



Pacific Neuroscience

Medical Group

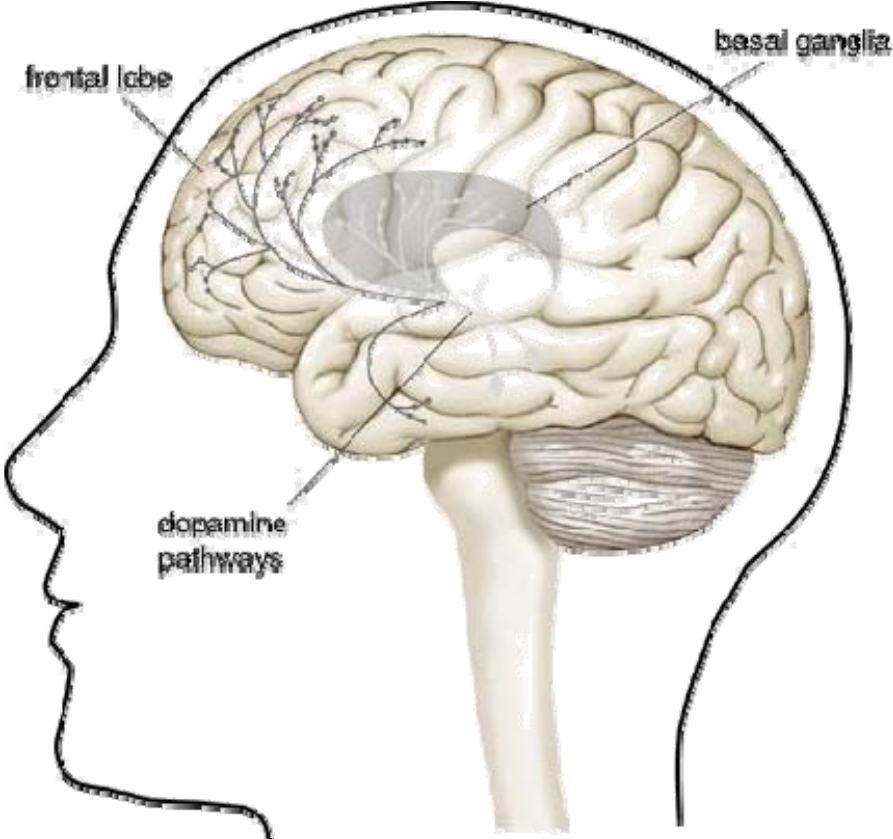
**Parkinson's 2007:
An update**

James P. Sutton, MD

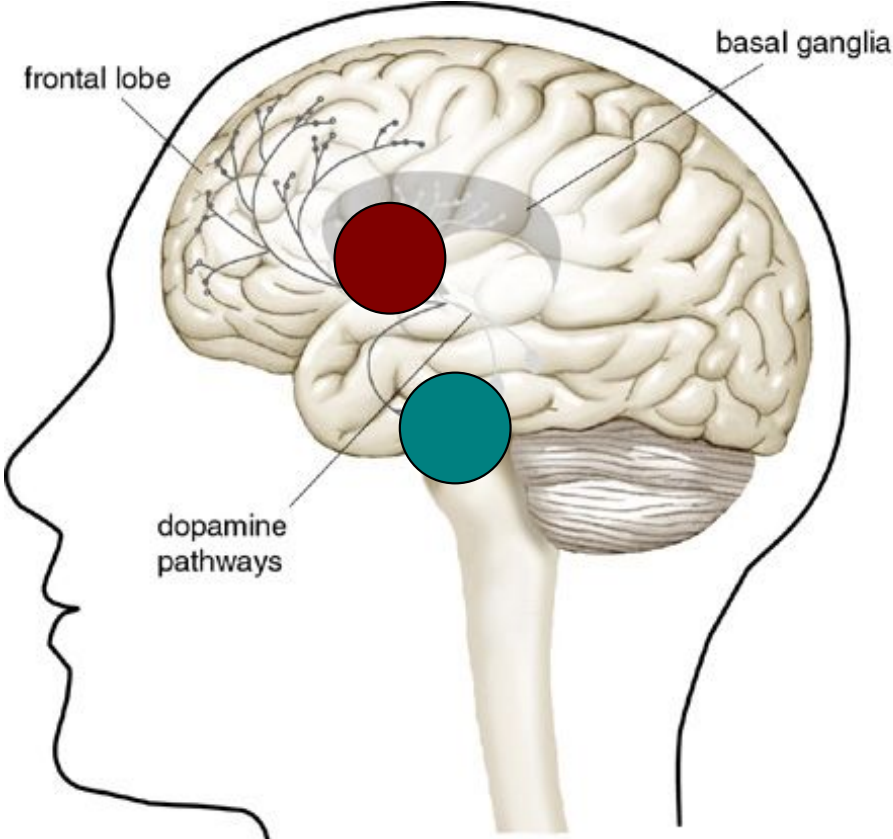


The basics: A review

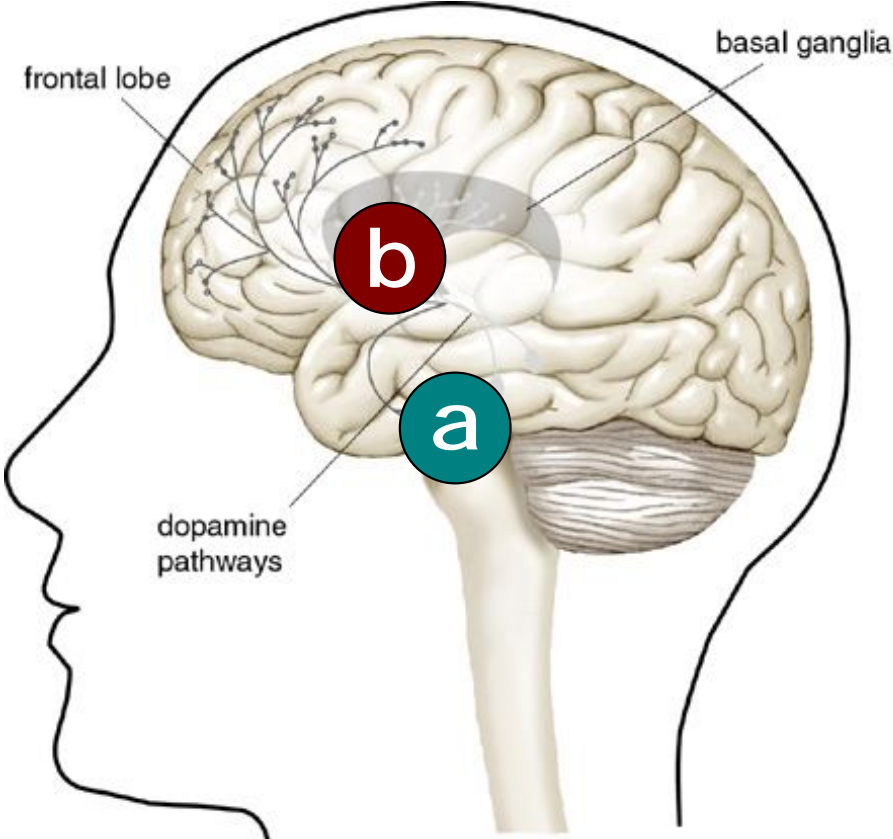
Basics

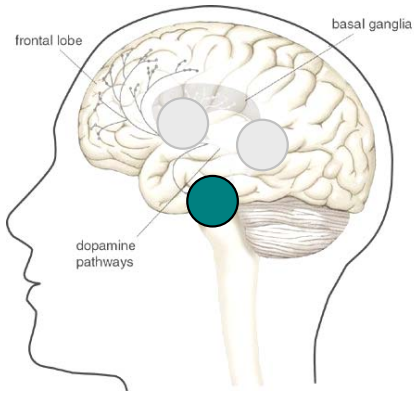


Basics



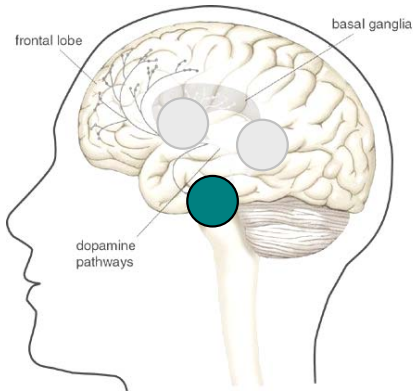
Basics





Substantia Nigra

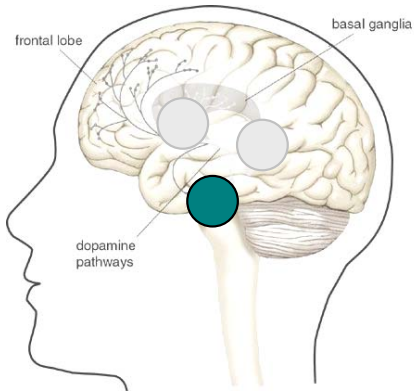




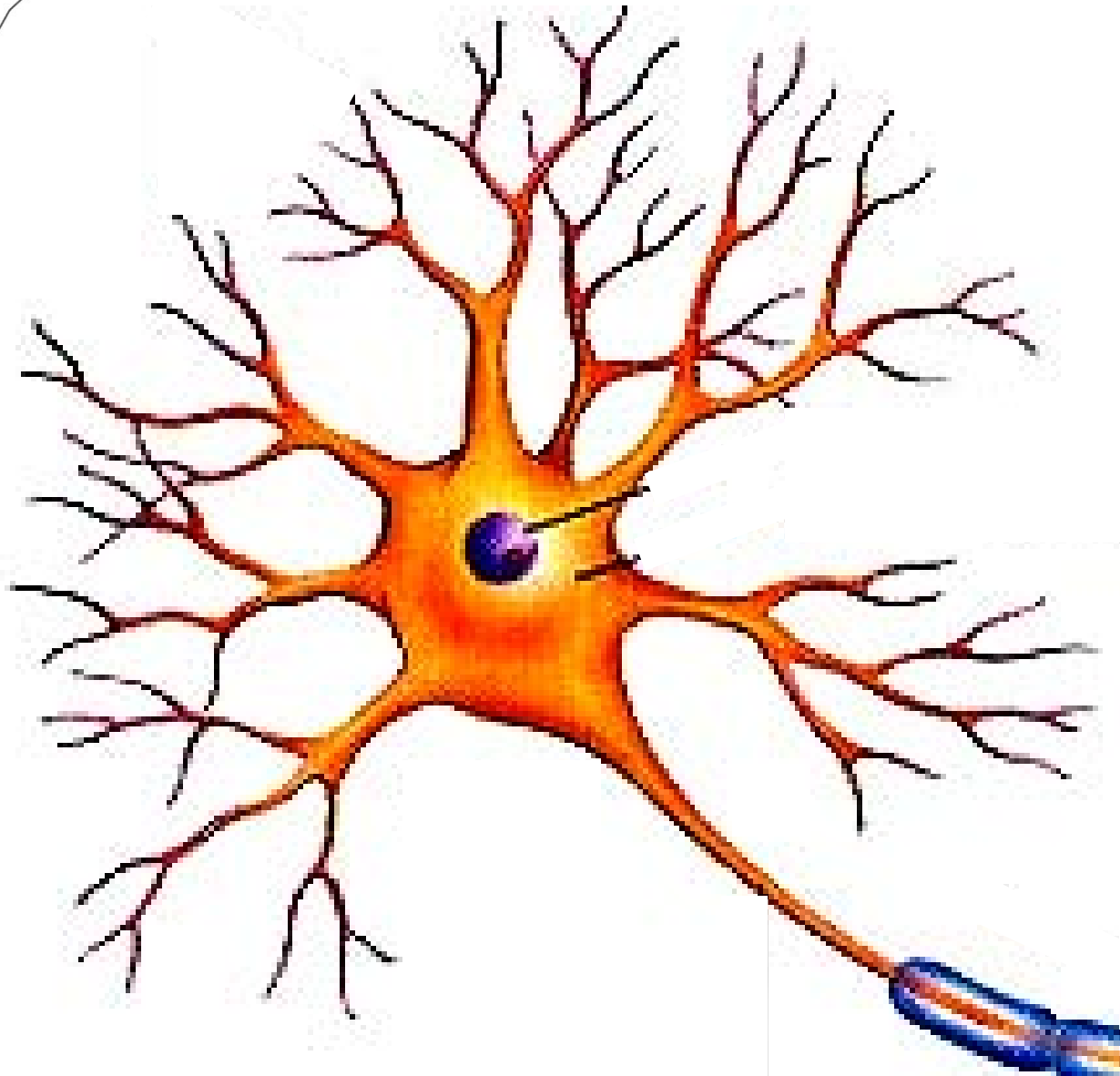
Substantia Nigra

- “The black substance”
- The “on”/“off” switch?
- 400,000 → 80,000 cells
- Dopamine loss

