Impulse Control Disorders in Parkinson's Disease

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Epidemiology

Terminology

- Impulse control disorders (ICDs) are group of psychiatric disorders in DSM-IV
  - Essential feature *"a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the person or to others"*
- ICDs increasingly accepted as term for major disorders reported to occur in PD (also "behavioural addictions")
  1. **Gambling**
  2. **Buying**
  3. **Sexual behaviors**
  4. **Eating**

Related Disorders in PD

- Dopamine dysregulation syndrome (DDS) (a.k.a. hedonistic homeostatic dysregulation) thought to differ from ICDs in important ways:
  - DDS more akin to substance abuse disorders
    - Involves medication misuse
  - Mood and behavioral disturbances often present
  - ICD behaviors not necessarily present
  - DDS more commonly occurs with “short-acting” agents (levodopa and sq apomorphine) than with dopamine agonists (DAs)
- Also punding / hobbyism

DOMINION Study: Phase I - Observational

- Study of frequency and correlates of 4 ICDs in PD
  - MAGS for gambling, MIDI for buying and sexual behavior, and DSM-IV criteria for binge-eating
- 46 PD centers in US and Canada
- 3090 patients ≤75 years old completed the ICD assessments
- 66% of patients were taking a dopamine agonist (DA)
  - Overall, 86.8% of patients were taking levodopa

Weintraub et al. *Archives of Neurology* 2010;67:589-595.

ICD Frequencies

- At least one ICD identified in **13.6%** of patients
  - 28.7% of ICD patients had ≥2 ICDs
- Frequencies of individual ICDs were:
  - Problem/pathological gambling = 5.0%
  - Compulsive sexual behavior = 3.5%
  - Compulsive buying = 5.7%
  - Binge-eating disorder = 4.3%

Current ICD Frequencies in DA- vs. Non-DA-Treated Patients

ICD type	DA treatment status	Current ICD N (%)	No current ICD N (%)	P value (CMH-test); odds ratio [95% CI]
Any ICD	No dopamine agonist	72 (6.9)	978 (93.1)	<.001
	Dopamine agonist	**348 (17.1)**	1692 (82.9)	2.72 [2.08;3.54]
Problem/pathological gambling	No dopamine agonist	24 (2.3)	1026 (97.7)	<.001
	Dopamine agonist	130 (6.4)	1910 (93.6)	2.82 [1.81;4.39]
Pathological gambling only	No dopamine agonist	17 (1.6)	1033 (98.4)	.004
	Dopamine agonist	72 (3.5)	1968 (96.5)	2.15 [1.26;3.66]
Compulsive sexual behaviour	No dopamine agonist	18 (1.7)	1032 (98.3)	<.001
	Dopamine agonist	90 (4.4)	1950 (95.6)	2.59 [1.55;4.33]
Compulsive buying	No dopamine agonist	30 (2.9)	1020 (97.1)	<.001
	Dopamine agonist	147 (7.2)	1893 (92.8)	2.53 [1.69;3.78]
Binge-eating disorder	No dopamine agonist	18 (1.7)	1032 (98.3)	<.001
	Dopamine agonist	114 (5.6)	1926 (94.4)	3.34 [2.01;5.53]

Current ICD Frequencies by DA Type

ICD type	Specific DA	Current ICD N (%)	No current ICD N (%)	P value (CMH-test); odds ratio [95% CI]
Any ICD	Ropinirole	101 (15.5)	550 (84.5)	.14
	Pramipexole	228 (17.7)	1058 (82.3)	1.22 [0.94;1.57]
Problem/pathological gambling	Ropinirole	37 (5.7)	614 (94.3)	.44
	Pramipexole	83 (6.5)	1203 (93.5)	1.17 [0.78;1.76]
Pathological gambling only	Ropinirole	24 (3.7)	627 (96.3)	.69
	Pramipexole	42 (3.3)	1244 (96.7)	0.90 [0.54;1.51]
Compulsive sexual behaviour	Ropinirole	28 (4.3)	623 (95.7)	.75
	Pramipexole	58 (4.5)	1228 (95.5)	1.08 [0.68;1.71]
Compulsive buying	Ropinirole	51 (7.8)	600 (92.2)	.58
	Pramipexole	87 (6.8)	1199 (93.2)	0.90 [0.63;1.30]
Binge-eating disorder	Ropinirole	28 (4.3)	623 (95.7)	.06
	Pramipexole	80 (6.2)	1206 (93.8)	1.53 [0.98;2.39]

22% of patients on pergolide (N=50) had an ICD.

Multifactorial Analysis of ICD Correlates

Variable*	Entire Study Population (N=3090)		
	Odds ratio [95% CI]	P value	PAR%&
Age (≤65 years vs. >65 years)	2.50 [1.98; 3.15]	<0.001	41.2%
Marital status (not married vs. married)	1.48 [1.16; 1.89]	0.002	7.4%
Country (living in United States)	1.62 [1.25; 2.10]	<0.001	27.9%
Current smoking (yes vs. no)	1.70 [1.07; 2.70]	0.02	2.9%
Family history gambling problems (yes vs. no)	2.08 [1.33; 3.25]	0.001	1.5%
DA treatment (yes vs. no)	2.72 [2.07; 3.57]	<0.001	49.3%
Levodopa treatment (yes vs. no)	1.51 [1.09; 2.09]	0.01	9.6%

* Clinical and demographic variables included were those with P value <0.10 on univariate analysis; data presented for significant results only; & **PAR% (population attributable risk percentage) for exposure variable = ([prevalence in the entire population – prevalence in unexposed population] / prevalence in entire population) x 100**. The PAR% is a univariate calculation, so the sum of the PAR% for multiple variables can exceed 100%.

Dose Effects

- Examining patients on a DA (N=2040)
  - On multivariable analysis there was no DA dosage effect
  - There was a levodopa dosage effect (P=0.008)
- Examining patients on levodopa only (N=991)
  - On multivariable analysis, higher levodopa dosages were associated with a current ICD (P=0.002)

Other Interesting Correlates

- ICDs more common in US (15.0%) than Canada (9.8%)
  - Specifically compulsive gambling and buying
  - Even after controlling for differences in medication exposure
- No sex differences in ICDs overall, but
  - Sexual behaviors far more common in men
  - Buying and binge-eating behaviors more common in women
- Family history of gambling problems more common in three of the four ICDs (all except sexual behaviors)

DOMINION Study: Phase II - Case-Control

- Case-control study of 564 patients
  - 282 ICD patients
  - 282 matched controls (sex, age, DA treatment)
- ICD+ versus matched ICD- patients were:
  - More functionally impaired ($p<0.0001$)
    - Despite similar UPDRS scores
  - More depressed and anxious, and had more obsessive compulsive symptoms (all p values <0.0001)
  - More impulsive decision-making ($p<0.0001$) and had higher novelty seeking scores ($p<0.05$)

Voon et al. *Annals of Neurology* (10.1002/ana.22356).

Neural Substrate

Possible Link Between PD, Dopamine Replacement Therapies, and ICDs

Necessary …

- Treatment with dopaminergic therapies
  - Dopamine agonists are more selective for D_3 subtype receptors
    - Other dopamine replacement therapies have more non-specific effects

But insufficient?

- Pre-morbid risk factors
  - Psychosocial, substance use exposure, temperament, genetic
- Executive impairment (neural circuitry)
- Decreased dopaminergic tone secondary to loss of substantia nigra (and to lesser degree the VTA) neurons
  - Other neurotransmitters?

