

## BACKGROUND

- ❖ Tolerance to deep brain stimulation (DBS) can be described as
  1. tremor rebound with a temporary increase of tremor intensity over the preoperative state after switching off DBS (Kronenburger 2006),
  2. habituation, which is the loss of sustained tremor control over a short duration of follow-up (Barbe 2011), or
  3. late therapy failure that may occur after at least one year of satisfactory control of tremor with DBS (Pilitsis 2008).
- ❖ Causes not completely understood. Theories include:
  - Natural disease progression
  - Inadequate electrode location
  - Resolution of microthalamotomy effects from surgery
  - Adaptation of neural networks to chronic localized stimulation (Barbe 2011).
- ❖ Existing research shows:
  - 13-40% of patients with essential tremor (ET) implanted in the thalamus (ViM) develop tolerance, despite proper lead placement (Pilitsis et al, 2008).
  - A prospective studies found 73% of ET patients experienced waning benefit of stimulation, as early as 3months following implantation (Shih et al, 2013)
  - Loss of acute benefit from programming in 54% of electrodes in ET patients with ViM stimulation by 10 weeks (Barbe et al, 2011)
  - Rebound is described in ET and Parkinson's disease (PD) (Hariz 1999) but is not well-characterized.

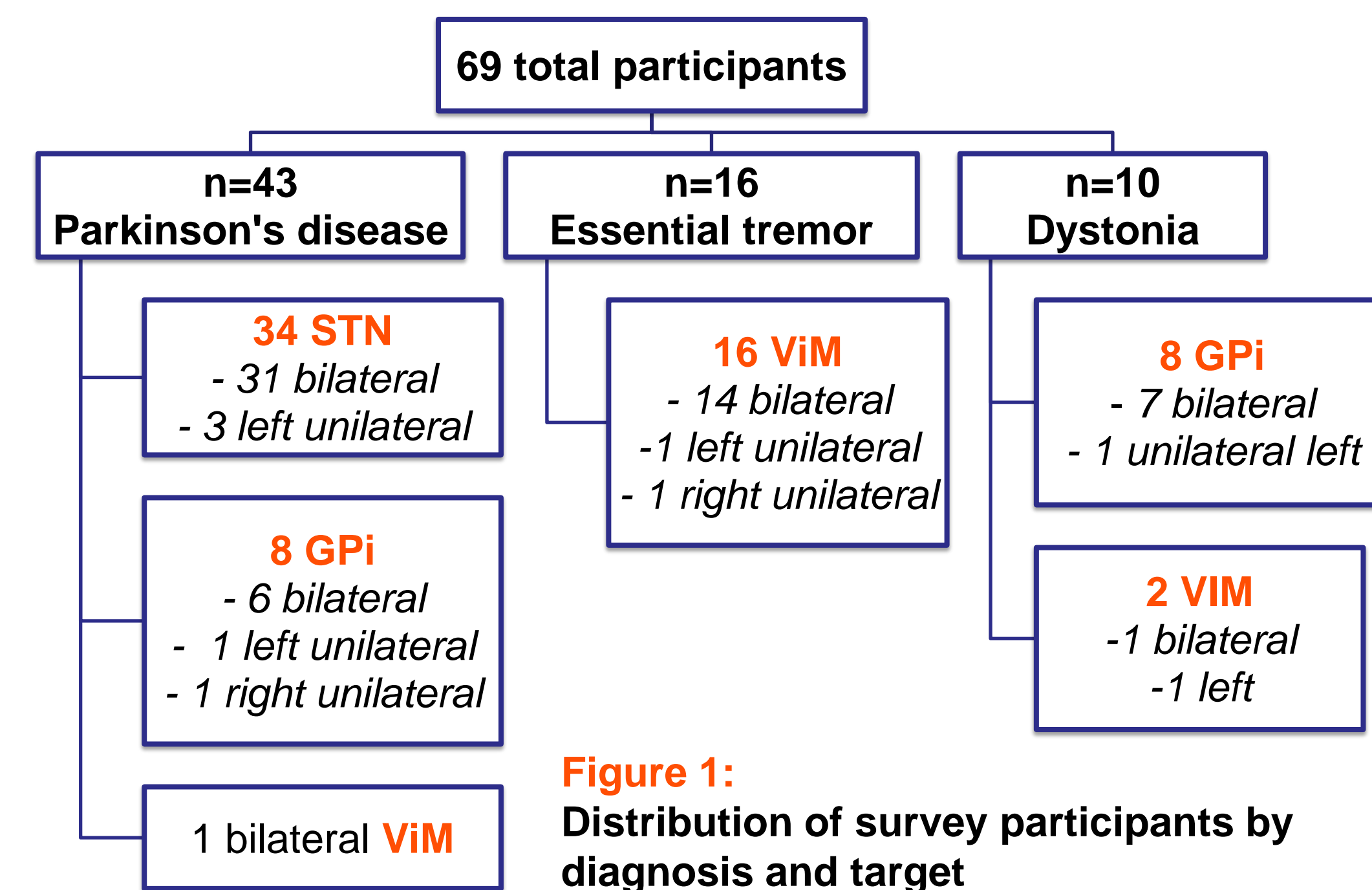
❖ **Objective: To determine factors and characteristics associated with development of tolerance to DBS across disease states and targets.**