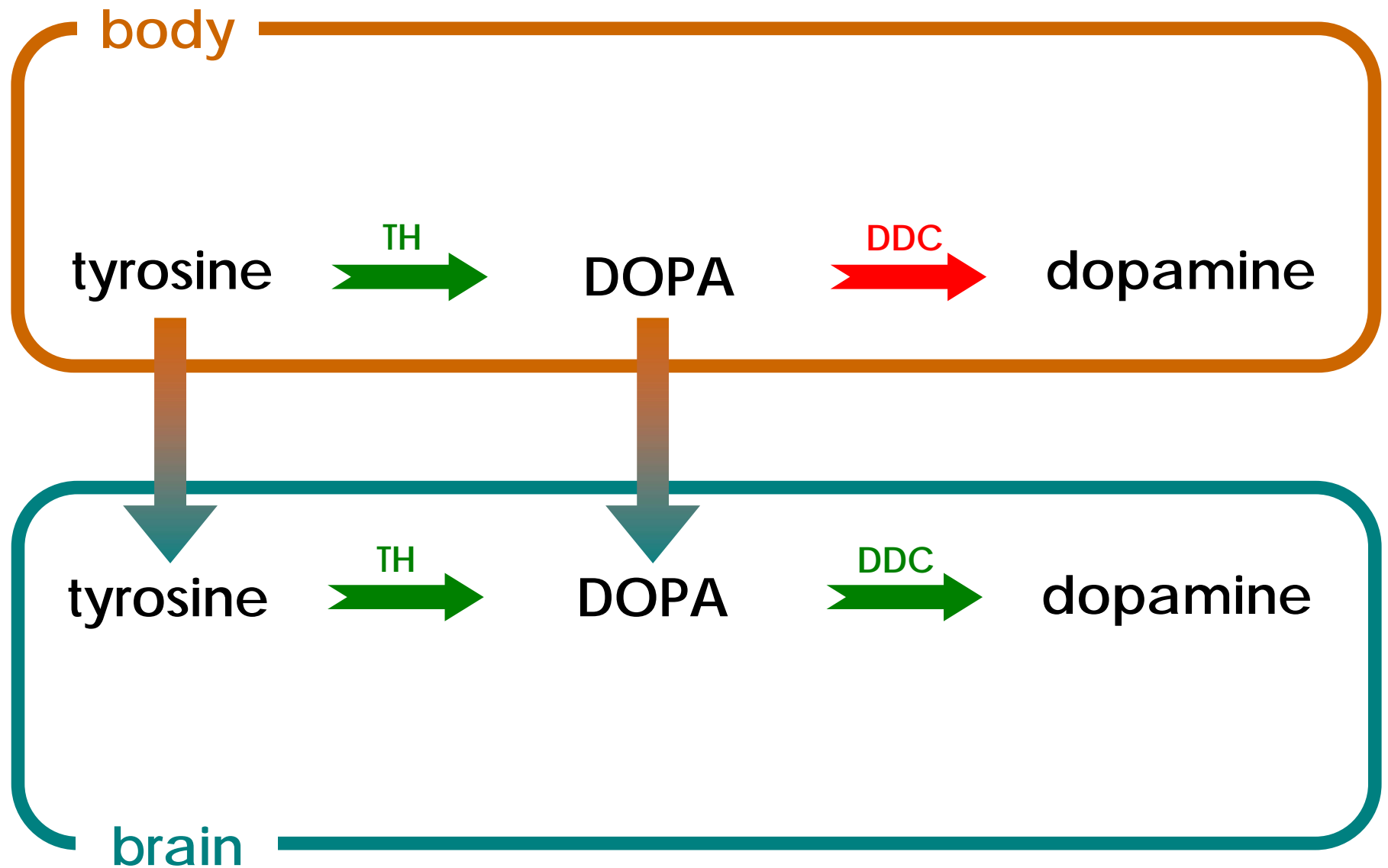




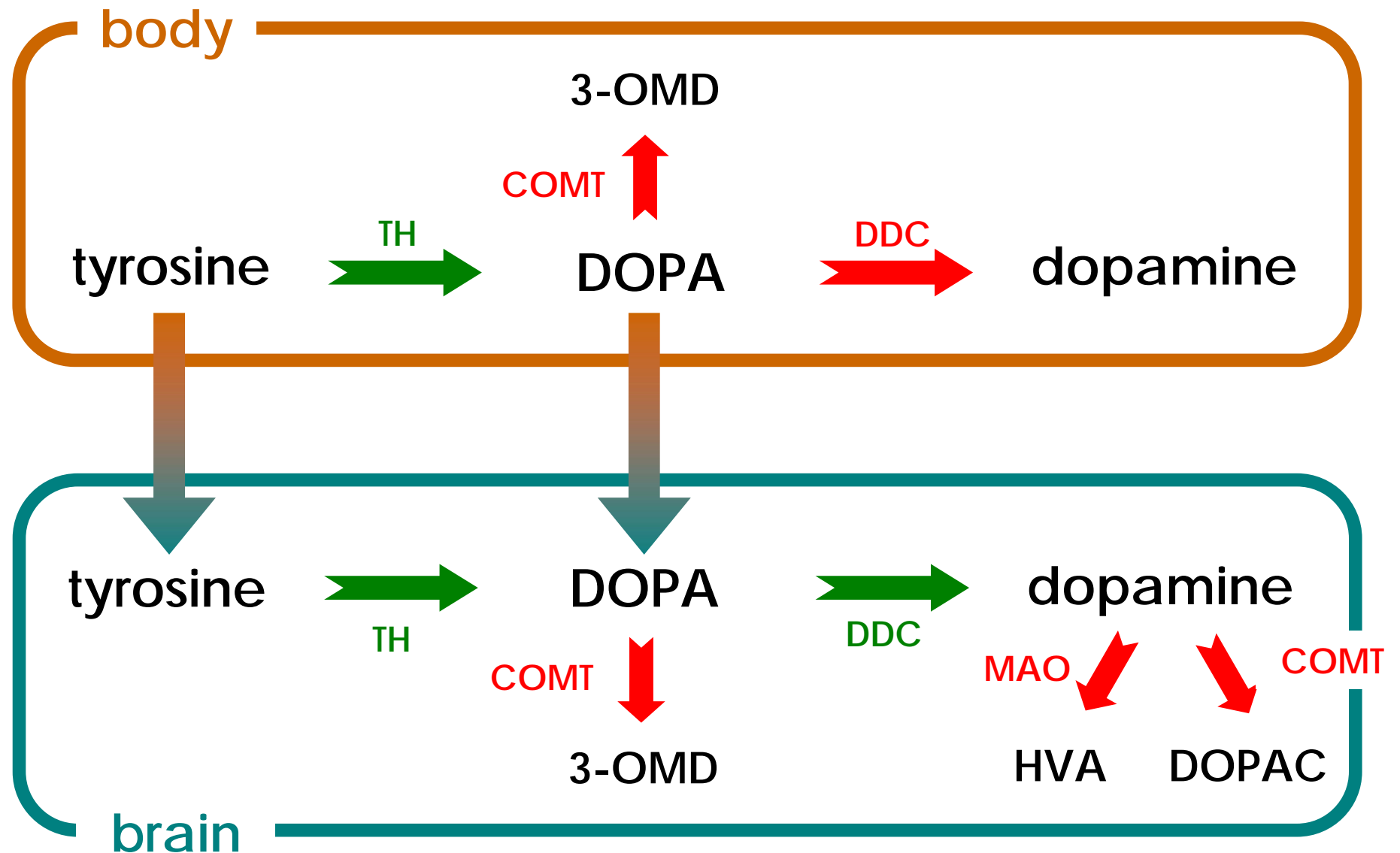
The Dopaminergic Neuron



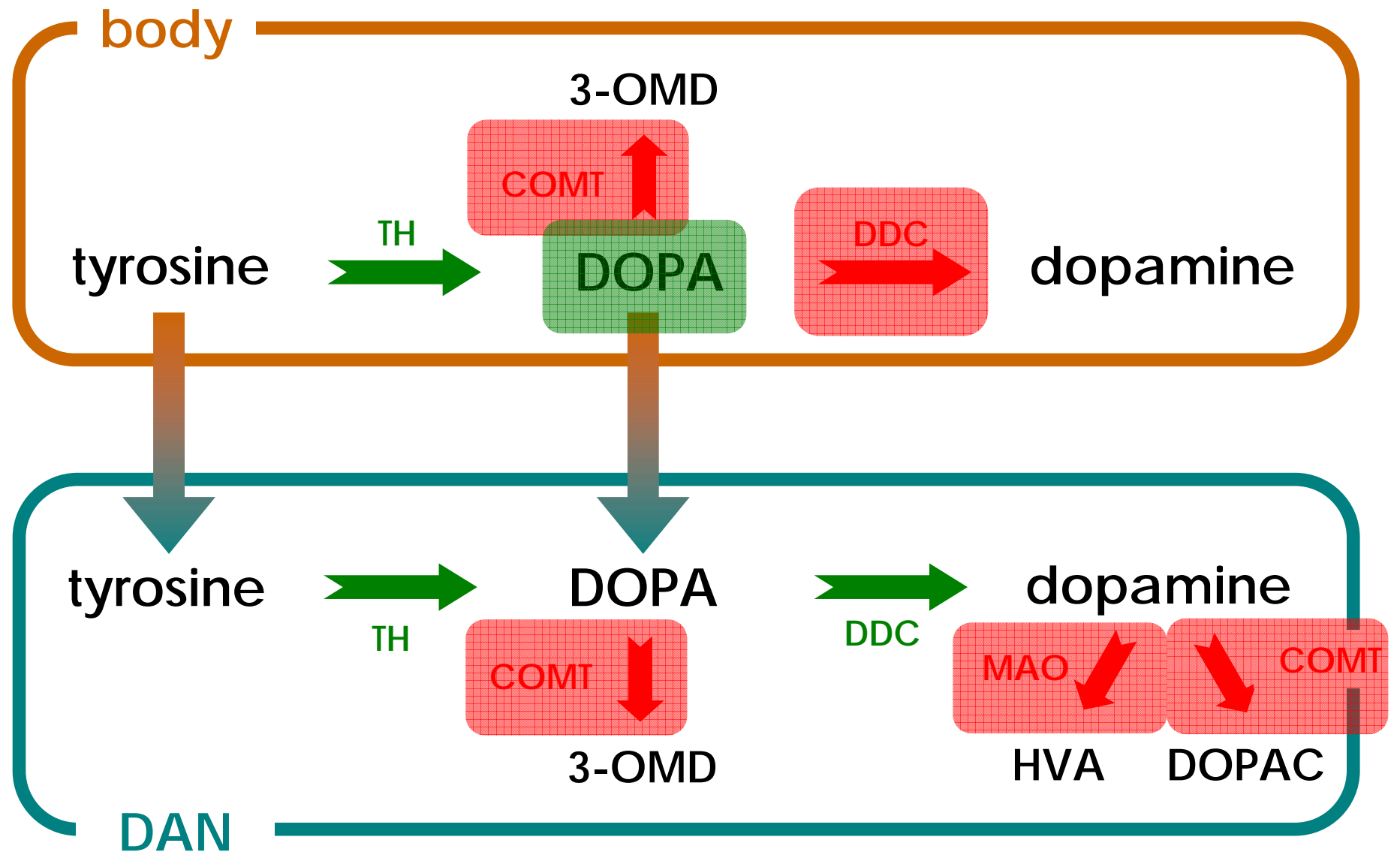
Dopamine Biochemistry I

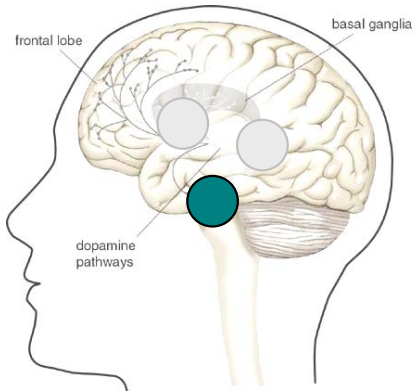


Dopamine Biochemistry II

