Deep Brain Stimulation

paper review · part II

Arseny Povolotsky

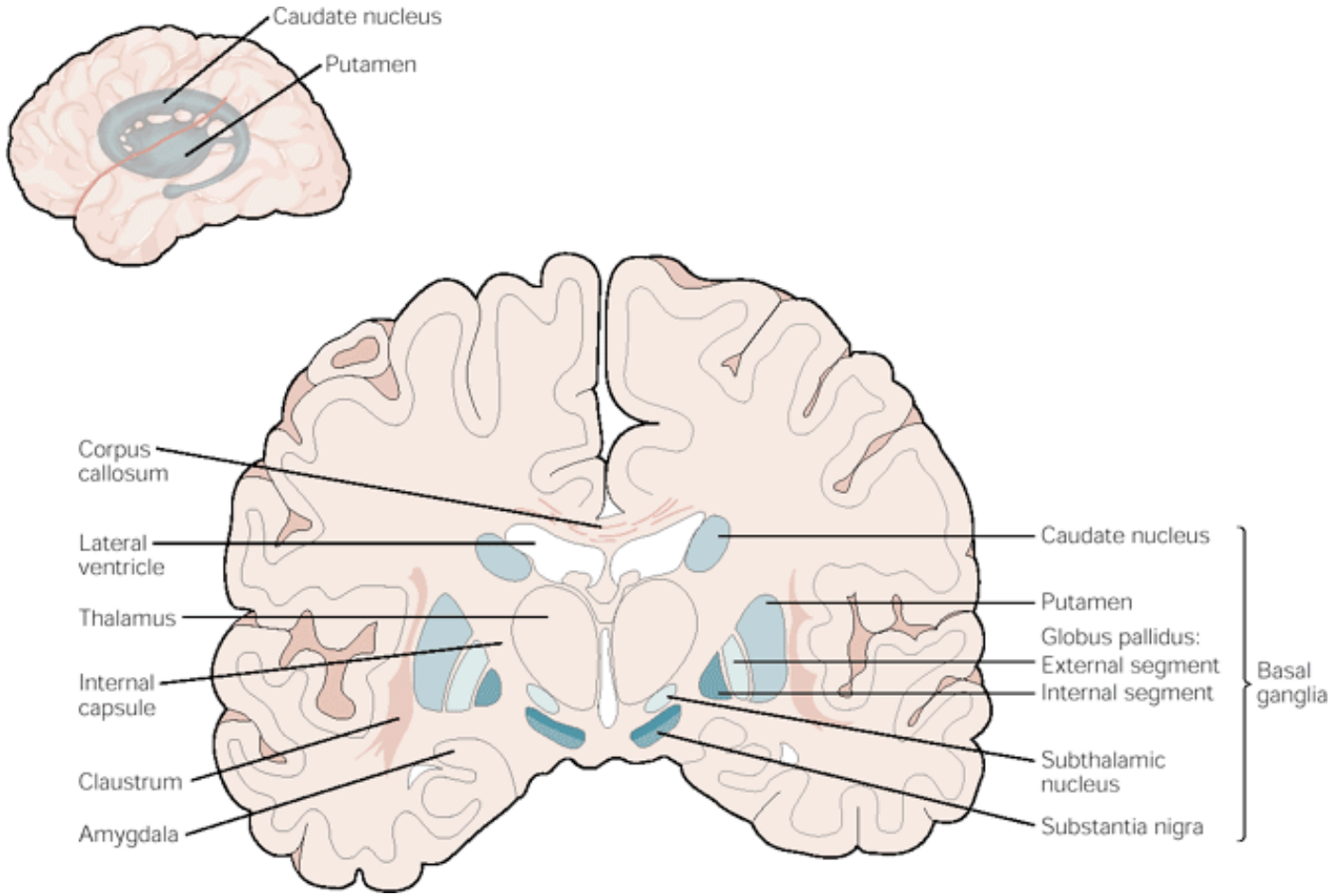
Outline

Optimal parameters

- Monopolar cathodic stimulation
- Pulse width: 60–200 μs
- Stimulus frequency: 120–180 Hz
- Stimulation amplitude: 1–5 V

Target Selection

Basal ganglia scheme



Target Selection
Globus pallidus internus

- Dramatic reduction of L-dopa induced dyskinesias
- Improvement of UPDRS[1] motor score: 30-50 %
- Levodopa dose did not change

[1] unified Parkinson's disease rating scale

Target Selection
Subthalamic nucleus

- Improvement of UPDRS motor score: 50–70%
- DBS markedly improves all cardinal symptoms of PD (akinesia, rigidity and tremor)
- Average levodopa dosage reduced by 50–65%
- Levodopa induced dyskinesias decrease
- Complete discontinuation of dopaminergic medication in 10–50% of patients

