Impulsive Compulsive Behaviors in Parkinson's disease: drug-related or disease progression?

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SNUH
SMG-SNU
BORAMAE MEDICAL CENTER

Behavioral Disturbances in PD

- Early literatures on the psychiatric and behavioral disturbances in PD patients with levodopa therapy; Psychosis, Delusion, Paranoia, Hypomania, Rapid mood cycling, Anxiety, insomnia, Aggression, Impulsive behaviors, Restlessness. Agitation, hypersexuality
  (Barbear 1969; Celesia 1970; Damasio 1971; Goodwin 1971; Quinn 1983; Harvey 1986; Uitti 1989)

- Hedonistic Homeostatic Dysregulation syndrome (Giovannoni, 2000)
- Dopamine Dysregulation Syndrome (Lawrence, 2003)
- Medication-related Impulse control and repetitive behaviors (Voon,2006)
  - Impulse control disorder
  - Compulsive medication use
  - Punding (Evans, 2004)
  - Obsessive compulsive behaviors

Pathological gambling
Hypersexuality, Zoophilia, Paraphilia
Compulsive buying
Binge eating
Kleptomania (Stealing)
Impulsive aggressive disorder
Trichotillomania (Pulling hair)
Problematic internet use

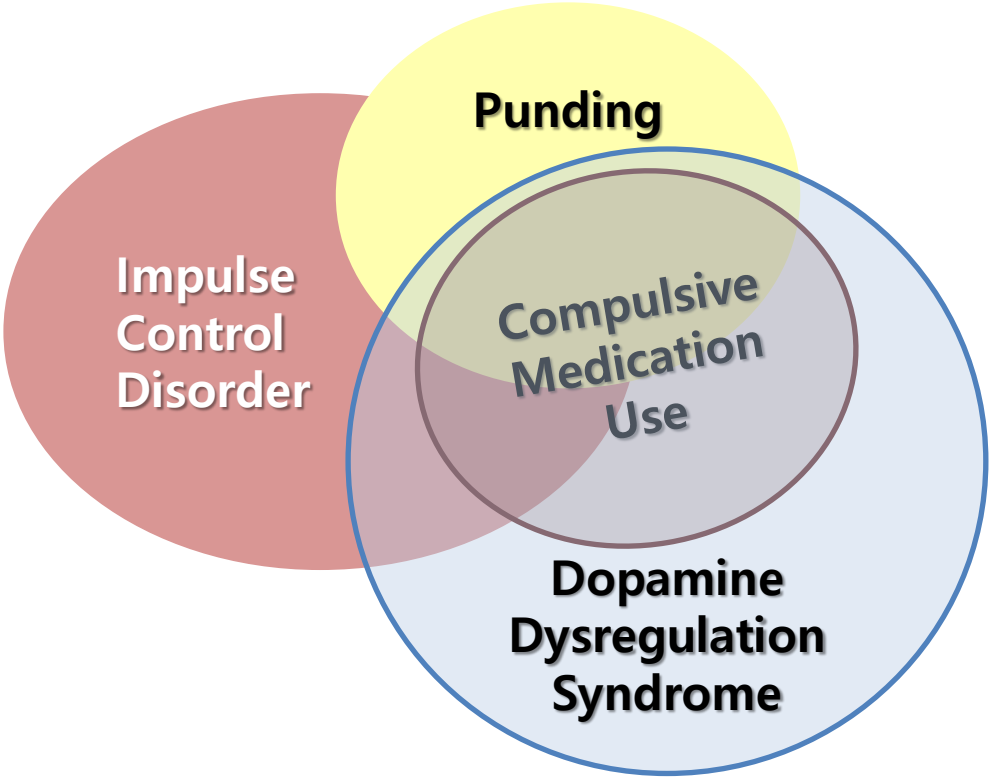
Punding

- **Repetitive stereotyped non-goal-oriented behaviors**
- described in amphetamine users
- premorbid interests
- may be socially disabling (Evans, 2010)
  - **less complex acts** : shuffling papers, reordering bricks, or sorting handbags
  - **more complex acts**: hobbyism (gardening, painting), cleaning, repairing things, writing, categorizing information, artistic drawing or craft-making, singing, playing a musical instrument, playing cards, fishing, excessive computer use, etc

Compulsive Medication (L-dopa) Use

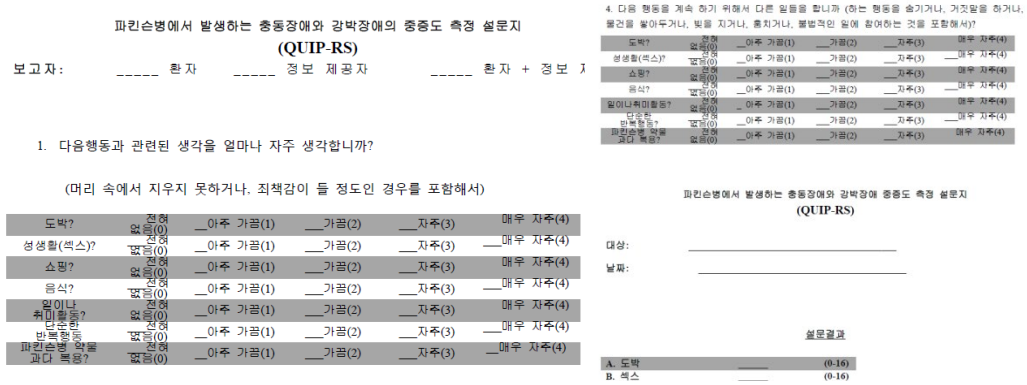
- Compulsive use of L-dopa well beyond the dose needed to optimally control motor disability (ex. Up to 3000 or 4000mg/d despite of severe dyskinesia)
- **Meet the criteria of Substance dependence or "Addiction"** (Evans, 2009)
- Nearly **always being associated with "dopamine dysregulation syndrome (DDS)"** (Voon, 2007)

VIDEO


Punding
Impulse Control Disorder
Compulsive Medication Use
Dopamine Dysregulation Syndrome

Prevalence of ICB (ICD and related behaviors)

- Large multicenter cross-sectional surveys on ICD; **10~14%** (Weintraub 2010; Lee 2010)
- Systematic surveys using QUIP including compulsive drug intake and punding; **15.5~35.9%** (Kim 2012; Lim 2011; Tanaka 2013; Callesen 2014)
- Low prevalence of pathologic gambling and High prevalence of eating and hypersexual behaviors in Korea. (Kim 2012; Lee 2014; Choi & Lee 2020)


파킨슨병에서 발생하는 충동장애와 강박장애의 중증도 측정 설문지
(QUIP-RS)
보고자: _____ 환자 _____ 정보 제공자 _____ 환자 + 정보 제

1. 다음행동과 관련된 생각을 얼마나 자주 생각합니까?
(머리 속에서 지우지 못하거나, 죄책감이 들 정도인 경우를 포함해서)

도박?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
성생활(섹스)?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
쇼핑?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
음식?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
일이나 취미활동?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
단순한 반복행동?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
파킨슨병 약물 과다 복용?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)

4. 다음 행동을 계속 하기 위해서 다른 일들을 참니까 (하는 행동을 숨기거나, 거짓말을 하거나, 물건을 팔아두거나, 빚을 지거나, 훔치거나, 불법적인 일에 참여하는 것을 포함해서)?

