



# Effect of constant-current pallidal deep brain stimulation for primary dystonia on cognition, mood and quality of life: Results from a prospective pilot trial

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## ABSTRACT

**Objective:** Knowledge on the effects of DBS on cognitive functions is limited and no data exists on the effects of constant-current DBS (CC-GPi-DBS), which appears to prevail over constant-voltage stimulation. Our aim was to prospectively assess the effect of Constant-Current-GPi-DBS, using an 8-contact lead, on cognition, mood and quality of life.

**Patients and Methods:** Ten patients aged 27–49 underwent prospective neuropsychological assessment using dedicated tests. Various cognitive domains (intelligence, executive functions, memory, attention, visuo-spatial perception, verbal intelligence) as well as emotional state and quality of life were examined preoperatively and 1, 6 and 12 months after continuous constant-current DBS.

**Results:** Patients performed preoperatively below average on information processing speed, phonemic verbal fluency and working memory. At 6-months there was an improvement in phonemic verbal fluency ( $p < .05$ ), which was retained at 12-months postoperatively ( $p = .05$ ). Results also showed marginal improvement in the Trail Making-A test ( $p = .051$ ) and the Stroop colour-word test ( $p < .05$ ). Despite improvement in Quality of Life (Physical and Mental Component improved by 32.42% and 29.46% respectively), patients showed no discernible change in anxiety and depression status.

**Conclusions:** CC-GPi-DBS for primary dystonia has no discernible negative impact on cognition and mood. If anything, we noted an improvement of certain cognitive functions.

## 1. Introduction

Dystonia is an extrapyramidal hyperkinetic motor syndrome with a wide phenotypical variety, characterized by sustained muscle contractions and abnormal postures. [1] Deep-Brain Stimulation (DBS) of the Globus pallidus internus (GPI) has emerged as a safe and reversible treatment for various forms of dystonia [2]. Our study population was treated with a novel 8-contact lead, using continuous constant-current (CC) stimulation. This “octrode” lead has 8 stimulation contacts and has the advantage of being able to facilitate the double number of possible stimulation sites in the same overall area as the commonly used four-contact leads. At the

same time, Constant-Current stimulation may provide a more “unwavering” electrical field than Constant-Voltage (CV) stimulation, which has been the mainstay of treatment so far. This may in turn enable superior control of the spread of the electrical stimulation [3].

The effect and safety of GPI-DBS for dystonia in respect to cognition has been shown in a limited number of case series. [4–9] All these studies have utilized *Constant-Voltage* stimulation with the common four-contact lead. In this study, we present the effect of *Constant-Current* GPI-DBS, using an 8-contact lead, on cognition, mood and quality of life during a one-year follow-up.

**Abbreviations:** DBS, Deep Brain Stimulation; CC, Constant Current; GPI, Globus Pallidus internus; CV, Constant Voltage; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; UDRS, Unified Dystonia Rating Scale; GDS, Global Dystonia Scale; TWSTRS, Toronto Western Spasmodic Torticollis Scale; CGI, Global Impression Scale; MMSE, Mini-Mental State; QoL, Quality of Life; VAS, Visual Analog Scale; ADHD, Attention Deficit Hyperactivity Disorder; VFT, Verbal Fluency Tasks; TMT, Trail Making Test; BSAT, Brixton Spatial Anticipation test; WAIS, Wechsler Adult Intelligence Scales; RBMT, Rivermead Behavioral Memory Test; BDI, Beck Depression Inventory

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## 2. Patients and methods

### 2.1. Procedure and clinical outcome measures

The here described neuropsychological evaluation was an ancillary part of the primary pilot trial. A detailed description of the parent study can be found elsewhere. [3] In short, 10 patients (6 females and 4 males, mean age  $35.8 \pm 9.2$  years) with medically refractory primary dystonia were selected for constant-current DBS of the posteroventral GPi using a novel 8-contact (octrode) lead. The majority (8/10) suffered from generalized dystonia, 1 from segmental dystonia and 1 patient from focal dystonia. Mean age of onset was  $18.5 \pm 9.1$  years and a mean disease duration of 17.3 years. Except for one patient suffering from hemidystonia who received unilateral electrodes, all other patients were implanted bilaterally.

