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Cognition in Parkinson's Disease and the Effect of Dopaminergic Therapy

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Disclaimer

No conflicts of interest to declare.

May 8, 2015

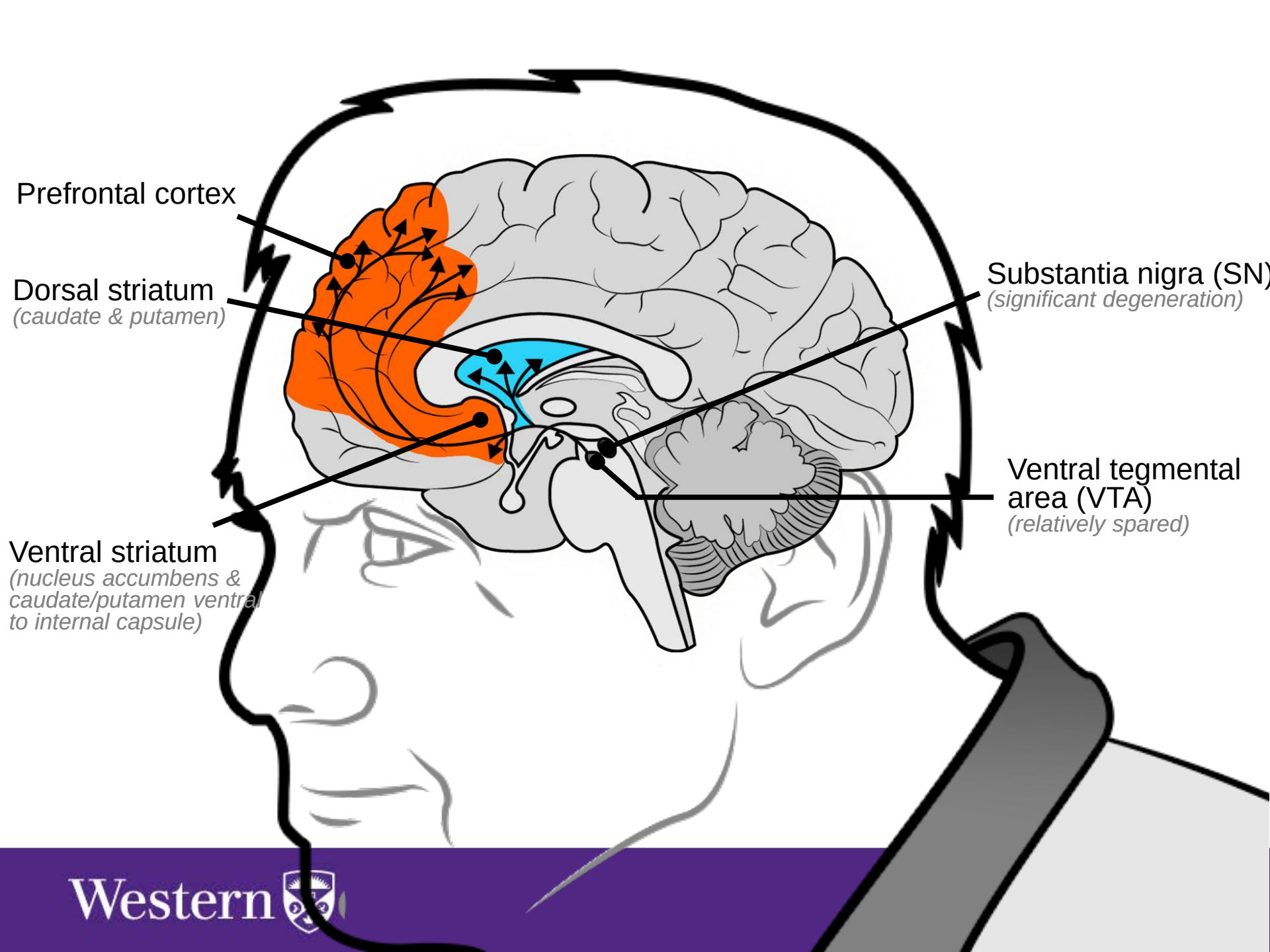
Overview

- Review cognitive changes in Parkinson's Disease (PD)
- Review the effect of dopamine replacement on cognitive function in PD
- Review possible mechanism for cognitive profile in PD

Background

Background

- Parkinson's Disease (PD) is a neurodegenerative condition with prominent motor symptoms:
  - Tremor
  - Bradykinesia
  - Rigidity
  - Postural instability (late)


Prefrontal cortex
Dorsal striatum
(caudate & putamen)
Ventral striatum
(nucleus accumbens &
caudate/putamen ventral
to internal capsule)
Substantia nigra (SN)
(significant degeneration)
Ventral tegmental
area (VTA)
(relatively spared)

Background

- Cognitive dysfunction is a major feature of PD
- 20-50% meet criteria for dementia (snapshot)
- Estimates as high as 80-90% (longitudinal)
- Milder cognitive dysfunction in vast majority

What is Cognition?

- Attention
- Perception
- Learning
- Memory
- Language
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
  - Sustained attention
  - Orienting/Alerting
  - Selective attention
  - Divided attention
- Perception
- Learning
- Memory
- Language
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
- Perception
  - Detection/Localization
  - Object Recognition
  - Visuospatial Processing
  - Sound Processing
- Learning
- Memory
- Language
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
- Perception
- Learning
  - Encoding (word, image, abstract)
  - Association (stimulus-response, stimulus-reward)
  - Rule
- Memory
- Language
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
- Perception
- Learning
- Memory
  - Storage
  - Recognition
  - Recall
- Language
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
- Perception
- Learning
- Memory
- Language
  - Speech Perception
  - Language Comprehension
  - Speech Production
  - Lexical Processing/Reading/Writing
- Executive Processing
- Emotional processing

What is Cognition?