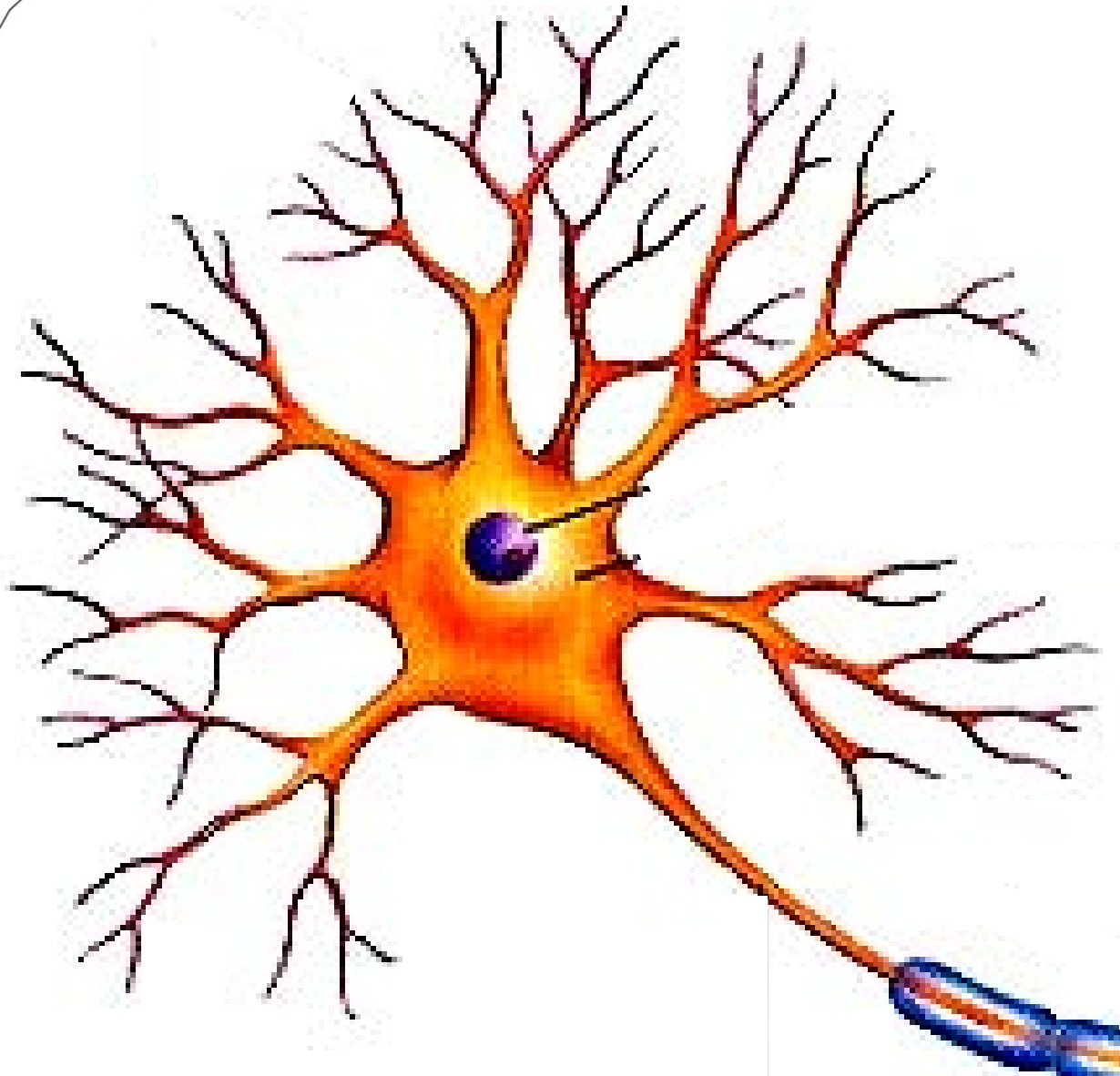


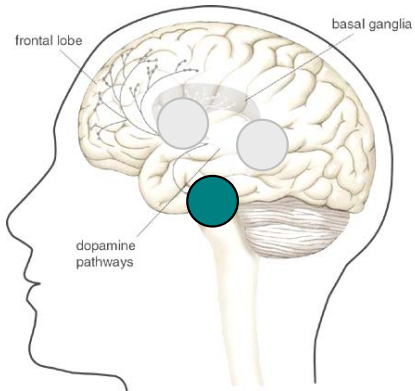
Dopamine Biochemistry III



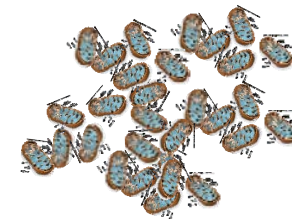
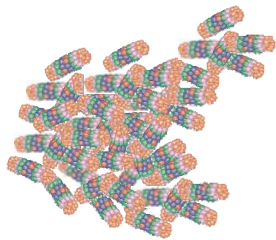
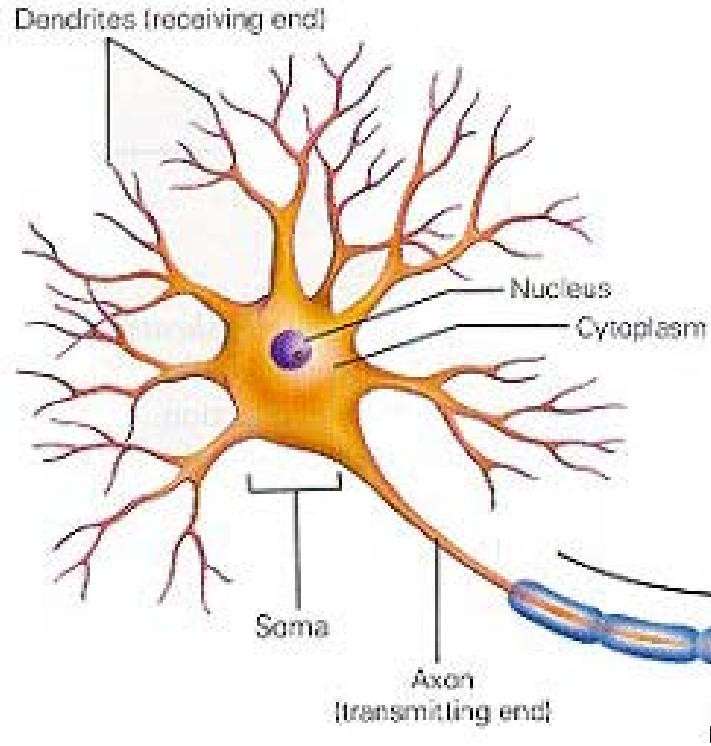


