



# My Strange Addiction

CAN DOPAMINE REPLACEMENT THERAPY CAUSE BEHAVIOURAL ADDICTIONS?

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# Acknowledgements

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Dr. David Euston

Dr. Darren Christensen

Dr. Aaron Gruber

Valerie Lapointe

Danika Dorchak

Dr. Kartik Iyer

Kathleen Ward

Kyler Fisher

Kenny Le May

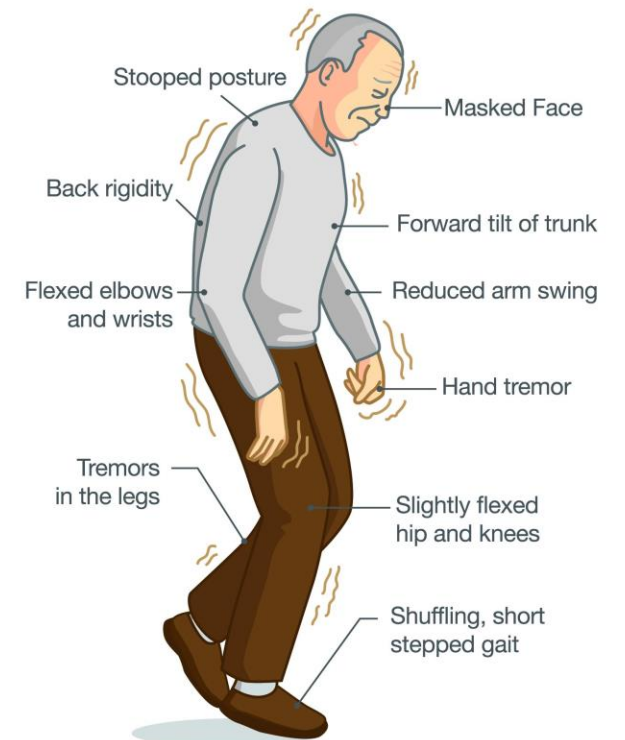




# Gambling Disorder and Parkinson's Disease

- Beginning in the early 2000s, clinicians treating patients with Parkinson's disease (PD) started reporting incidences of *de novo* Gambling Disorder (GD) in their patients
- PD is a progressive neurological disorder caused by dopamine cell death and is characterized by motor and non-motor symptoms
- GD appears to be linked to dopamine medication
  - Problematic behaviours often resolve after either dopamine medication cessation or a reduction in dosage

## Parkinson's Disease Symptoms



# Parkinson's Disease Treatment

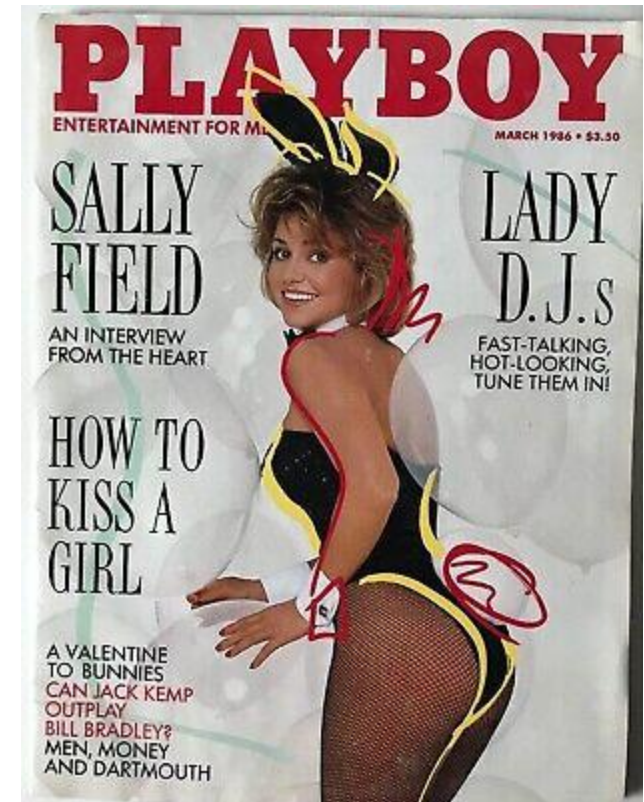
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- The primary treatment of PD involves dopamine replacement therapy (DRT)
  - DRT generally includes the dopamine precursor levodopa/carbidopa
    - Promotes dopamine synthesis and release
  - Dopamine Agonists (DA)
    - Act directly on dopamine receptors and bypass the requirement for functioning presynaptic terminals

# DRT and Behavioural Addictions

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- Association between PD and GD falls in line with reports since the 1980s of other disorders linked to DRT
  - A minority of PD patients developed cognitive and behavioural disturbances that mirror that of drug addiction, a condition called dopamine dysregulation syndrome
  - The other major behavioural side effect noted early on was hypersexuality in mostly male PD patients