Impaired Decision Making in PD – Gambling Task and Executive Abilities

Results of the neuropsychological test battery of the Parkinson's patients (PD group) and the healthy controls (control group, CG)

Domain/test		Max	PD		CG		T	P
			mean	sd[1]	mean	sd[1]		
General cognitive state								
Mini Mental State Examination (MMSE)		30	28.2	(1.7)	⩾ 27			
DemTect (transformed total score)		18	15.1	(2.1)	16.5	(1.6)	−2.37	0.02
Memory								
Subtest Word list of the DemTect	immediate recall	20	12.2	(2.5)	13.6	(2.1)	−1.91	0.06
	delayed recall	10	4.0	(2.0)	4.7	(1.2)	−1.34	0.18
Digit span	reversed	6	4.0	(0.9)	5.2	(0.4)	−5.44	<0.001
Executive functions and information processing								
Modified Card Sorting Test (MCST)	categories	t-scores[2]	40.3	(10.2)	54.0	(4.9)	−5.41	<0.001
	errors	t-scores[2]	43.0	(8.9)	53.2	(1.7)	−5.03	<0.001
	perseverations	t-scores[2]	50.5	(7.6)	55.0	(5.4)	−2.15	0.037
Controlled oral word association 'F', 'A', 'S'		/	35.0	(13.8)	35.7	(14.8)	−0.14	0.88
	'supermarket'	/	22.8	(5.5)	28.2	(4.1)	−3.52	0.001
Subtest 4 'reasoning' of the LPS[3]		t-scores	43.5	(13.6)	67.0	(8.7)	−6.50	<0.001
Subtest 7 'visual-spatial abilities' of the LPS[3]		t-scores	51.9	(15.6)	na[4]			

[1] sd = standard deviation.
[2] norm scores of [35].
[3] LPS = 'Leistungsprüfsystem' (German intelligence test battery, see text).
[4] na = not administered.

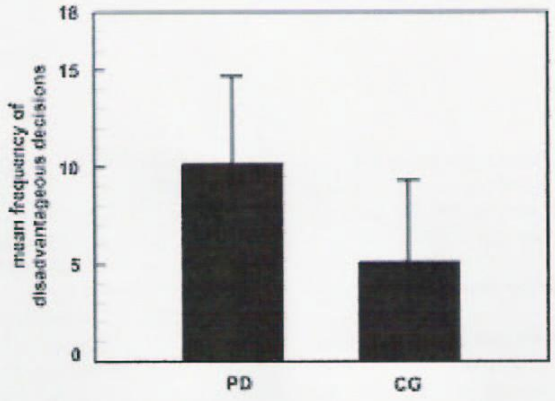
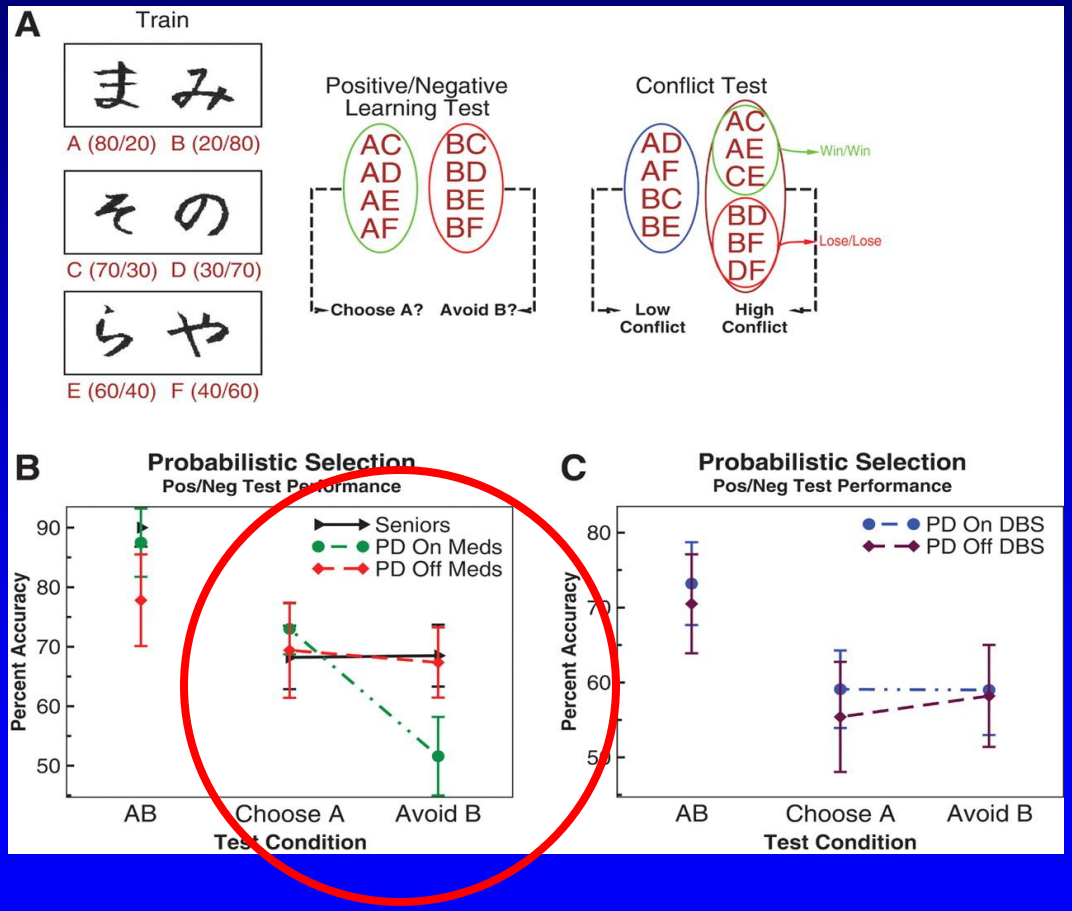


Fig. 1. Frequency of disadvantageous decisions (mean and standard deviation) in the Game of Dice Task of patients with Parkinson's disease (PD) and the healthy control group (CG).

"Frequency of disadvantageous choices correlated with impairment on Card Sorting Test - hypothesized that decision-making deficits related to impairments in two fronto-striatal loops, the limbic-orbitofrontal-striatal loop for feedback processing and the dorsolateral prefrontal-striatal loop involved in executive functions."

Brand et al. *Behavioral Neurology* 2004;15:77-85

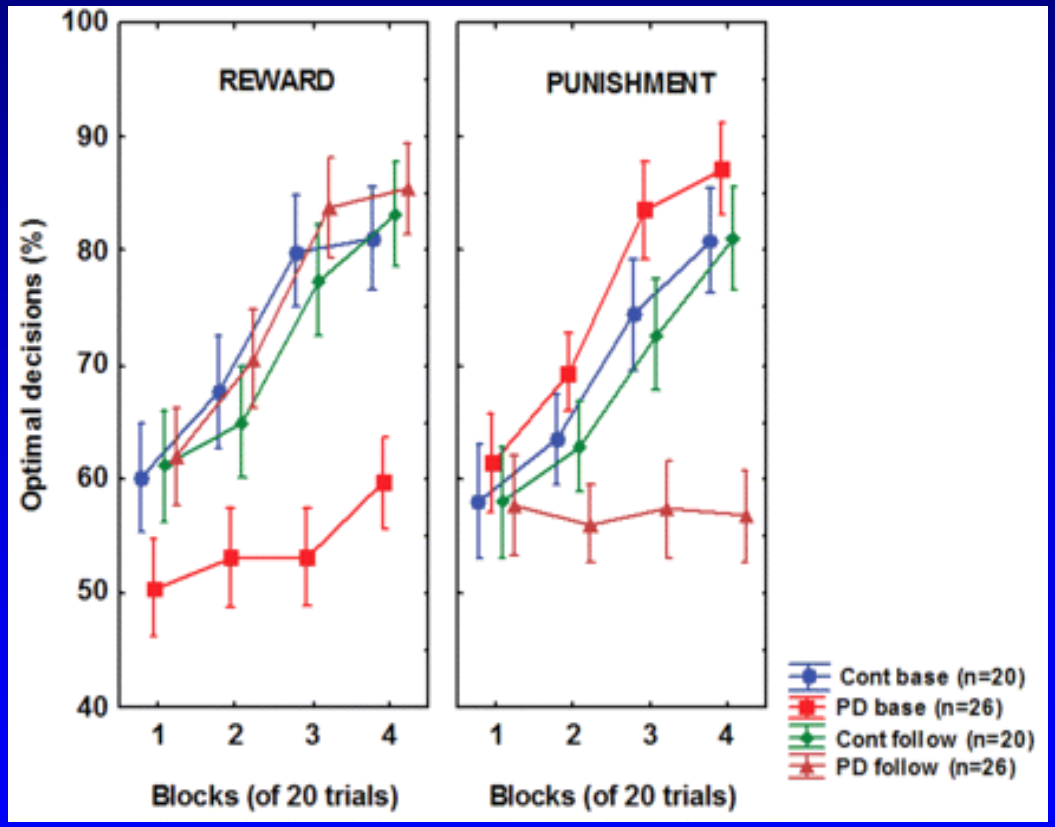
"Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism"



"Dopaminergic medication, by tonically elevating dopamine levels and stimulating D2 receptors, prevents learning from negative decision outcomes. This mechanism may explain pathological gambling behavior in patients treated with D2 agonists."