도박?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
성생활(섹스)?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
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일이나 취미활동?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
단순한 반복행동?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)
파킨슨병 약물 과다 복용?	전혀 없음(0)	_아주 가끔(1)	__가끔(2)	__자주(3)	매우 자주(4)

파킨슨병에서 발생하는 충동장애와 강박장애 중증도 측정 설문지
(QUIP-RS)
대상: _____
날짜: _____

설문결과

A. 도박	_____	(0-16)
B. 섹스	_____	(0-16)

2. 다음 행동에 대해 스스로 과도하
못할 때, 불안하거나 짜증이 나는

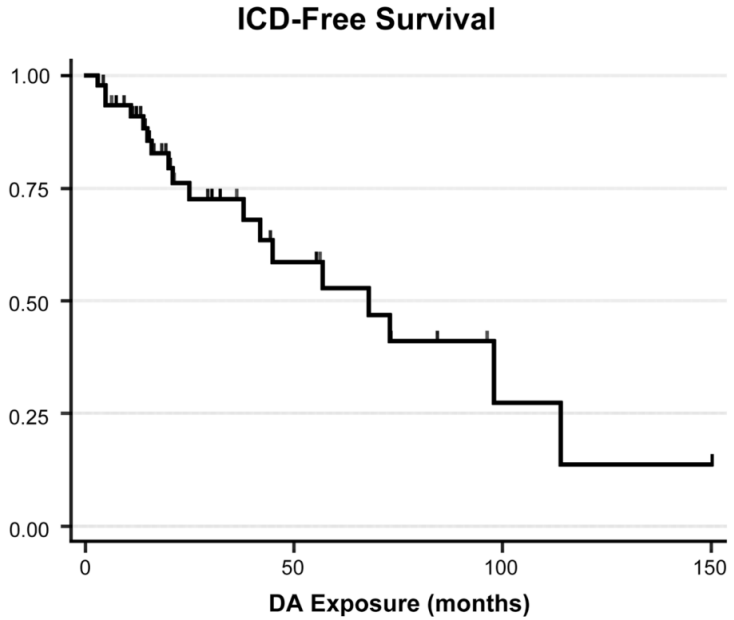
도박?	전혀 없음(0)	_아
성생활(섹스)?	전혀 없음(0)	_아
쇼핑?	전혀 없음(0)	_아
음식?	전혀 없음(0)	_아
일이나 취미활동?	전혀 없음(0)	_아
단순한 반복 행동?	전혀 없음(0)	_아
파킨슨병 약물 과다 복용?	전혀 없음(0)	_아

3. 다음 행동을 스스로 조절하기가
중단하기 힘든 경우를 포함해서)?

도박?	전혀 없음(0)	_아
성생활(섹스)?	전혀 없음(0)	_아
쇼핑?	전혀 없음(0)	_아
음식?	전혀 없음(0)	_아
일이나 취미활동?	전혀 없음(0)	_아
단순한 반복행동?	전혀 없음(0)	_아
파킨슨병 약물 과다 복용?	전혀 없음(0)	_아

K-QUIP-RS domain	Guttman split-half coefficient	Spearman's rank correlation	
		rS	*p*
Gambling	0.908	0.392	<0.001
Hypersexuality	0.079	0.539	<0.001
Buying	0.863	0.551	<0.001
Eating	0.708	0.723	<0.001
Hobbyism/punding	0.830	0.820	<0.001
DDS	0.347	0.379	<0.001
Summed score for ICD	0.726	0.887	<0.001
Total K-QUIP-RS score	0.808	-	-

Incidence in prospective cohort

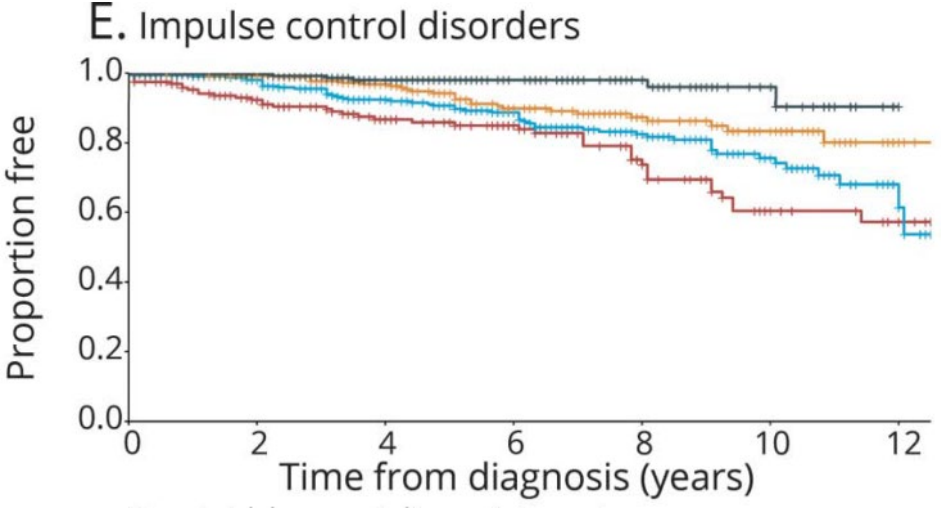


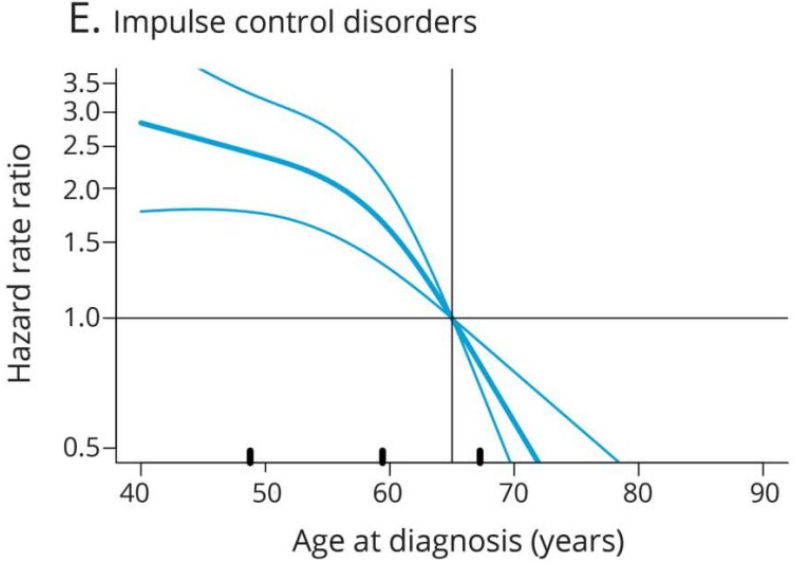
(Bastiaens, 2013; N=164, 4Y FU)

- However, the timing of new-onset ICDs in PD is highly variable.
- Even after DBS with concomitant reduction of Das

- Risk factors in large sample studies: cigarette smoking, caffeine use, alcohol abuse disorder, family history of alcohol or drug use disorder