Gambling

Food and  
Eating

Shopping

**Behavioural  
Addictions**

Internet  
and  
Gaming

Work and  
Exercise

Sex and  
Pornography

# DRT and Behavioural Addictions

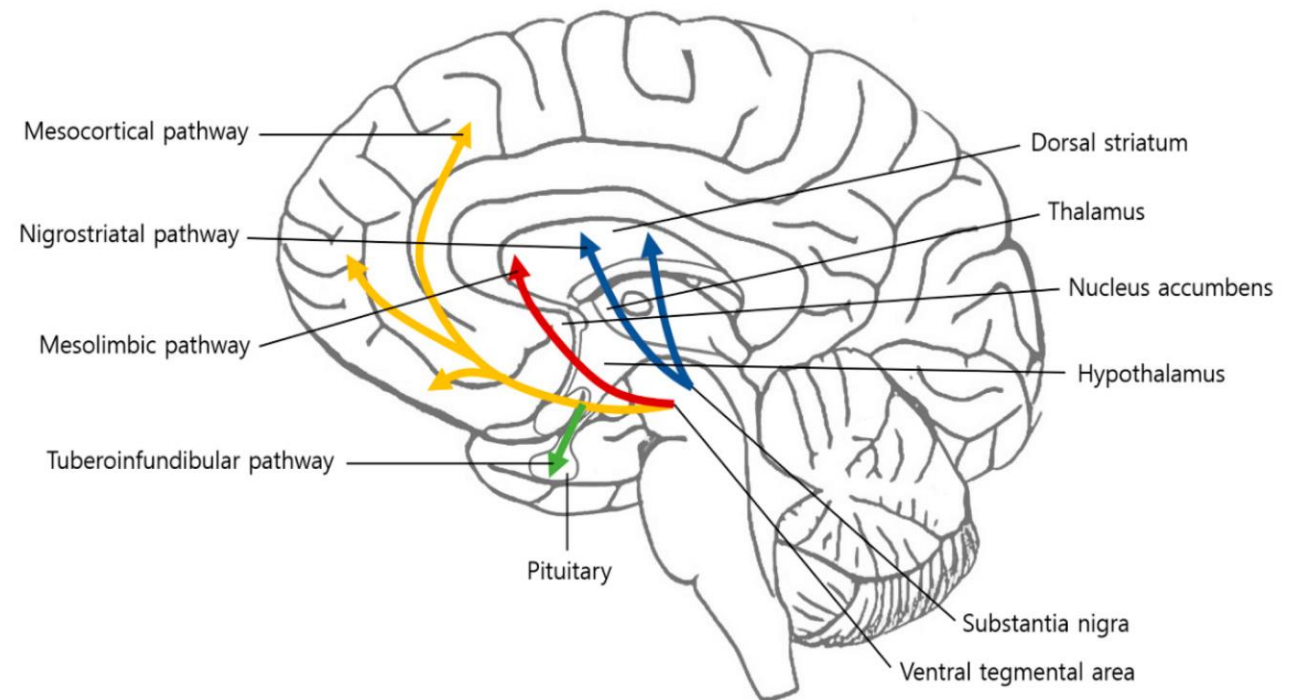
- Prevalence studies indicated markedly higher prevalence rates of gambling and other behavioural addictions compared to the general population
- Often underreported due to fear of embarrassment, low levels of insight, and difficulty connecting medication changes with behaviour

Reference	Screening Target	Sample Size	Overall Prevalence	DA Prevalence
Bostwick et al. (2009)	GD and HS	267	2.6%	13.2%
Callesen et al. (2013a)	ICD	490	35.9% life 14.9% cur	n.r.
Corvol et al. (2018)*	ICD	411	46.1%	51.5%
Crockford et al. (2008)	GD	140	5.7%	14.1%
Driver-Dunckley et al. (2003)	GD	1884	0.48%	0.7%
Garcia-Ruiz et al. (2014)	ICD	233	n.r.	39.1%
Grosset et al. (2006)	GD	388	4.4%	8%
Hassan et al. (2011)	ICD	321	n.r.	24%
Isaias et al. (2008)	ICD	100	n.r.	28%
Lee et al. (2010)	ICD	1167	10.1%	10.8%
Lu et al. (2006)	GD	~200	n.r.	7%
Pontone et al. (2006)	ICD	100	9%	13.8%
Ribacoba et al. (2010)	GD	106	2.8%	n.r.
Singh et al. (2007)	ICD	300	n.r.	19.3%
Vela et al. (2016)**	ICD	87	58.3%	66.2%
Voon et al. (2006)	GD	297	3.4%	7.2%
Weintraub et al. (2006b)	ICD	272	6.6%	n.r.
Weintraub et al. (2010)	ICD	3090	13.6%	17.1%