Frank et al. *Science* 2007;318:1309-1312.

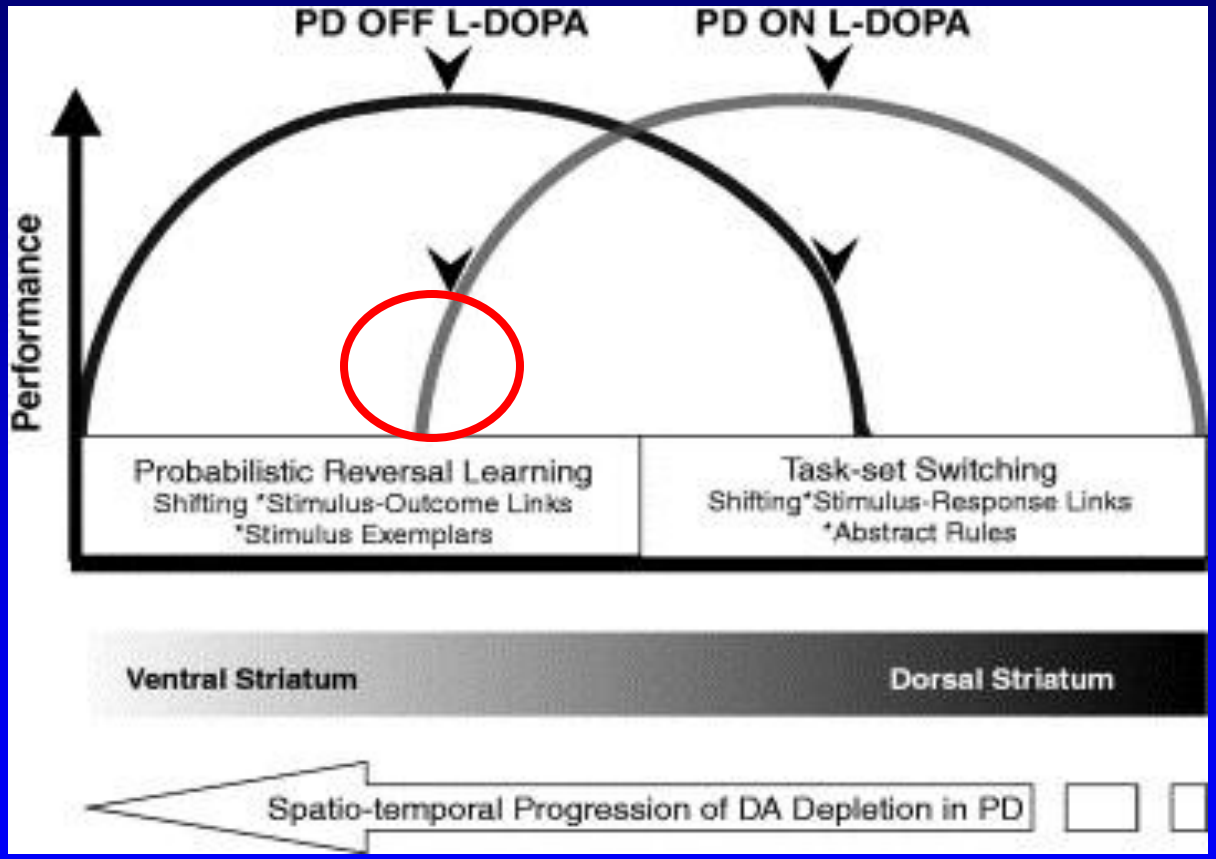
Reward-Punishment Learning and Dopamine Agonists in PD



"DA administration in young patients with PD resulted in enhanced reward processing, and decreased punishment processing….may shed light on the cognitive and personality bases of ICDs."

Bódi et al. *Brain* 2009;132:2385-2395.

Schematic of Dopaminergic "Over-dose" Hypothesis of Ventral Striatum in PD



"It is hypothesised that this dissociation reflects the finding that the dopamine levels are depleted to a greater extent in the dorsal striatum compared with the ventral striatum."

Cools. *Neuroscience and Biobehavioral Reviews* 2006;30:1-23.

Neural Substrate – PD ICDs

Relevant Genetic Associations

Risk factors	Crude OR[a,b] (CI)	*P*	Adjusted OR[b,c] (CI)	*P*
Age at onset < 45 yr	2.56 (1.08-6.11)	0.0337	2.09 (0.82-5.28)	0.1204
PD duration > 10 yr	1.88 (1.06-3.31)	0.0303	1.44 (0.77-2.67)	0.2522
Agonist use	1.90 (0.96-3.75)	0.0646	1.49 (0.67-3.34)	0.3286
Total LEDD > 850 mg/day	2.35 (1.34-4.15)	0.0030	1.88 (1.00-3.55)	0.0515
Agonist LEDD > 100 mg/day	1.91 (1.06-3.46)	0.0322	1.14 (0.54-2.41)	0.7303
Genotype[d]	2.60 (1.30-5.20)	0.0069	2.57 (1.27-5.21)	0.0087

[a] Crude OR is adjusted for age and sex.
[b] Analyses are conducted using multivariate logistic regression.
[c] The adjusted ORs are adjusted for other 5 risk factors as well as age and sex.
[d] Either *DRD3* p.S9G AA genotype or *GRIN2B* c.366C>G genotype.
Abbreviations as Table 1. OR, odds ratio; CI, confidence interval.

DRD3 = D3 receptor
GRIN = glutamate *N*-methyl- D-aspartate (NMDA) receptor

Lee et al. 2009;24:1803-1810.

Personality Risk Factor for ICDs in PD?

Table. Characteristics of Patients With Parkinson Disease With and Without Pathological Gambling