Postsurgical testing was conducted while patients were on continuous constant-current stimulation, with DBS parameters being optimized for each patient up until month 12 (Mean settings at month 12: Amplitude: 2.54 mA, Pulse Width: 205.5 $\mu$ sec, Frequency: 137.8 Hz). Patients were evaluated on their medications, which remained unchanged for the entire duration of the study. The clinical efficacy of DBS was evaluated with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), the Unified Dystonia Rating Scale (UDRS), the Global Dystonia Scale (GDS) and the Toronto Western Spasmodic Torticollis Scale (TWSTRS), when applicable. The Clinical Global Impression Scale (CGI) was utilized to evaluate the overall clinical severity and improvement after surgery. A gross assessment of the general level of cognitive ability was performed during the preoperative screening with the Mini-Mental State Examination (MMSE), as it was part of the study inclusion/exclusion criteria. Quality of Life (QoL) was measured with the RAND Short Form 36 (SF-36) and pain with the Visual Analog Scale (VAS).

### 2.2. Neuropsychological measures

A comprehensive paper-and-pencil neuropsychological assessment of intelligence, memory, attention, visuo-spatial perception, executive functions, and emotional state was performed prior to surgical electrode implantation as well as 1, 6, and 12 months post-operatively. Each patient was evaluated by one of two licensed neuropsychologists (EL and EA). Some of the tests were complementary and specifically selected because they do not require a verbal response.

#### 2.2.1. Executive functions

The Brown Attention Deficit Hyperactivity Disorder self-rated scales were used to assess patients' subjective perceptions of organizing and prioritizing (Brown-ADHD Organization), focusing, sustaining and shifting attention to tasks (Brown-ADHD Attention), sustaining effort (Brown-ADHD Effort), utilizing working memory (Brown-ADHD Memory) and managing frustration and modulating emotions (Brown-ADHD Affect). Tests of executive functions included the Stroop test (reading word, reading colour names in black and naming colour of word-different), the phonemic and semantic Verbal Fluency Tasks (VFT), the Trail Making Test (TMT-A: connect points marked with consecutive numbers and TMT-B: connect consecutive numbers alternating with consecutive letters of the alphabet) and the Brixton Spatial Anticipation test (BSAT) for detecting and following game rules. The BSAT is perceptually simple and does not require a verbal response; as such, it is suitable for patients with an impaired motor aspect of speech production.

#### 2.2.2. Intelligence

The "Vocabulary" and "Matrix Reasoning" subsets of the Wechsler Adult Intelligence Scales (WAIS-III) were used as measures of crystallized and fluid intelligence. The Raven's Advanced Progressive Matrices (Set I) were also included as measures of fluid intelligence i.e. the

capacity to reason and solve novel problems without any knowledge from the past.

#### 2.2.3. Memory

The Digit Span (Forward & Backward) test from the WAIS-III battery was used to evaluate verbal short-term / working memory, and the Rivermead Behavioral Memory Test (RBMT-E, a battery including multiple tests) was applied to assess verbal, visual, and visuospatial learning.

#### 2.2.4. Personality and mood

Self-rated mood and psychiatric state were evaluated with the Greek version of the Beck Depression Inventory (BDI). [10] The intensity and individual differences of how frequently anxiety, anger, depression and curiosity are experienced as personality traits were appraised using the trait form of the State-Trait Personality Inventory.

### 2.3. Data analysis

Statistical analyses were performed with the SPSS software package (IBM SPSS Statistics for Windows, version 21, IBM Corp., Armonk, N.Y., USA). Differences in raw scores across time points for mood and neuropsychological tests were assessed using the nonparametric Friedman test for repeated measures, followed by post hoc comparisons with the Wilcoxon signed-rank test when the Friedman test showed an overall effect of time. Due to the small sample size, we used raw scores rather than standard scores, because they show more variation across observations and increase statistical power. The results were considered significant if  $p < 0.05$ . Given the small sample size inherent in a pilot study, post hoc tests were not corrected for multiple comparisons, so results should be interpreted with caution. The neuropsychological and mood scores after 1, 6 and 12 months of stimulation were compared with the preoperative scores with the Wilcoxon signed-rank test. In addition, we calculated non parametric Spearman's correlations between education, duration of symptoms and neuropsychological measures.