n.r. not reported

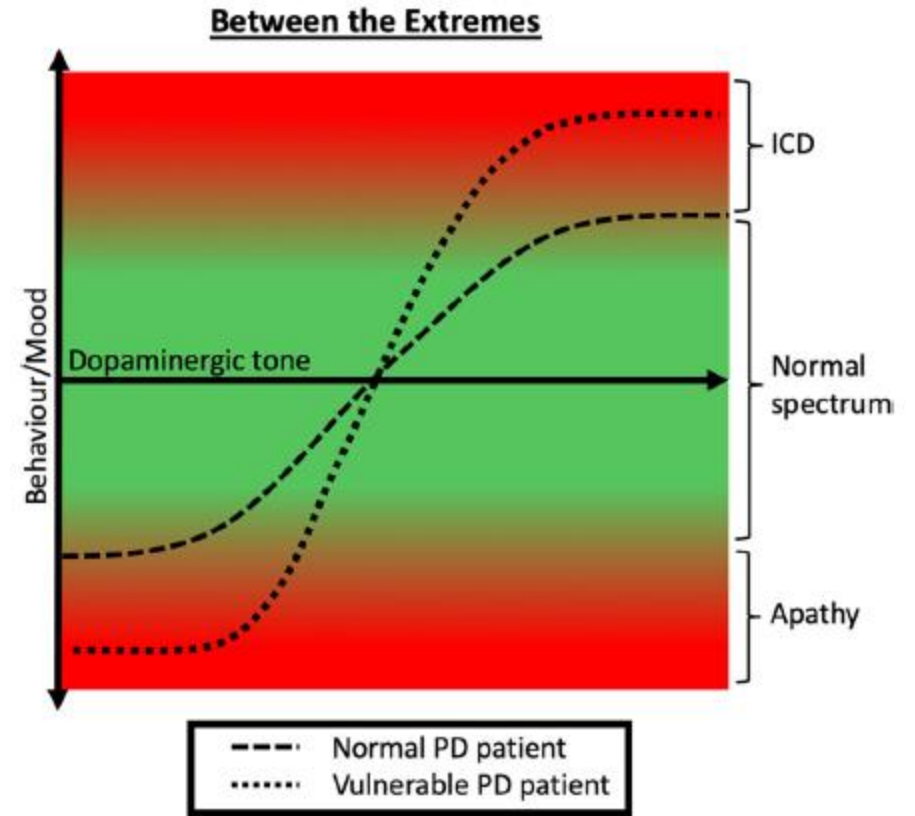
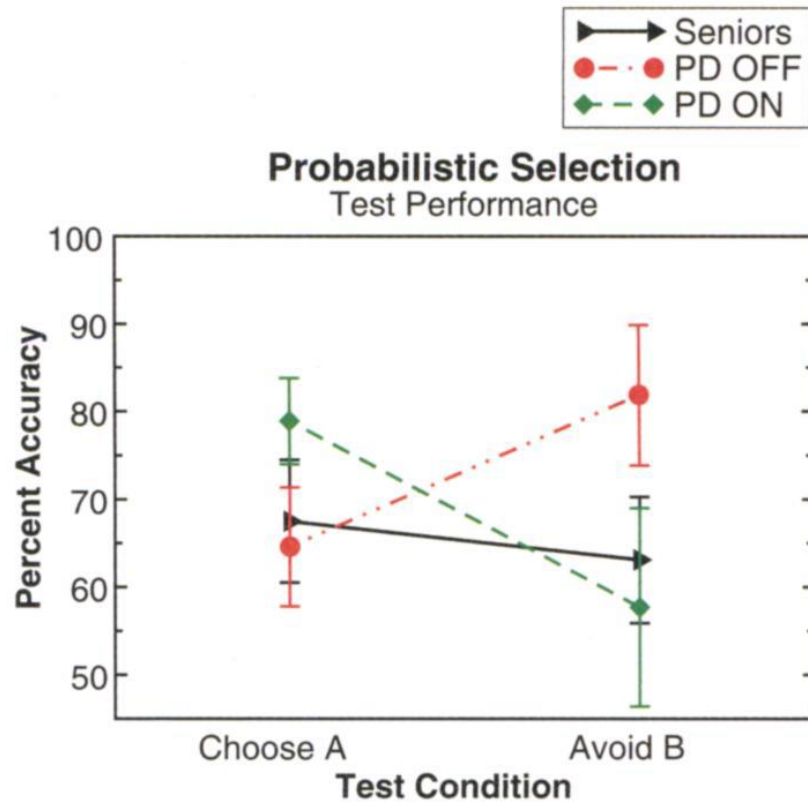
# DRT and Behavioural Addictions

- Motor symptoms result from nigrostriatal dopaminergic neuronal loss
- Nonmotor symptoms involve dysfunctions within a wide range of neural structures involved in reinforcement learning, motivation, decision-making, inhibition, and cognition