Characteristic	Patients With PD and PG (n = 21)	PD Control A Group* (n = 42)	*P* Value†	PD Control B Group‡ (n = 286)	*P* Value§
Men, No. (%)	15 (71)	21 (50)	.16	172 (60)	.36
Age, mean (SD), y	60.2 (8.9)	65.7 (9.9)	.03	65.8 (11.2)	.007
Age at PD onset, mean (SD), y	50.9 (8.8)	58.4 (10.1)	.006	57.8 (8.5)	<.001
PD duration, mean (SD), y	9.2 (5.2)	6.9 (4.2)	.07	8.0 (9.6)	.57
Patients receiving levodopa alone, No. (%)	0	11 (26.1)	NA	150 (52.4)	NA
Patients receiving dopamine agonist monotherapy, No. (%)	1 (4.8)	1 (2.4)	.38‖	24 (8.6)	.14‖
Patients receiving dopamine agonist adjunctive therapy, No. (%)	20 (95.2)	30 (71.4)	.01‖	105 (37.6)	<.001‖
Pergolide, No. (%)	7 (33.3)	10 (23.8)	.70¶	21 (7.5)	.17¶
Pramipexole, No. (%)	5 (23.8)	12 (28.6)	.70¶	48 (17.2)	.17¶
Ropinorole, No. (%)	8 (38.1)	15 (35.7)	.70¶	36 (12.9)	.17¶
LEDD, mean (SD), mg/d	874.2 (495.6)	746.9 (322.5)	.20	746.7 (442.3)	.21
Dopamine agonist LEDD, mean (SD), mg/d	268.3 (194.3)	192.1 (105.3)	.69	209.0 (123.1)	.07
Hoehn and Yahr score, mean (SD)	2.0 (0.5)	2.2 (0.8)	.29	NA	NA
UPDRS-III score while "on," mean (SD)	15.2 (6.9)	22.1 (13.9)	.42	NA	NA
Patients with left-hemisphere PD onset, No. (%)	16 (76.2)	15 (44.1)	.03	NA	NA
MMSE score, mean (SD)	27.4 (3.2)	28.6 (1.5)	.51	NA	NA
Frontal Assessment Battery score, mean (SD)	15.4 (2.2)	15.5 (1.5)	.65	NA	NA
Apathy scale score, mean (SD)	5.6 (2.6)	8.0 (0.9)	.39	NA	NA
Patients with current or past depression, No. (%)	6 (28.6)	11 (26.8)	.80	NA	NA
Beck Depression Inventory score, mean (SD)	12.4 (6.0)	10.3 (7.9)	.30	NA	NA
Patients with medication-induced hypomania or mania, No. (%)	6 (30.0)	0	.001	NA	NA
Patients with any anxiety disorder, No. (%)	6 (30.0)	21 (50.0)	.25	NA	NA
Patients smoking >1 pack-year, No. (%)	10 (47.6)	11 (26.1)	.13	NA	NA
Patients with personal or immediate family history of alcohol use disorder, No. (%)	12 (60.0)	8 (19.0)	.002	NA	NA
Barratt Impulsivity Scale 11 score, mean (SD)				NA	NA
Attention subscale	16.9 (3.8)	15.6 (4.1)	.36	NA	NA
Motor subscale	20.9 (5.6)	17.3 (4.4)	.02	NA	NA
Planning subscale	27.0 (6.0)	21.1 (4.6)	.002	NA	NA
Total	65.2 (12.2)	54.1 (10.1)	.006	NA	NA
Novelty seeking score, mean (SD)	20.3 (6.6)	10.9 (4.2)	<.001	NA	NA
Harm avoidance score, mean (SD)	12.8 (5.3)	16.5 (6.9)	.17	NA	NA

Abbreviations: LEDD, levodopa equivalence daily dose; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease; PG, pathological gambling; UPDRS, Unified Parkinson's Disease Rating Scale.
*Control A indicates controls assessed for current study.
†*P* value for patients with PD and PG vs PD control A group.
‡Control B indicates control data from prevalence study.[1]
§*P* value for patients with PD and PG vs PD control B group.
‖Compared with levodopa monotherapy.
¶Compared with other dopamine agonist.

"The novelty seeking differences were due to lower control scores in PD patients without compulsive behaviors compared with patients with PG who scored similarly to the general population."

Voon et al. *Arch Neurol* 2007;64:212-216

Executive Impairment in PD Pathological Gambling

TABLE 3. *Cognitive compares between patients with PD with and without pathological gambling*

	PD + PG (n = 15)	PD − PG (n = 15)	F	P
MMSE	27.3 ± 1.9	28.27 ± 1.2	2.768	0.107
Neuropsychiatric parameter				
HAM-D score	11.47 ± 5.57	9.73 ± 8.25	0.454	0.506
Depression: yes/no (HAM-D score = 15/16)	4/11	2/13	0.833	0.361
Neuropsychological parameter				
a) Frontal Functions				
FAB	12.4 ± 2.2	15.7 ± 1.5	21.827	0.001[a]
1) Cognitive flexibility				
WCST-global score	105.3 ± 15.3	80.4 ± 38.9	5.334	0.029[b]
Phonological fluency	22.3 ± 11.1	34.8 ± 10.1	10.297	0.003[a]
Semantic Fluency	14.6 ± 3.3	18.7 ± 4.2	8.747	0.006[b]
2) Spatial and verbal working memories				
Corsi's test	4.5 ± 0.9	5.3 ± 1	6.293	0.018[b]
Verbal span	3.6 ± 0.8	3.9 ± 0.7	1.411	0.245
3) Logical abstract thinking				
RCPM	24.1 ± 5.9	29 ± 3	8.288	0.008[b]
4) Spatial planning				
ROCF-copy task	22.4 ± 8	29.5 ± 4.9	8.353	0.007[b]
5) Set-shifting				
TMT: B-A	141.1 ± 56.5	79.5 ± 37.7	12.355	0.002[a]
b) Memory				
Immediate Recall	41.1 ± 10.6	47.9 ± 10.4	3.196	0.085
Delayed recall	8.3 ± 2.7	10.2 ± 3.1	3.002	0.094
ROCF-delayed recall task	7.9 ± 3.7	13 ± 6.9	6.295	0.018[b]

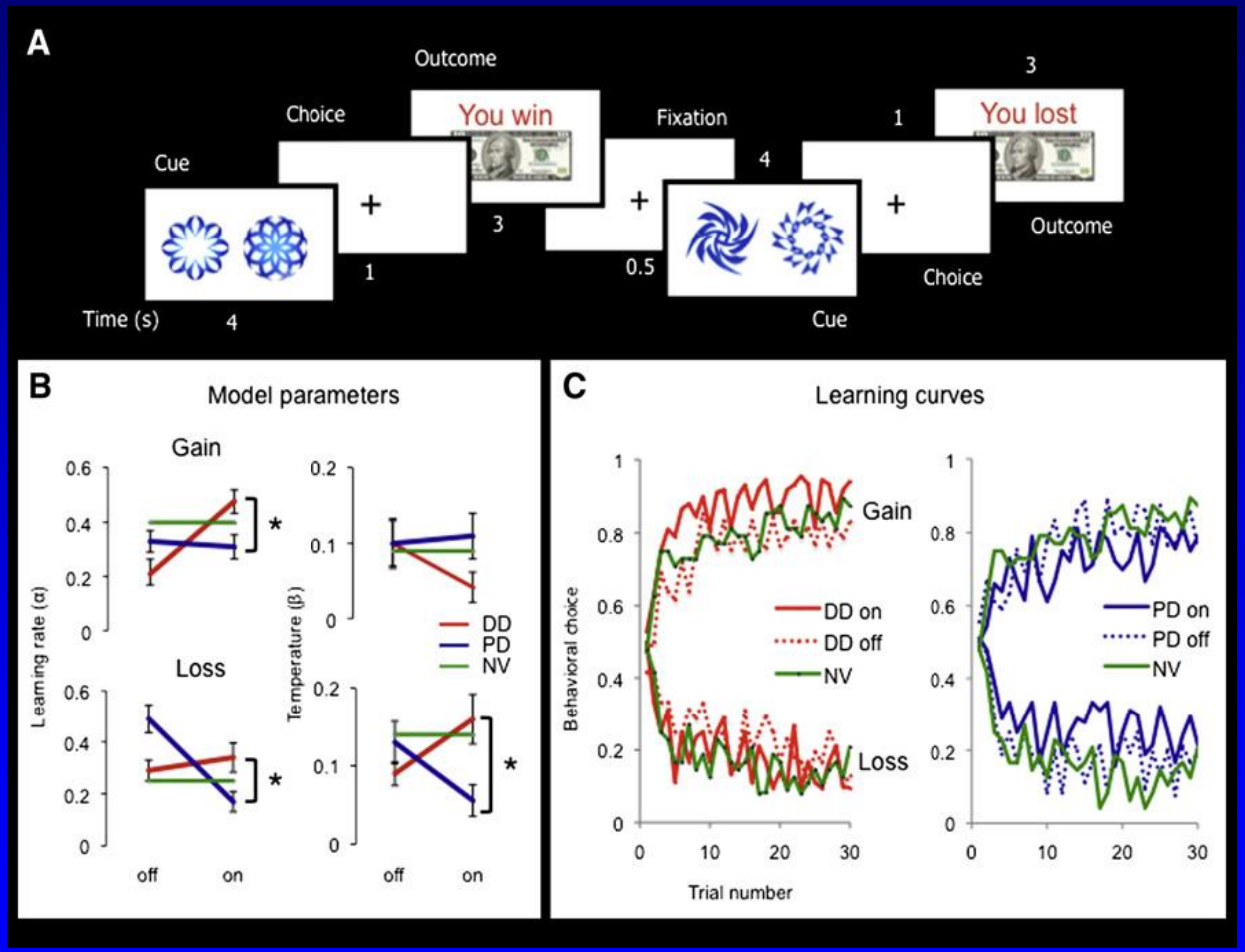
MMSE, Mini mental state examination; HAM-D, Hamilton depression rating scale; RCPM, Raven's colored progressive matrices; ROCF, Rey-Osterrieth complex figure test; TMT, trail making test.
[a]$P < 0.004$ (bonferroni's correction).
[b]$P < 0.050$.