## METHODS

- ❖ Prospective questionnaire study with retrospective chart review in a 3-month cross-sectional population of a tertiary Movement Disorders Center
- ❖ Inclusion criteria:
  - > 18 years old
  - diagnosis of ET, PD, or dystonia as determined by a movement disorders specialist,
  - lead implantation in the ViM, globus pallidus interna (GPi), or the subthalamic nucleus (STN)
- ❖ Exclusion criteria
  - Stimulator in place < 6 months
- ❖ Prospective evaluation included a Clinician-administered survey either in person or by phone consisting of 8-items:
  - whether the patient experienced habituation or rebound,
  - patient rating of their symptom control
  - patient satisfaction with the treatment
  - a patient-rated version of the Clinical Global Impression Scale compared the positive effects of the DBS with the effects of losing the benefit of an adjustment
- ❖ Retrospective chart review to identify diagnosis, disease onset, stimulator placement date, target and laterality for all patients who agreed to complete surveys

- ❖ Information was extracted to a database for analysis. Statistical methods included **2-tailed Fisher's exact test** to compare incidence of tolerance across disease states and targets, **Mann Whitney U** to compare self-report measures in patients with and without tolerance, **Kruskal-Wallis** and **ANOVA\*** to compare self-report measures among those experiencing tolerance across disease states and targets, and **2-tailed t-test\*** to compare patient characteristics.

## RESULTS



**Figure 1:** Distribution of survey participants by diagnosis and target

**Table 1: Patient Characteristics**

|   | ViM                            | STN            | GPi                  |
|---|--------------------------------|----------------|----------------------|
| <b>Gender</b>                               | M: 14<br>F: 5                  | M: 20<br>F: 14 | M: 5<br>F: 11        |
| <b>Current Average Age</b>                  | 70 years                       | 64 years       | 61 years             |
| <b>Disease treated by DBS</b>               | ET: 17<br>PD: 1<br>Dystonia: 1 | PD: 34         | PD: 8<br>Dystonia: 8 |
| <b>Average Disease duration</b>             | 33 years                       | 15 years       | 19 years             |
| <b>Average Duration of DBS implantation</b> | 5 years                        | 5 years        | 5 years              |
| <b>N Bilateral</b>                          | 16                             | 31             | 13                   |

**Table 2: Characteristics of patients experiencing habituation**

| Target           | Mean age (years) at time of survey |        |     | Mean disease duration (years) at time of survey |        |     | Mean time (years) since DBS at time of survey |        |     |
|------------------|------------------------------------|--------|-----|---|--------|-----|---|--------|-----|
|                  | +habit                             | -habit | P   | +habit  | -habit | P   | +habit  | -habit | P   |
| <b>ViM (n=9)</b> | 68.2                               | 74.6   | 0.2 | 32.9  | 39.3   | 0.4 | 4.6   | 6.1    | 0.5 |
| <b>STN (n=7)</b> | 62.3                               | 64.2   | 0.6 | 14.6  | 15.1   | 0.8 | 4.7   | 4.6    | 0.9 |
| <b>GPi (n=3)</b> | 56                                 | 62.2   | 0.3 | 21.3  | 17.8   | 0.5 | 7.3   | 3.9    | 0.2 |

**Table 3: Characteristics of patients experiencing rebound**

| Target            | Mean age (years) at time of survey |          |     | Mean disease duration (years) at time of survey |          |     | Mean time (years) since DBS at time of survey |          |     |
|-------------------|------------------------------------|----------|-----|---|----------|-----|---|----------|-----|
|                   | +rebound                           | -rebound | P   | +rebound  | -rebound | P   | +rebound                                      | -rebound | P   |
| <b>ViM (n=10)</b> | 68.8                               | 71.9     | 0.5 | 34.3  | 32       | 0.8 | 6.1   | 4.4      | 0.4 |
| <b>STN (n=11)</b> | 62.6                               | 64.3     | 0.6 | 15.5  | 14.8     | 0.7 | 5   | 4.5      | 0.6 |
| <b>GPi (n=1)</b>  | 66                                 | 60.7     | 0.6 | 17  | 18.6     | 0.9 | 3   | 4.7      | 0.7 |

