International Parkinson and Movement Disorder Society

MDS-ES Winter course
Liverpool

Deep Brain Stimulation for Dystonia

Selection criteria, adequate targeting, short and long term results

Marie Vidailhet

ICM Paris Brain Institute
Department of Neurology and Sorbonne Université
Salpêtrière Hospital, Paris, France

marie.vidailhet@aphp.fr

1

More than 20 years of literature and experience…

DBS is still a difficult decision
with evolving therapeutic strategy
and still uncertainty on therapeutic results
Including long term effects

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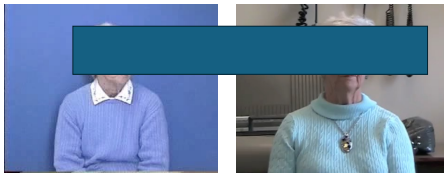
2

> 30 years of experience and 'historical " results still relevant..

Courtesy Pr Elena Moro Grenoble

Among Pionneers

Pr Pierre Pollak and Pr Benabid



Pre – operative

10 years follow-up stimulation ON (GPI bilateral)

"Precision medicine" :
DBS targeting "soft spot" and specific network

3

❖ DBS is still a difficult decision

DECISION-MAKING PROCESS

A. Clinical

Young age at onset
Shorter duration

Body distribution
limbs, neck, trunk, face

Phenomenology
Phasic movements vs tonic postures, Myoclonus

Isolated or combined dystonia
- myoclonus dystonia ++
- dystonia parkinsonism

Genetics

multidisciplinary meeting

Informed decision between doctors & patient

THERAPEUTIC STRATEGY TO MEET GOAL EXPECTATION

B. Anatomo-functional

Targeting
(GPi, STN, Thalamus)

Anatomical specificities

Connectome ?

Stimulation parameters

Adaptive stimulation ?

4

EXPECTATIONS VERSUS RESULTS

STILL SOME UNCERTAINTY

Schrodinger'cat

Therapeutic outcome

- → **Phenomenology, body distribution, target**
- → **Timing :** beneficial effects evolves over time
- → **Genetic disorders :** inter-individual differences in patients with same mutations
- → **Prediction** Still uncertainty on the amount of improvement

SINGULARITY OF EACH PATIENT
Extrinsic / intrinsic individual factors
Development / lifetime = adaptation / maladaptation
Optimal "time window"

5

Genetic factors : "the good, the bad, and the evil ?"
Body distribution may be a positive or limiting factor

A) Body distribution, example : oro-mandibular dystonia

B) Genetic specificities : example THAP1 or TUBB4

THAP1 dystonia patients with GPi DBS, median follow up 4 years, average BFMDS improvement of 49% BUT **limited improvements in speech**

Reasons for poorer and more variable DBS response in **THAP1** dystonia may be, in part, related to **prominent bulbar** (oromandibular) involvement

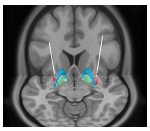
6

Limiting factor: Orofacial and speech dystonia

THAP1 mutations:
- frequently oromandibular and laryngeal dystonia
- moderate to good response on motor function **but marginal benefit on speech.**

- By curtersy orf Lubeck's team

Choreo-acanthocytosis VPS13A gene
- significant improvement of chorea dysarthria

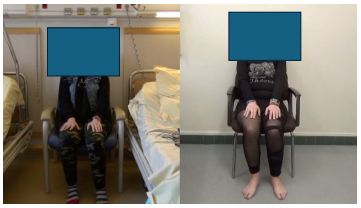


- The tips of the electrodes are located in the GP bordering the putamen bilaterally.

7

Whispering dysphonia in *TUBB4A*-related disorders responsive to bipallidal deep brain stimulation

Courtoisie
Dr Cecile Delorme
(Paris, Salpêtriere)



Gpi right 1- 60µs 130Hz 2,7V
Gpi left 9- 60µs 130Hz 2,7V

Improvement movement BFM scale 55%

Whispering dysphonia in TUBB4A-related disorders responsive to bipallidal deep brain stimulation.
Delorme C, Roze E, Karachi C, Vidailhet M, Hainque E.Eur J Neurol. 2021 Mar;28(3):1082-1083.