## 3. Results

At the Month 12 assessment, 6 patients (60%) were responders with 5 of those patients having sustained the response achieved at the Month 6 assessment. At one year the relevant scores were 14.25 for BFMDRS, 16.3 for UDRS and 15.9 for GDS, representing an improvement of 54%, 55.2% and 48.9% respectively. Nearly 84% of the overall improvement occurred by the end of first month after stimulation-onset, thus documenting an early response to treatment. Axial symptoms responded the best. In regard to Quality of Life, the Physical Health scale and Mental Health scales showed equivalent improvements from baseline, a mean of 30.54% and 33.12% at Month 6, which was sustained by the Month 12 Visit, means of 32.42% and 29.46% respectively. An analytical report can be found in our previous publication. [3]

### 3.1. Preoperative results

As a group, patients performed at baseline (prior to surgery) below average on tasks of information processing speed (TMT-A: 692 and TMT-B: 1192), phonemic verbal fluency (24,6, SD: 144) and working memory (WAIS digit span: 131). Non-parametric Spearman's calculations between education, duration of symptoms and neuropsychological outcomes showed that the duration of symptoms was positively correlated with the outcome of the Trail Making-B Test ( $r = 0.803$ ,  $p < 0.01$ ), and negatively correlated with the Stroop word test ( $-0.929$ ,  $p < 0.01$ ), Stroop colour test ( $-0.970$ ,  $p < 0.01$ ), and Stroop colour-word test ( $-0.826$ ,  $p = < 0.01$ ). Moreover, years of education were positively correlated with phonemic verbal fluency ( $r = 0.692$ ,  $p < 0.05$ ) with semantic verbal fluency ( $r = 0.829$ ,  $p < 0.01$ ) with the Stroop