**Table 4: Patient self-report measures on efficacy, satisfaction, and global impression of change with DBS in patients reporting habituation by stimulator target**

|            | Overall efficacy of DBS |        |        | Overall satisfaction with DBS |        |              | Patient global impression of change |        |               |
|------------|-------------------------|--------|--------|-------------------------------|--------|--------------|-------------------------------------|--------|---------------|
|            | +habit                  | -habit | P      | +habit                        | -habit | P            | +habit                              | -habit | P             |
| <b>ViM</b> | 3                       | 1.4    | 0.0601 | 5.1                           | 6.8    | <b>0.012</b> | 6.8                                 | 2.4    | <b>0.0048</b> |
| <b>STN</b> | 3.1                     | 1.5    | 0.067  | 5                             | 6.5    | 0.12         | 8                                   | 2.8    | <b>0.0027</b> |
| <b>GPi</b> | 1.7                     | 1.4    | 0.41*  | 6.3                           | 6.5    | 0.85*        | 5.3                                 | 2.2    | <b>0.036*</b> |
| <b>K-W</b> | 0.722                   |        |        | 0.654                         |        |              | 0.811                               |        |               |

**Table 5: Patient self-report measures on efficacy, satisfaction, and global impression of change with DBS in patients reporting rebound by stimulator target**

|               | Overall efficacy of DBS |          |             | Overall satisfaction with DBS |          |       | Patient global impression of change |          |              |
|---------------|-------------------------|----------|-------------|-------------------------------|----------|-------|-------------------------------------|----------|--------------|
|               | +rebound                | -rebound | P           | +rebound                      | -rebound | P     | +rebound                            | -rebound | P            |
| <b>ViM</b>    | 2.8                     | 1.4      | 0.142       | 5.4                           | 6.7      | 0.112 | 6.2                                 | 2.6      | <b>0.013</b> |
| <b>STN</b>    | 2.3                     | 1.6      | <b>0.01</b> | 5.8                           | 6.3      | 0.087 | 4.8                                 | 3.4      | 0.162        |
| <b>GPi</b>    | 1                       | 1.5      | 0.4*        | 6                             | 6.5      | 0.67* | 1                                   | 2.9      | 0.45*        |
| <b>ANOVA*</b> | 0.6*                    |          |             | 0.8*                          |          |       | 0.4*                                |          |              |

❖ 27.5% (n = 19) reported symptoms of habituation

❖ Analysis by target:

- 20.6% (n = 7) STN
- 47.4% (n = 9) ViM
- 18.8% (n = 3) GPi (P = 0.103)\*

❖ Analysis by disease state:

- 20.9% (n = 9) PD
- 50% (n = 8) ET
- 20% (n = 2) dystonia (P = 0.107)\*

\*2-tailed Fisher's exact test

❖ 31.9% (n = 22) reported symptoms of rebound

❖ Analysis by target:

- 32.3% (n = 11) STN
- 52.6% (n = 10) ViM
- 6.3% (n = 1) GPi (P = 0.011)\*

❖ Analysis by disease state:

- 25.6% (n = 11) PD
- 56.3% (n = 9) ET
- 20% (n = 2) dystonia (P = 0.064)\*

\*2-tailed Fisher's exact test

\*Because of small sample size for GPi and Dystonia patients, a parametric approach (t-test, ANOVA) was used for analysis instead of a nonparametric approach (Mann Whitney U, Kruskal-Willis).

## CONCLUSIONS

- ❖ Presence of habituation and rebound should be considered when performing clinical evaluations on any patient treated with DBS.
  - tolerance to stimulation is not unique to ViM stimulation or ET, though it may be more common in this target and this disease.
  - Factors such as age, disease duration, and duration of DBS therapy do not appear to play a significant role.
  - recurrent symptoms other than tremor (e.g. bradykinesia, rigidity, dystonia) may be experienced.
- ❖ Tolerance to DBS influences patient perceptions of DBS efficacy and satisfaction
  - Patients experiencing habituation generally seemed to have significantly lower self-reported efficacy of DBS and significantly lesser satisfaction with DBS therapy than those who did not experience habituation.
  - Rebound symptoms led to significantly lower satisfaction and PGI in the ViM group, but did not differ by disease state
    - ✓ However, rebound itself may be a less-recognized phenomenon (by both patients and clinicians) since most patients leave DBS therapy on all the time.
- ❖ A unique finding in our survey study was the laterality experienced by multiple patients implanted bilaterally.
  - 80% of patients implanted bilaterally who experienced worse tolerance unilaterally did so on the left side.
  - No direct association between handedness and laterality was found.
- ❖ Study limitations: retrospective nature, lack of objective assessments to confirm patient reports of tolerance, and small sample size, especially among dystonia patients.
- ❖ Further, prospective studies, including larger Ns of dystonia patients and investigations into laterality of tolerance symptoms, are warranted.

## REFERENCES

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