8

Positive factor

Good response : Cervical dystonia

> 30 years of experience and "old" results still relevant

Courtesy Pr Elena Moro Grenoble

Among Pionneers

Pr Pierre Pollak and Pr Benabid

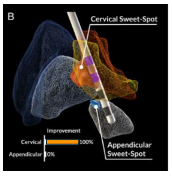
Pre – operative

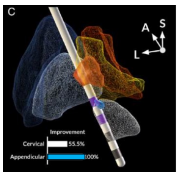
10 years follow-up stimulation ON (GPI bilateral)

Important : DBS targeting "soft spot" (Gpi) and specific network

9

Targeting : « soft spot » Optimal stimulation area associated with optimal outcome for patients





Axial versus appendicular
(neck versus limbs)

10

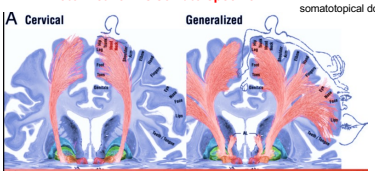
Specific networks
Tracts associated with optimal outcome for patients

motor network is somato-specific

Track from the whole somatotopical domain

Somato-specific DBS modulation

modulation of corticofugal tracts from the somatomotor head and neck region
Horn A, et al PNAS 2022



Functional connectivity

Increased functional connectivity between the neck and trunk representation (area 4 of the precentral gyrus) **and the cerebellar Vermis** (6 and 7b). Zito G, et al Parkinsonism Relat Disord 2022

11

Both GPi- and STN-DBS can effectively improve cranio-cervical motor symptoms

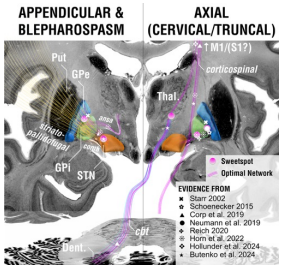
Cranio-cervical dystonia
2 non randomized cohorts:
GPi-DBS (n = 38) and STN-DBS (n = 40)

STN group, greater improvement in motor symptoms compared with the GPi group (50 % vs 34%.
the STN group showed greater improvement in the eye

Comparison of Pallidal and Subthalamic Stimulation for Cranial Cervical Dystonia: A 4-Year Follow-up Study.
Huang J, Xie H, Jiang Y et al H. Neurosurgery. 2025 Oct 9.

12

Axial (neck/ trunk) and appendicular (limbs) dystonia
Optimal therapeutic targeting and network involvement



Stimulation of the dorsolateral STN associated with improvement in limb dystonia and blepharospasm.

Engaging dystonia networks with STN stimulation. Butenko K et al. PNAS . 2025):e2417617122.

13

Optimal therapeutic targeting and network involvement for axial (neck/ trunk) and appendicular (limbs) dystonia.

Optimal treatment for **appendicular symptoms** may be achieved by modulating a network that involves the classical **basal ganglia thalamocortical loop in the sensorimotor domain.**

Optimal treatment for **axial symptoms**, such (**cervical or truncal dystonia**) , seem to be better treated by modulating projections from phylogenetically older motor areas to midbrain regions such as the **interstitial nucleus of Cajal, as well as cerebello-thalamocortical projections to the same areas.**

14

Therapeutic results
Including long term effects

15

”old ” results still relevant...
Body distribution: generalized, segmental dystonia

Progressive improvement of dystonia severity (motor score)

generalized dystonia
- by 44% at 6 months
- by 70% at 3 years and by 67% at 5 years

segmental dystonia showed a relatively stable change –54at 6 months, –60% at 3 years, –49% at 5 years,

but heterogeneous results from one patient to another

Motor improvement observed at 1 year (51%) was maintained at 3 years (58%).
Improvement in quality of life (SF-36 questionnaire) similar 1 and 3 years.