"The results indicate an association between pathological gambling and frontal lobe dysfunctions in nondemented patients with PD."

FAB = Frontal Assessment Battery

Santangelo et al. *Movement Disorders* 2009;24:899-905

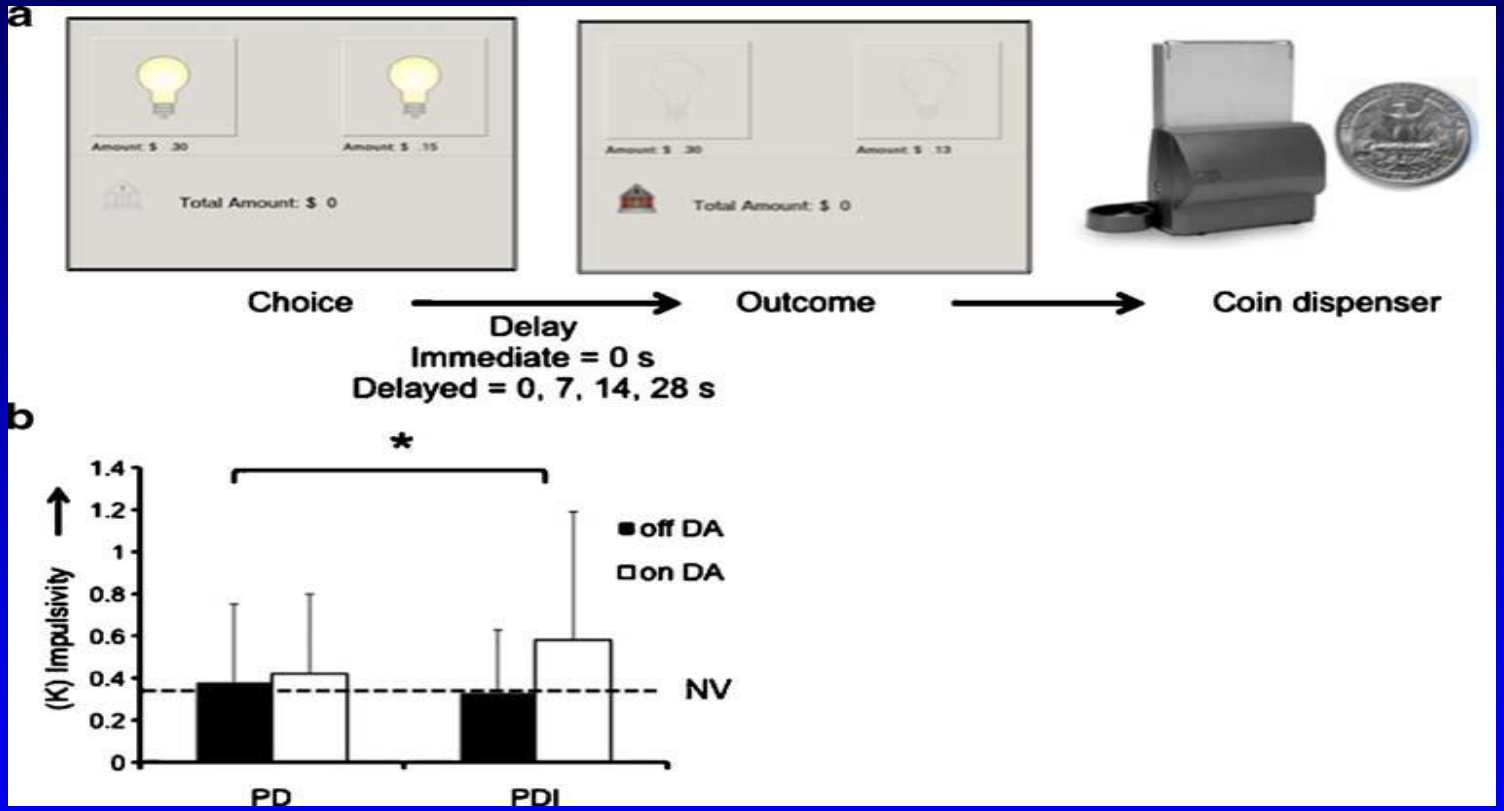
Altered Reward Learning with ICDs



In PD ICD patients, DA exposure increases reward learning and learning rates.

Voon et al. *Neuron* 2010;65:135-142

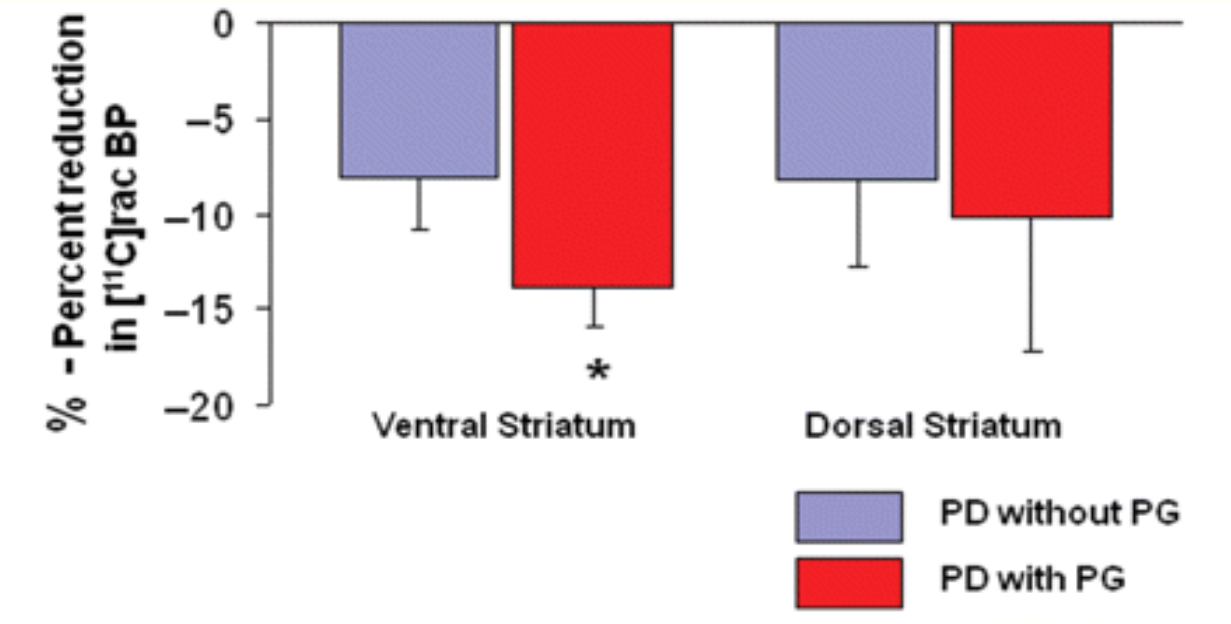
Increased Choice Impulsivity with ICDs



K is the steepness of the temporal discounting curve and is used as the measure of choice impulsivity. A higher K represents higher choice impulsivity. **PD=ICD-; PDI=ICD+**