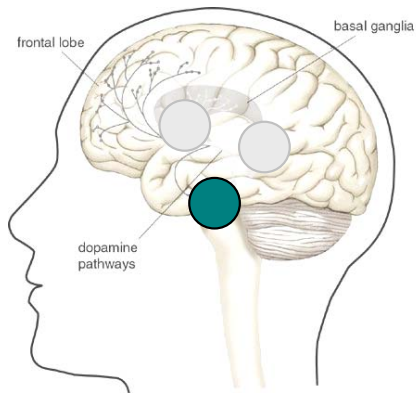
Substantia Nigra: Keeping Clean



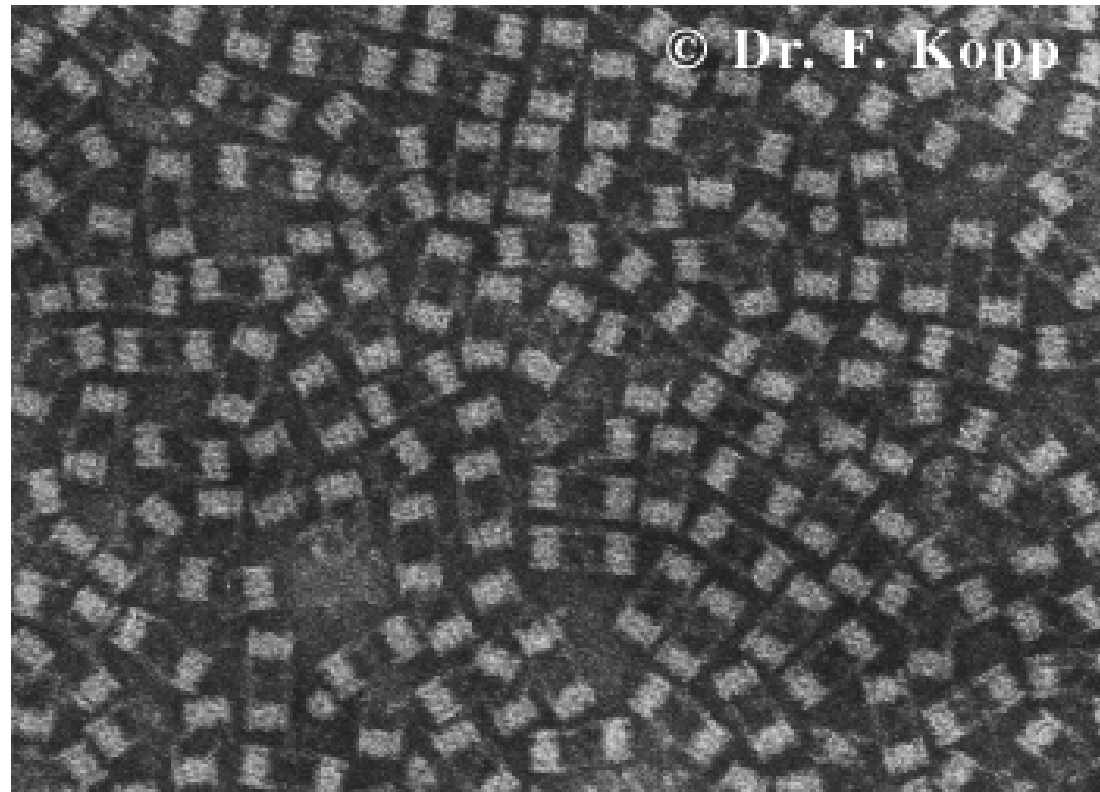


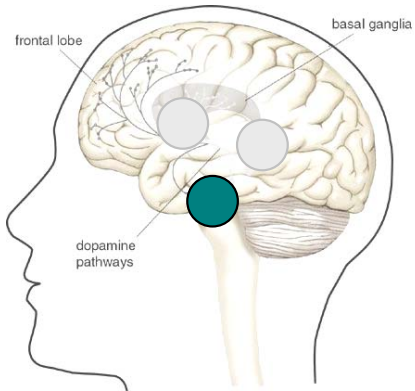
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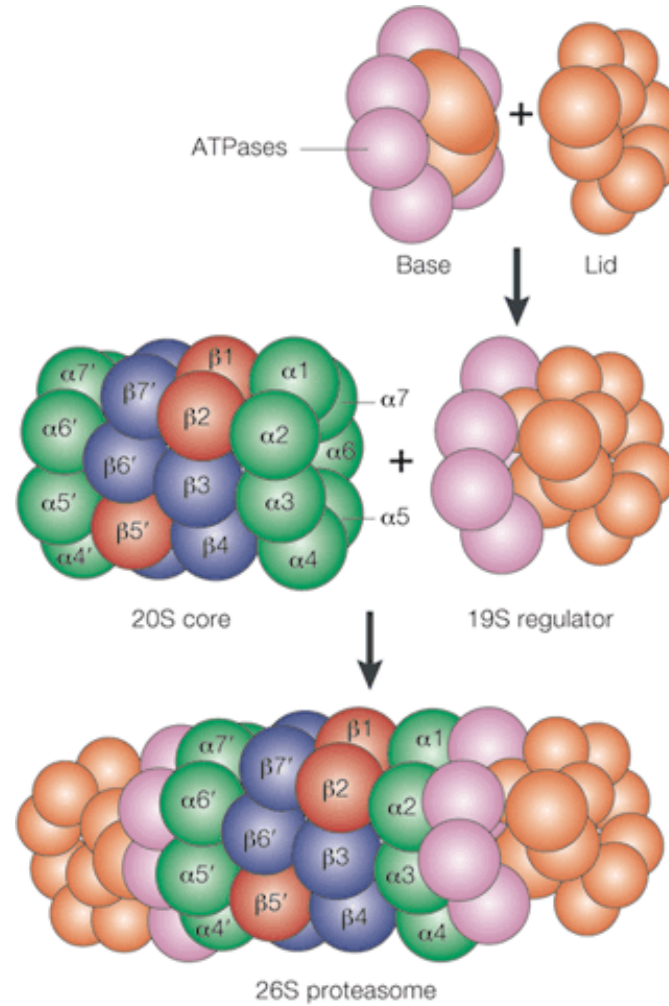