- Attention
- Perception
- Learning
- Memory
- Language
- Executive Processing
  - Decision making
  - Reasoning (abstract, moral)
  - Planning, Generation (sequence, word, object)
  - Judgment
- Emotional processing

What is Cognition?

- Attention
- Perception
- Learning
- Memory
- Language
- Executive Processing
- Emotional processing
  - Emotion recognition/production
  - Theory of mind/perspective taking
  - Empathy

Cognitive Profile in PD: Historical

- Non-Amnestic
- Visuospatial Processing
- Fronto-executive
- Subcortical

Pubmed: Parkinson's disease and…

- Cognition 4080
- Attention 2498
- Perception 1740
- Learning 2989
- Memory 2786
- Language 1297
- Executive function 672
- Emotional processing 172

Cognitive Profile

Preserved:

- Simple reaction time/detection
- Verbal working memory/holding words/numbers in mind, online
- Learning*
  - Encoding (words, abstract images)
  - Associative (stim-reward; stim-response)
  - Sequence
- Time estimation
- Generation (sequence, object uses)*
- Planning*

Cognitive Profile

Impaired:

- Selectively attending (only to less salient targets)
- Manipulating contents of working memory
- Figure copying/mental rotation*
- Retrieval (recall/recognition)
- Prospective remembering
- Suppressing automatic actions/responses
- Set shifting*
- Task switching*
- Generation (words)*
- Motor planning*
- Facial emotional recognition (negative)
- Theory of mind attributions

Challenges to studying Cognition in PD

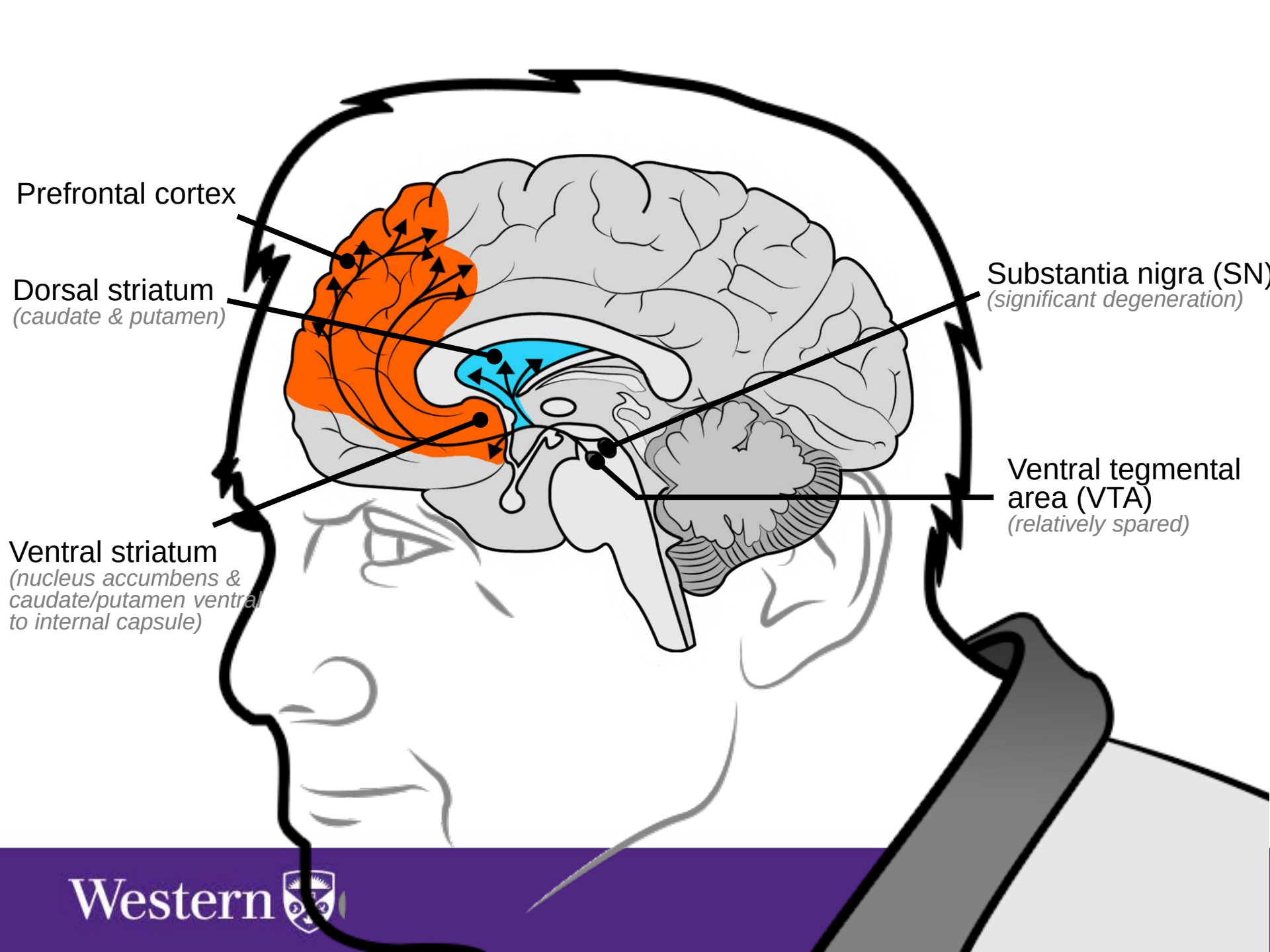
- dopamine replacement medications can improve some aspects of cognition and worsen others
- progressive disease
- medications have different effects on cognition depending on the stage of disease

Cognitive Profile: Worsened by Dopaminergic Therapy

- Learning
  - Encoding (words, abstract images)
  - Associative (stim-reward*; stim-response)
  - Sequence
- Time estimation
- Generation (sequence, object uses)*
- Planning*