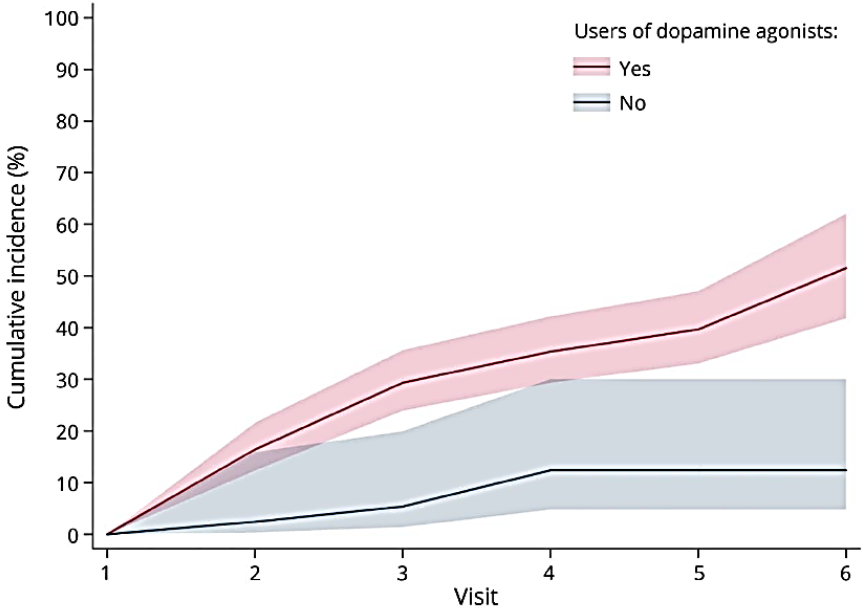
Age and time course of long-term nonmotor complications in PD

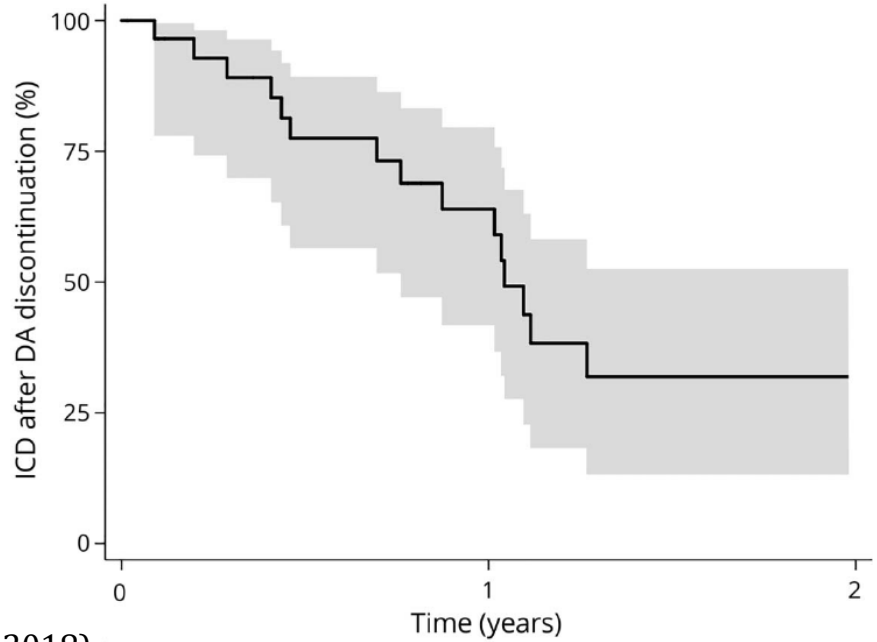




(Prange, 2018)

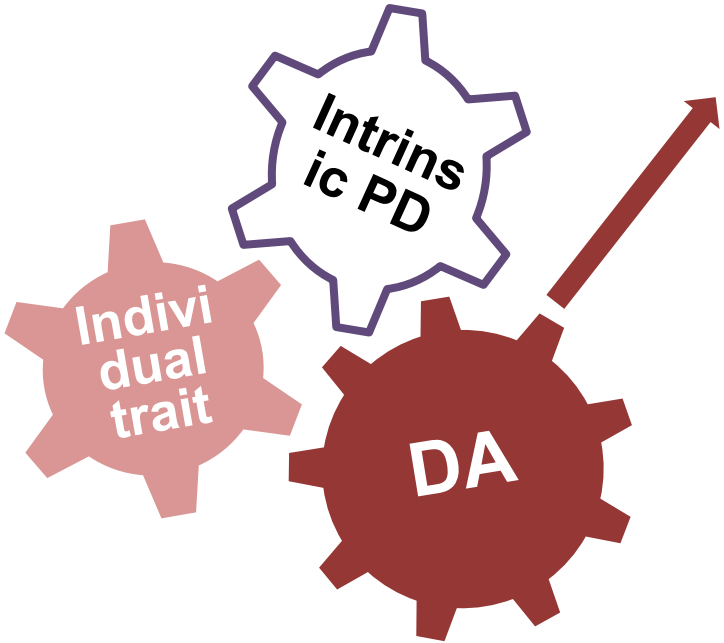
Longitudinal change of ICD in PD





(Covel, 2018)

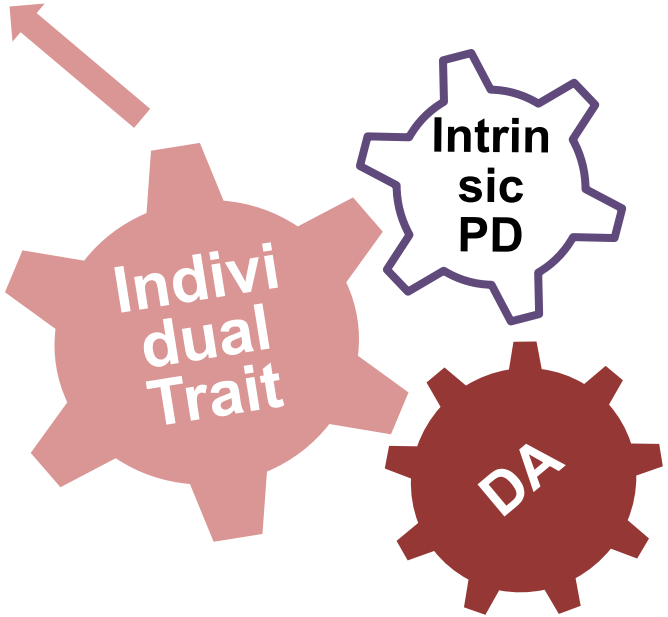
Factors associated with ICD in PD



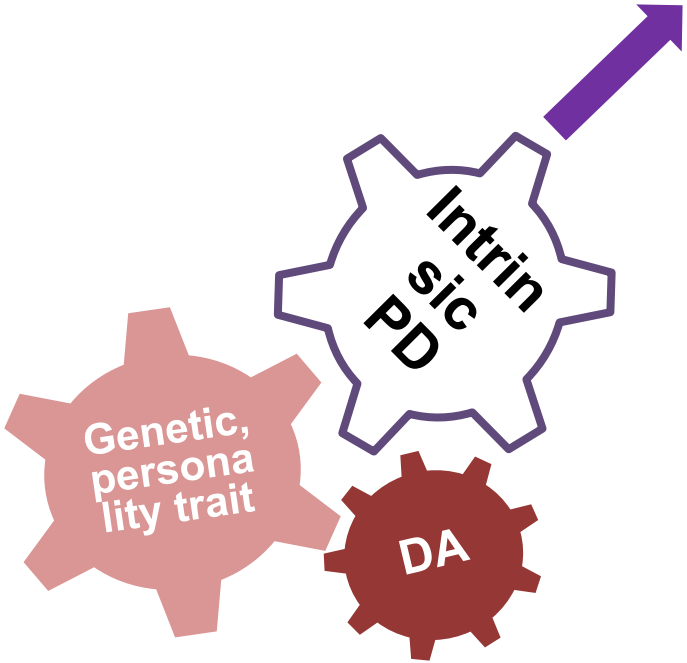
- **Dopamine agonist** use: X10↑(Weintraub 2006)
- **High dose** DA: X3-4↑(Lee 2010; Bastiaens, 2013), no difference (Weintraub 2006)
- Dopamine agonists with higher affinity to mesolimbic dopamine receptors, D3 (Grosset 2006): pramipexole, ropinirole, no class difference
- ICD in patients with RLS, fibromyalgia, and P-plus syndrome patient taking dopamine agonists (Voon 2011; Holman 2009; O'Sullivan 2010)
- Improvement of ICD by cessation of DA or reduction of dosages (Mamikonyan 2008; Voon 2007; Thobois 2010; Lee 2019)

