Basal Ganglia Cognitive Disorders and the Effects of Deep Brain Stimulation.

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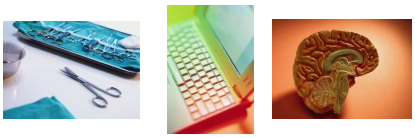

Outline

1. How does Parkinson's disease affect cognitive processing?
2. What is the role of the subcortical circuits in accounting for cognitive changes in PD?
3. What consequences does DBS have on cognitive processing and subcortical circuits?
4. Implications and future directions.

How does Parkinson's disease affect cognitive processing?

- Visuospatial deficits.
- Memory:
  - Impairments of delayed recall, temporal ordering, and conditional associate learning.
- Attention:
  - Digit span fairly intact but attentional tasks requiring speeded cognitive processing or internal guidance impaired.
  - Covert attention impaired.
- Mood:
  - Depression is common.
- Emotional processing impaired.
- Frontal/executive functions:
  - impairments in working memory, trial-and-error learning, planning, response monitoring, set shifting.

How does Parkinson's disease affect language processing?

• Difficulties interpreting ambiguity and figurative language.

• Reduced verbal fluency abilities.

• Impaired naming and definitional abilities and more difficulties generating and naming verbs than nouns **(Probs with semantics).**

• Reduced performance when comprehending complex sentences (e.g., object-relative sentences – "the ball that the man kicked was impossible to stop") **(Probs with syntax).**

What does a person with PD say about their communication?

Direct impact on socialization, from apprehension at interaction to social withdrawal.

Miller et al., 2006

Principal components of the striatal circuitry

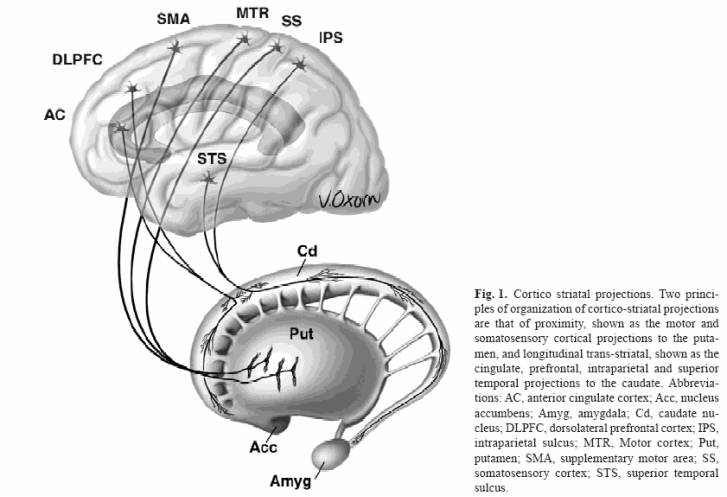

Fig. 1. Cortico striatal projections. Two principles of organization of cortico-striatal projections are that of proximity, shown as the motor and somatosensory cortical projections to the putamen, and longitudinal trans-striatal, shown as the cingulate, prefrontal, intraparietal and superior temporal projections to the caudate. Abbreviations: AC, anterior cingulate cortex; Acc, nucleus accumbens; Amyg, amygdala; Cd, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; IPS, intraparietal sulcus; MTR, Motor cortex; Put, putamen; SMA, supplementary motor area; SS, somatosensory cortex; STS, superior temporal sulcus.

Saint-Cyr, 2003

Three nonmotor circuits

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Ant Cingulate Circuit. involved in
- attention-based semantic processing
- Processing of negative stimuli
- Response initiation
- Intention
- Inhibition of prepotent response
- Conflict monitoring

DLPFC. mediates executive cognitive functions such as
- Set shifting
- Complex problem solving
- Activation of remote memories
- Organizational strategies
- Working memory

Orbitofrontal Cortex. associated with functions requiring frontal monitoring of the limbic system such as
- Disinhibition
- Making decisions based on reinforcement/ reward schedule
- Impulse control
- Perseveration
- Mood and
- Personality