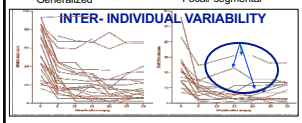
Vidailhet M et al Lancet Neurol 2007
Volkmann et al Lancet Neurol 2012

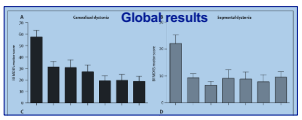
16

TIME TRAVELS IN DIVERS PACES WITH DIVERS PERSONS
William Shakespeare, *in « As you like it »*

Generalized | Focal/ segmental

INTER- INDIVIDUAL VARIABILITY





Good response as a group (> 40%)

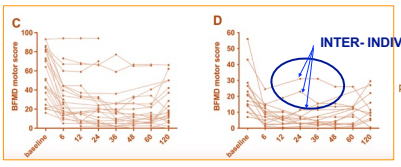
Generalized, segmental and focal dystonia
Predictive factors: young age, early DBS disease duration, disease severity

Interest of “Spaghetti plots” representation

Interest on Long term follow-up
Adverse effects
- Dysarthria
- Gait difficulties, freezing, falls
- Parkinsonism

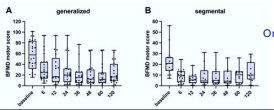
17

10 years later : ISOLATED DYSTONIA



INTER- INDIVIDUAL VARIABILITY

One-third experienced primary or secondary **treatment failure.**

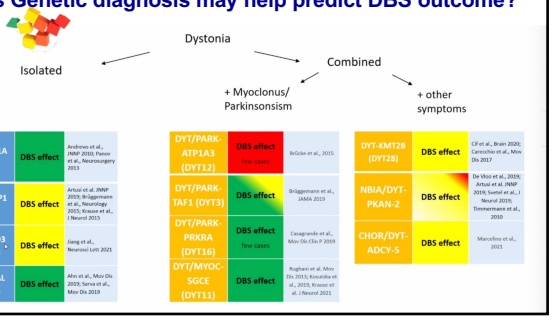


One-third experienced primary or secondary **treatment failure.**

Krause P et al Mov Disord 2025

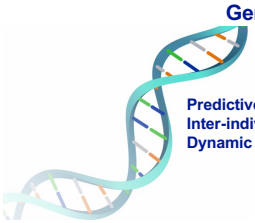
18

Does Genetic diagnosis may help predict DBS outcome?



19

Genetic factors



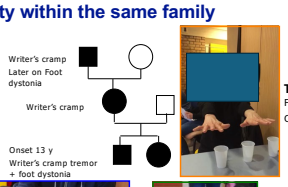
Predictive factors of therapeutic response ?
Inter-individual variabilité
Dynamic process

20

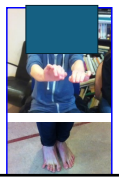
Heterogeneity within the same family

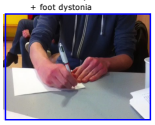
Focal segmental dystonia with Torsin A mutation (DYT1)

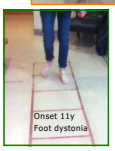
DYT1: Presenting symptom = (lower or upper) limb dystonia,
- progresses towards generalized or multifocal form (65%)
- purely segmental (10%) and focal (24%)



Torsin A mutation
Focal dystonia
Onset at adolescenc





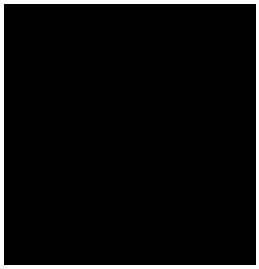


Phenotypic differences in Dyt1 between ethnic groups Neurol Neurosci Rep 2012 Beom Seok Jeon

21

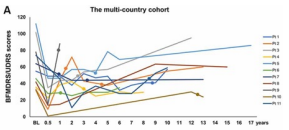
Heterogeneity between subjects with the same mutation

Torsin A



22

Heterogeneity over time : Torsin A mutation::



Individual changes of the BFMDRS-M movement scale

circles on each line indicate additional GPi or subthalamic nucleus (STN) implantations.