Factors associated with ICD in PD

- Novelty seeking trait, **Impulsivity**, Depression, Anxiety, Anger, Obsessive-compulsive traits, **Alexithymia** (Pontone 2006; Voon 2007; Isaias 2008; Voon 2011; Goerlich-Dobre 2014)
- Genetic variants for dopamine, serotonin, glutamate receptors: *DRD3* S9G, *GRIN2B* C366G, *HTR2A* T102C (Lee 2009; Lee 2012)
  cf. *DRD2*-controversial in PD-ICD
- History of smoking, alcohol use disorder, substance use disorder (Voon 2007; Voon 2011; Valença 2013)

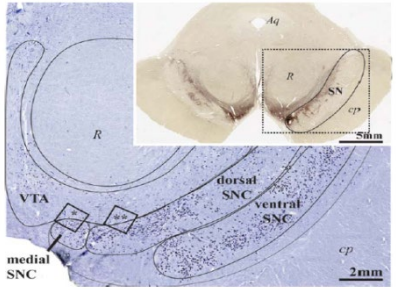


Factors associated with ICD in PD



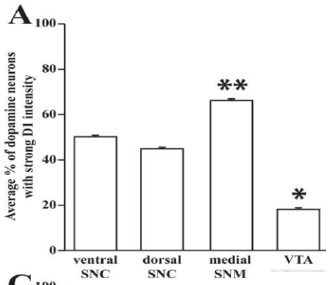
- young age at onset, right-sided predominance of symptom (Voon 2007; Lee 2009)
- Alterations in Reward Learning & Decision Making: **mesolimbic dopamine system dysfunction:**
  - ✓ Biased representation of reward and sensitivity to rewards and risk taking
  - ✓ More impulsive on decision making
- Characteristic pattern of **dopaminergic system degeneration** in PD
  - ✓ relative preservation of extrastriatal vs. striatal dopaminergic fibers
- Dysfunctional frontostriatal inhibitory network

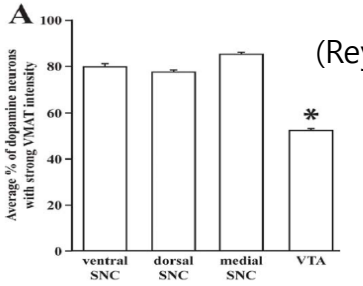
Different expression of DR, DAT, VMAT in the SNc and VTA



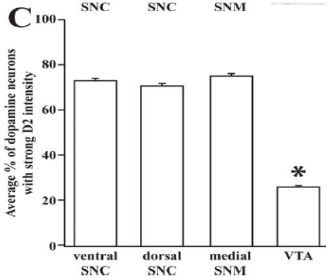
↑ D1, relative low auto-D2, ↓ DAT in mSNc

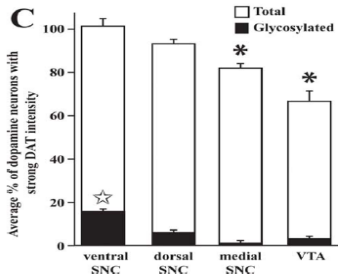
: inefficient negative feedback machinery for dopamine release regulation

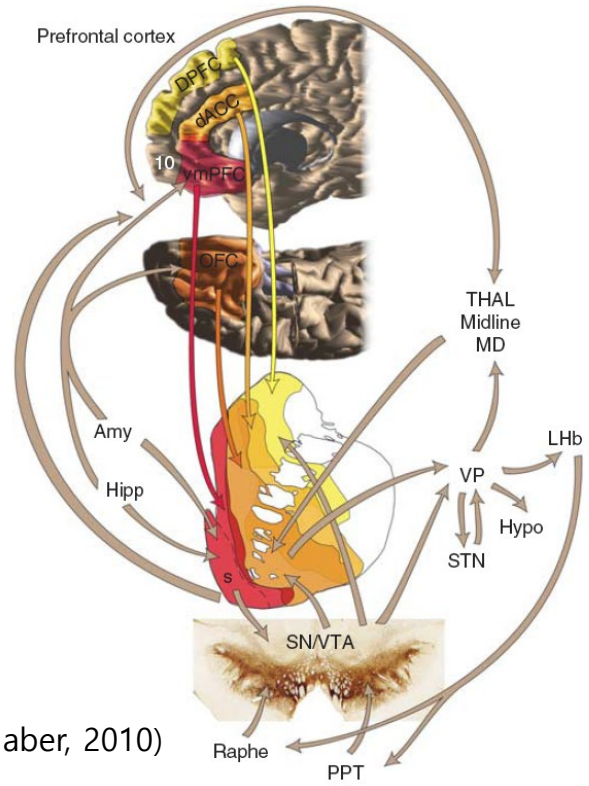




(Reyesr, 2013)

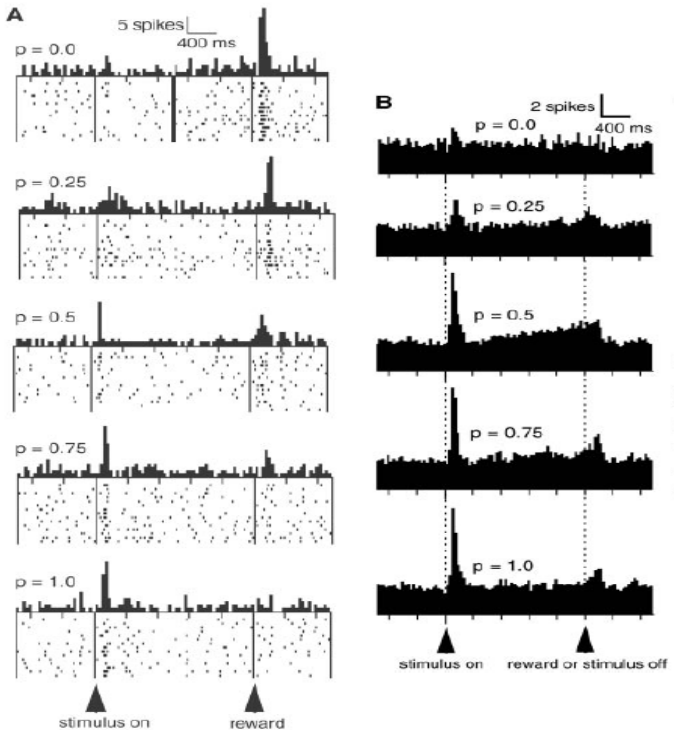




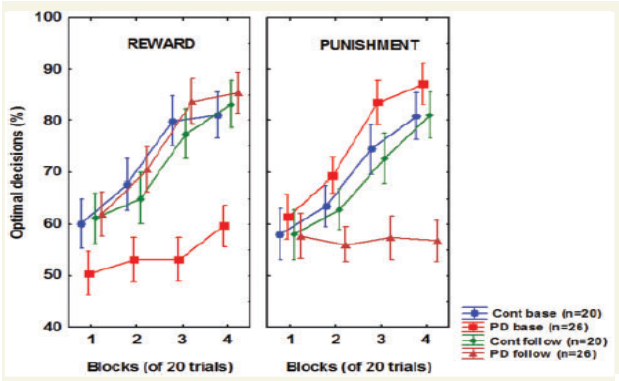


(Haber, 2010)