Zgaljardic et al., 2003

Three nonmotor circuits

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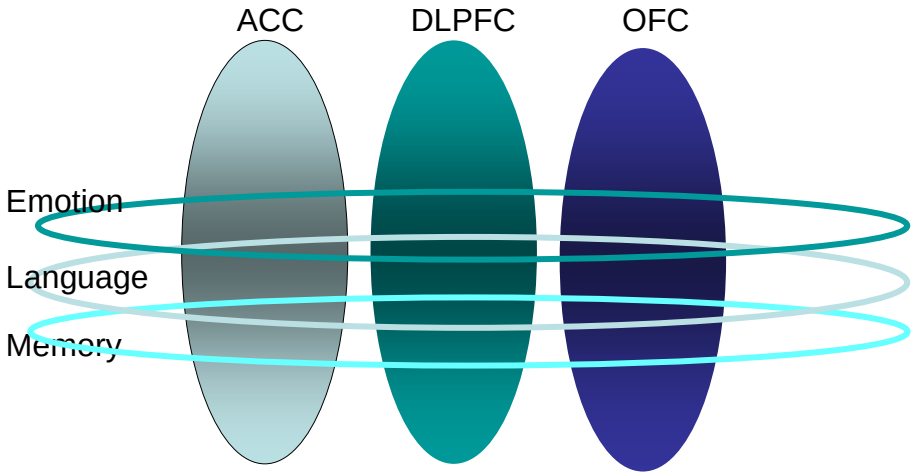


Outcomes of DBS.

- Include
  - Greater mobility,
  - Higher scores on activity of daily living,
  - Reduced stigma and
  - Reduced bodily discomfort.

- But there are some negative outcomes to the surgery.
  - Reduced verbal memory, executive functioning and/or working memory
  - changes in emotional and affective functioning, including
    - depression
    - hypomania or
    - Anxiety
  - Language
    - Verbal fluency.

The research to date has focused on

Studies of:

- Mood and emotional processing post STN DBS
- Inhibitory and interference control
- Memory and learning
- Attention and frontal-executive processing
- Lexical-semantic processing using verbal fluency tasks

Variable results

Effect of DBS on cognition

Mood and emotion processing

- Positive influence on self-reported mood state and emotional story recall (Schneider et al., 2003).
- Negative effect on negative emotion recognition in faces (Dujardin et al., 2004)

Verbal fluency

- Verbal fluency declines with STN stimulation (e.g. De Gaspari et al., 2006)
- Verbal fluency does not change with DBS (e.g. Jahanshahi et al., 2000)

Our research.

To investigate the effects of DBS (in a cohort of PD participants) on language processes that rely primarily on different subcomponent cognitive processes.

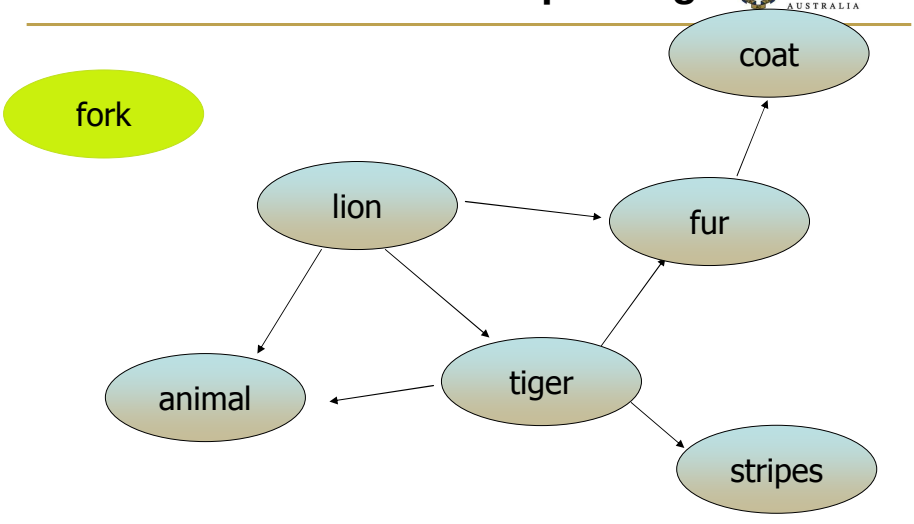
Some studies to date:

- Semantic and emotional priming and its control
- Semantic switching in a homophone generation task
- Noun and verb generation and selection from competing alternatives

Cohort characteristics.