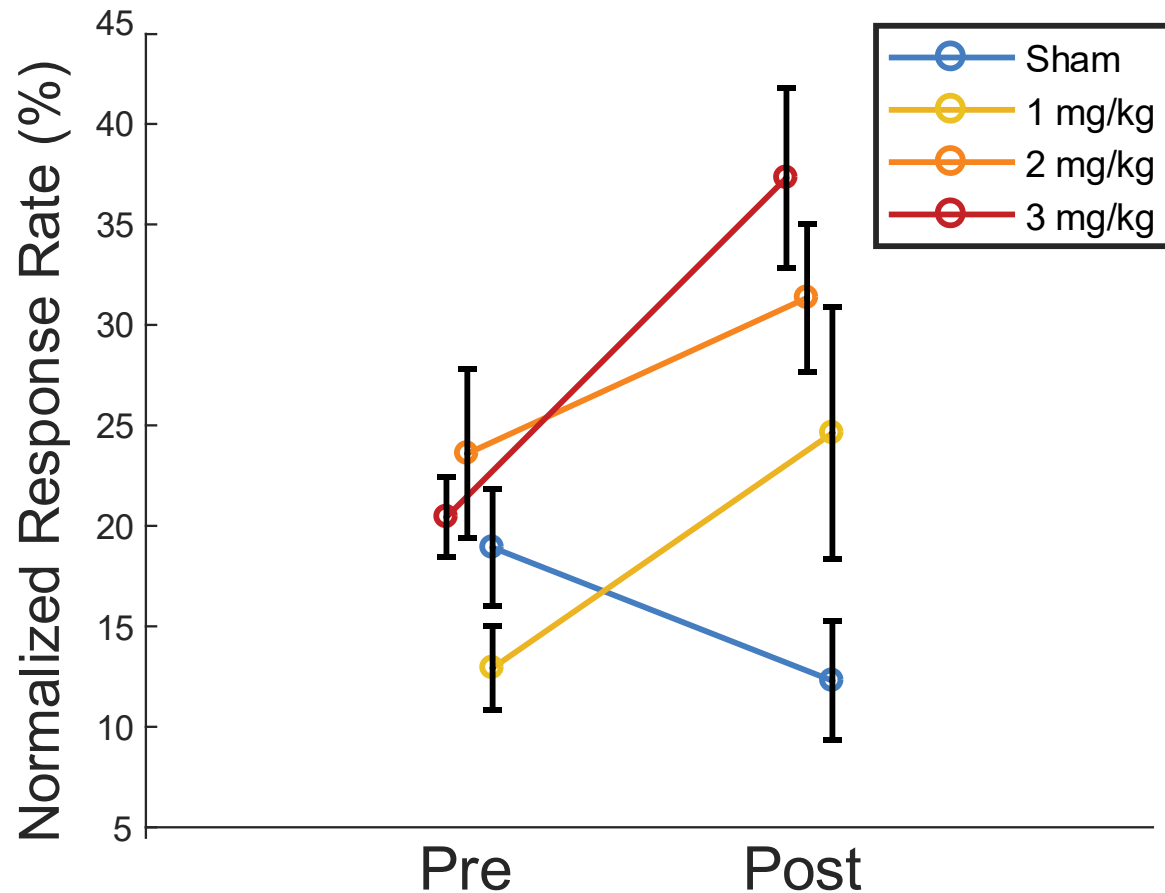


# DRT and Learning

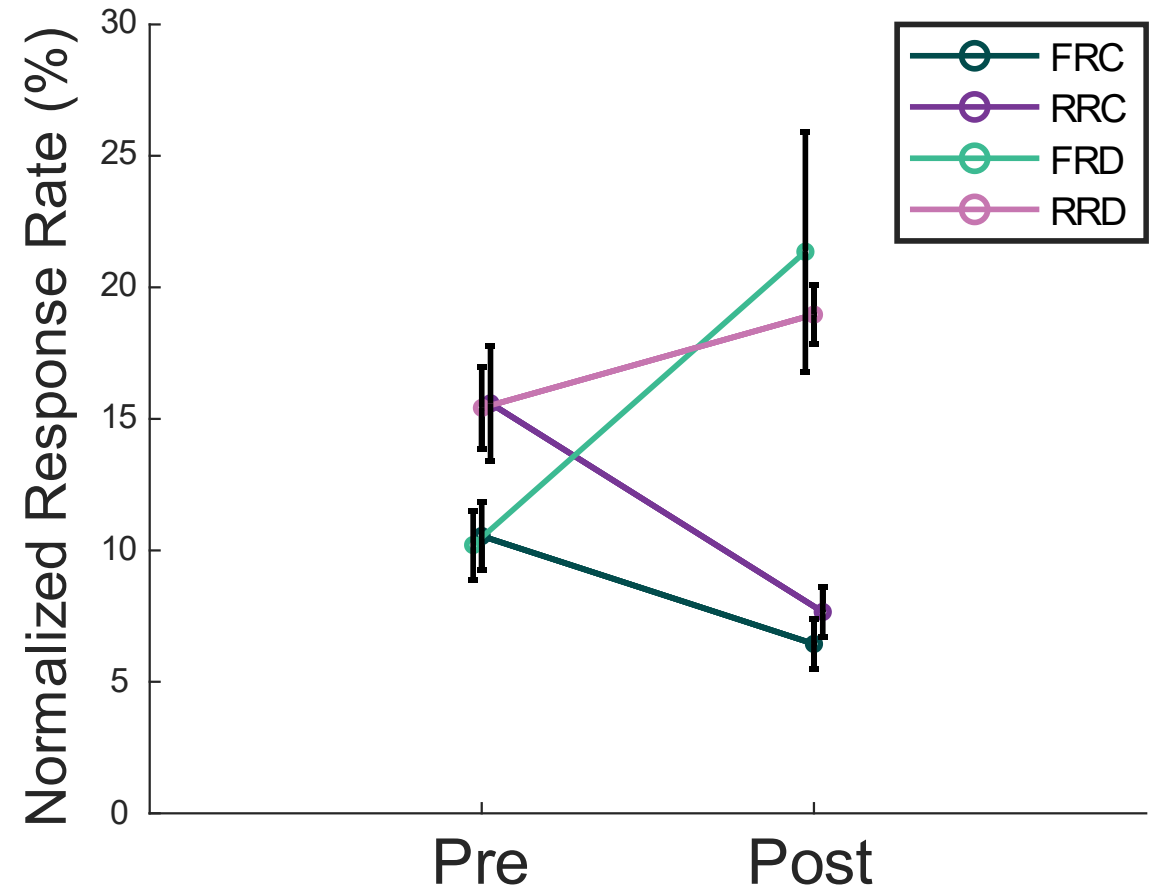


# Results – Cued No-Reward Responding

## Experiment 1

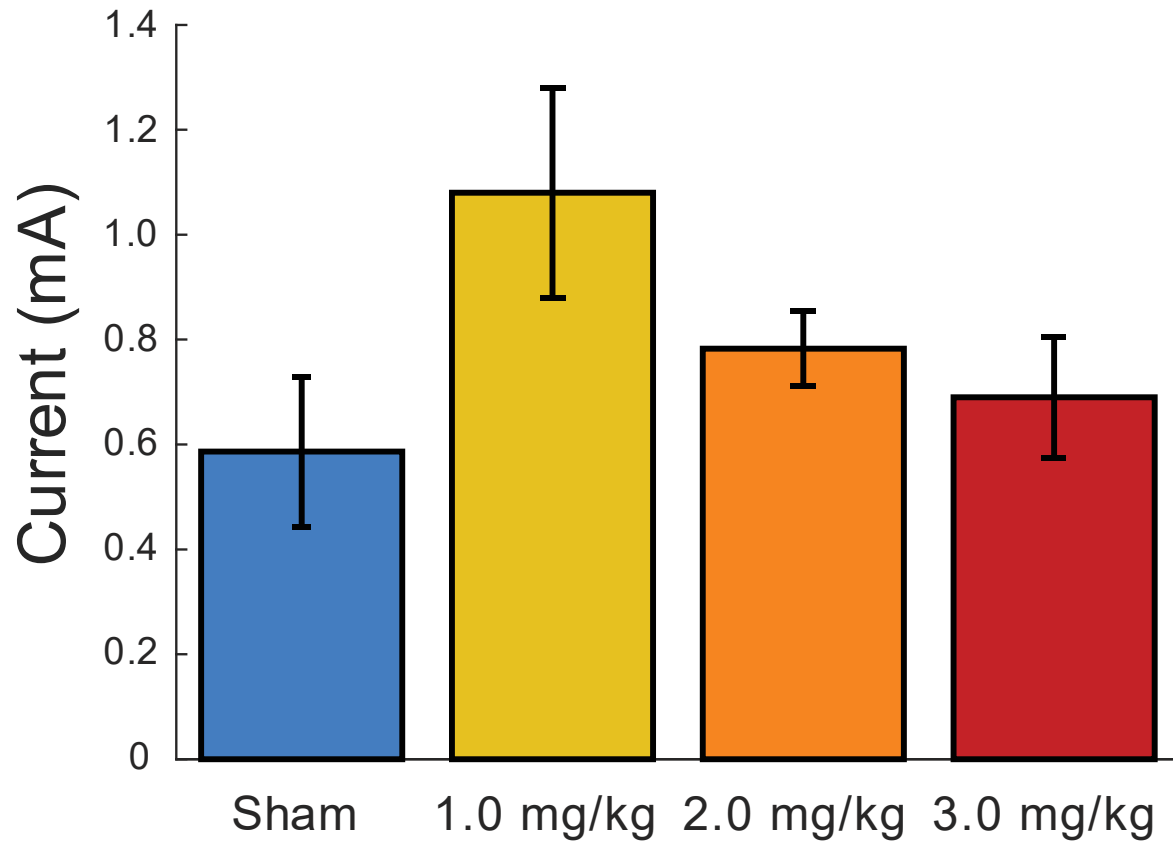


## Experiment 2

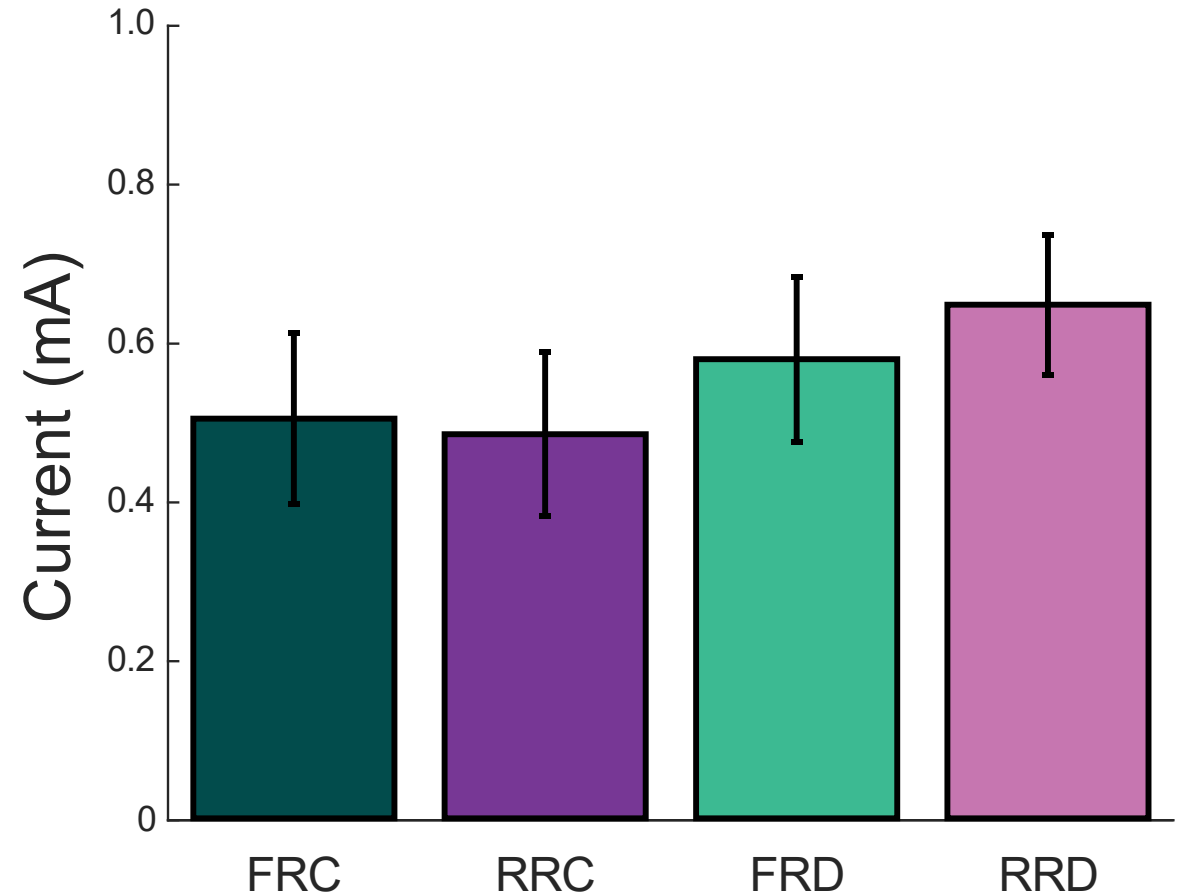


# Results – Progressive Aversion

## Experiment 1

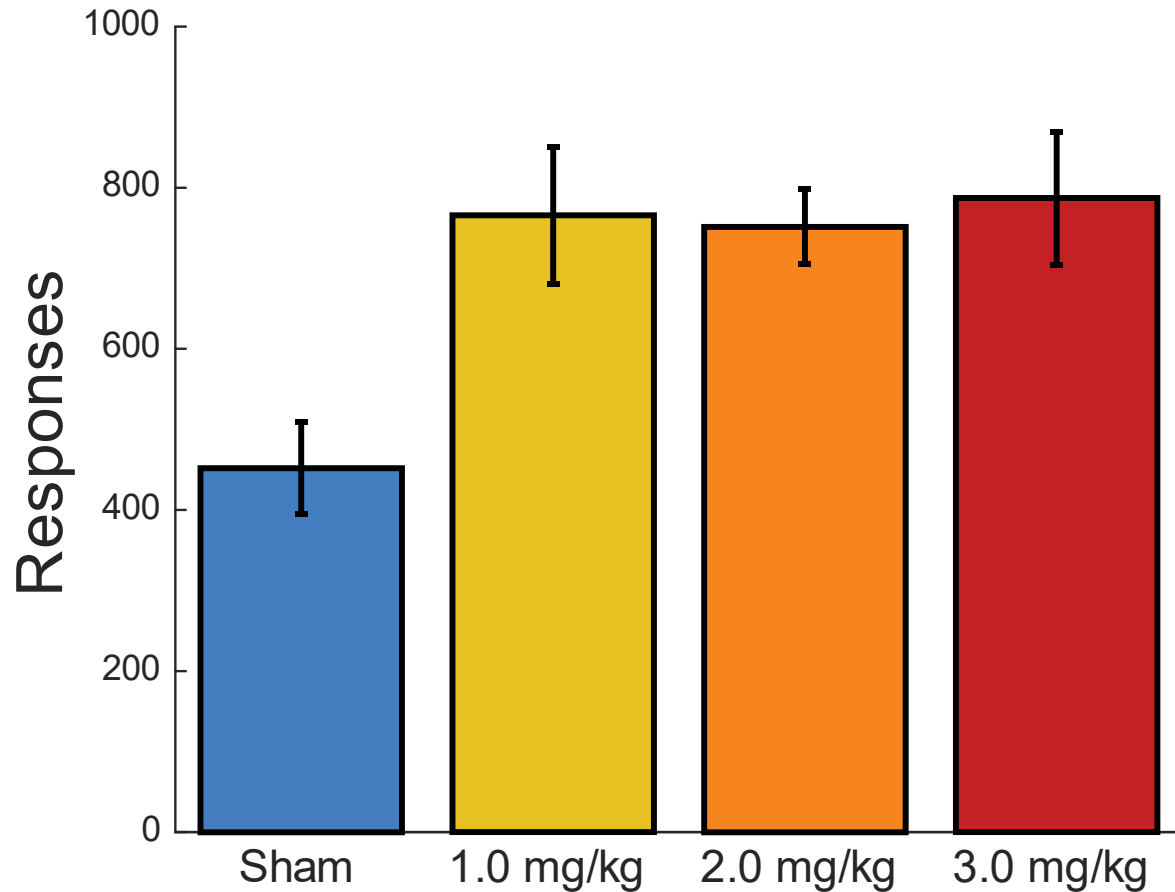


## Experiment 2

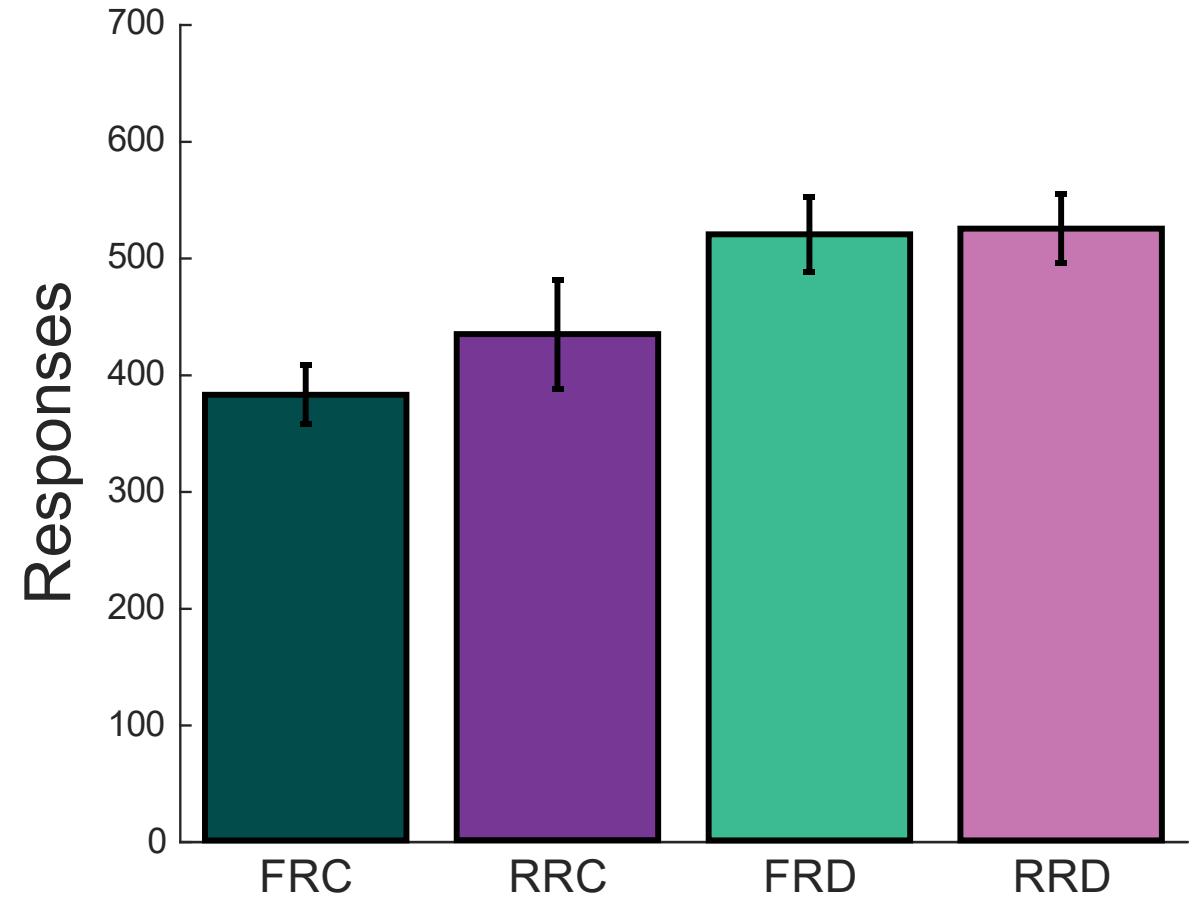


# Results – Progressive Ratio

## Experiment 1



## Experiment 2





# Considerations and Conclusions

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- DAs appear to disrupt reward learning and motivational processes which promote narrowed reward-seeking behaviours
- The effect is not gambling-specific but appears to have the most impact on behaviours linked with repeated, high-intensity positive reinforcement and hedonistic pleasure