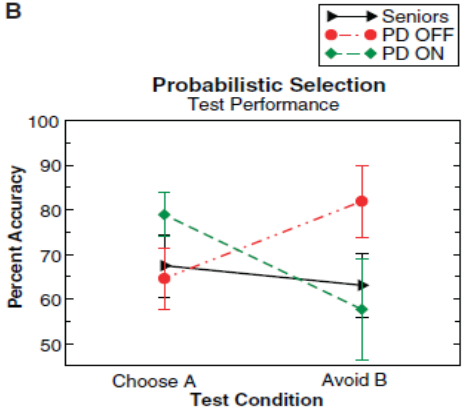
Reward learning alterations in PD



Dopamine replacement therapy alters normal physiologic release of dopamine in the mesolimbic system during reward reinforcement learning process (Fiorillo 2003; Frank 2004)

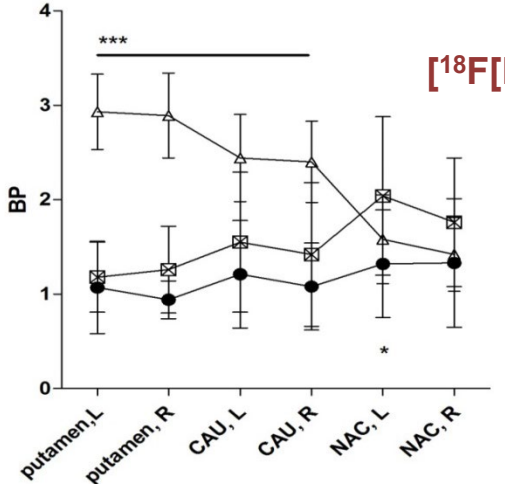


Dopamine agonist reverse reward learning pattern in drug-naïve PD (Bodi 2009)



Increased sensitivity to rewards, insensitivity to punishments (Kobayakawa 2010)

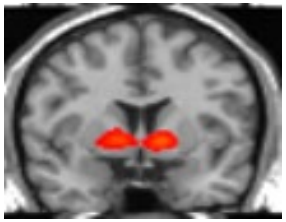
Hyperdopamine in the ventral striatum in PD+ICD



[^{18}F[FP-CIT dynamic PET study

PD-ICD
PD nonICD
normal control

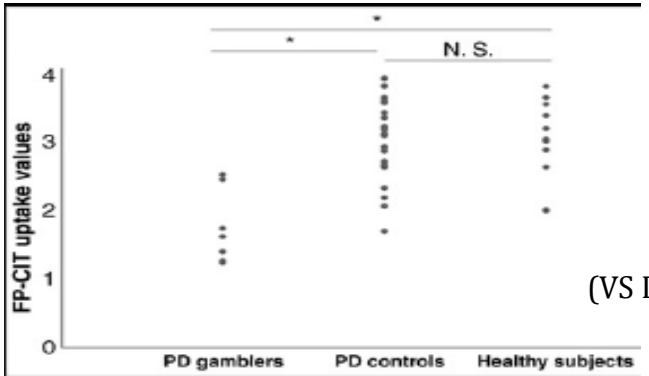
(Lee, 2014)



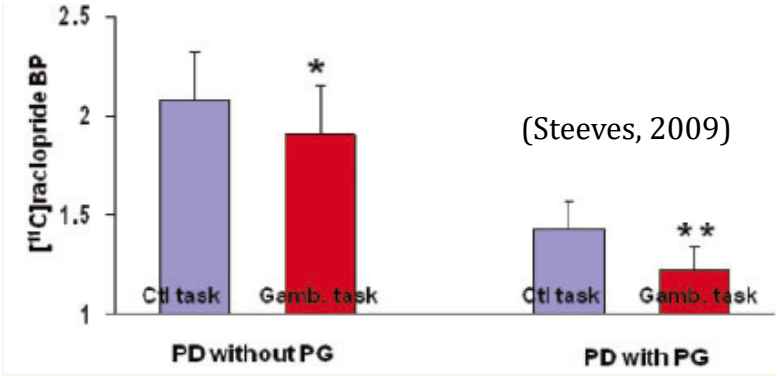
PD ICD < PD control, p<0.005

"Downregulation as a sensitization to reward-related behaviors"
- an early event of addiction formation (Koo, 2010)

"Hyperdopamine in synapse"



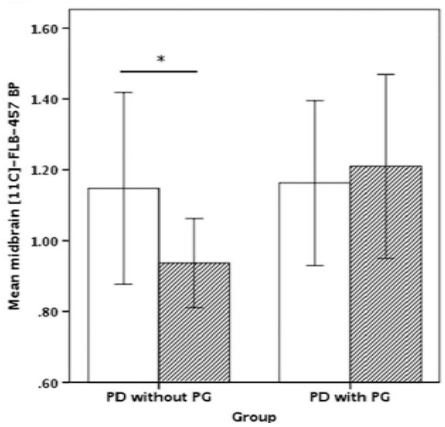
(VS DAT, Cilia 2010)

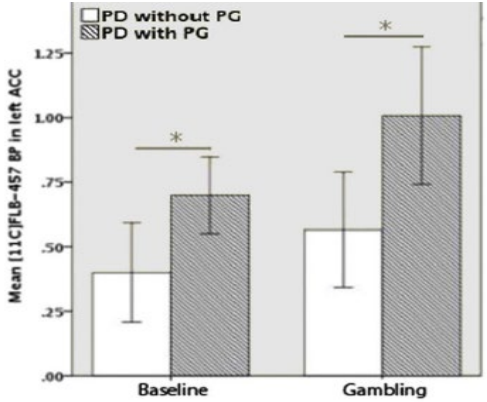


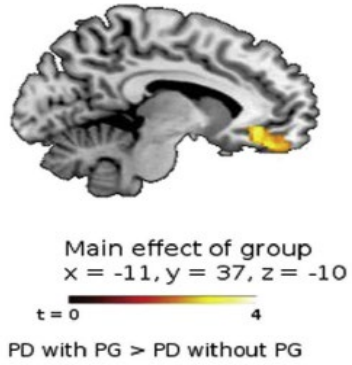
(Steeves, 2009)

Extrastriatal dopamine homeosis in PD+PG

[^{11}C]FLB-457 PET scan during gambling task





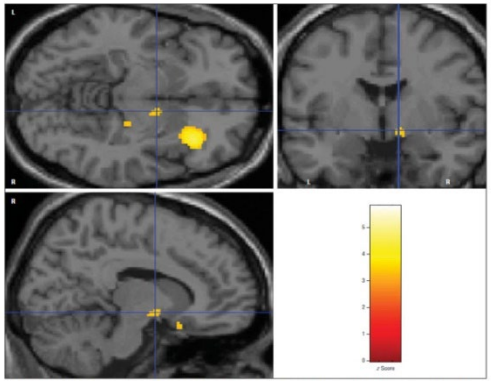


↓ D2 auto-Rc occupancy during gambling task → ↓ negative feedback to DA release in the midbrain