**Table 1**  
 Presurgical and postsurgical scores for executive functions, intelligence, memory and mood.

|                                   | Pre-surgery  |              | 1 month post-surgery |              | 6 months post-surgery |              | Pre vs 1 month post-surgery comparison |          | 1 month post-surgery |             | 6 months post-surgery |            | Pre vs 6 months post-surgery |          | 12 months post-surgery |             | Pre vs 12 months post-surgery |            |          |
|-----------------------------------|--------------|--------------|----------------------|--------------|-----------------------|--------------|--|----------|----------------------|-------------|-----------------------|------------|------------------------------|----------|------------------------|-------------|-------------------------------|------------|----------|
|                                   | Mean (SD)    | (SD)         | Mean (SD)            | (SD)         | Mean (SD)             | (SD)         | p-values                               | p-values | Mean (SD)            | (SD)        | Mean (SD)             | (SD)       | p-values                     | p-values | Mean (SD)              | (SD)        | Mean (SD)                     | (SD)       | p-values |
| <b>EXECUTIVE FUNCTIONS</b>        |              |              |                      |              |                       |              |  |          |                      |             |                       |            |                              |          |                        |             |                               |            |          |
| Brown ADHD Organization Attention | 24.4(16.5)   | 24.4(16.5)   | 35.5 (22.5)          | 35.5 (22.5)  | 33.4(23.1)            | 33.4(23.1)   | .123                                   | .123     | 36.0 (16.6)          | 36.0 (16.6) | —                     | —          | n/a                          | n/a      | 38.5 (12.6)            | 38.5 (12.6) | 40.3(17.3)                    | 40.3(17.3) | .500     |
| Brown ADHD Effort                 | 5.5(4.8)     | 5.5(4.8)     | 7.0 (6.4)            | 7.0 (6.4)    | 7.3 (6.6)             | 7.3 (6.6)    | .343                                   | .343     | 12.9 (6.9)           | 12.9 (6.9)  | —                     | —          | n/a                          | n/a      | 12.7 (5.7)             | 12.7 (5.7)  | 16.6(5.9)                     | 16.6(5.9)  | .715     |
| Brown ADHD                        | 5.7 (4.7)    | 5.7 (4.7)    | 8.8(5.9)             | 8.8(5.9)     | 7.8 (5.9)             | 7.8 (5.9)    | .155                                   | .155     | 8.0 (1.4)            | 8.0 (1.4)   | —                     | —          | n/a                          | n/a      | 7.3 (3.3)              | 7.3 (3.3)   | 10(1)                         | 10(1)      | .066     |
| Brown ADHD Effort                 | 6.4 (4.2)    | 6.4 (4.2)    | 8.5(5.3)             | 8.5(5.3)     | 7.0 (4.7)             | 7.0 (4.7)    | .231                                   | .231     | 13.1 (4.3)           | 13.1 (4.3)  | 12.4(3.5)             | 12.4(3.5)  | .337                         | .337     | 13.7 (3.7)             | 13.7 (3.7)  | 14.4(3.5)                     | 14.4(3.5)  | .832     |
| Brown ADHD Affect Memory          | 4.7 (3.8)    | 4.7 (3.8)    | 5.9 (2.9)            | 5.9 (2.9)    | 6.4 (4.9)             | 6.4 (4.9)    | .129                                   | .129     | 9.1 (3.9)            | 9.1 (3.9)   | 7.8.1(2.1)            | 7.8.1(2.1) | .249                         | .249     | 8.1 (3.6)              | 8.1 (3.6)   | 7.6(2.7)                      | 7.6(2.7)   | .068     |
| COWAT Phonemic (total)            | 24.6 (14.4)  | 24.6 (14.4)  | 26.4 (16.2)          | 26.4 (16.2)  | 30.1(14.2)            | 30.1(14.2)   | .396                                   | .396     | 8.2 (3.8)            | 8.2 (3.8)   | 6.4(2.0)              | 6.4(2.0)   | .075                         | .075     | 7.4 (3.3)              | 7.4 (3.3)   | 7.3(2.7)                      | 7.3(2.7)   | .092     |
| COWAT Semantic (total)            | 49.8 (17.0)  | 49.8 (17.0)  | 45.2(19.1)           | 45.2(19.1)   | 49.1 (25.7)           | 49.1 (25.7)  | .314                                   | .314     | 12.0 (4.2)           | 12.0 (4.2)  | 12.7(3.0)             | 12.7(3.0)  | .462                         | .462     | 14.4 (1.6)             | 14.4 (1.6)  | 14.6(0.7)                     | 14.6(0.7)  | .068     |
| Trail Making Test (TMT) A         | 69.2 (82.1)  | 69.2 (82.1)  | 60.5(56.3)           | 60.5(56.3)   | 50.5 (34.4)           | 50.5 (34.4)  | .374                                   | .374     | 11.5 (5.1)           | 11.5 (5.1)  | 12.7(3.1)             | 12.7(3.1)  | .686                         | .686     | 13.4 (3.2)             | 13.4 (3.2)  | 13.3(2.8)                     | 13.3(2.8)  | .414     |
| Trail Making Test (TMT) B         | 119.2 (75.2) | 119.2 (75.2) | 166.8(128.8)         | 166.8(128.8) | 124.3 (84.4)          | 124.3 (84.4) | .123                                   | .123     | 5.4 (1.8)            | 5.4 (1.8)   | 5.3(1.6)              | 5.3(1.6)   | .655                         | .655     | 6 (0.0)                | 6 (0.0)     | 6.0(0.0)                      | 6.0(0.0)   | 1.00     |
| Stroop Test (word)                | 79.1 (19.9)  | 79.1 (19.9)  | 80.8 (17.2)          | 80.8 (17.2)  | 76.7 (18.2)           | 76.7 (18.2)  | .575                                   | .575     | 5.4 (1.8)            | 5.4 (1.8)   | 5.4(1.6)              | 5.4(1.6)   | .317                         | .317     | 6 (0.0)                | 6 (0.0)     | 5.7(0.7)                      | 5.7(0.7)   | .317     |
| Stroop Test (colour)              | 60.5 (18.0)  | 60.5 (18.0)  | 62.5(13.8)           | 62.5(13.8)   | 60.3 (18.0)           | 60.3 (18.0)  | .574                                   | .574     | 18.8 (5.7)           | 18.8 (5.7)  | 21.0(6.0)             | 21.0(6.0)  | .406                         | .406     | 21.3 (5.2)             | 21.3 (5.2)  | 20.9(5.8)                     | 20.9(5.8)  | .259     |
| Stroop Test (colour-word)         | 35.5 (12.6)  | 35.5 (12.6)  | 37.1(13.7)           | 37.1(13.7)   | 37.8 (18.9)           | 37.8 (18.9)  | .233                                   | .233     | 29.5 (5.4)           | 29.5 (5.4)  | 28.4(3.1)             | 28.4(3.1)  | .362                         | .362     | 27.8 (4.8)             | 27.8 (4.8)  | 26.3(8.2)                     | 26.3(8.2)  | .261     |
| Stroop Test (CWexp-CW)            | - .75 (7.9)  | - .75 (7.9)  | -.87(11.3)           | -.87(11.3)   | 3.5 (11.5)            | 3.5 (11.5)   | .116                                   | .116     | 20.1 (8.4)           | 20.1 (8.4)  | 22.1(6.0)             | 22.1(6.0)  | .389                         | .389     | 23.4 (8.3)             | 23.4 (8.3)  | 22.3(6.9)                     | 22.3(6.9)  | .673     |
| Brixton                           | 12.3 (5.1)   | 12.3 (5.1)   | —                    | —            | 14.0 (6.5)            | 14.0 (6.5)   | n/a                                    | n/a      | 19.0 (5.1)           | 19.0 (5.1)  | 20.3(7.1)             | 20.3(7.1)  | .326                         | .326     | 19.7 (6.1)             | 19.7 (6.1)  | 20.2(7.3)                     | 20.2(7.3)  | .312     |
| Depression Beck                   | 8.5 (6.1)    | 8.5 (6.1)    | 8.2(5.9)             | 8.2(5.9)     | 8.5 (6.1)             | 8.5 (6.1)    | .635                                   | .635     | 6.7 (6.0)            | 6.7 (6.0)   | 6.7(6.0)              | 6.7(6.0)   | .154                         | .154     | 10.1(8.4)              | 10.1(8.4)   | 10.1(8.4)                     | 10.1(8.4)  | .722     |