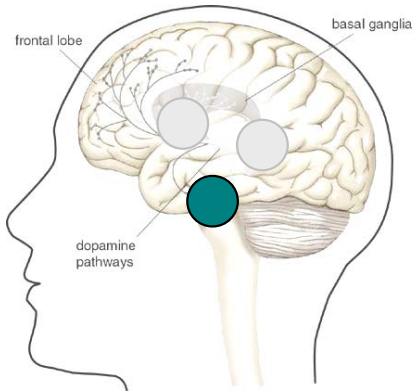
Proteasomes: the trash cans



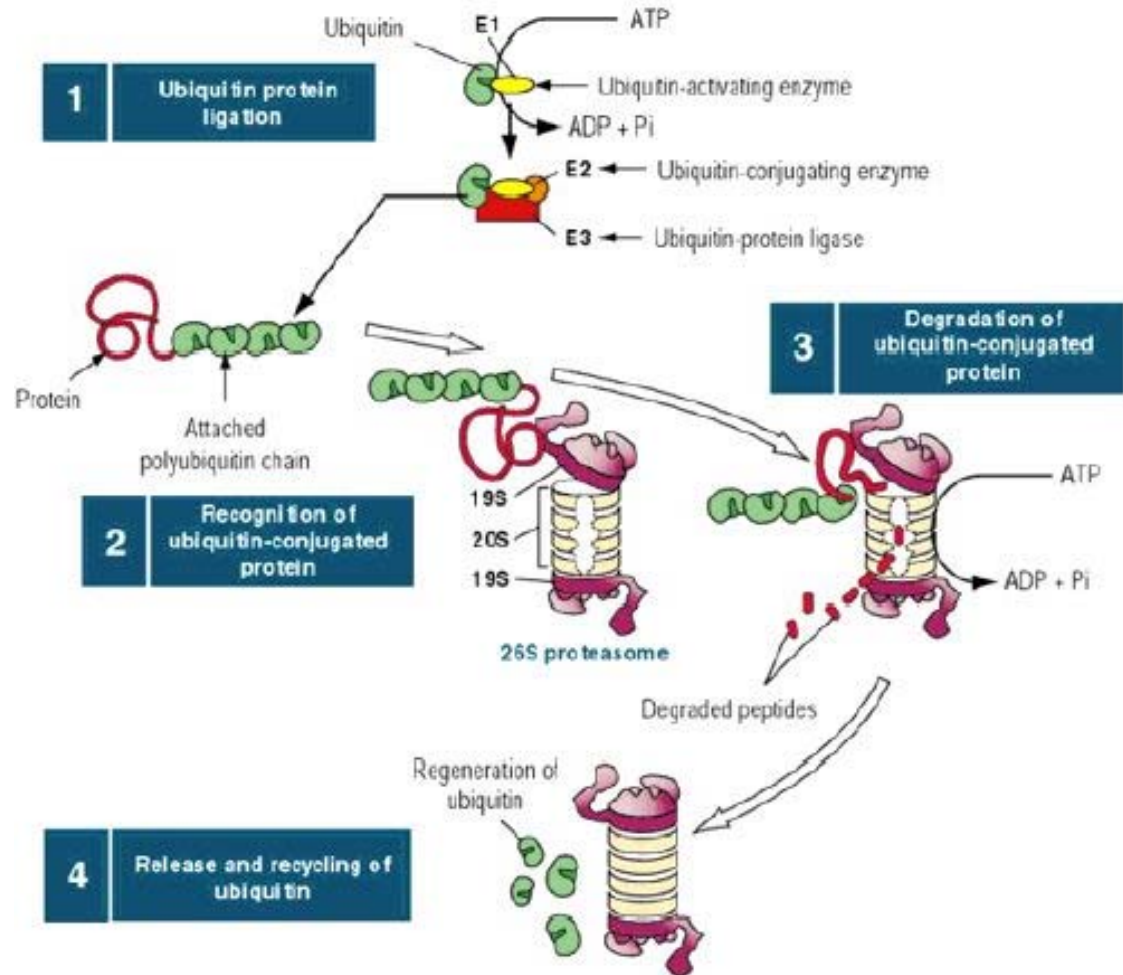


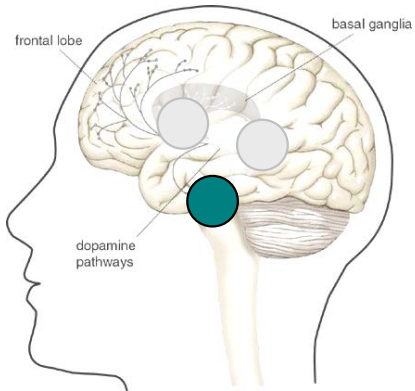
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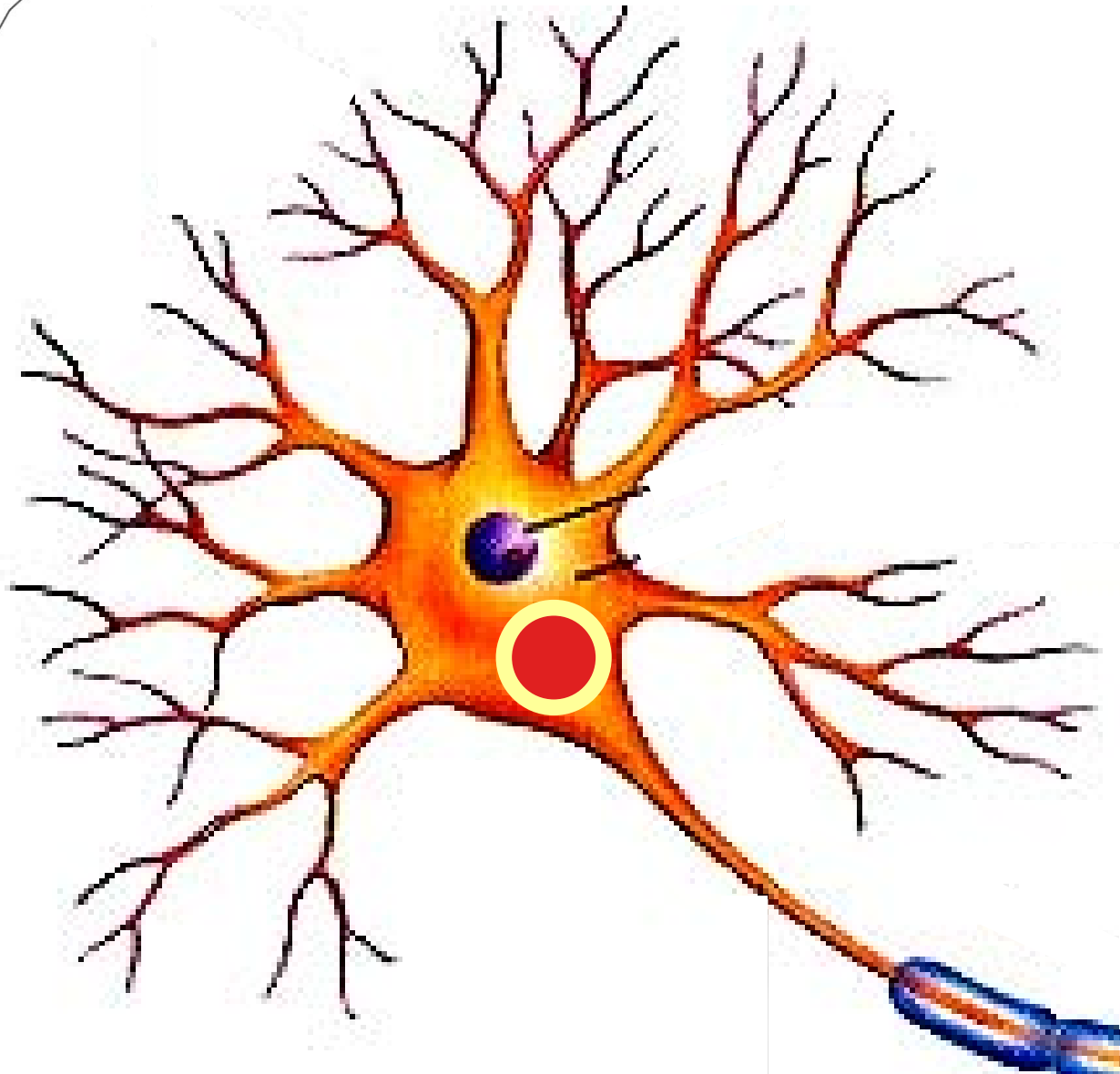


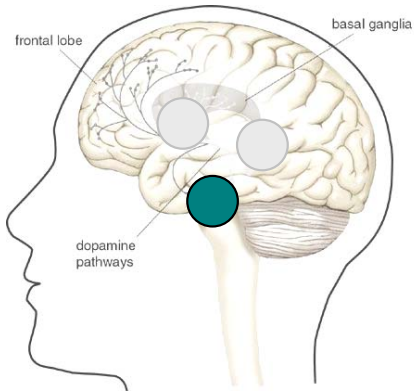
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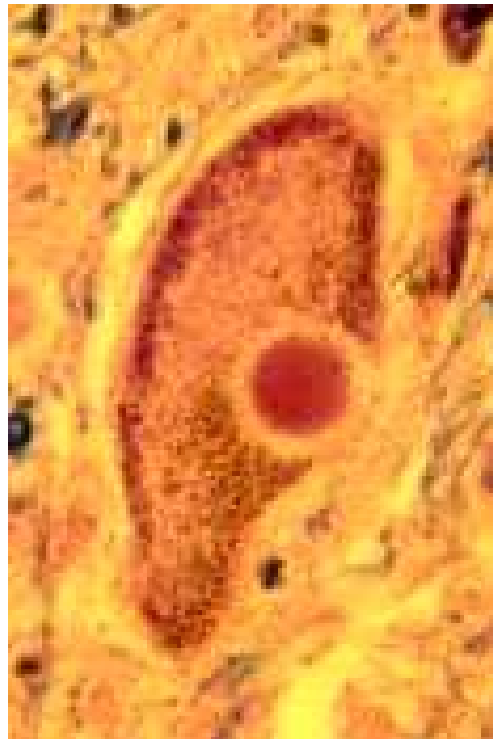


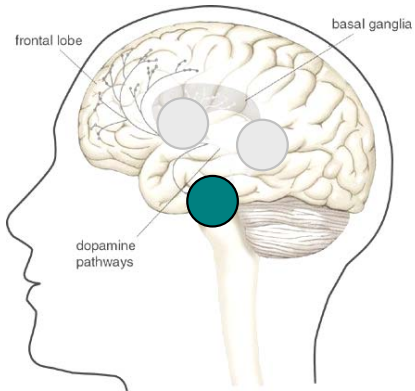
The Lewy body: Toxic Trash



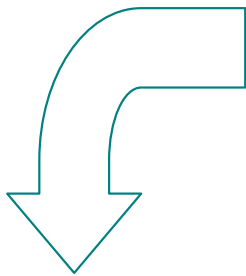


The Lewy body: Toxic Trash

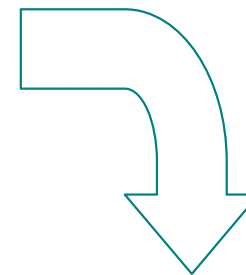
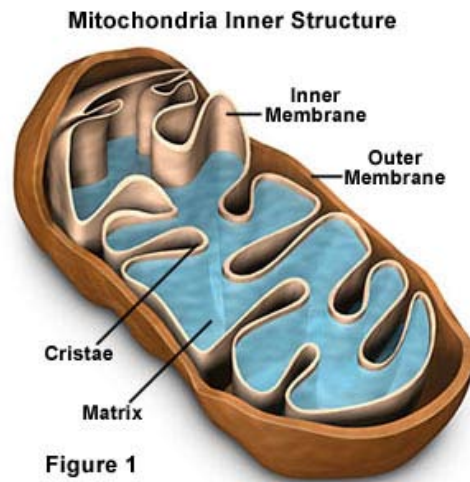