Cognitive Profile: Improved by Dopaminergic Therapy

- Selectively attending (only to less salient targets)
- Manipulating contents of working memory
- Retrieval (recall/recognition)
- Prospective remembering
- Suppressing automatic actions/responses
- Set shifting/task switching*
- Generation (words)*
- Motor planning*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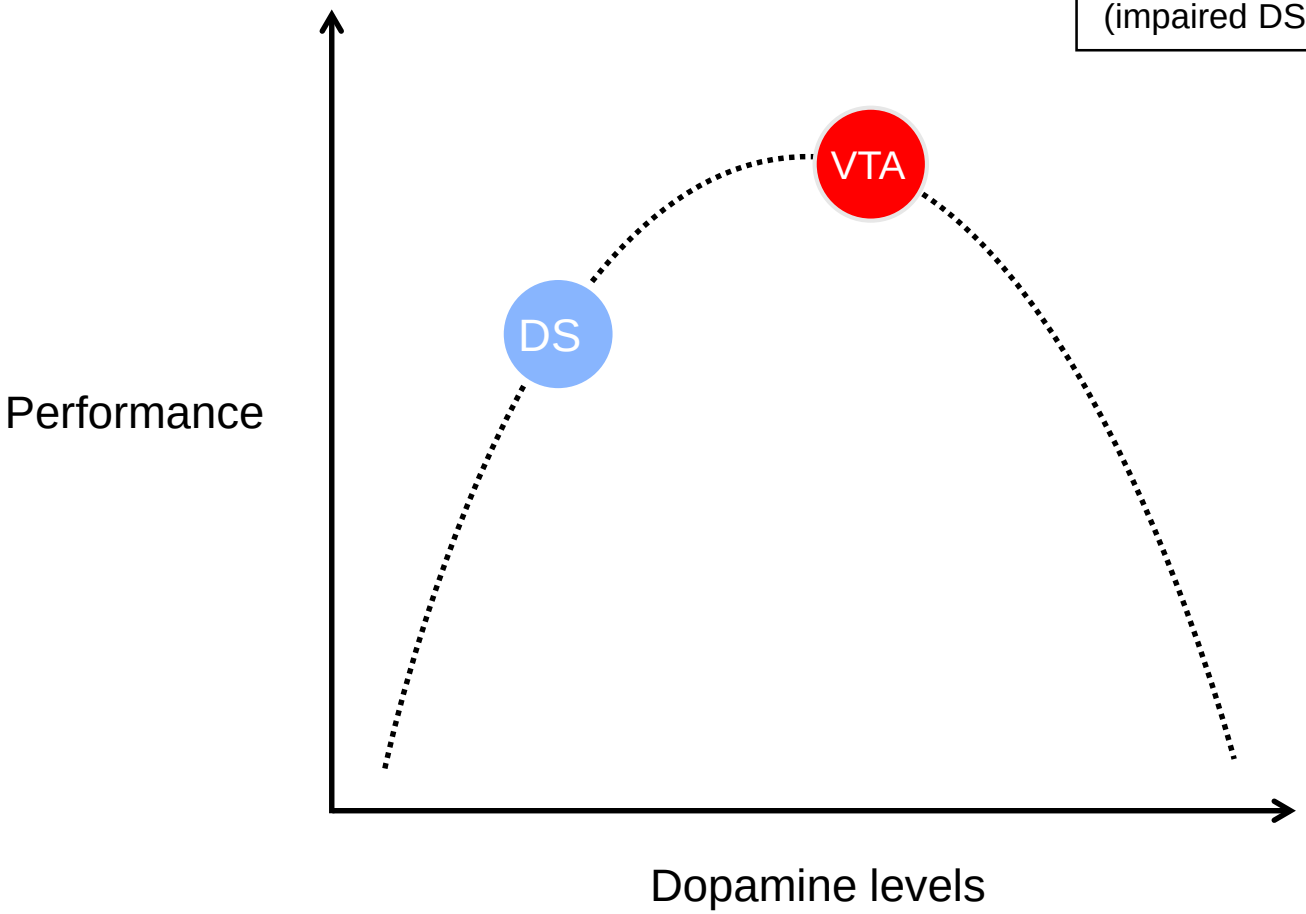
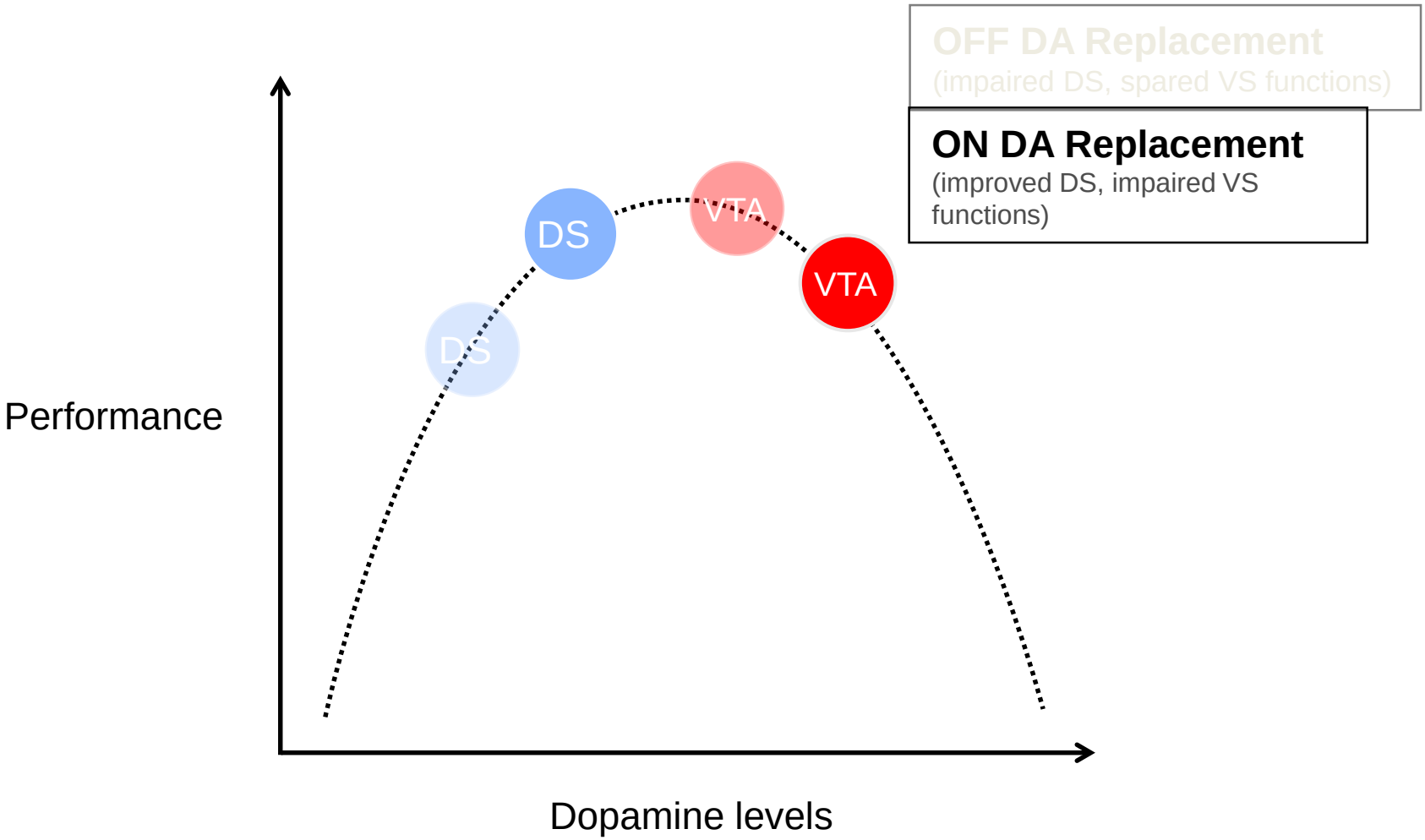
OFF DA Replacement
(impaired DS, spared VS functions)