colour-word test ( $r = 0.785$ ,  $p < 0.05$ ), with vocabulary ( $r = 0.915$ ,  $p < 0.01$ ) and with route immediate recall ( $r = 0.853$ ,  $p < 0.01$ ) and route delayed recall ( $r = 0.839$ ,  $p < 0.01$ ).

### 3.2. Postoperative results

There was no significant difference in any of the neuropsychological measures at one-month post-surgery compared to baseline performance. At the 6-months follow-up there was an improvement in phonemic verbal fluency ( $p < .05$ ) compared to baseline, and this improvement was retained at 12-months postoperatively ( $p = .05$ ). In parallel, results showed improvement with a marginal statistical significance in the Trail Making A test ( $p = .051$ ) and the Stroop colour-word test ( $p < .05$ ), compared with baseline. Detailed neuropsychological test results are provided in Table 1.

## 4. Discussion

This study reports on the medium- and long-term neuropsychological outcomes following constant-current DBS for primary dystonia.

Although psychiatric comorbidities, especially depression and anxiety, are common in dystonia, it is widely held that cognitive functions remain largely intact. [11–14] Nonetheless, various authors have reported, among others, deficits of visuospatial working memory, extra-dimensional set-shifting, complex movement planning, sustained attention, semantic fluency and dual task performance [13,15–20]. Our study showed that as a group, patients at baseline performed below average on executive function tasks, namely information processing speed (Trails A and B), phonemic verbal fluency and working memory (digit span). By and large, however, patients with primary dystonia have not shown executive cognitive difficulties with sufficient consistency so as to make a clear statement regarding executive cognitive deficits. This may be due to the clinical –and potentially also pathophysiological– heterogeneity of dystonia which is compounded by the fact that some of the deficits detected may be related to the patients' effort and attention-shifting in controlling dystonia and anticholinergic medication but also on the wide variety of neuropsychological batteries used.