- 18 participants with PD (13 males) and 19 controls (13 males, mean age 62.2, mean education 13.8)
- Tested at least 4 months post electrode implantation and had stable stimulator settings. Tested in on and off conditions (counterbalanced) with at least 6 weeks between testing sessions.
- For the off condition, stimulators were off for at least one hour before testing.

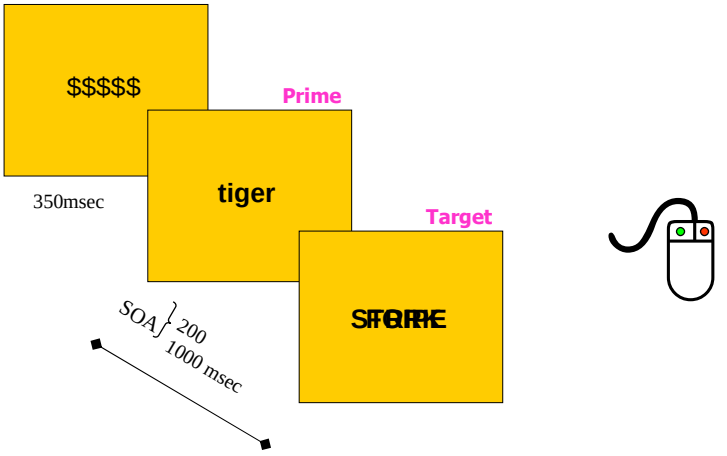
Let's talk about semantic priming



Semantic priming

- Refers to a reaction time advantage in identifying a particular word when it is preceded (or primed) by a related word.
- Can be investigated subconsciously or when other cognitive systems are active.
- Assessed via computerized tasks.