Tsuboi T, Cif L Front. Hum. Neurosci., 2020

Malignant'' forms

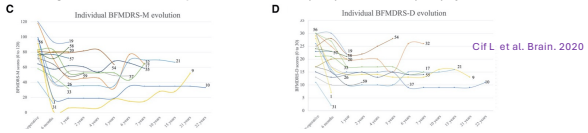
8% of patients with Torsin A mutation with a **more aggressive phenotype**

- **younger age at onset** (mean, .0 vs. 8.4 years)
- **faster disease progression** (generalization of dystonia within 2.5 years after disease onset).
- **cranial involvement**,
- associated with long-term suboptimal responses to DBS (but indistinguishable initially)
- **secondary worsening of dystonia started between 6 months and 3 years** following DBS.

23

KMT2B

The greatest BFMDRS-M improvements for trunk (53%) and cervical (50%) dystonia



Cif L et al. Brain. 2020

Individual changes over 5 years post implantation.

- **1 year follow-up**, **>50%** of subjects showed BFMDRS-M and BFMDRS-D improvement of >30%.
- **long-term >5 years**, n = 8), improvement of **>30%** in 5/8 (BFMDRS-M) and 3/8 (BFMDRS-D)
- **Improvement of gait dystonia decreased** from 20.9% at 1 year to 16.2%

at last assessment, no patient maintained a fully independent gait.

24

Dynamic process but Unknown mechanisms
Example : myoclonus dystonia

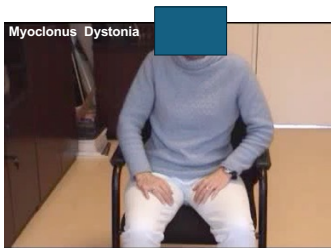
Epsilon sarcoglycan gene : **remission of myoclonus and dystonia after** > 10 years Gpi DBS.

KCNN2 gene : 38-year-old female with severe dystonic and myoclonic symptoms

Bilateral DBS targeting the internal segment of the globus pallidus (GPi) resulted **in marked and sustained symptom improvement,** notably reducing dystonic posturing and myoclonic movements over the 24-month follow-up period.

25

Myoclonus dystonia : Diagnosis and therapeutic options



Onset in childhood or adolescence
- Almost always < 20 years
- Median age at onset = 6 years

Myoclonus > dystonia
- can be present at rest (70%)
- increases with posturing and action (95%)
- predominates in the upper body (90%)

Non motor: anxiety, depression, OCD

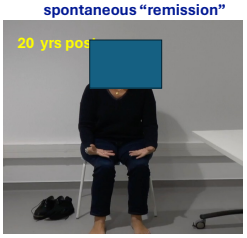
Roze E Current Opinion Neurology 2019

Mutation or deletion within the SGCE gene

account for about 40-50% of myclonus-dystonia patients

26

No more DBS (GPi) stimulation (removed) - spontaneous "remission"



Myoclonus dystonia SCGE mutation

Roze E, et al Mov Disord. 2015
Kosutzka Z et al Mov Disord. 2019

27

Parkinsonism …

***AOPEP* (also known as *C9orf3*).**

Recessive isolated-dystonia syndrome.
from childhood to late adulthood (sixth decade of life),

Biallelic AOPEP Loss-of-Function Variants Cause Progressive Dystonia with prominent Limb Involvement. Zech et al. Mov Disord 2022

20 years post-bilateral GPI-DBS:
Freezing of gait, postural instability, and hypokinesia

DAT scan : Dopaminergic denervation
Poorly improved by L-Dopa

Dystonia improvement with bilateral pallidal stimulation

28

CONCLUSIONS / PERSPECTIVES

The end of the beginning…

More than 20 years of literature and experience
"anatomo-functional" signature of dystonia (connectome)

Dynamic process: therapeutic response to DBS
evolution over time (inter- individual differences)
"remission" (myoclonus dystonia)
from hyperkinetic to hypokinetic (parkinsonism)

29

30