Voon et al. *Psychopharmacology* 2010;207:645-659

Altered Striatal Dopamine Release with Pathological Gambling

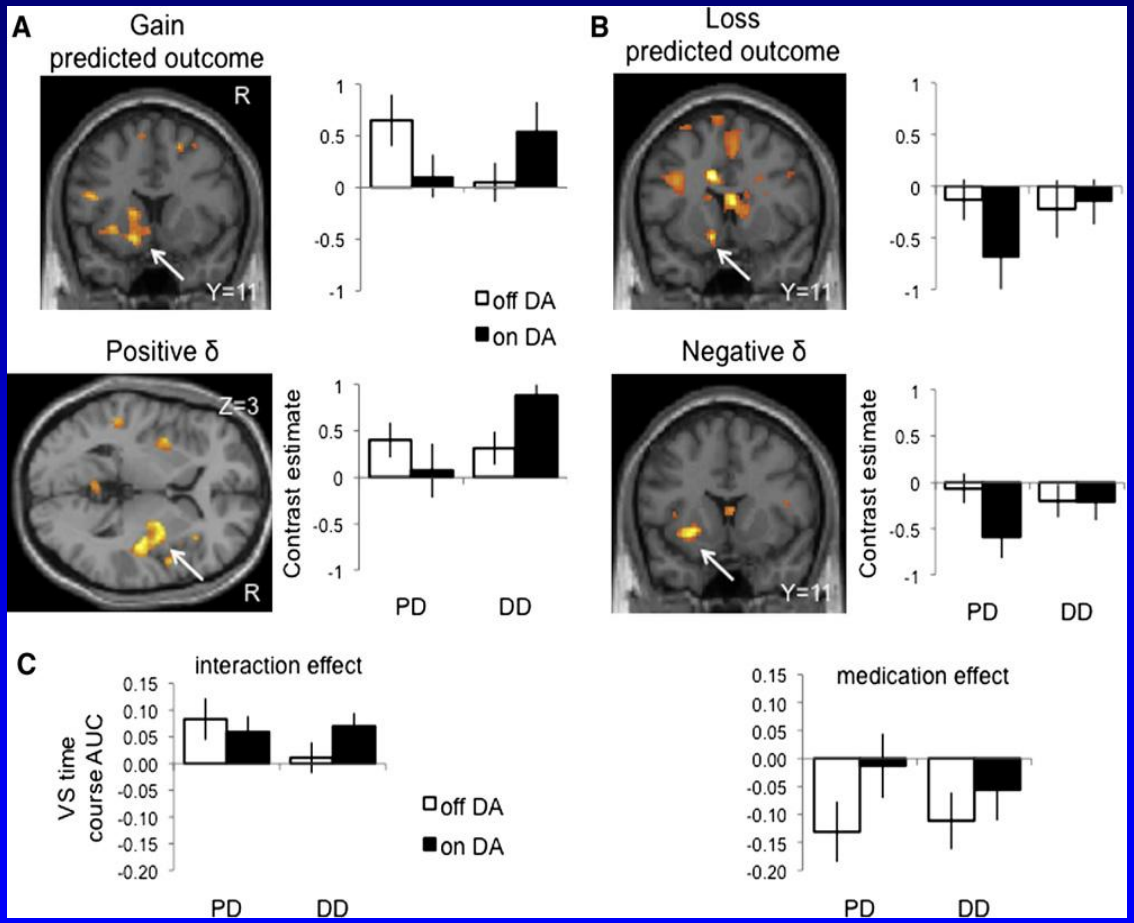


"Patients with PG demonstrated greater decreases in binding potential in the ventral striatum during gambling,... likely reflecting greater dopaminergic release."

Percent reduction in [^{11}C] raclopride-binding potentials during gambling (as compared to control task) in PD patients with and without PG. *Paired *t*-test, $P = 0.01$.

Steeves et al. *Brain* 2009;132:1376-1385.

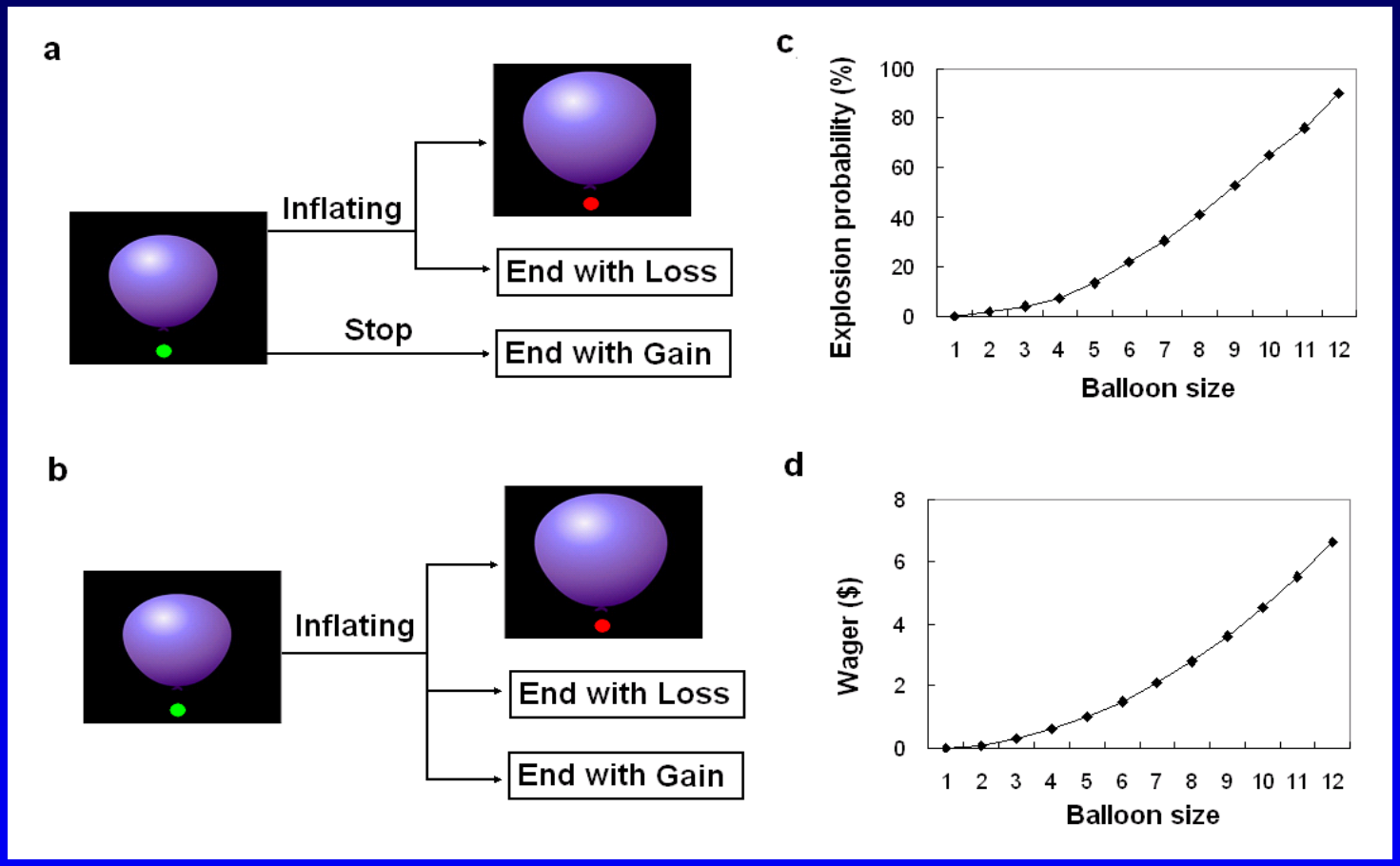
Increased Striatal Activation & Reward Prediction Error / Outcomes with ICDs



In ICD patients, DA exposure increases striatal reward prediction error (RPE) and predicted outcomes.

Voon et al. *Neuron* 2010;65:135-142.