Mitochondria: the fuel cells

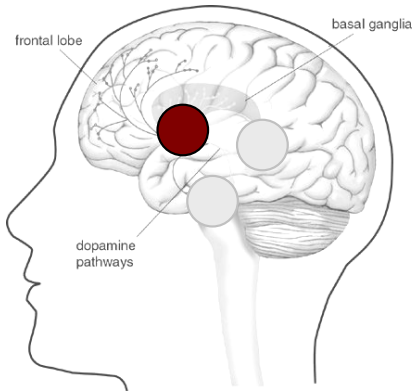


cell fatigue



cell suicide

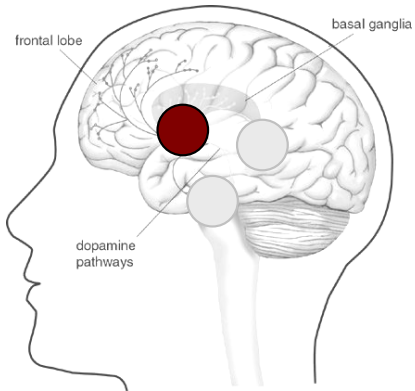




The Striatum

- “The striped object”
- The control center?
- Many inputs and outputs
- Cells in the striatum are healthy!
- The medium spiny neuron

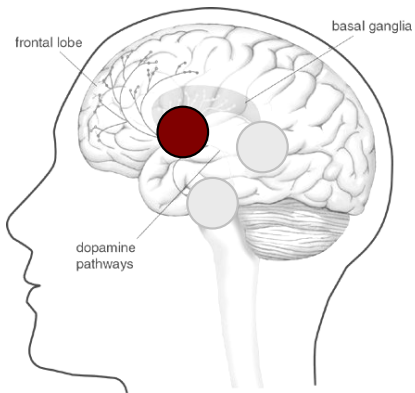




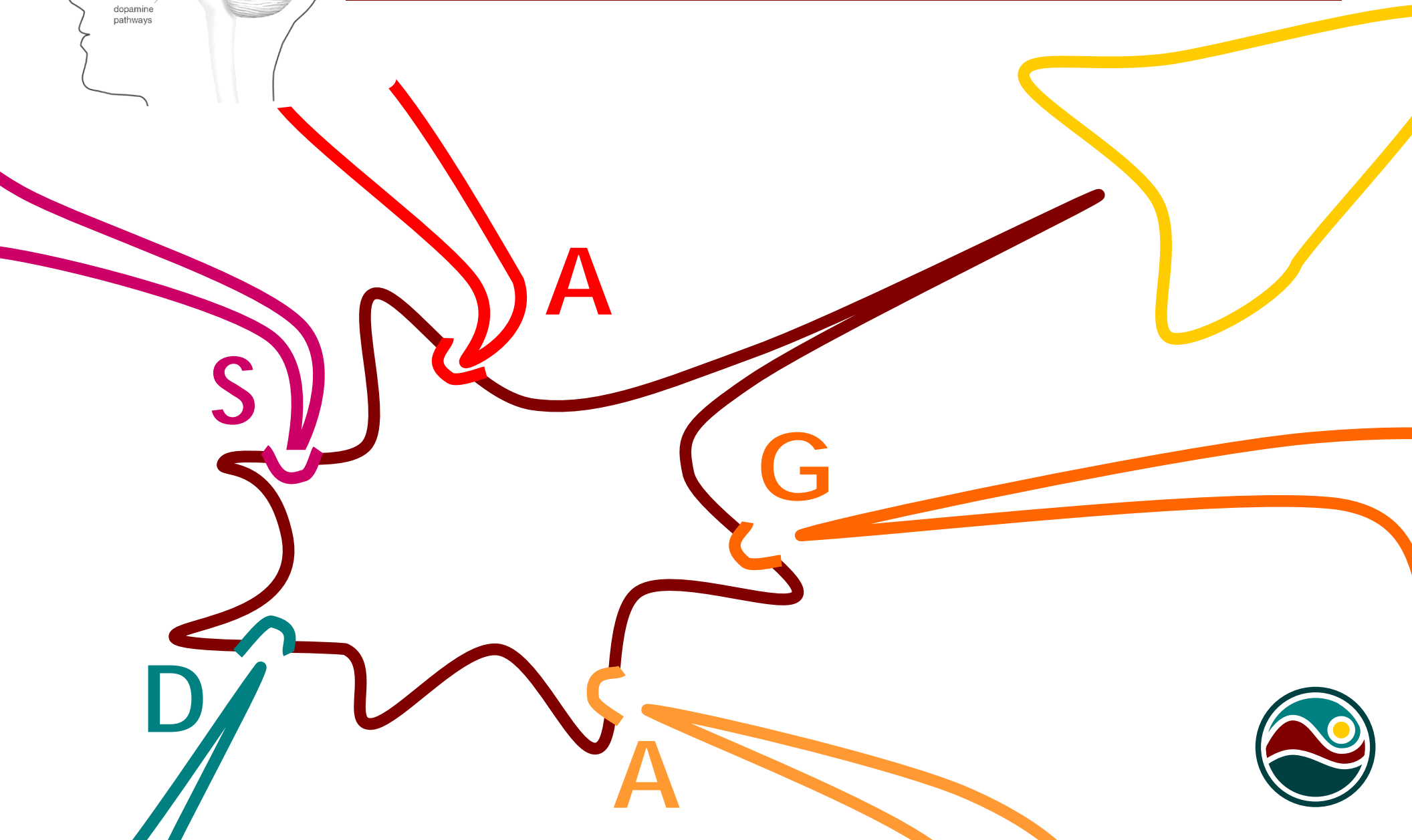
The Striatum

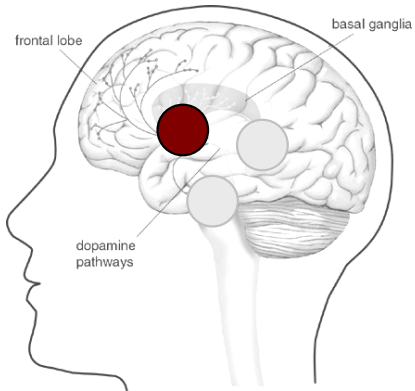
The medium spiny neuron



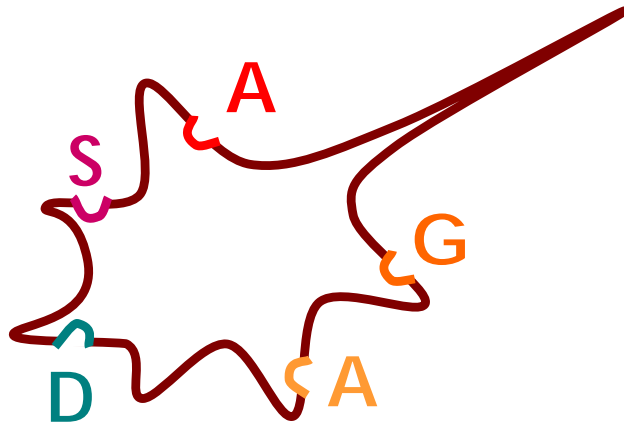


The Striatum





The Striatum



Dopamine

Acetylcholine

Glutamate

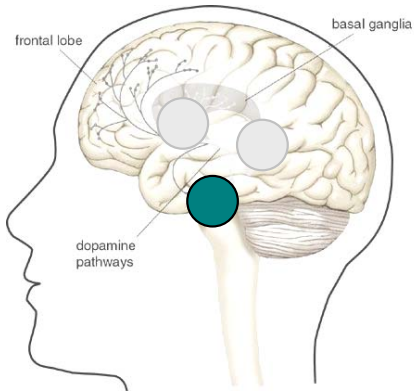
Adenosine

Serotonin





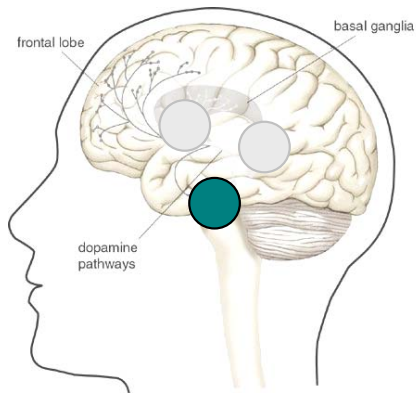
2007: What's new



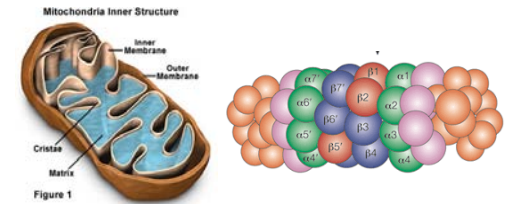
Strategies

1. Protect
2. Replace
3. Enhance
4. Bypass



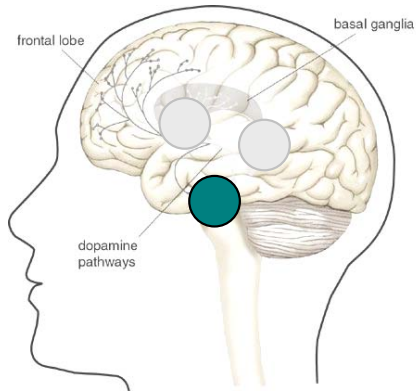


Protect

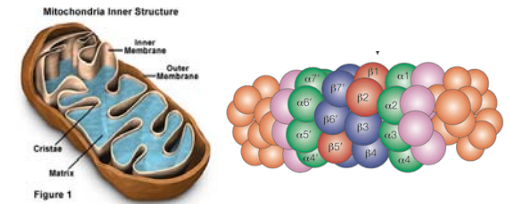


stage	mitochondria	proteasome
established	none	none
just in	none	none
soon	none	none
research	rasagiline CoQ10 creatine	siRNA



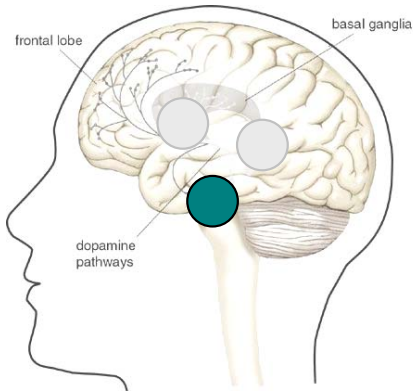


Protect



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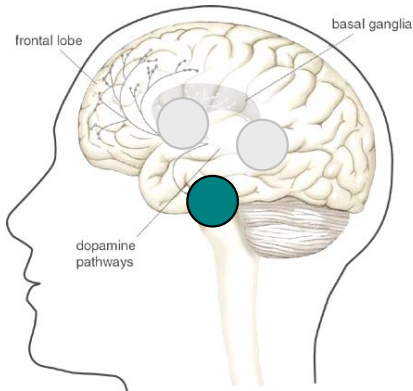