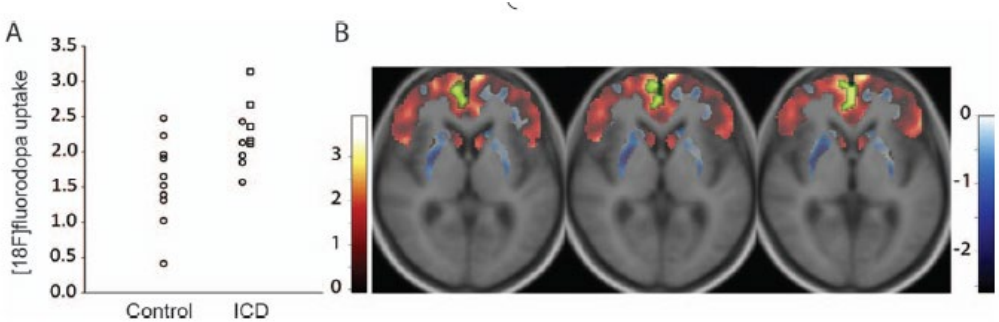
↓basal DA levels or ↑D2/D3 in the OFC, ACC in PD+PG

(Ray, 2012)

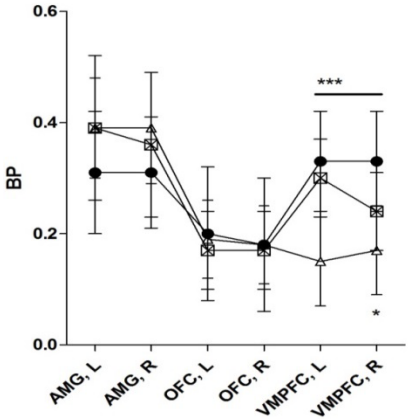
High basal OFC dopaminergic activities in PD+ICD

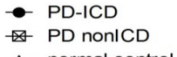


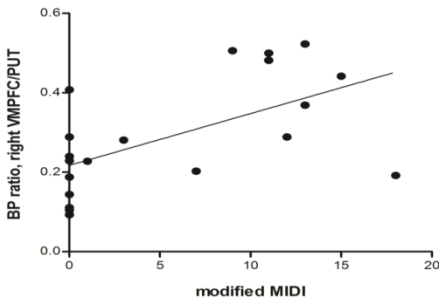
(CBF, Cilia, 2008)



(AADC, Jousta, 2012)

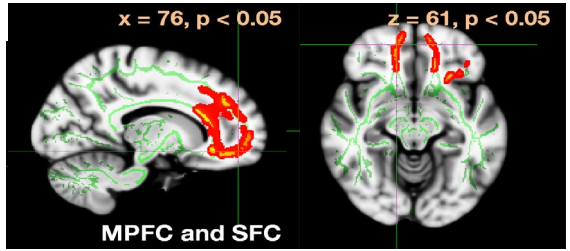




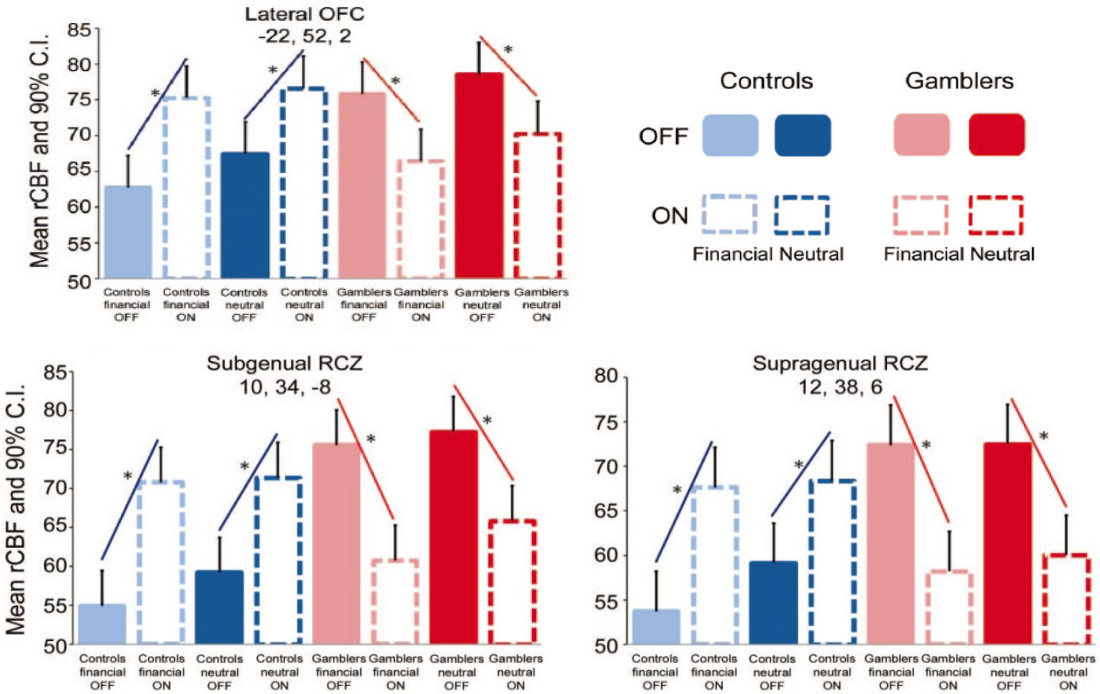


(DAT, Lee, 2014)

(FA, Yoo & Lee, 2015)



Apomorphine-induced deactivation of inhibitory networks in PD + PG



The role of OFC & RCZ

✓ Med OFC: reward-based decision making

✓ **Lat OFC**: punishment-based decision making, suppression of previously rewarded behavior (Rolls, 2000)

✓ **RCZ (ACC)**: monitoring functions to prevent negative consequences

(Eimeren, 2010)

Adjustment of drugs as soon as identifying the problem can help the patients

- Of 18 subjects, 15 (83.3%) participated in the FU (mean 29.2 mo)
- 12 (80.0%) patients discontinued or significantly decreased DA
- All experienced full or partial remission of ICD symptoms
- 10 (83.3%) patients no longer met diagnostic criteria for an ICD.

(Mamikonyan, 2008)

TABLE 2. *Changes in levodopa equivalent daily dosages (LEDDs) and UPDRS score over time*

	Time 1 (mean [SD])	Time 2 (mean [SD])	Average % change	Statistic (*Z* score [*P* value])*
Dopamine agonist LEDD	358.7 (179.4)	170.2 (233.3)	−52.6	−3.1 (0.002)
Levodopa daily dosage	349.7 (381.3)	482.3 (358.9)	+37.9	−1.9 (0.05)
Total LEDD	708.3 (482.9)	652.5 (465.3)	−7.9	−0.5 (0.64)
UPDRS motor score[a]	22.6(8.7)	24.6(10.2)	+8.8	−1.3(0.19)

Problems: DA withdrawal and apathy

Severe apathy after switching of ropinirole to levodopa/carbidopa due to ICD(compulsive shopping, unrealistic compulsive religious behavior)

Dopamine Agonist Withdrawal Syndrome (DAWS): 15~19% in patients after discontinuing DA . Higher dose → Greater risk

Akathisia, anxiety, panic attacks, depression, dysphoria, agitation, insomnia, dizziness, nausea, irritability, fatigue, orthostatic hypotension, diaphoresis, generalized pain, and drug cravings

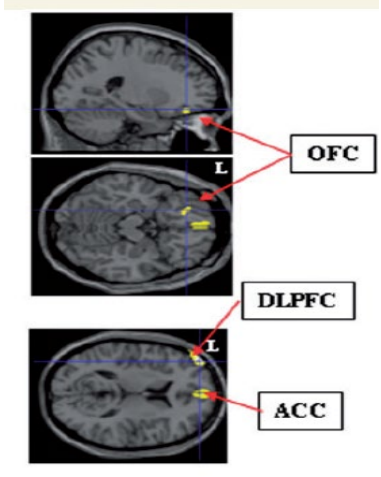
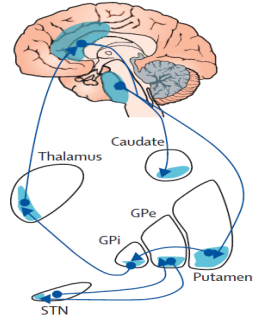