- Importantly, the reinforcer is often abstract and difficult to satiate via normal regulatory homeostatic feedback mechanisms

# Considerations and Conclusions

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- When gambling it may be important to pay attention to alcohol consumption or the use of other drugs that increase tonic dopamine release
- There is a high comorbidity between GD and substance abuse



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END



# DRT and Other Disorders

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- Restless legs syndrome
  - A sensorimotor disorder that involves unpleasant sensations in the legs combined with a strong urge to move the legs in order to alleviate those feelings
- Fibromyalgia
  - A condition involving widespread chronic feelings of pain and fatigue.
- Both of these conditions are treated with DAs, particularly restless legs syndrome



# DRT and Other Disorders

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- Moore et al. (2014)
  - Identified 1580 people with ICDs and comorbid PD, restless legs syndrome, or hyperprolactinemia from a public database of 2.7 million reported adverse events related to drug use
  - 44.9% were prescribed DAs; 55.1% were prescribed other dopaminergic medications
  - GD was the most frequently reported adverse event (39.7%), followed by hypersexuality, compulsive shopping, and walkabout

# DRT and Other Disorders

- Initially, there appeared to be a greater rate of ICDs in the PD population

- After controlling for the medication dose the difference was non-significant

Pharmacological Agent	Pharmacological Target	Maximum Recommended Dosage		
		Parkinson's Disease	Restless Leg Syndrome	Hyperprolactinemia