Target Selection
GPi vs STN

STN-DBS is considered superior to GPi-DBS

Better clinical results for most outcome variables

Worldwide most used target

STN is worldwide most used target for surgical therapy of PD

Adverse effects

- Surgery related
- Hardware failure
- Stimulation related
- Medication changes related

Adverse effects
Surgery related

Severe morbidities
- Intra-cranial haemorrhage
- Chronic subdural hematoma
- Venous infarction

Overall risk
1–3%

How to minimize risk?
Careful trajectory planning is mandatory

Adverse effects
Hardware failure

Possible failures
- Lead migration
- Lead extension fracture
- Short/open circuit
- Pulse generator malfunction

Overall risk
5–25%

Expertise increases
Hardware problems become less frequent

Adverse effects
Stimulation related

Acute, but reversible side effects

- dysarthria
- paraesthesia
- tonic muscle contraction
- . . .

These side effects are very useful

Acute stimulation induced dyskinesias indicates
correct placement of stimulation electrode

Mechanisms of stimulation

HFS mimics effects of ablation

However, the fundamental mechanisms of high-frequency stimulation are still not fully elucidated

Frequency is a key factor

Experimental and clinical data shows stimulation frequency represents a key factor with respect to effect of DBS

Mechanisms of stimulation

Main hypotheses

1. Inactivation of voltage dependent ion-channels
   $\Rightarrow$ depolarization blocking of neuronal transmission
2. Efferent high-frequency pattern
   $\Rightarrow$ jamming of information
3. Inhibitory afferents to the target nucleus
   $\Rightarrow$ synaptic inhibition
4. Neurotransmitter depletion
   $\Rightarrow$ synaptic failure

Theoretical models

Why do we need them?

- To help understanding the mechanism of DBS
- To predict (and thus beware of) some adverse effects

How they are built?

Simplifying assumptions:

- Finite element field of the electric field generated by electrode
- Homogenous isotropic extracellular environment
- Simplified multicompartment cable model of neuron

Theoretical models

Prediction of activation pattern

- DBS induces a complex pattern of activation and inhibition of the local cells near the electrode
- Firing of the cell body of directly stimulated neurons is not necessarily representative for their efferent output
- Stimulation-induced functional decoupling between cell body and efferent projections

Theoretical models

Prediction of the volume of tissue influenced by DBS

Why do we need them?

- DBS targets are relatively small
- Adjacent structures can induce adverse effects if co-stimulated

Major drawbacks in modeling

- Highly anisotropic medium
- Disturbances of the distribution of the electric field

Results

- Minor variations in the range of 1mm in the electrode location within STN can have substantial changes of the activation profile
- Target exploration prior to electrode implantation is needed

Neuroprotection issues

STN hyperactivity is a hallmark of PD

STN hyperactivity

$\Downarrow$

STN-mediated glutamatergic excitotoxicity on neurons of SNc

How DBS can help?

STN-DBS might reduce glutamatergic drive

$\Downarrow$

Neuroprotection effect

Summary

DBS is an important treatment option

- Marked benefits
- Minimal morbidity
  - Number of aspects are not improved

Key for successful intervention

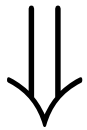
- Careful patient selection
- Precise electrode implantation