Rasagiline

- Rasagiline is an MAO inhibitor
- MAO inhibitors may have neuroprotective effects
- TEMPO study (2002; PSG, TEVA)
 - N = 404
 - improves early disability
- ADAGIO study (2005 →; TEVA)
 - N = 1000
 - Results: 2008 or later

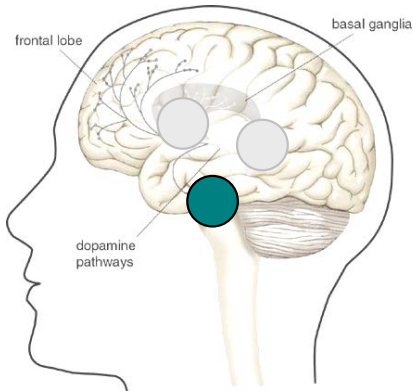




Coenzyme Q 10

- Coenzyme Q 10 is a mitochondrial cofactor
- Mitochondrial cofactors may have neuroprotective effects
- QE II study: (2002; PSG)
 - N = 80
 - 1200 mg/day helps 44%
- QE III study: (2007 →; PSG)
 - N = 800?
 - Results: 2010 or later

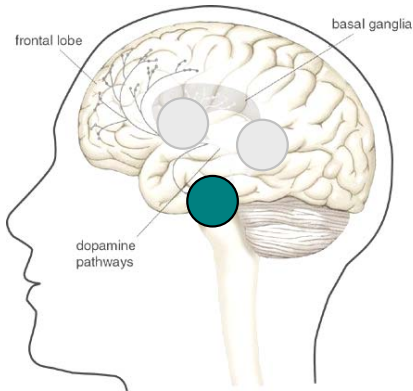




Creatine

- Creatine is a mitochondrial cofactor
- Mitochondrial cofactors may have neuroprotective effects
- NET-PD futility study: NIH
- NET-PD final study (2007 →; NIH)
 - N= 1720
 - Results: 2010 or later

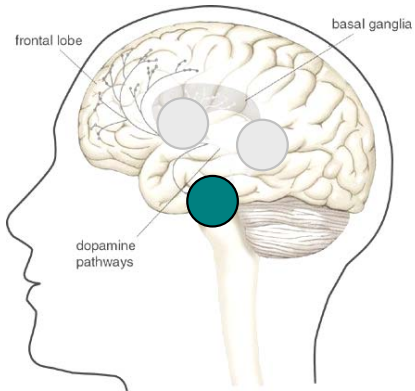




siRNA

- Small interfering RNA (siRNA) is a tool for “silencing” genes
- Discovered in 1998
- 2006 Nobel Prize
- Recently shown to work in a rodent model of Huntington’s disease
- Expect a report in a PD model soon

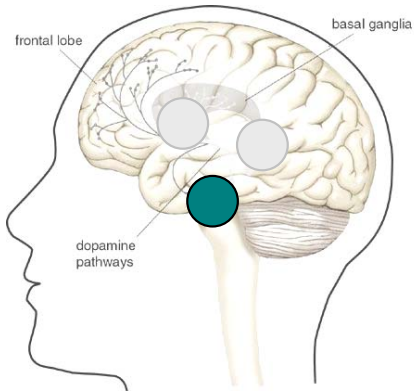




Replace

stage	therapy
established	none
just in	none
soon	none
research	stem cells retinal cells

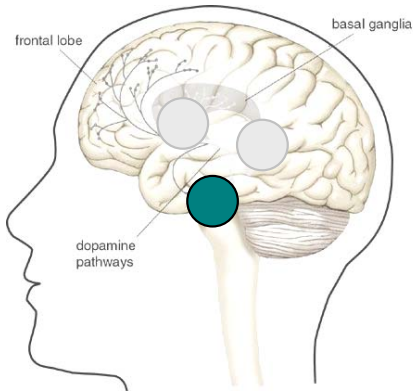




Replace

stage	therapy
established	none
just in	none
soon	none
research	stem cells retinal cells

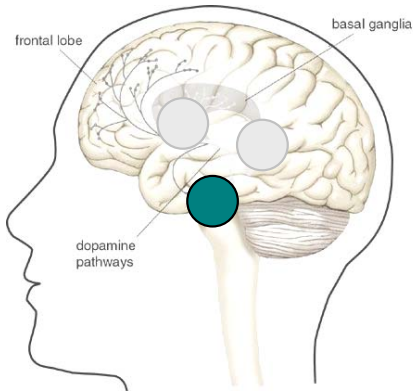




Stem Cells

- Stem cells might or might not be a way to replace dopaminergic neurons
- Stem cells might be more important as a research tool
- Political obstacles persist, but...
- Neural stem cells (NSC)
 - Kim et al 2006
 - Kim et al 2007
- Results: don't ask

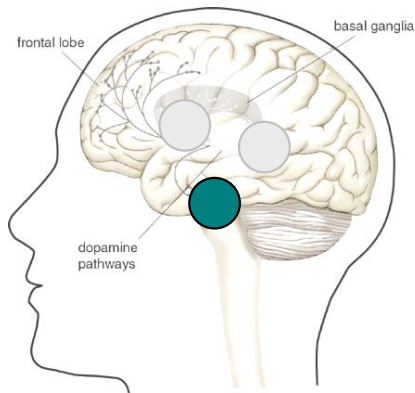




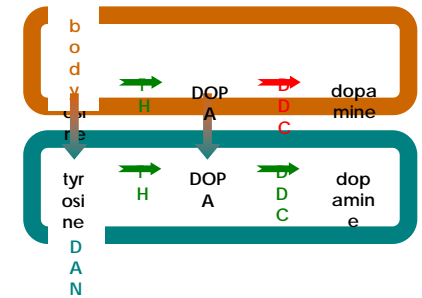
Retinal Epithelial Cells

- The human retina is rich in dopamine
- Retinal epithelial cells can be bound to synthetic microbeads
- Spheramine
- Human clinical trials are in progress
- Results: 2009 or later



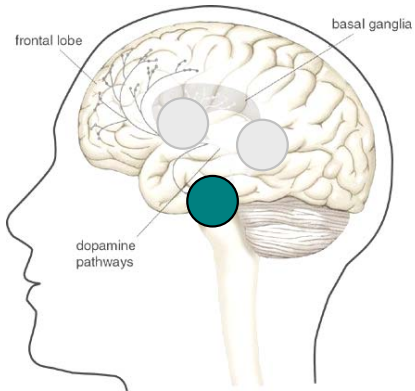


Enhance

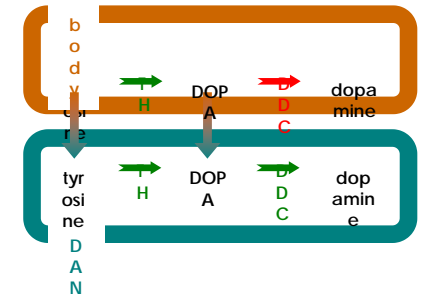


stage	dopamine precursors	enzyme inhibitors
established	<p>Slnemet</p> <p>Slnemet CR</p> <p>Parcopa</p>	<p>Eldepryl</p> <p>Lodosyn</p> <p>Comtan / Stalevo</p> <p>Tasmar</p> <p>Zelapar</p> <p>Azilect</p>
just in	none	none
soon	none	none
research	none	none



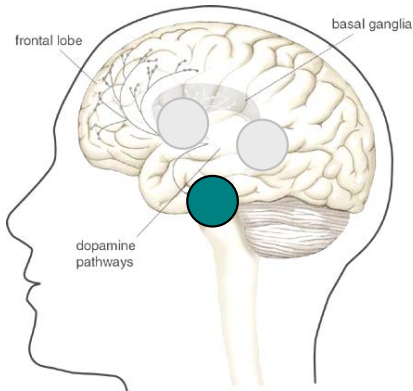


Enhance



stage	dopamine precursors	enzyme inhibitors
established	Slnemet Slnemet CR Parcopa	Eldepryl Lodosyn Comtan / Stalevo Tasmarr Zelapar Azilect
just in	none	none
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research	none	none

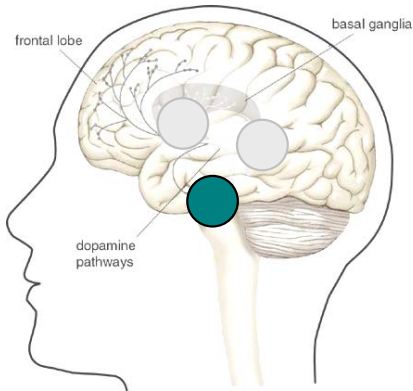




Parcopa

- Parcopa is orally dissolving carbidopa / levodopa
- Since levodopa is absorbed in the duodenum, this should not be any better than regular carbidopa / levodopa
- The clinical data do not suggest it is any better
- However, a significant number of patients report it works faster

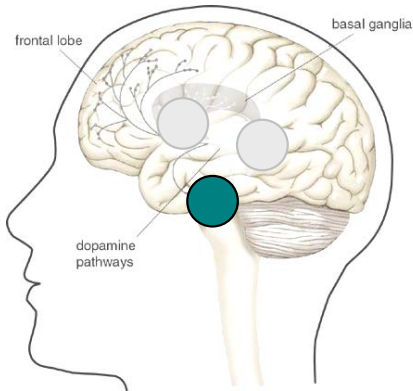




Zelapar

- Zelapar is orally dissolving selegiline
- Since selegiline ordinarily undergoes extensive first- pass metabolism in the liver, this ought to be a marked Improvement
- The clinical data do not suggest it is any better
- However, our patients report remarkable improvement