OFF DA Replacement
(impaired DS, spared VS functions)
ON DA Replacement
(improved DS, impaired VS functions)
DS
VTA
DS
VTA
Performance
Dopamine levels

Challenges to studying Cognition in PD

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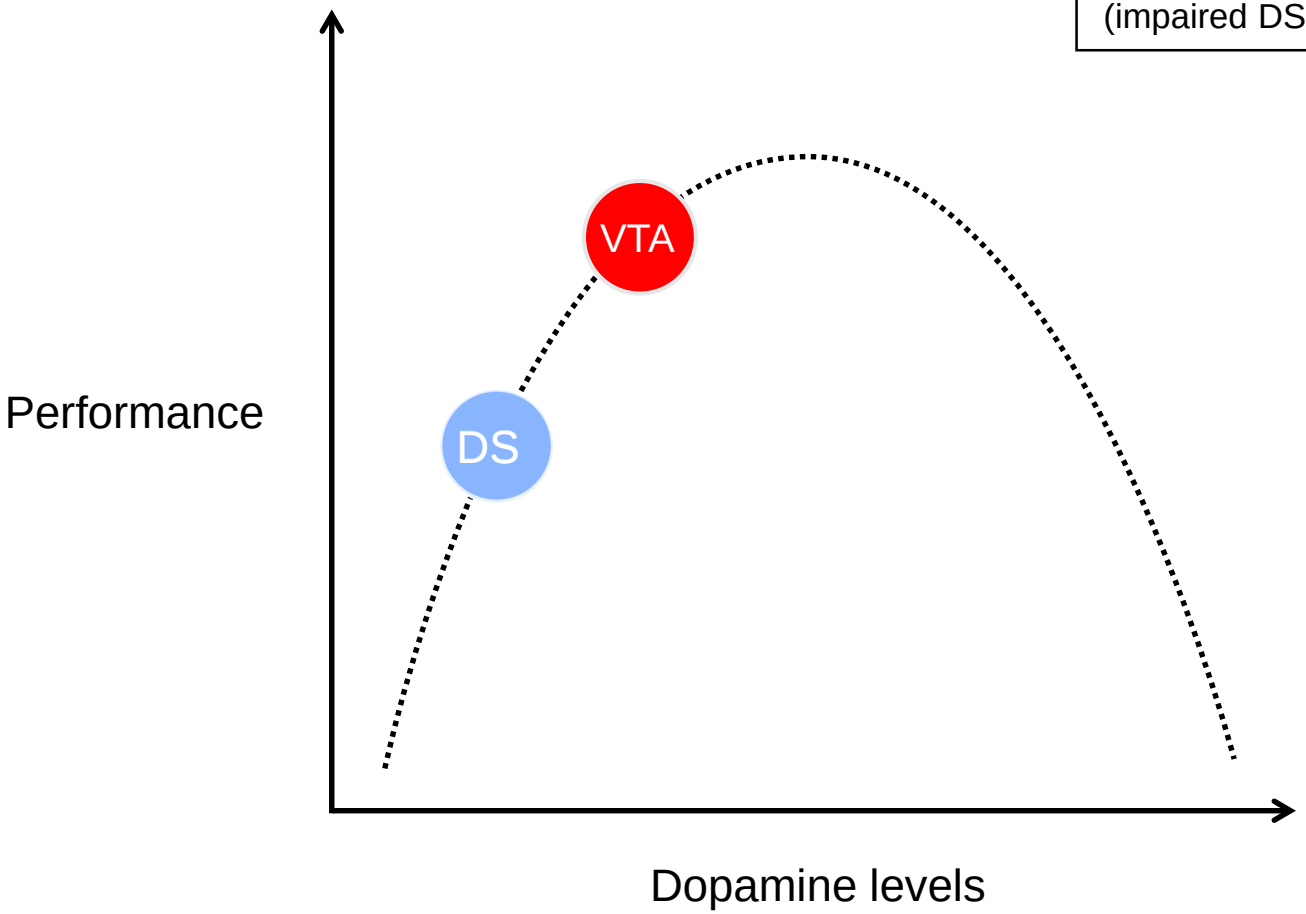