Principles of high-frequency stimulation

- Little is known
- Empirically determined parameters

Looking to the future

Extensive research needs further to be done

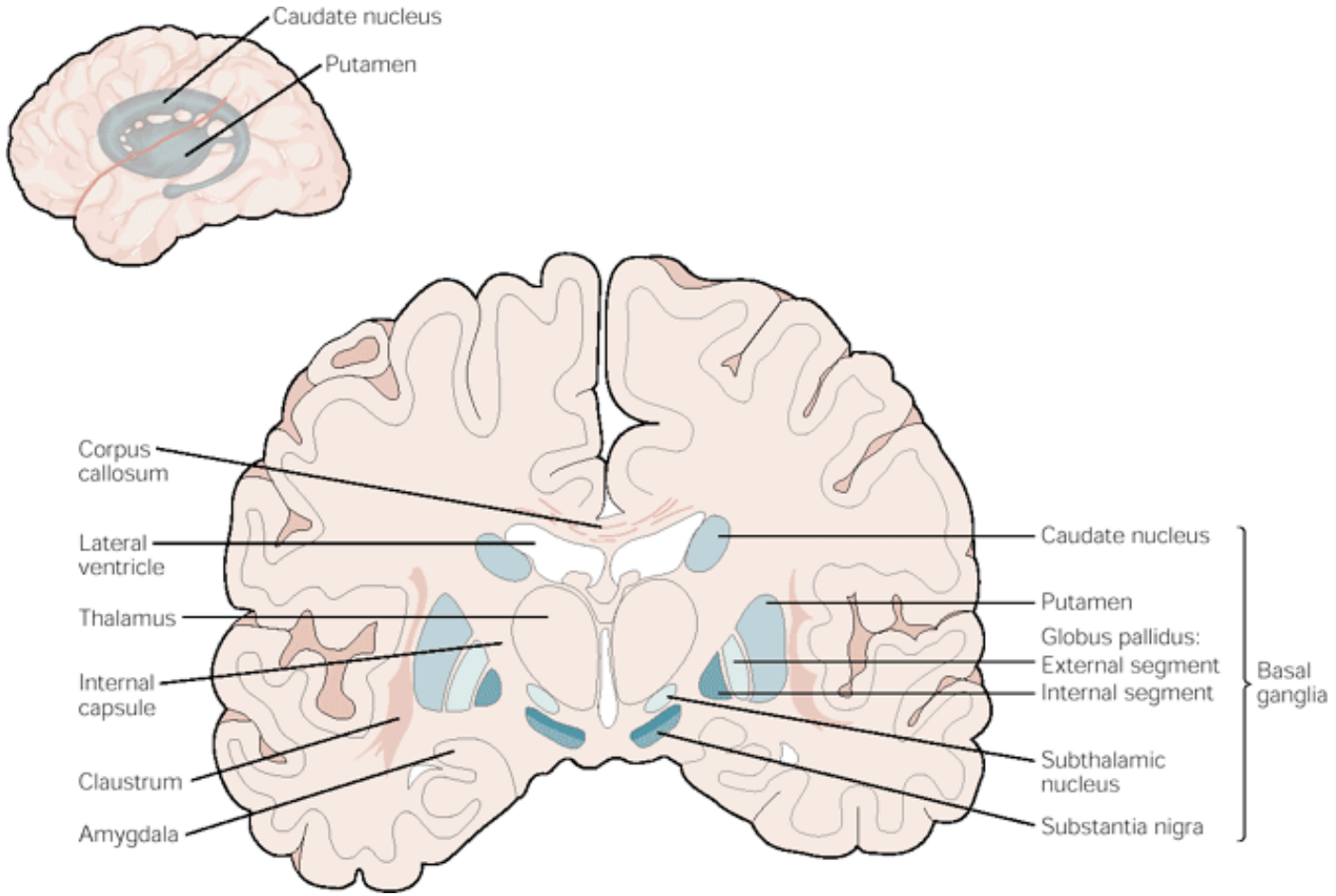


- Better understanding of disease pathophysiology
- Better target selection

- Possible applications beyond PD's treatment

Thank you!

Appendix A
Basal Ganglia



Appendix B
Glossary

Akinesia

Inability to initiate movement due to difficulty selecting and/or activating motor programs in the central nervous system.
http://en.wikipedia.org/wiki/Akinesia

Bradykinesia

Slowness in the execution of movement, a feature of a number of diseases, most notably Parkinson's disease and other disorders of the basal ganglia.
http://en.wikipedia.org/wiki/Bradykinesia

Appendix B
Glossary

Dopamine

A hormone and neurotransmitter occurring in a wide variety of animals. In the brain, dopamine functions as a neurotransmitter, activating the five types of dopamine receptor - D1, D2, D3, D4 and D5, and their variants.
http://en.wikipedia.org/wiki/Dopamine

Dyskinesia

Involuntary movements, similar to a tic or chorea. In the context of Parkinson's disease, dyskinesias are often the result of chronic levodopa (L-dopa) therapy.
http://en.wikipedia.org/wiki/Dyskinesia

Appendix B
Glossary

Excitotoxicity

Pathological process by which nerve cells are damaged and killed by glutamate and similar substances. Occurs when receptors for the excitatory neurotransmitter glutamate are overactivated.
http://en.wikipedia.org/wiki/Excitotoxicity

Glutamate

One of the 20 proteinogenic amino acids (GAA/GAC codons), the most abundant fast excitatory neurotransmitter in the mammalian nervous system.
http://en.wikipedia.org/wiki/Glutamate

Appendix B
Glossary

Levodopa

L-DOPA (3,4-dihydroxy-L-phenylalanine) is an intermediate in dopamine biosynthesis. In clinical use, levodopa is administered in the management of Parkinson's disease.
http://en.wikipedia.org/wiki/Levodopa

Neuroprotection

Mechanisms within the nervous system which protect neurons from apoptosis or degeneration.
http://en.wikipedia.org/wiki/Neuroprotection

Appendix C
Abbreviations

PD	Parkinson's disease
DBS	Deep brain stimulation
HFS	High-Frequency Stimulation
STN	SubThalamic Nucleus
GPi	Globus Pallidus internal
GPe	Globus Pallidus external
SNc	Substantia Nigra pars Compacta
Vim	Ventralis intermedius
PPN	PedunculoPontine Nucleus
UPDRS	Unified Parkinson's Disease Rating Scale