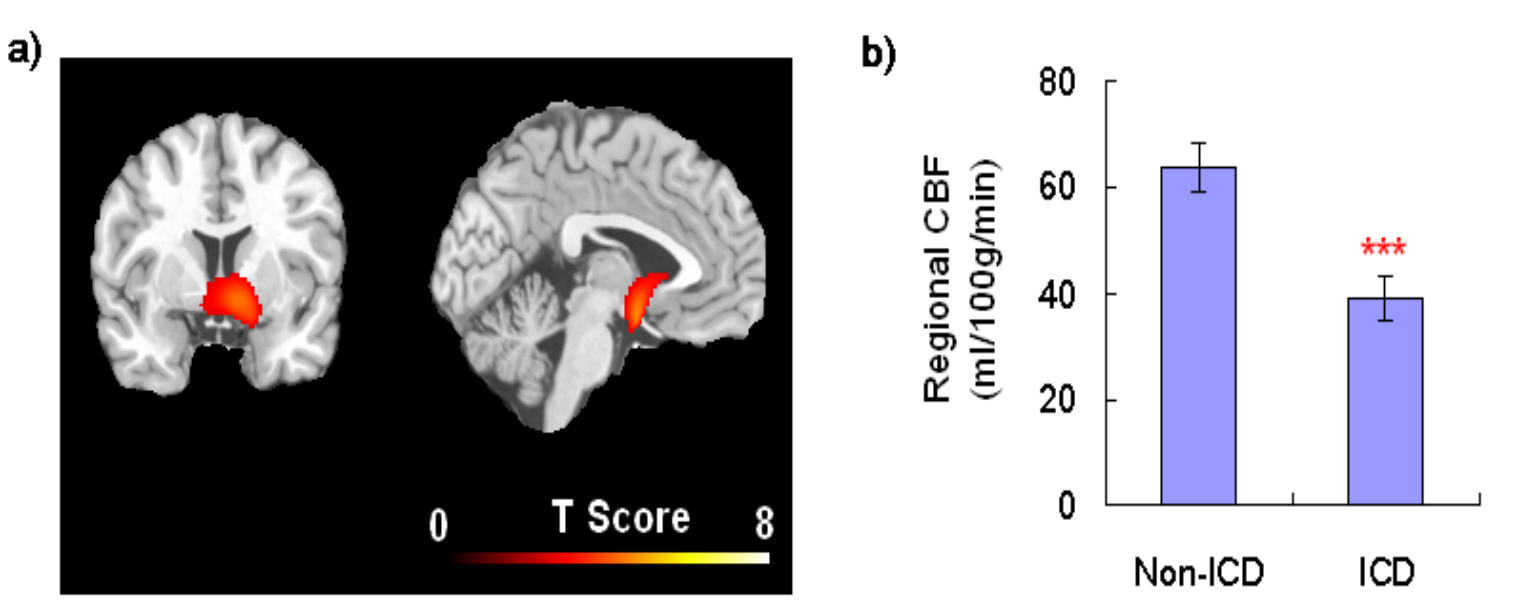
Risk Taking in ICD Patients



Balloon Analog Risk Task (BART)

Rao et al. *Movement Disorders* 2010; .

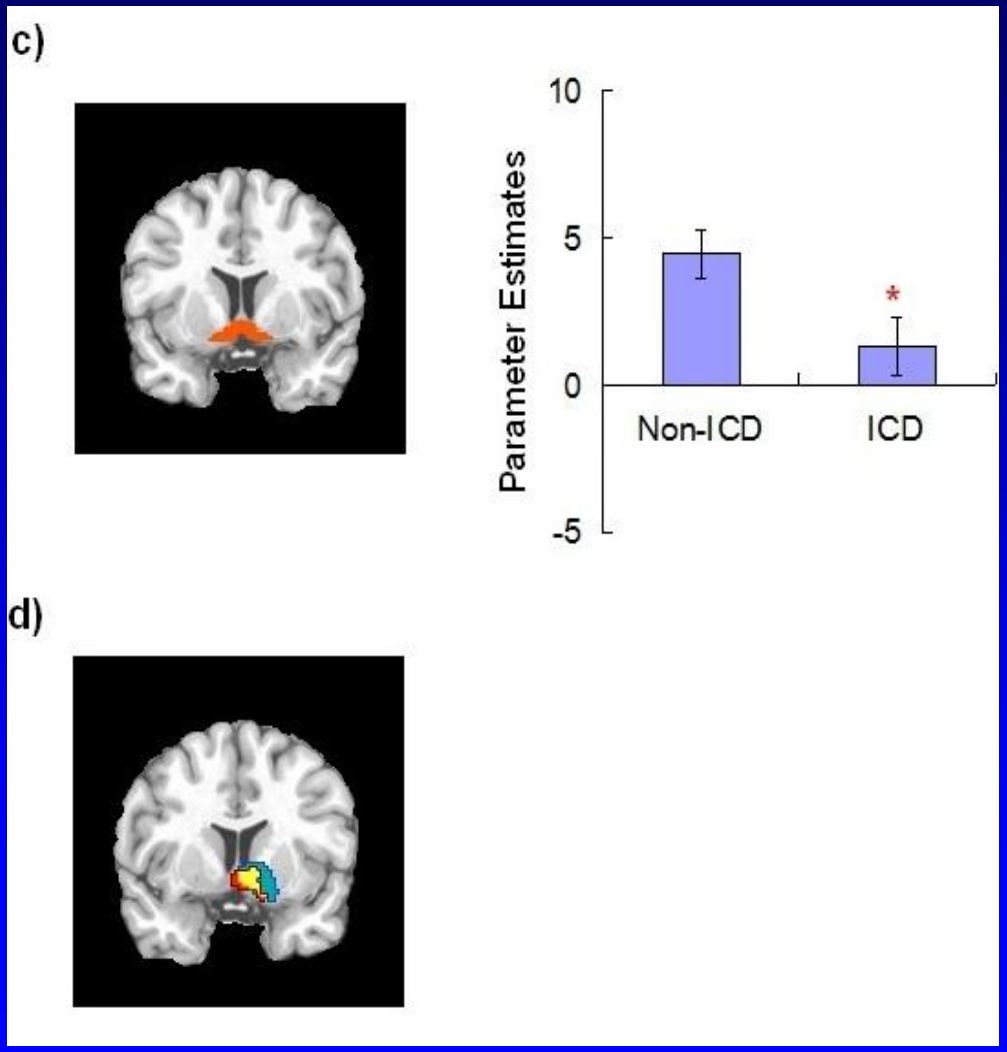
Resting Cerebral Blood Flow



(a) Resting perfusion imaging data showing significant CBF differences in the ventral striatum between ICD and non-ICD PD patients (threshold set as cluster corrected for $P < 0.05$)

(b) Quantitative analysis showing regional **resting CBF in the right ventral striatum decreased for the ICD group compared with the non-ICD group** (error bar represents standard error, ***$P < 0.001$)

Activation During Risk Taking



(c) The ventral striatum region of interest (ROI) and parametric estimates in ventral striatum showed significantly lower BOLD activation levels for ICD group compared with the non-ICD group (error bar represents standard error; *P < 0.05)

(d) **BOLD activation differences in the right ventral striatum overlapped with resting CBF differences** (red = BOLD, blue = CBF, yellow = both).

Clinical Management

Screening for ICDs & Related Disorders

- QUIP valid as self-administered screening instrument for ICDs & related disorders in PD
- Simple and short (<5 minutes)
- Brief version (13 questions) may perform as well as the full
- Follow-up clinical interview needed for screen + patients
- Clinical interview should focus on all ICDs and related behaviors

Movement Disorders
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Validation of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

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QUIP-Rating Scale

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Reported by: ____ Patient ____ Informant ____ Patient and Informant

Patient / Subject: _____

Date: _____

1. How much do you think about the following behaviors (such as having trouble keeping thoughts out of your mind or feeling guilty)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

2. Do you have urges or desires for the following behaviors that you feel are excessive or cause you distress (including becoming restless or irritable when unable to participate in them)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

3. Do you have difficulty controlling the following behaviors (such as increasing them over time, or having trouble cutting down or stopping them)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

4. Do you engage in activities specifically to continue the following behaviors (such as hiding what you are doing, lying, hoarding things, borrowing from others, accumulating debt, stealing, or being involved in illegal acts)?