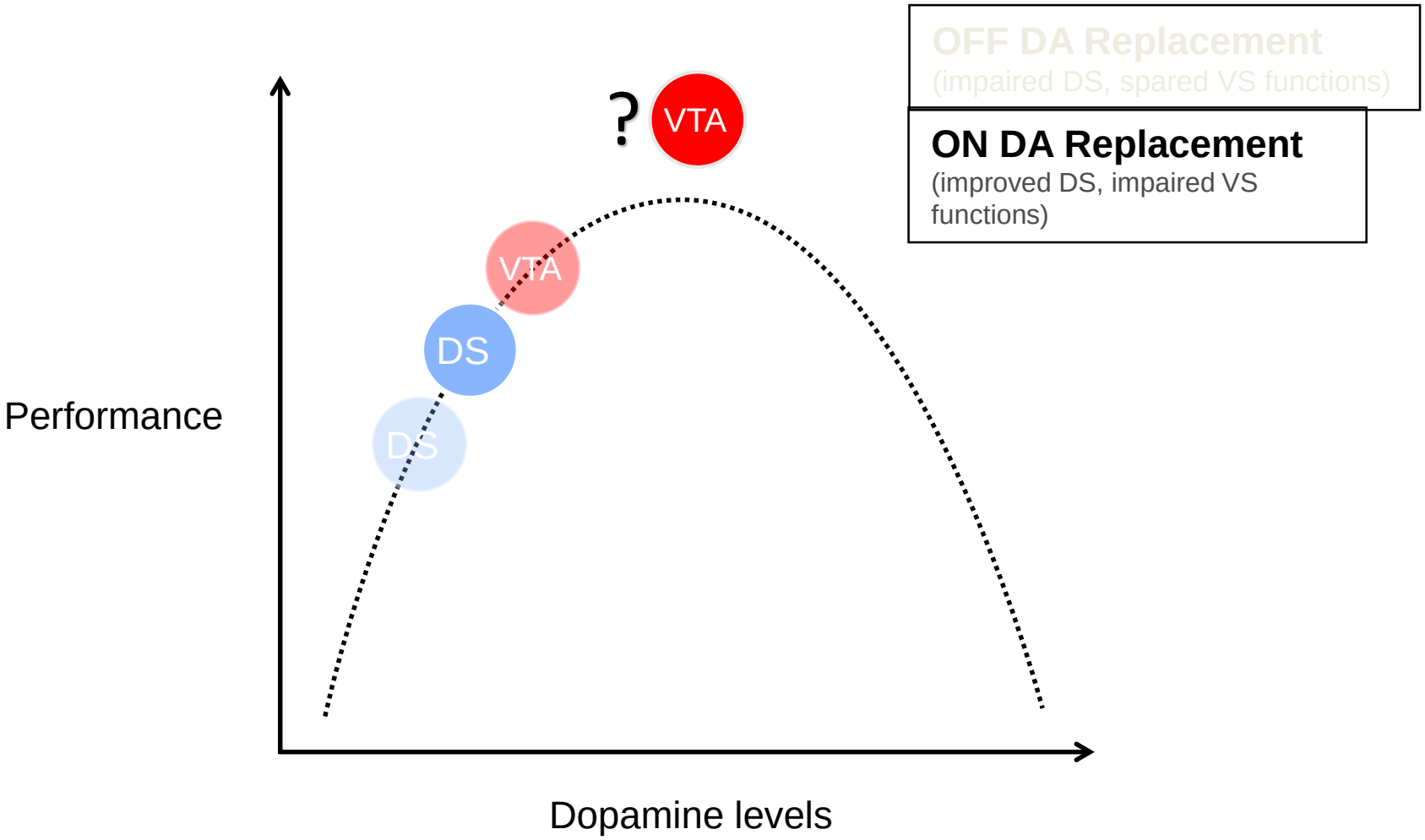
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(impaired DS, spared VS functions)
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?
VTA
VTA
DS
DS
Performance
Dopamine levels

Mechanisms of cognitive dysfunction

- Early mild (pre-clinical) cognitive impairment:
  - Dopamine deficiency to DS
  - Overdose of VTA-innervated brain regions
  - Other neurotransmitter depletion
- Late clinical cognitive impairment (MCI-PDD):
  - More significant dopamine deficiency to DS
  - Dopamine deficiency to VTA-innervated brain regions
  - Worsening serotonergic, acetylcholinergic depletion
  - Cortical Lewy body deposition