In our primary dystonia population, constant-current DBS lead to an improvement in phonetic verbal fluency ( $p < .05$ ) and a marginal improvement in the Trail Making A test and the Stroop colour-word test compared with baseline. Dinkelbach et al. examined 13 patients with primary cervical dystonia treated with GPI-DBS for a period of 12 months and noted a decrease in the number of produced words in a verbal fluency task (RWT) which involved alternating categories (a task requiring the person to alternate between categories in producing words). [4] They found this decline to be unrelated to the degree of clinical improvement of cervical dystonia. Total verbal fluency as well as letter (phonemic) and category (semantic) fluency remained unaffected. This finding of deteriorated aspects of verbal fluency is in line with a single case in a multicentre study of 10 patients with cervical dystonia by Kiss et al. [21] Interestingly, in a recent study involving 12 patients with primary and secondary dystonia who underwent GPI-DBS, de Gusmao et al. noted a trend towards decreased semantic verbal fluency that did not attain statistical significance [9]. Jahanshani et al. did employ the alternating versions of the verbal fluency test, in addition to the phonemic and semantic versions, in their series of 14 patients with primary generalized dystonia but found no change [11]. In contrast, our study documented an improvement in phonemic verbal fluency at 6 months after surgery; this benefit was retained at the 12-month follow-up. Arguably, this change could reflect an improvement in the motor aspect of articulation. Since there was no change in semantic fluency, we hypothesize that this finding is not due to articulation, but due to improved access of the phonemic process. The findings by Dinkelbach et al. were limited to the “alternating categories” subset of semantic verbal fluency; as we did not perform this particular

subtest, a direct validation of this result is not possible. Alternating fluency deficits have been linked with frontostriatal lobe dysfunction and have been documented in patients with Parkinson's Disease. [22] It is conceivable that lesions in the electrode tract, current overflow or disease progression disrupting the neighbouring dorsomedial GPI, as part of the fronto-subcortical circuits, may account for this adverse effect [23]. At this point, the effect of GPI-DBS in verbal fluency remains unclear. If there is an impact from treatment, then it is unlikely to affect the patient's everyday verbal communication.

Our data support the notion of marginally ( $p = .051$ ) improved performance in TMT-A and in the Stroop colour-word test ( $p < .05$ ). Hålbjerg et al. evaluated 13 patients with primary dystonia and 2 patients with tardive dystonia who were treated with bilateral GPI-DBS and observed no significant effect on cognitive scores and neuropsychiatric measures. They did note, however, a slight improvement on the TMT-A. [6] Part A of the Trail Making Test is generally presumed to be a test of visual search and motor speed skills; expectedly, motor speed measures contribute to the performance on the TMT-A [24]. It could be that the overall improvement of the motor aspect of dystonia –which could have positively affected visual scanning as well– may have led to the decreased performance times in the TMT-A. The Stroop Color-and-Word test assesses the ability to inhibit cognitive interference which occurs by simultaneously processing incongruent attributes of the same stimulus and is considered to measure, among others, selective attention, cognitive flexibility and processing speed. [25] In attempting to explain the marginal improvement of our patients (Baseline: 35.5, SD: 12.6 vs 42.7, SD: 14.1 at 12 months), it is impossible to rule out that attention processes originally involved in motor control were redirected to perform tasks involving cognitive functions after surgery.

Reduction of antidystonic medication after surgery can mask any deterioration in cognition, or even lead to improvement of cognitive function, since it is known that most antidystonic drugs can potentially induce cognitive impairment. [26] This was not the case in our study, however, since medication remained unchanged during the 12-month evaluation period. This allows us to assume that the cognitive changes observed postoperatively may indeed have been due to treatment effects.