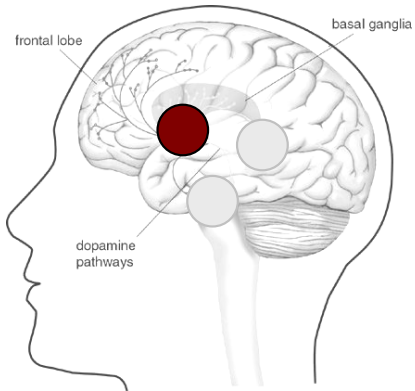




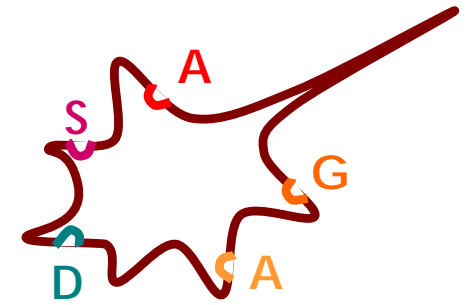
Azilect (rasagiline)

- Azilect is an irreversible MAO inhibitor, quite similar to selegiline
- However, we have better data for rasagiline
- The clinical data suggest it is no better than selegiline, except for a possible neuroprotective effect
- Our patients report variable results



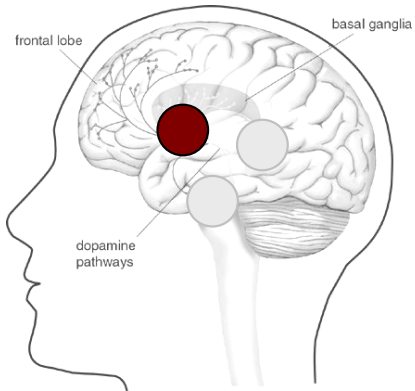


Bypass

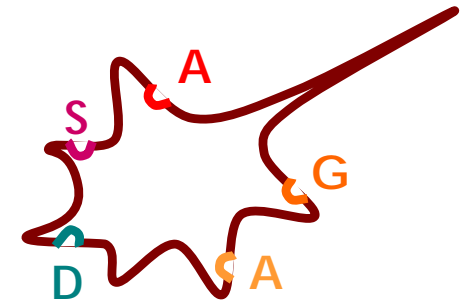


stage	dopamine	acetylcholine	glutamate	adenosine	serotonin
established	Parlodel Permax Mirapex Requip	Cogentin Artane	Symmetrel	none	none
just in	Apokyne	none	none	none	none
soon	Neupro	none	none	none	none
research	Mirapex Requip	none	E2007	KW6002	SLV308



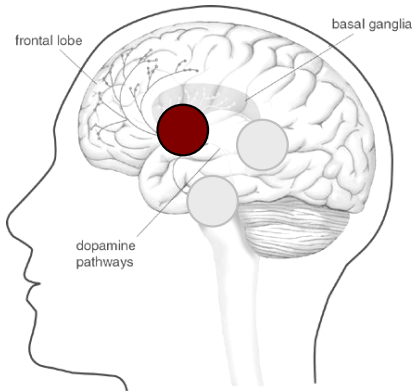


Bypass



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soon	Neupro	none	none	none	none
research	Mirapex Requip	none	E2007	KW6002	SLV308

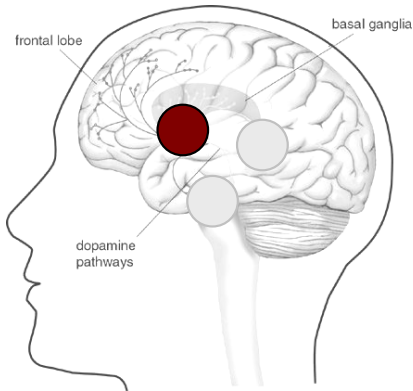




Mirapex (pramipexole)

- 10 years of post-marketing experience
- Research continues
- PramiBID
 - 5 visits over 12 weeks
 - seeking volunteers now
- Mirapex CR
 - 12 visits over 34 weeks
 - open-label extension
 - seeking volunteers soon

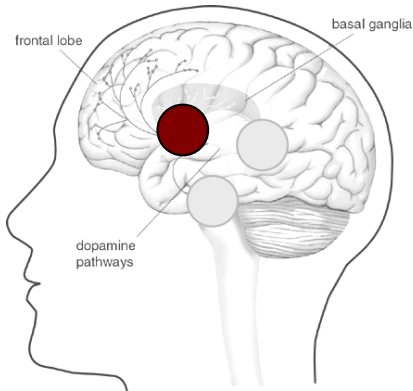




Requip (ropinerole)

- 10 years of post-marketing experience
- Research continues
- Ropinerole CR, now in extended open-label phase
- > 5 years and continuing
- Closed to enrollment

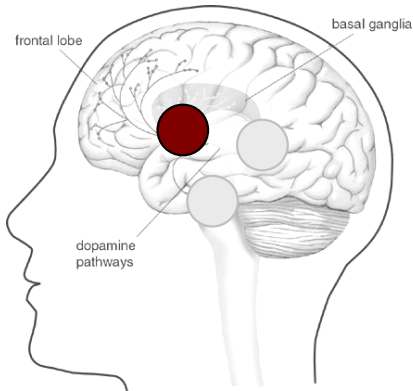




E2007

- A novel glutamatergic agent
- AMPA receptor antagonist
- may reduce “off” time
- Phase II: promising
- The PACE study (phase III)
 - 10 visits over 24 weeks
 - open-label extension
 - seeking volunteers now

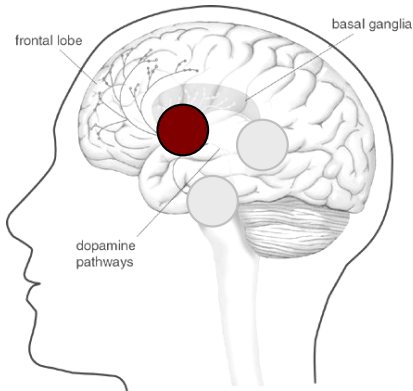




KW6002

- A novel adenosinergic agent
- A2a receptor antagonist
- In animal models, reduces “off” time and reduces dyskinesias
- In human studies, reduces “off” time
- > 5 years of experience at Pacific Neuroscience medical group
- Closed to enrollment





SLV308

- **A novel mixed agonist**
 - dopaminergic (D2, partial)
 - serotonergic (5HT-1a)
 - adrenergic (α 1/ α 2)
- **In animal models, reduces the signs of parkinsonism**
- **Vermeer study for early PD**
 - 14 visits over 24 weeks
 - open-label extension
 - seeking volunteers now





Decisions: What to do?

Decisions

- Volunteer?
- Protect?
- Replace?
- Enhance?
- Bypass?



Research



Parkinson's Research at Pacific Neuroscience

- Actively enrolling (or starting soon)
 - Vermeer (SLV308, Solvay) (early PD)
 - PramiBID (Mirapex, BIPI) (early PD)
 - Mirapex CR (Mirapex, BIPI) (early PD)
 - PACE (E2007, Eisai) (for patients with wearing-off)
- Ongoing (closed to enrollment)
 - ADAGIO (rasagiline, TEVA)
 - KW-6002-US-025 (KW6002, Kyowa)
 - POSTCEPT



Research



Protect?

- Exercise?
 - Yes, yes, yes
- Nutrition
 - Eat well, eat a lot
- CoQ10?
 - Wait
- Creatine?
 - Wait



Replace?

- Nothing yet (sigh)



Enhance?

- Levodopa
- Enzyme inhibitors
 - selegiline
 - entacapone
 - tolcapone
 - carbidopa
- Energizers
 - Coq10? (wait)



Bypass?

- Agonists
 - pramipexole
 - ropinerole
- Other spiny neuron agents
 - amantadine
 - anticholinergic



Comparison of early treatment options

class	side effects		cost	convenience
	peripheral	central		
levodopa	nausea orthostasis	dyskinesia hallucinations sleepiness	cheap	Tid empty stomach
agonists	nausea orthostasis edema	hallucinations gambling shopping? sleepiness	expensive	tid titration is complex
spiny	edema	hallucinations	cheap	bid
MAO	anorexia	Insomnia	vanes	once a day



Management of side effects

nausea	edema	orthostasis	hallucinations
<ul style="list-style-type: none">• Take medication with meals• Take levodopa with a light non-protein snack• Tigan• domperidone	<ul style="list-style-type: none">• Elevate legs• Stockings• Midodrine?• Reduce the agonist	<ul style="list-style-type: none">• Increase salt and fluids• Stockings• Elevate HOB• Proamatine• Fludrocortisone• Physostigmine	<ul style="list-style-type: none">• Reduce dose• clozapine• quetiapine





thank you

Appendix 1: References

The following images were obtained from various web sites, using Google's image search function. Images were modified and adapted for use in this educational program. All images belong to their respective creators and/or owners, and are presumed to be protected under copyright law. They should not be used other than for educational purposes.

1. Sagittal view of the brain
2. Cross section of midbrain in normal and PD brains
3. Neuron
4. Micrograph of dopaminergic neuron with Lewy body.
5. Proteasome
6. Mitochondria
7. EM of proteasomes
8. Ubiquitin-proteasome pathway

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Medication names (updated 2007)

	Generic	Brand	Other
levodopa & enzyme inhibitors	levodopa	Laridopa	
	carbidopa	Lodosyn	
	carbidopa/levodopa regular	Sinemet	
	carbidopa/levodopa controlled release	Sinemet CR	
	carbidopa/levodopa orally dissolving tablet	Parcopa	
	entacapone	Comtan	
	tolcapone	Tasmar	
	carbidopa/levodopa/entacapone	Stalevo	
	selegiline, deprenyl regular	Eldepryl	
	selegiline orally dissolving tablet	Zelapar	
	rasagiline	Azilect	
dopamine agonists	bromocriptine	Parlodel	
	pergolide	Permax	
	ropinerole	Requip	
	pramipexole	Mirapex	
	rotigotine transdermal system	Neupro	
	apomorphine subcutaneous	Apokyn	
study drugs	creatine		
	coenzyme Q10 (coQ10)		
	retinal ganglion cells		spheramine
	istradefylline		KW6002 E2007 SLV308