Table 4 Predictors of apathy: multivariate analysis

Parameters	Hazard ratio	Confidence Interval 95%	P
Delta anxiety (BAI) per unit	1.054	[1.019; 1.090]	0.002
Non-motor fluctuations yes versus no	2.754	[1.348; 5.626]	0.005

← mesolimbic denervation in patients with severe apathy after medication switch

(Thobois, 2010)



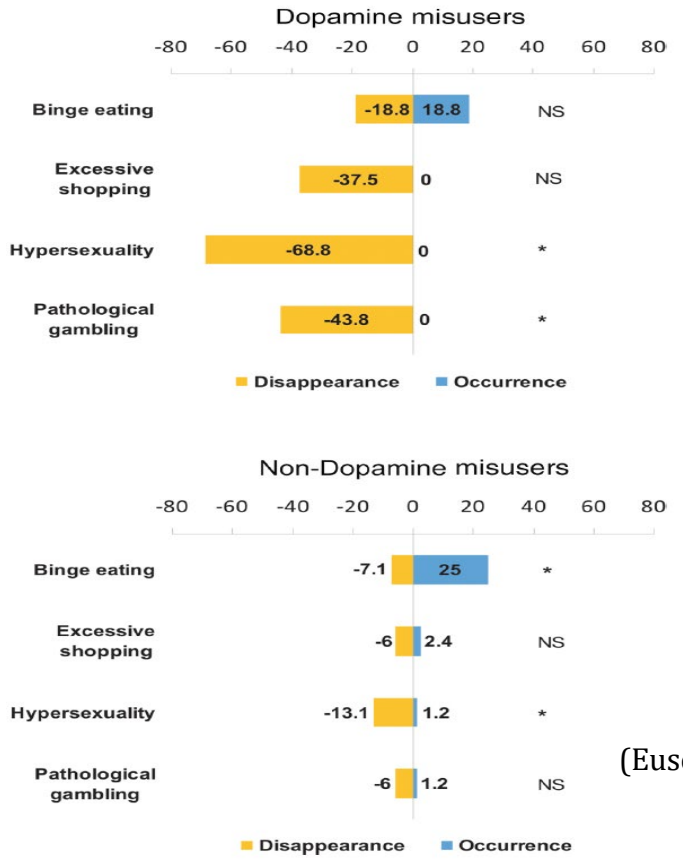
Effect of STN DBS on ICD and DDS

VIEWPOINT

Should Impulse Control Disorders and Dopamine Dysregulation Syndrome Be Indications for Deep Brain Stimulation and Intestinal Levodopa?

Michael S. Okun, MD[1]* and Daniel Weintraub, MD[2,3]

"DA and high dose dopaminergic medications are contributors to ICD in PD. However, DBS is not a convincing resolution despite marked reduction or cessation of all dopaminergic drugs after DBS"



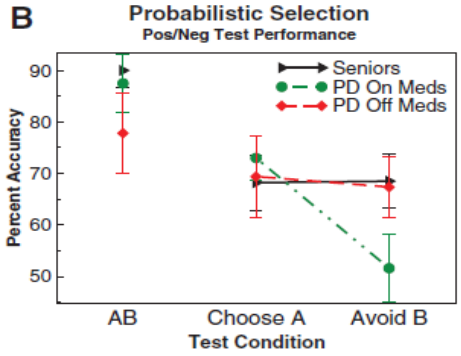
(Eusebio, 2013)

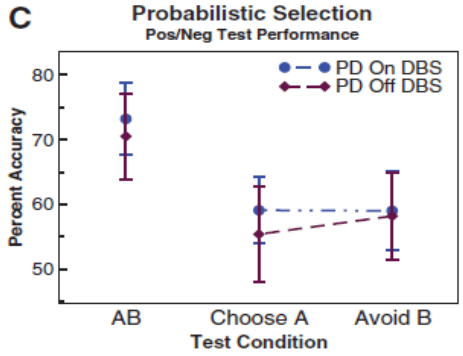
STN DBS can increase impulsivity in PD

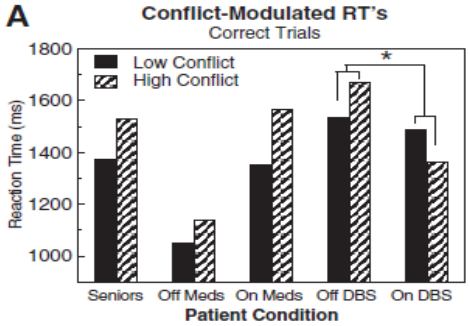
Hold Your Horses: Impulsivity, Deep Brain Stimulation, and Medication in Parkinsonism

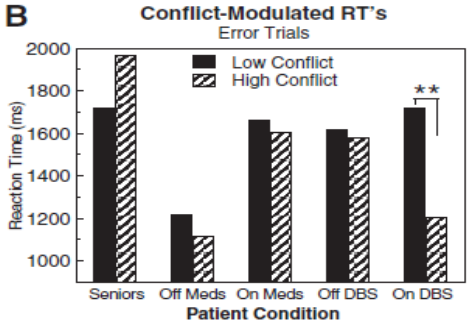
Michael J. Frank,[1]* Johan Samanta,[2,3] Ahmed A. Moustafa,[1] Scott J. Sherman[3]

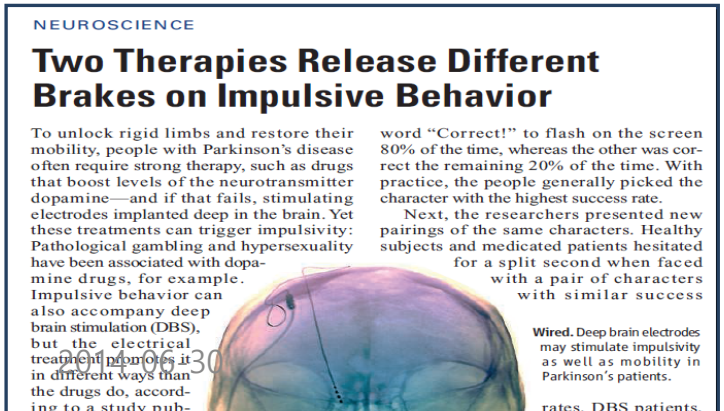
Dopaminergic medication altered patients' relative tendency to learn from positive versus negative outcomes without affecting conflict-induced slowing.
In contrast, DBS induced speeded high-conflict choices, without affecting learning biases.











NEUROSCIENCE

Two Therapies Release Different Brakes on Impulsive Behavior

To unlock rigid limbs and restore their mobility, people with Parkinson's disease often require strong therapy, such as drugs that boost levels of the neurotransmitter dopamine—and if that fails, stimulating electrodes implanted deep in the brain. Yet these treatments can trigger impulsivity: Pathological gambling and hypersexuality have been associated with dopamine drugs, for example. Impulsive behavior can also accompany deep brain stimulation (DBS), but the electrical treatment promotes it in different ways than the drugs do, accord-

word "Correct!" to flash on the screen 80% of the time, whereas the other was correct the remaining 20% of the time. With practice, the people generally picked the character with the highest success rate.