Before diagnosis -

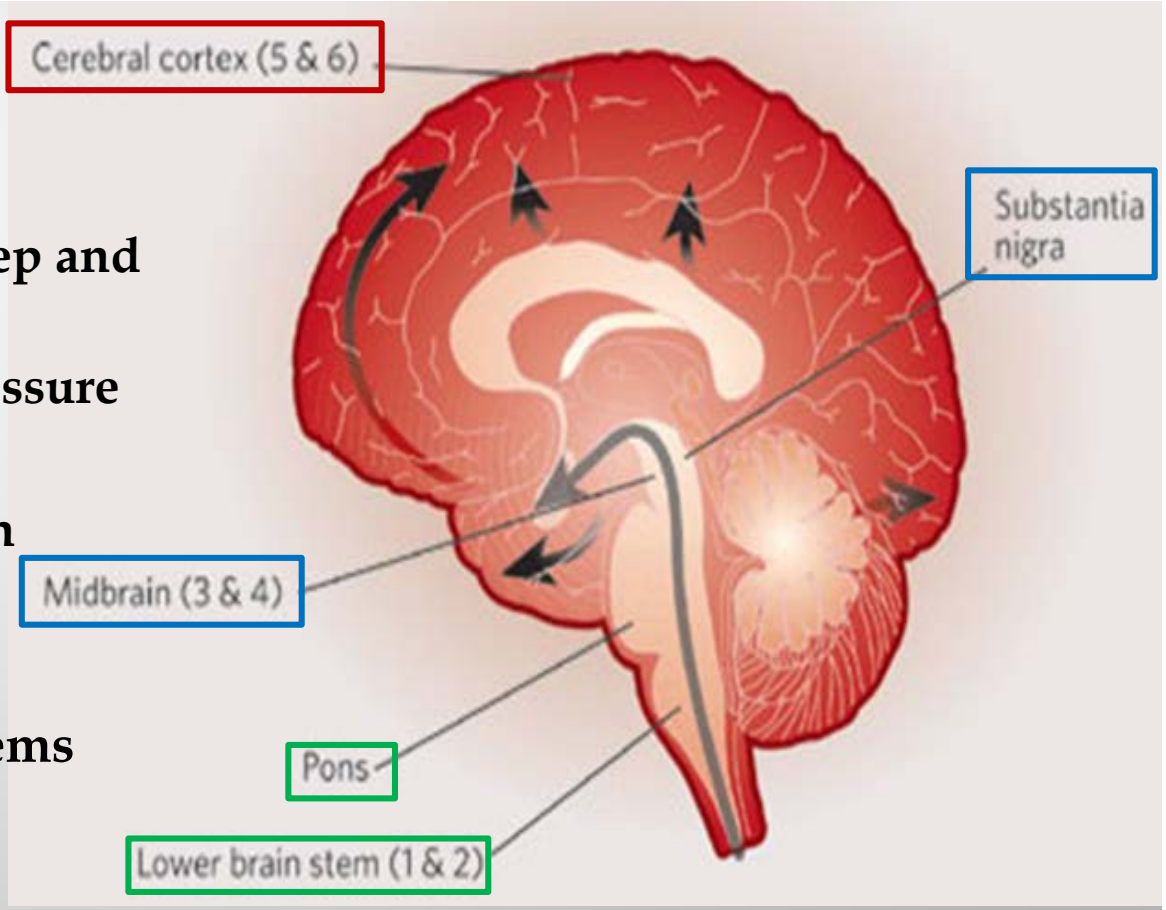
Stages 1 & 2 :

- loss of smell
- disturbance of sleep and wakefulness
- lowered blood pressure
- constipation
- anxiety/depression

At diagnosis -

Stages 3 & 4:

- movement problems
- subtle thinking problems



Later disease - Stages 5 & 6:

- worsening movement problems
- more significant thinking problems/dementia
- worsening anxiety/depression
- hallucinations/paranoia/delusions (i.e., false beliefs)

Cognitive Profile in PD: Historical

- Non-Amnestic
  - Encoding spared (early)
  - Retrieval impaired
  - Episodic memory very commonly impaired
- Visuospatial Processing
  - not predominant (tests often incorporate many cognitive processes)
  - inconsistent findings (esp. mental rotation)
- Fronto-executive
  - Too broad
  - Some impaired; some spared
    - Cognitive flexibility/control most prominent

Summary of Cognition in PD

- Cognitive dysfunction even at early stages
  - attentional modulation
  - cognitive flexibility/control
  - episodic memory
- Some cognitive dysfunctions are remedied by dopaminergic therapy
  - evidence that these are mediated by DS
- Others are caused by dopaminergic therapy (esp. early in disease)
  - evidence that these are mediated by VTA-innervated brain regions
- More widespread cognitive dysfunction late in disease
  - striatal/dopaminergic, cortical, acetylcholinergic origins