A Semantic Priming Trial



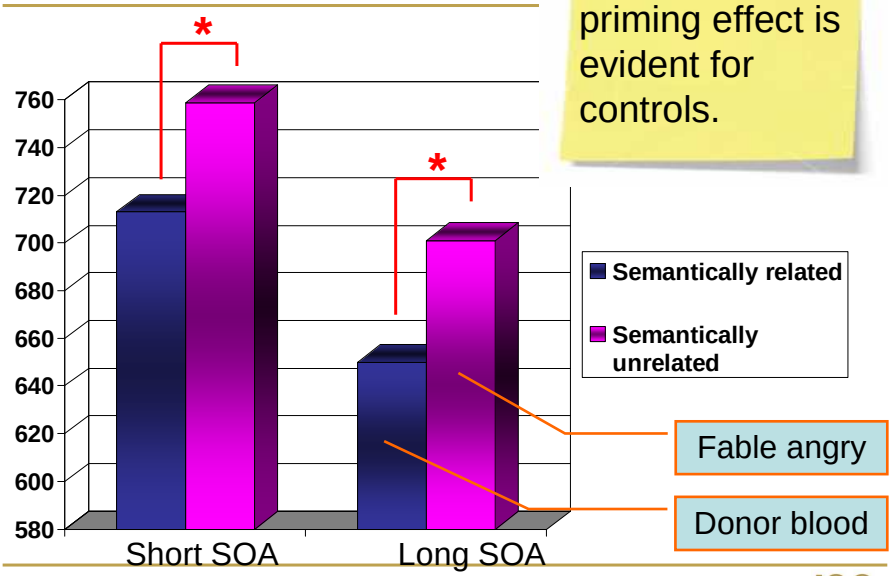
Repeated variables

Semantic relatedness

Related	Prime	Target
Yes	**donor**	**blood**
No	**fable**	**angry**

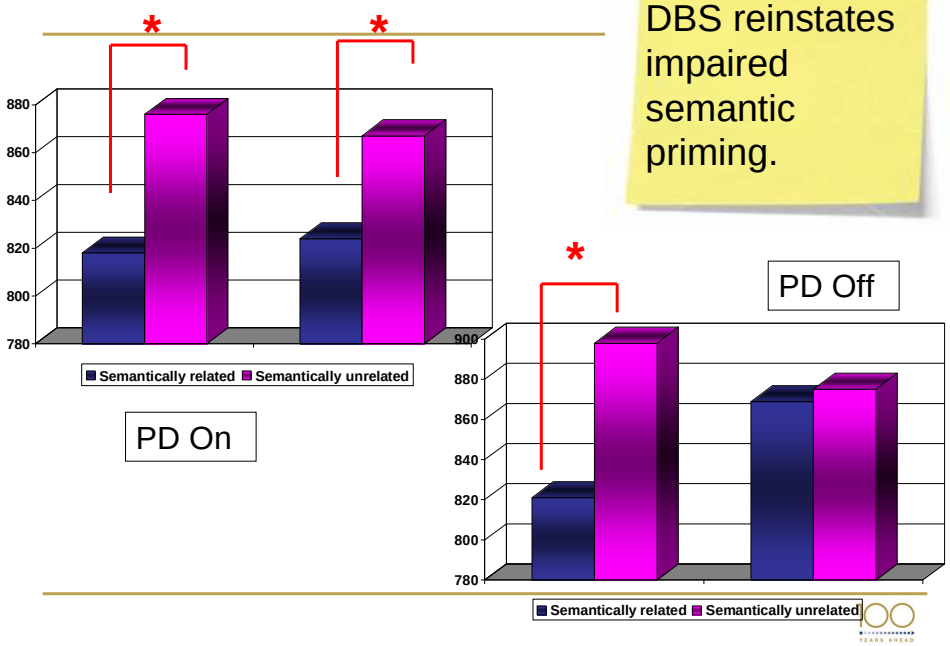
Castner et al., Brain 2007

Semantic priming – Control Group



Semantic priming effect is evident for controls.

Semantic priming – PD Group



DBS reinstates impaired semantic priming.

Imaging semantic priming

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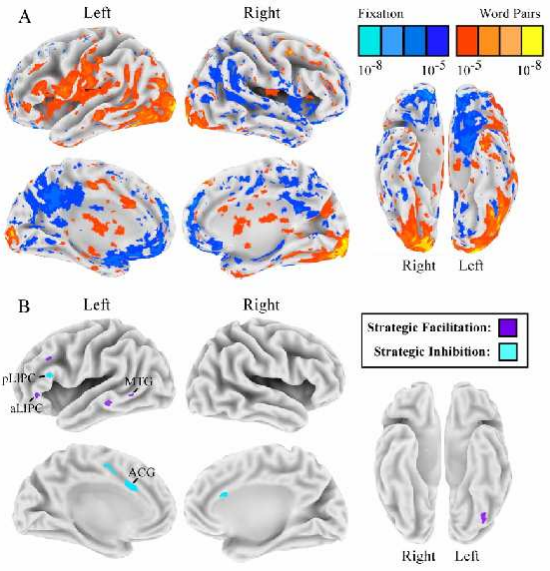

spoon

fork

Gold et al. 2006.

DBS may act to re-establish controlled semantic priming via ACC basal ganglia-thalamocortical neuromodulation.

Experiment 2

Let's revisit Paris……

Your task is to generate as many different meanings of the word "slip":

boat

fall

slip

lingerie

Homophone meaning generation

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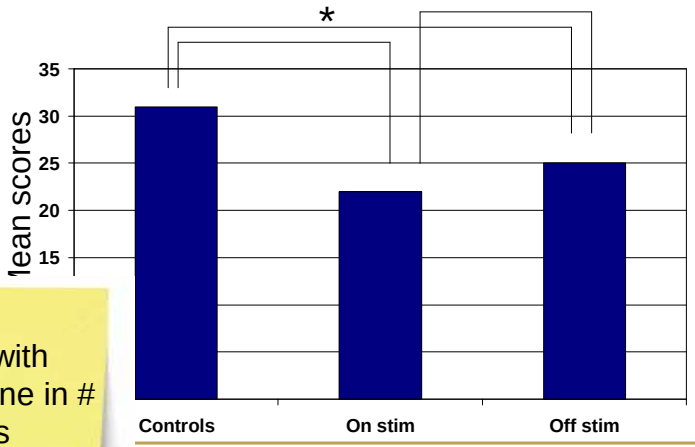
Generate as many definitions as possible for the word slip etc.