Next, the researchers presented new pairings of the same characters. Healthy subjects and medicated patients hesitated for a split second when faced with a pair of characters with similar success

Wired. Deep brain electrodes may stimulate impulsivity as well as mobility in Parkinson's patients.

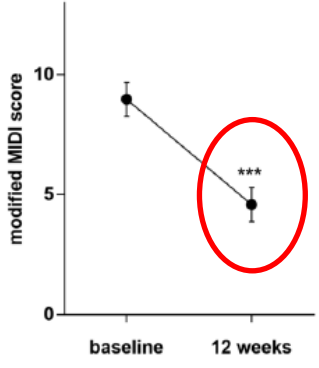
rates. DBS patients,

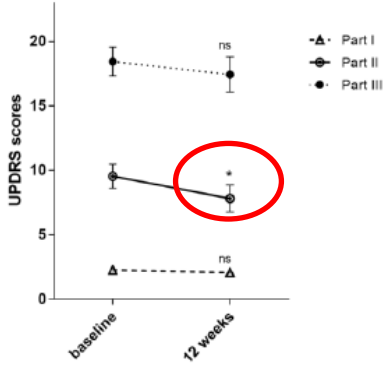
RESEARCH PAPER

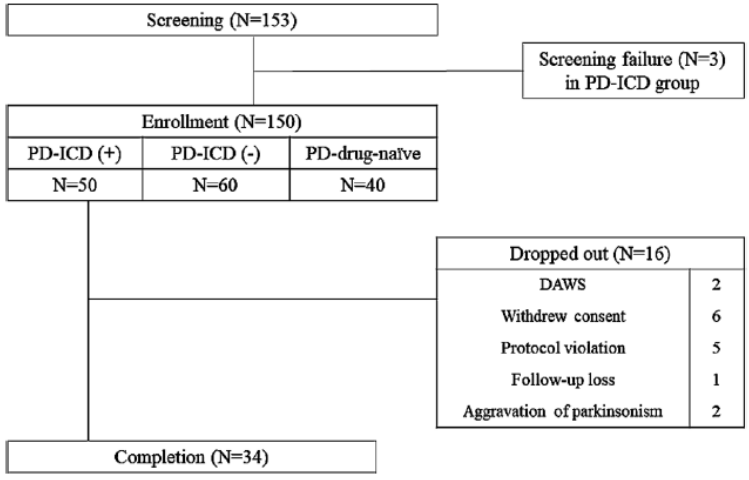
Behavioural and trait changes in parkinsonian patients with impulse control disorder after switching from dopamine agonist to levodopa therapy: results of REIN-PD trial

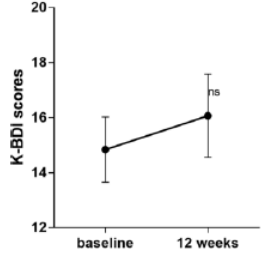
Jee-Young Lee,[1] Beomseok Jeon,[2] Seong-Beom Koh,[3] Won Tae Yoon,[4] Ho-Won Lee,[5] Oh Dae Kwon,[6] Jae Woo Kim,[7] Jong-Min Kim,[8] Hyeo-Il Ma,[9] Hee-Tae Kim,[10] Jong Sam Baik,[11] Jinwhan Cho,[12] (REIN-PD Investigators)

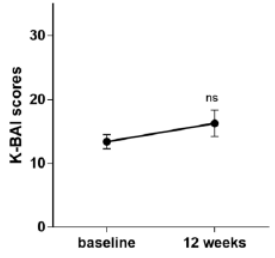
- Improved ICB and ADL after switching DA to levodopa, but underlying neuropsychiatric traits no changed.

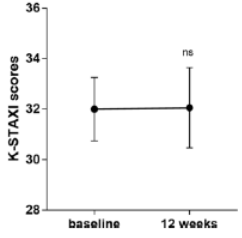


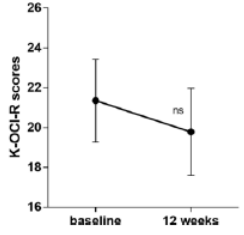


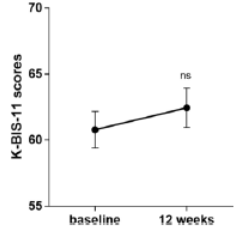






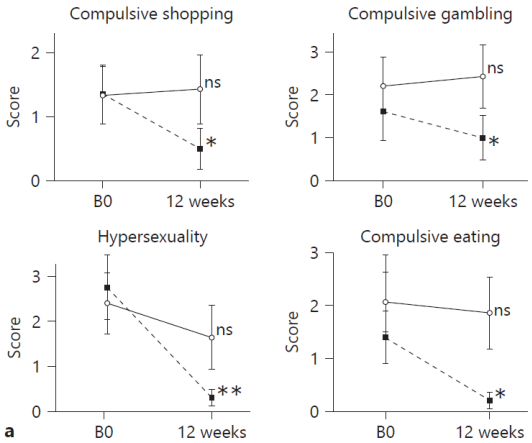






Lee J-Y, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**90**:30–37. doi:10.1136/jnnp-2018-318942

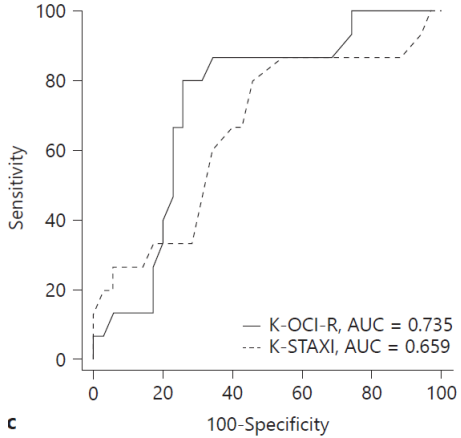
Characteristics of PD patients with refractory ICD



Characteristics	Poor-outcome group (n = 15)	Good-outcome group (n = 20)	Total-ICD group (n = 50)	$p^{\dagger}$	$p^{\ddagger}$
Total LED, mg/day	1,436.9 (858.0)	978.7 (696.1)	1,125.2 (689.9)	0.064	0.084
Levodopa daily dose, mg/day	831.7 (637.2)	550.3 (508.3)	610.4 (516.1)	0.240	0.112
Agonist LED, mg/day	229.6 (145.6)	283.4 (177.7)	258.6 (163.4)	0.419	0.494
K-BAI	16.9 (8.6)	11.8 (6.3)	13.8 (8.1)	0.043*	0.177
K-BDI	14.3 (8.2)	14.6 (8.0)	15.2 (8.6)	0.934	0.726
K-STAXI[§]	36.3 (11.3)	27.7 (5.2)	32.0 (8.7)	0.007*	0.193
Total K-BIS-11	65.7 (11.3)	57.6 (12.3)	62.8 (11.9)	0.080	0.441
Total K-OCI-R	28.9 (12.8)	17.8 (14.2)	21.3 (14.3)	0.009*	0.054
Total K-NPI	23.4 (18.0)	13.2 (10.5)	17.3 (14.7)	0.064	0.199

No difference in ICD subtypes or number of ICB

Co-existing higher level of 'obsessive compulsiveness' associates with poor outcome



(Choi & Lee, 2020)

In Summary,

- Both the medications and disease progression contribute to development of ICD in PD.
- Underlying traits may predispose individuals and relates to poor prognosis
- Both dopaminergic medications and DBS which are essential treatment for motor disability in advanced PD patients, can make them more impulsive and vulnerable to ICB.
- Switching dopamine agonist into levodopa can improve ICB, but DAWS and recurrence of ICB should be closely monitored.

Thank you for your attention!