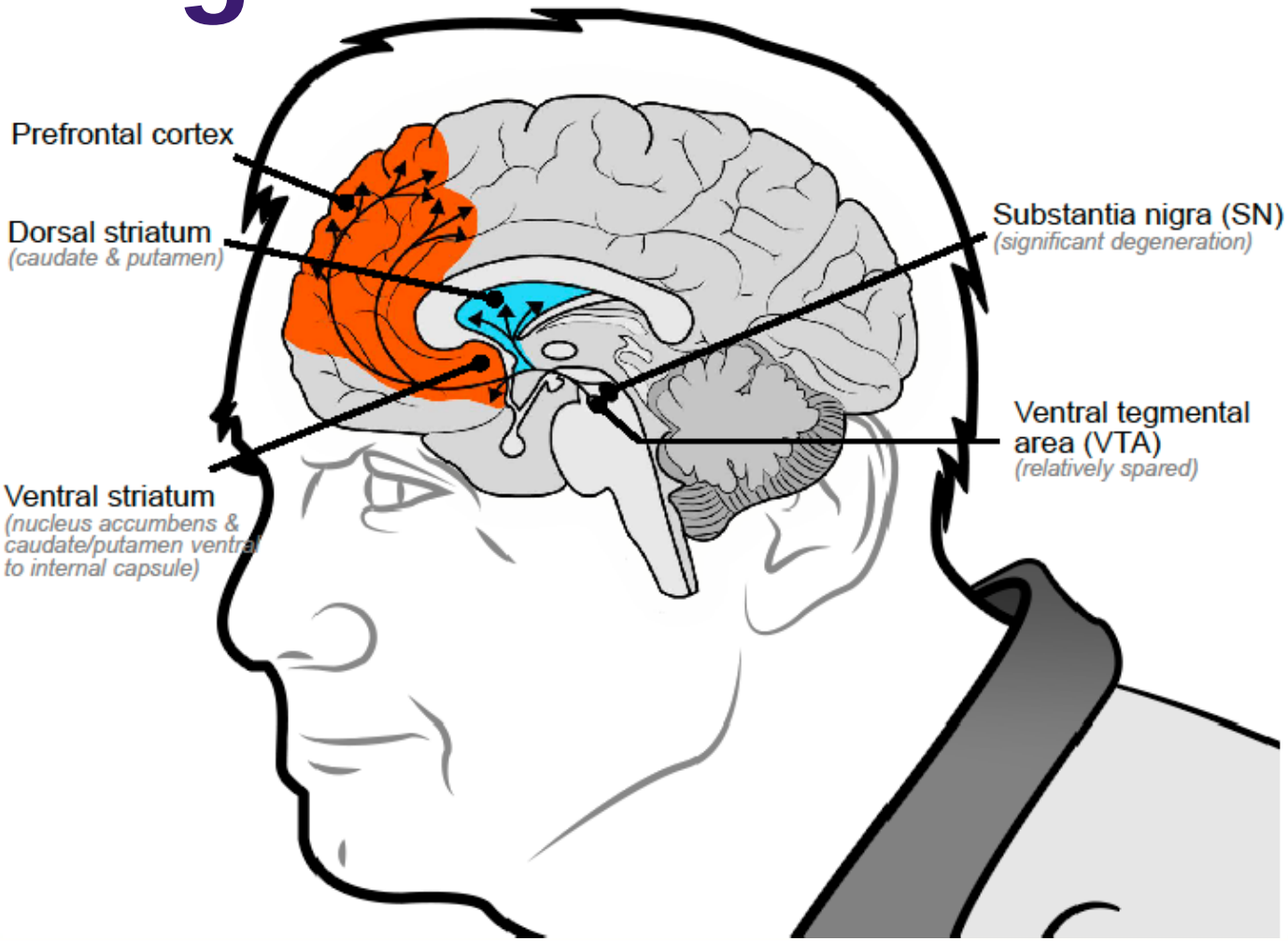
Future Directions

- Clarify cognitive profile, and effect of dopaminergic therapy on different cognitive processes in early vs. late PD
  - cohort studies
  - longitudinal designs more definitive in understanding evolution of cognitive profile
- Clarify pathophysiology of deficits in PD
  - studies of PD patients ON-OFF meds using neuroimaging techniques
  - can mechanisms of cognitive symptomatology suggest new treatments
- Understand the relation between deficits revealed in lab to real-world function

Background

- DA deficit and BG pathology could be a major factor in cognitive dysfunction in PD
- DA replacement seems to help certain cognitive functions, but hinder others
- This is likely related to different segments of BG mediating different cognitive functions and responding differently to treatment

Background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Background

- In PD, SN is more affected that VTA
- Since dorsal striatum (DS) receives dopaminergic input from SN, it is more affected than ventral striatum (VS)
- DS dysfunction is responsible for motor sx
- Dopamine replacement improves DS function (motor sx), but may worsen VS function
- VS may suffer from ‘dopamine overdose’ with dopaminergic medications

Background

- DS and VS mediate different cognitive functions
- If DS function improves and VS function worsens with DA-ergic medication, one can expect varying changes to cognitive function with treatment in PD

Dorsal Striatum

Dorsal Striatum

- Denser DA inputs
- Numerous dendrites and spines on medium spiny neurons (MSNs)
- Rapid and maximal DA stimulation through wide range of input firing frequency and intensity

Dorsal Striatum

- High concentration of dopamine transporter (DAT)
- Synaptic DA rapidly cleared
- Short DA stimulation durations
- Rapid, flexible, more absolute or ‘binary’ response
- Implications:
  - Important for deciding between alternatives
  - Important in performance

Dorsal Striatum

- DS connected to effector regions:
  - Frontal eye fields
  - Dorsal and rostral premotor cortex
  - Supplementary and primary motor cortex
- Connections also to:
  - Dorsolateral prefrontal cortex
  - Somatosensory cortex
  - Parietal association cortex

Dorsal Striatum

- MSNs receive few projections from each cortical neuron
- DS ideally positioned to sum diverse influences on responding
  - Vast numbers of neurons making small contributions
  - Concordance among many inputs to influence excitation status of MSNs

Dorsal Striatum

- Single MSNs affect numerous cortical neurons
- Thus, DS coordinates activity in disparate cortical regions
- DS is ideally suited for selecting some stimuli and suppressing others

Ventral Striatum

Ventral Striatum

- Subtle cytoarchitectural and neurochemical differences:
  - Smaller neurons
  - Fewer, more spaced out dendrites and spines
  - Less significant dopaminergic input
- Result: receptor stimulation leads to slower and of lower more variable intensity vs DS
- More graded incremental VS response

Ventral Striatum

- Lower DAT concentration → longer duration of DA stimulation
- VS well suited for associating stimuli or events (even across time) in a graded fashion essential for probabilistic or associative learning and for binding events that are temporally coincident into episodes

Ventral Striatum

- VS connections to brain regions involved in encoding and associating salient features of the environment:
  - Anterior cingulate
  - Orbitofrontal cortex
  - Anterior temporal cortex
  - Hippocampus
  - Insula
  - Amygdala
  - Hypothalamus

Ventral Striatum

- Like DS, high degree of convergence
- VS receives information about:
  - Top-down, goal-directed attentional bias
  - Bottom-up object and event salience
  - Multimodal representations of objects and events
  - Current motivational state of the organism

Ventral Striatum

- Like DS, high degree of convergence
- VS receives information about:
  - Top-down, goal-directed attentional bias
  - Bottom-up object and event salience
  - Multimodal representations of objects and events
  - Current motivational state of the organism
- Thus, VS could be important in learning and encoding

Dorsal Striatum: Cognitive Testing

Dorsal Striatum Lesions

- DS lesions impair:
  - Set shifting and task switching
  - Category judgements
  - Suppression of irrelevant information and responses
  - Reversal of previously acquired stimulus-reward relations
  - Planning
  - Visuospatial processing
  - Explicit and implicit memory

Dorsal Striatum Lesions

- DS lesions spare:
  - Working memory
  - Language
  - Word and face recognition
  - Explicit and implicit learning

Dorsal Striatum in Ctrls

- Consistent with lesions studies, shifting sets and changing stimulus-reward or stimulus response mappings increase DS activity