Gambling?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Sex?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Buying?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Eating?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Performing tasks or hobbies?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Repeating simple activities?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)
Taking your PD medications?	Never(0)	Rarely(1)	Sometimes(2)	Often(3)	Very often(4)

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS)

Instruction Sheet

TIME FRAME

Either past 4 weeks or any 4-week period in a designated time frame

FREQUENCY OF SYMPTOMS

Never (0) = not at all
Rarely (1) = less than 2 hour a day on average
Sometimes (2) = 1-2 hours a day on average
Often (3) = 2-4 hours a day on average
Very often (4) = greater than 4 hours a day on average

DESCRIPTION OF BEHAVIORS

A. Gambling (casinos, internet gambling, lotteries, scratch tickets, betting, or slot or poker machines)

B. Sex (making sexual demands on others, promiscuity, prostitution, change in sexual orientation, masturbation, internet or telephone sexual activities, or pornography)

C. Buying (too much of the same thing or things that you don't need or use)

D. Eating (eating larger amounts or different types of food than in the past, more rapidly than normal, until feeling uncomfortably full, or when not hungry)

E. Hobbyism (specific tasks, hobbies or other organized activities, such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)

F. Punding (repeating certain simple motor activities, such as cleaning, tidying, handling, examining, sorting, ordering, collecting, hoarding, or arranging objects, etc.)

G. Medication Use (consistently taking too much of your Parkinson's medications, or increasing on your own, without medical advice, your overall intake of Parkinson's medications)

Current Management Options

- Do nothing
  - Assess clinical significance
  - Some patients unable or reluctant to make adjustments to PD pharmacotherapy
- Alterations to PD pharmacotherapy
  - Changes to DA therapy
  - Not clear what role levodopa adjustments might play
- Consider deep brain stimulation (DBS)
- Psychopharmacology

Changes in Dopaminergic Therapy and UPDRS Motor Scores Over Time

	Time 1 (mean [SD])	Time 2 (mean [SD])	Average % Change	Statistic (Z score [P value])[1]
Dopamine agonist LEDD	358.7 (179.4)	170.2 (233.3)	- 52.6%	-3.1 (.002)
Levodopa LEDD	349.7 (381.3)	482.3 (358.9)	+ 37.9%	-1.9 (.05)
Total LEDD	708.3 (482.9)	652.5 (465.3)	- 7.9%	-0.5 (.64)
UPDRS motor score[2]	22.6 (8.7)	24.6 (10.2)	+8.8%	-1.3 (.19)

[1] Wilcoxon Signed Ranks Test

[2] N=14 (UPDRS scores unavailable for 1 patient)

Mamikonyan et al. *Movement Disorders* 2008;23:75-80.

Deep Brain Stimulation?

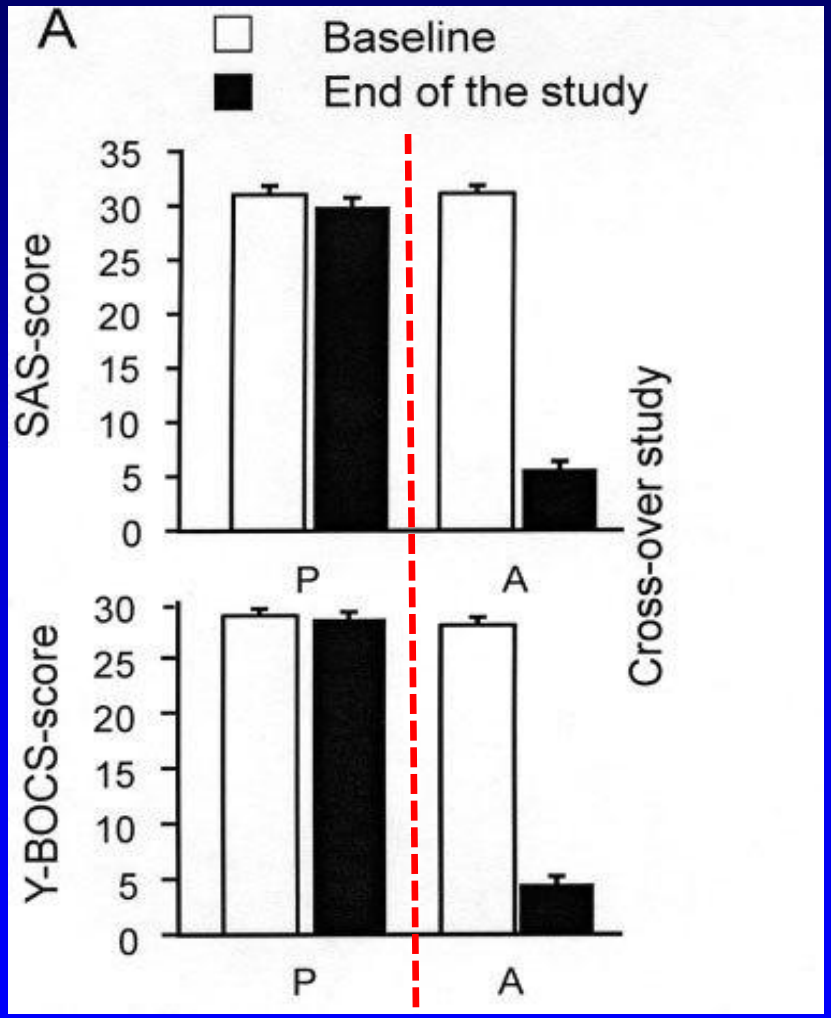
- 7 patients with pathological gambling underwent DBS
- Pre-surgery levodopa equivalent dose = 1,390 mg/day
  - Post-surgery 74% reduction in overall LEDD
- PG resolved postoperatively in all patients over mean of 18 months (range 0-48)
- However, emerging case report literature of ICDs starting post-DBS surgery

Ardouin et al. *Movement Disorders* 2006;21:1941-1946.

Psychopharmacology

- Antidepressants (SSRIs), atypical antipsychotics (APs), and anticonvulsants used clinically
  - Case reports for atypical APs in treatment of ICDs in PD
- Need for medications that will allow patients to stay on PD medications and not worsen parkinsonism
  - Specific D_3-receptor antagonists?
  - Opioid and glutamate antagonists?

Amantadine for Gambling in PD



Symptom Assessment Scale (SAS) and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score changes during the crossover. Both scores are reduced by amantadine ($p < 0.001$ compared to baseline).

A = amantadine
P = placebo

Thomas et al. *Annals of Neurology* 2010;68:400-404.

DOMINION - Amantadine Data

ICD type	Amantadine treatment status	Current ICD N (%)	No current ICD N (%)	P value (CMH-test); odds ratio [95% CI]*
Any ICD	No amantadine use (N=2357) Amantadine use (N=728)	292 (12.4) 128 (17.6)	2065 (87.6) 600 (82.4)	<0.001 1.49 [1.19;1.87]
Problem/pathological gambling	No amatadine use Amantadine use	100 (4.2) 54 (7.4)	2257 (95.8) 674 (92.6)	<0.001 1.78 [1.27;2.50]
Compulsive sexual behaviour	No amantadine use Amantadine use	71 (3.0) 37 (5.1)	2286 (97.0) 691 (94.9)	0.001 1.70 [1.13;2.56]
Compulsive buying	No amantadine use Amantadine use	119 (5.0) 58 (8.0)	2238 (95.0) 670 (92.0)	0.005 1.60 [1.15;2.22]
Binge-eating disorder	No amantadine use Amantadine use	100 (4.2) 32 (4.4)	2257 (95.8) 696 (95.6)	0.90 1.03 [0.68;1.54]

Weintraub et al. *Annals of Neurology* 2010;68:963-968.

Ongoing Clinical Trial

- Michael J. Fox Foundation grant
- Randomized clinical trial of naltrexone for ICDs
  - Naltrexone is a competitive opioid receptor anatagonist
    - Primarily kappa and mu receptors
  - Modulatory role for mu and delta opioid peptides in the nigrostriatal dopaminergic pathway
- 48 subjects with ≥1 of 4 common ICDs randomized to naltrexone or placebo
  - 17 subjects enrolled so far

Conclusions PD - I

- ICDs in PD are
  - Relatively common
  - A range of ICDs occur
  - ICDs often co-morbid
  - Associated with DA use as a class
  - Associated with levodopa and amantadine use to lesser extent
  - Dose effects for levodopa
  - Psychiatric co-morbidity common

Conclusions PD - II

- May have several other “pre-morbid” risk factors
- Altered reward-punishment learning with DA exposure
- Increased impulsivity in reward choices
- Alterations in ventral striatal activity
- Alterations in dopaminergic system
  - Striatal dopamine activity
  - Genetic associations

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