STN stim associated with overall decline in # of definitions

100 YEARS AHEAD

Imaging ambiguous words

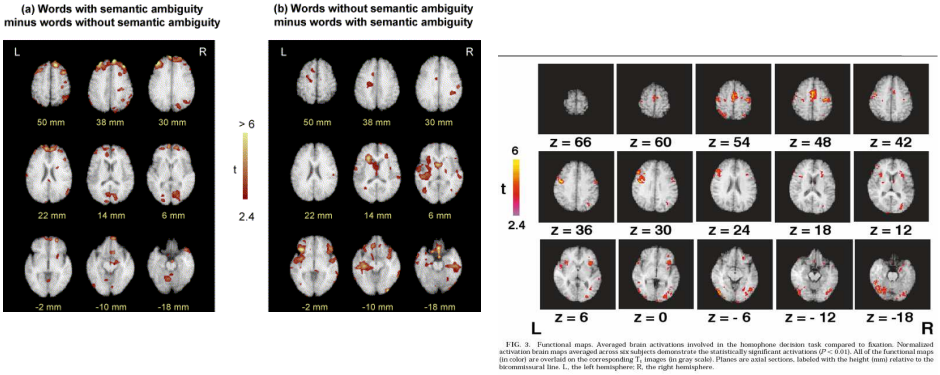


FIG. 3. Functional maps. Averaged brain activations involved in the homophone decision task compared to fixation. Normalized activation brain maps averaged across six subjects demonstrate the statistically significant activations ($P < 0.01$). All of the functional maps (in color) are overlaid on the corresponding T_1 images (in gray scale). Planes are axial sections, labeled with the height (mm) relative to the bicommissural line. L, the left hemisphere; R, the right hemisphere.

