Unimpaired PDs resembled CON

Lewis et al., 2003c

Correlation analysis comparing signal intensity with the RT constant for the task, performed on those ROIs that showed underactivity

- Significant neg correlation within the caudate for retrieval and manipulation contrasts in the impaired PDs, but not in the unimpaired PDs or CON
- Significant neg correlations within the DLPFC and VLPFC with executive impairment during manipulation, but not in the unimpaired PDs or CON
- Occipitioparietal cortices showed no sig correlations for any group

Lewis et al. 2003c

Conclusions

- fMRI can be used to identify the neural locus of the selective executive deficit in a subgroup of early PDs
- This impairment is related to specific underactivity in regions of the basal ganglia and frontal cortex, and preferentially effects processes that support the manipulation of information in working memory
- This effect was seen in a executively impaired subgroup of PDs, but not in an unimpaired subgroup (who resembled CON)
- The fact that working memory deficits have been shown previously to be sensitive to the effects of controlled L-dopa withdrawal in PDs suggests a predominantly dopaminergic substrate for the deficits reported here

Lewis et al., 2003c

Future research (like ours)

- The results of this study
  - highlight the need for better characterization of PD patient subgroups and their impairments, both cognitively and motorically, and
  - may explain why previous studies have sometimes produced apparently conflicting results

Lewis et al. 2003c

Fronto-striatal cognitive deficits at different stages of Parkinson's disease

Owen et al. (1992)

Christie Chung

7/26/06

PD vs. Frontal Lobe Dysfunction

- Deficits in attention set formation and set shifting, e.g., WCST (fewer sorting categories and more perservative errors)
- Smaller deficits in PD
- Frontal lobe damage – lack normal executive control (e.g., Tower of London)

- Frontal lobe patients impaired in accuracy and latency of thinking (Computerized Tower of London test)
- Mixed results in PD:

  Taylor et al. (1986) PD impaired in tasks that involve “self-directed behavioral planning”

  Saint-Cyr et al. (1988) found no deficit in Tower of London task

Set-shifting impairments reflect…

- Deficits in planning?
- Impairment in memory function?
  - Corsi’s block-tapping task (Milner, 1971)
  - Self-ordered search task (Petrides & Milner, 1982)

Present Study

- Examined planning ability in 3 subgroups of PD patients
- Take into account progressive nature of PD
- Medication (L-Dopa)
- Same cognitive tests used in Owen et al. (1990) on frontal lobe patients

Participants

- 15 non-medicated PD (early PD; mean = 18 mths; H&Y -- 3 stage I, 10 stage II, 2 stage III)
- 15 medicated (L-dopa), mild PD (H&Y -- 3 stage I, 12 stage II)
- 14 medicated (L-dopa), severe PD (H&Y -- 8 stage III, 6 stage IV)
- 3 groups controls (N=44) matched on age and NART IQ

Sample Characterization

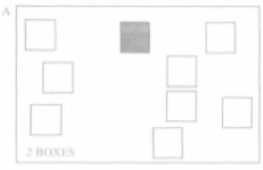
- MMSE ≥ 24
- Kendrick Object Learning Test (KOLT) ≥ 23
- GDS -- PD (mild) = 8.61
  PD (severe) = 15.14

Cambridge Neuropsychological Test Automated Battery

- 'Motor screening test'
- Spatial short-term memory task
- Spatial working memory (WM) task
- Planning task (Tower of London)
- Pattern recognition
- Attentional set-shifting test

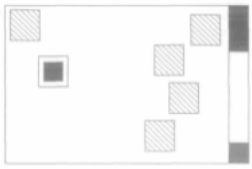
Spatial short-term memory task

- Computerized Corsi's Block-tapping task (Milner, 1971)
- Highest level achieved -- spatial span



Spatial WM task

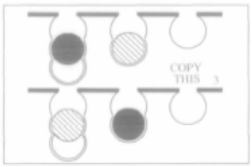
- ‘Open up’ boxes to collect blue tokens inside and fill empty column on the side



- ‘between search error’
- ‘within search error’

Computerized Tower of London task

- Based on Tower of Hanoi problem



- Rearrange balls in bottom display to match top display
- Baseline estimates measured in yoked control condition -- follow sequence on top half of screen

Pattern recognition task

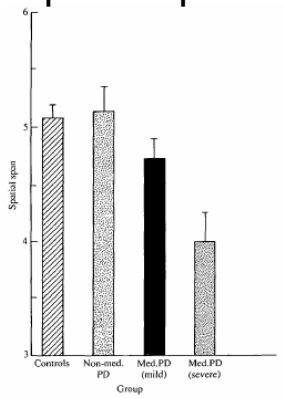
- Presentation phase:
  - 12 ‘target’ colored patterns
  - 3 s each, one at a time
- Recognition phase:
  - 12 pairs of colored patterns
  - pick pattern they have already seen