Dorsal Striatum in Ctrls

- Other processes that activate DS:
  - Responding to colour vs word in Stroop task
  - Pictures named in a second language vs. first language
  - Previously informative stimuli disregarded
  - Learned (vs. random) motor sequences
  - Familiar items in episodic recognition test

Dorsal Striatum in Ctrls

- Other processes that activate DS:
  - Category judgements
  - Rewarded vs unrewarded stimuli and responses
  - Distinguishing and estimating different time durations

Dorsal Striatum in Ctrls

- DS appears to be involved in performance rather than learning

Ventral Striatum: Cognitive Testing

Ventral Striatum Lesions

- Few lesion studies
- Anterograde amnesia following L nucleus accumbens bleed
    - Normal testing on:
        - Retrospective verbal memory
        - Dividing and shifting attention
        - Wisconsin card sorting
        - Tower of London
        - Working memory
        - Language
        - Encoding/retrieval of nonverbal info

Ventral Striatum Lesions

- VS appears to involved in encoding associations with left VS lateralized for language
- Other examples:
  - Anger recognition deficits
  - Behavioural deficits, hyperactivity
  - Deficits in reversing previously acquired stimulus-reward contingencies
  - Encoding facial emotional expressions

Ventral Striatum in Ctrls

- VS activity seems to correlate to the degree to which a motor sequence is implicitly learned
- VS activity greatest in early learning and preferential for positive feedback
- This stimulus-reward learning occurs even without intention or consciousness
- Once learning is established VS activity drops off

Ventral Striatum in Ctrls

- VS activity seems to correlate to the degree to which a motor sequence is implicitly learned
- VS activity greatest in early learning and preferential for positive feedback
- This stimulus-reward learning occurs even without intention or consciousness

Ventral Striatum in Ctrls

- Once learning is established, VS activity drops off… unless:
  - Unexpected rewards delivered for previously unrewarded stimuli or reward omitted for previously rewarded items
  - Punishment after errors
  - Reversal learning experiments when criterion is reversed and selection of previously rewarded stimuli now elicits negative feedback

Ventral Striatum in Ctrls

- VS is differentially activated by
  - Salient stimuli
  - Valued stimuli
  - Novel stimuli
- Differential VS activity reflects both magnitude and probability of reward
- In summary, VS appears to be engaged when stimulus signals possibility of new learning

Ventral Striatum in Ctrls

- VS is also associated with more impulsive choices and riskier choices
- VS activity is greater for immediate rewards vs. long-term benefits

Summary of DS versus VS: Cognitive Testing

DS versus VS: Cognition

- DS:
  - Complex planning tasks
  - Tracking whether an item belongs in one category or another
  - Whether an item is rewarded versus unrewarded
  - Whether an item is familiar versus novel
  - Time discrimination and estimation
  - Visuospatial processing

DS versus VS: Cognition

- VS:
  - Multiple aspects and forms of learning
  - Orienting attention to salient, novel, or valued stimuli
  - Mediates motivation
  - Facilitating approach behaviours
  - Facial emotional processing

Effect of Dopamine Replacement on Cognition

DA Replacement

- Recall that…
  - DS is depleted of DA at all stages of PD
  - VS is relatively unaffected
  - Hypothesis: VS is overdosed with DA replacement and its function impaired

DA Replacement

- Enhanced by dopaminergic therapy:
  - Motivation* (VS)
  - Impulsivity* (VS)
  - Selective attention (DS)
  - Selective responding (DS)
  - Complex planning (DS)
  - Category judgements (DS)
  - Time estimation (DS)
  - Visuospatial processing (DS)
  - Explicit and implicit retrieval (DS)
  - Set shifting (DS)
  - Task switching (DS)
  - Spatial working memory
  - Manipulating contents of working memory

  - ** enhanced to a pathological degree*

DA Replacement

- Improvements are mostly seen in processes mediated by DS

DA Replacement

- Unchanged by dopaminergic therapy:
  - Complex planning (DS)
  - Set shifting (DS)
  - Task switching (DS)
  - Nonspatial working memory
  - Set shifting
  - Task switching

DA Replacement

- Impaired by dopaminergic therapy:
  - Implicit and explicit learning (VS)
  - Reversal learning (VS)
  - Orienting to stimuli (VS)
  - Time estimation (DS)
  - Reaction time
  - Production of self-generated sequences
  - Generation of alternate uses of common objects

DA Replacement

- Impairments are mostly seen in processes mediated by VS

DA Replacement

Table 1: Cognitive functions that are enhanced, unchanged, or impaired by dopaminergic therapy, grouped according to their association with dorsal striatum, ventral striatum, or other brain regions.

	Enhanced by dopaminergic therapy	Unchanged by dopaminergic therapy	Impaired by dopaminergic therapy
Ventral striatum	*Motivation *Impulsivity		Implicit and explicit learning Reversal learning Orienting to stimuli
Dorsal striatum	Selective attention Selective responding Complex planning Category judgements Time estimation Visuospatial processing Explicit and implicit retrieval Set shifting Task switching	Complex planning Set shifting Task switching	Time estimation
Other brain regions	Spatial working memory Manipulating contents of working memory	Nonspatial working memory Set shifting Task switching	Simple reaction time Production of self-generated sequences Generation of alternate uses of common objects

* Are enhanced to a pathological degree.

Summary

Summary

- Cognitive dysfunction is a feature of PD
- Cognitive functions are increasingly attributed to striatum
- Dopamine replacement improves cognitive processes mediated by the dopamine-depleted DS
- Dopamine replacement impairs cognitive processes mediated by the relatively spared VS

Summary

- Titration of PD therapy is usually geared to the DS-mediated motor sx of PD
- Cognitive functions associated with VS may suffer as a result
- Clinicians should bear in mind the potential for DA overdose of the VS and associated symptoms when managing PD medications

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