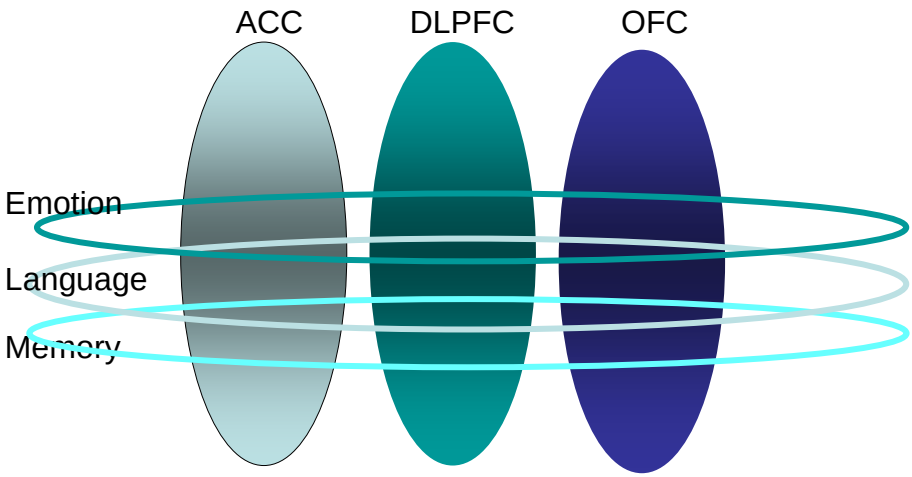
Summary: Activation in DLPFC and IFG

Conclusions

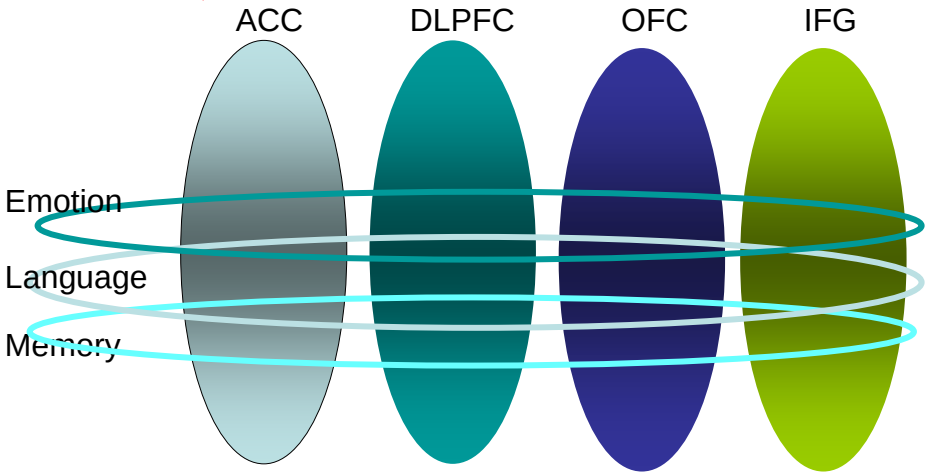
DBS may act to impair semantic switching via DLPFC basal ganglia-thalamocortical neuromodulation

But what about the IFG?

Three nonmotor circuits



Four ~~Three~~ nonmotor circuits

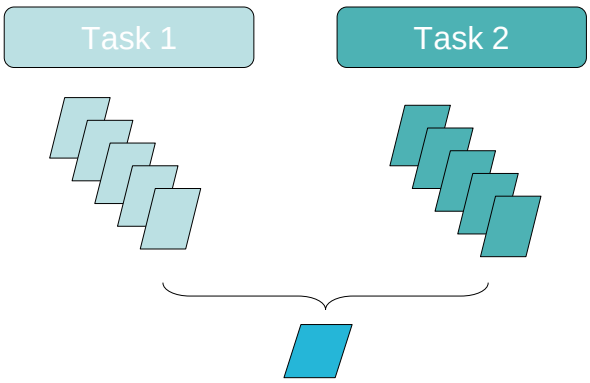


Chenery, Angwin et al., 2008

Implications and future directions.

Link imaging and investigation of component processes across cognitive domains.

Deconstruction of tasks critical to identify common substrates among tasks and across domains.



Collaborators:

Professor Peter Silburn
Dr. David Copland
Dr. Terry Coyne and Dr. Felicity Sinclair
Dr. Andrew Bradley and Dr. Paul Meehan
Dr. Joanna Castner
Professor Bruce Crosson

Thank you
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Experiment 2 Verb generation

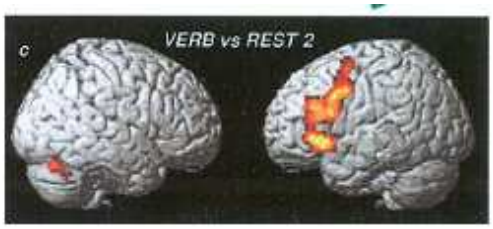
- 4 experimental conditions
- Example of one condition:
  - Given a noun and asked to respond with a semantically related verb (fork – eating)
  - Given the word “axe”
    - 87% of controls responded with ‘chopping’
    - 13% of controls said ‘cutting’
    - ➔ **high selection constraint**
  - Given the word “banana”
    - 17% of controls said ‘peeling’
    - 17% of controls said ‘eating’
    - ➔ **low selection constraint**

Verb generation

- Selection constraint was correlated with errors in this condition only for PD participants ON stimulation
  - (i.e., ⇧ errors when selecting from more competing alternatives)

Imaging verbs

In humans, producing verbs activated …..



Left Inferior, middle and superior frontal gyrus

Hamzei et al., 2003

Conclusions

DBS may act to impair selection from competing alternatives via a basal ganglia-thalamocortical neuromodulation

➔perhaps via a further nonmotor circuit not previously identified??