Attentional set-shifting test

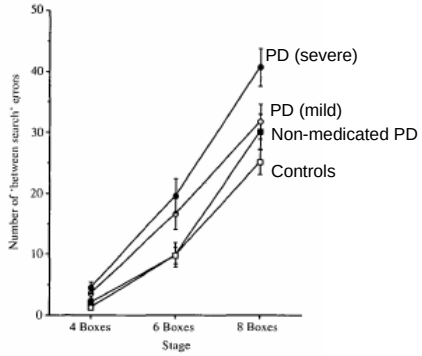
- Learn a series of discriminations where one of two dimensions was relevant using feedback (purple-filled shapes or white lines)
- Auditory tone and visual feedback

1) Simple discrimination (SD)
2) Contingencies reversed (SDR)
3) (C-D) compound stimuli formed but still have to respond to previous relevant dimension
4) CD (dimensions are superimposed)
5) CDR
6) IDS - intra-dimensional shift
7) EDS - extra-dimensional shift
8) EDR

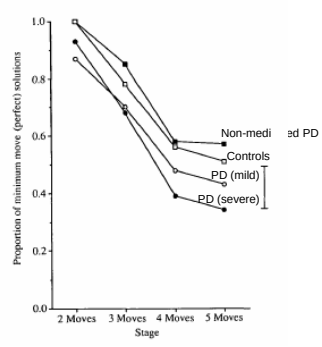
Severe PD impaired on spatial span task



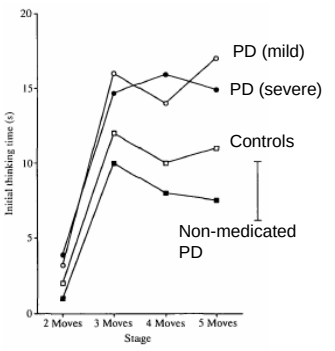
Medicated PD showed more 'between search errors'



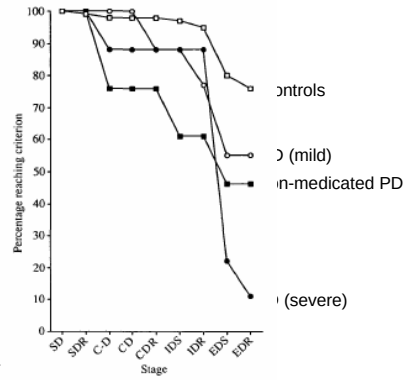
Accuracy on Tower of London test decreased with PD



PD w/ Medication increases thinking time



PD impairs attentional set-shifting



Summary of Results

- Accuracy deficits on Tower of London test of planning only seen in medicated PD (severe)
- Medicated PD (mild, severe) prolonged initial thinking (planning) times prior ro first move
- Frontal lobe patients -- also impaired on accuracy, but unimpaired in initial thinking time

Prolonged thinking time…

- Correlate of ‘bradyphrenia’
- In medicated PD (mild) -- speed-error trade-off
- Medicated PD -- differed in accuracy but equally slow
  - ‘psychic akinesia’
  - Delays in switching between representations

- Spatial working memory and spatial span also play roles in planning on Tower of London test
- Medicated PD impaired on spatial WM and Tower of London
- PD's reduced spatial span also affected performance on Tower of London test (not in frontal lobe patients)

Inter-correlations

- Controls -- accuracy on Tower of London test positively related to initial thinking time
- Controls and PD -- significant correlation between total errors on spatial WM and accuracy on Tower of London test
- Pattern recognition and attentional set-shifting did not correlate with anything

TABLE 2. SUMMARY OF RESULTS

	Non-medicated Parkinson's disease	*Medicated Parkinson's disease (mild)*	*Medicated Parkinson's disease (severe)*	*Frontal lobe*
Pattern recognition	√	√	√	√
Span	√	√	X	√*
Spatial working memory ('between search' errors)	√	X	X	X*
Minimum move solutions (Tower of London)	√	√	X	X*
Initial thinking time (Tower of London)	√	X	X	√*
Subsequent thinking time (Tower of London)	√	√	√	X*
Attentional set-shifting	X	X	X	X**

√ = unimpaired; X = impaired. *Owen *et al.*, 1990; **Owen *et al.*, 1991.

Depression….

- GDS scores correlated with initial movement times at levels 3 and 5 on Tower of London test, and subsequent movement times at levels 2, 3, 4, 5.
- No significant correlations between GDS and initial thinking time.

Involvement of frontal cortex

- Spatial WM - dorsolateral frontal
- Set-shifting - orbitofrontal and dorsolateral regions
- Results of striatal pathology

Conclusions

- Results are important for staging of cognitive decline at different stages of PD
- Non-medicated PD only impaired on attentional set-shifting -- limited anatomical focus for cognitive impairments in early PD
- As PD prgresses, more extensive regions of fronto-striatal cicuitry become disrupted