levodopa/carbidopa	dopamine precursor	420 mg/day	n.t.	n.t.
pramipexole	D3>D2	4.5 mg/day	.5 mg/day	n.t.
ropinirole	D3>D2	8 mg/day	4 mg/day	n.t.
pergolide	5-HT <sub>1A</sub> >D3>D2	3-5 mg/day	n.t.	0.1 mg/day
cabergoline	D2=D3>5-HT	3 mg/day	n.t.	1 mg/biw
selegiline	MAO-B inhibitor	10 mg/day	n.t.	n.t.
bromocriptine	α <sub>1</sub> >D2=D3	100 mg/day	n.t.	15 mg/day
amantadine	DRI and DRA	322 mg/day	n.t.	n.t.
entacapone	COMT inhibitor	1600 mg/day	n.t.	n.t.
tolcapone	COMT inhibitor	300 mg/day	n.t.	n.t.

- These reports suggest that DRT (particularly DAs) has the capacity to induce GD and other ICDs independent of the neuropathology for which the drug is being used

# DRT and Behavioural Addictions

- PD patients may be uniquely *protected* against ICDs
  - Characterized by low levels of novelty-seeking, accompanied by thoughtful, careful decision-making and a calm temperament

**Table 1. Possible Site of Striatal Dopamine Dysfunction Causing Different Motor and Cognitive Symptoms in Parkinson's Disease**

Cortical Origin of the Cortico-Striatal Loop	Striatal Region	Effect of Low Dopamine	Effect of High Dopamine
primary motor	putamen	bradykinesia, clumsiness	dyskinesia
accessory motor	rostral putamen	akinesia	stereotypies, tics
limbic	ventral striatum	“parkinsonian personality,” mental rigidity, neophobia	“addictive personality,” impulsivity, novelty seeking, impaired reversal learning
prefrontal	caudate	dysexecutive syndrome, impaired planning (sequential actions to reach a goal), working memory, and cognitive flexibility	compulsive disorders, punding (excessive engagement in goal-directed behavior)

This model is of necessity overly simple as dopamine dysfunction also occurs in cortical areas in PD.