Constant-Current pallidal stimulation had a positive effect on Quality of Life (QoL); at month 12, Physical and Mental Component scales improved by 32.42% and 29.46% respectively. The SF-36 is a generic measure of QoL that has been widely validated for use across a range of settings and patients. Although normative data for the SF-36 health survey lack for the Greek population, published norms for other countries suggest that the mean baseline values for our group were below the ones reported in the literature. This is in concordance with previous reports of impaired QoL in dystonia patients compared to the general population. [27] After treatment, mean Physical and Mental Health Component values (52.8 and 47.6 respectively) approached the mean values reported worldwide [28,29]. Our study supports the body of the literature that shows post-surgical improvement in most QoL domains and contrasts those studies that report diminished impact to the emotional component [5,30].

In our study, patients showed no discernible change in their neuropsychiatric status, including anxiety and depression, despite significant improvement of dystonia. This finding is in consonance with data from previous studies which showed no significant change in mood after GPI-DBS, although some authors did report mild to modest improvement on depression scales. [5,6,8,13,31,32] A possible explanation for this is that most patients who receive DBS undergo preoperative screening for depression and that absence of a psychiatric comorbidity usually belongs to the inclusion criteria for DBS [33]. Whether neuropsychiatric outcomes are a liability remains unclear; Meoni et al. found that pallidal stimulation is safe even for patients with a history of preexisting psychiatric issues and that the majority of psychiatric illnesses remain unchanged or subside after stimulation. [31] In a meta-analysis of 808 articles, the reported rates of depression (2–4%), mania

(0.9–1.7%), emotional changes (0.1–0.2%) and the prevalence of suicidal ideation/suicide attempt (0.3–0.7%) as adverse effects associated with pallidal DBS were low, but existent [34]. At present, it seems safe to say that psychiatric disorders of dystonia patients show a relative stability after DBS-treatment. Nevertheless, a discernible risk of life-threatening depression and completed suicide (0.16–0.32%) does exist and appears to be difficult to predict; in that context, regular psychiatric assessment after surgery is recommended [34].

The fact that anxiety and depression remained practically stable despite significant improvement of dystonia is an intriguing one, especially given the fact that surgery improved not only the physical but also the emotional component of QoL. An interesting hypothesis involves the “set-point” or “dynamic equilibrium” theory, that essentially claims that emotional well-being is a sum of hereditary characteristics, including personality traits. Major life events are viewed as having only a transitory effect, with overall happiness always shifting back or close to a predetermined “set point”. In a milestone study of happiness and disability, Brickman and colleagues first argued on the presence of a “hedonic treadmill”, where reactions to both positive and negative events are temporary—across time, people adjust to extreme good or bad fortune, returning to their individual set-point level of happiness, although sometimes not completely. [35,36] The implausibility of this theory lies with the fact that even if such adaptation occurs, it should occur over a certain timespan. We examined our patients at months 6 and 12 and noticed no adaptation phenomena; mood and anxiety remained unchanged, much less increase initially as one would expect, only to settle to the previous baseline value with time. Alternatively, one could speculate that there is a “critical mass” of disability which may be detrimental to those aspects of life that define a patient’s well-being, such as social life or employment. Interestingly, similar observations have been made in patients successfully treated from other chronic disorders: Karlsson et al. studied the ten-year trends in QoL after treatment for severe obesity and found that although improvements in QoL were associated with the magnitude of weight loss, anxiety remained stable. Furthermore, Long-lasting weight reduction in the severely obese had a general long-standing positive outcome on QoL but no significant impact on overall mood and anxiety [37]. Finally, notwithstanding the positive effects of DBS on motor function, treatment presents patients with new challenges such as concern about being dependent on the stimulator, having to deal with interfering side effects from deep brain stimulation or undergoing surgery for battery replacement. It is unknown how these new issues affect mood and state of mind.

This is the first study to report on the neuropsychological outcomes after Constant-Current GPi-DBS. Our study has strong internal validity, as the surgical procedure was performed by the same neurosurgeon and neuropsychological examinations by the same two neuropsychologists. The neuropsychological battery was comprehensive, covering a wide range of neuropsychological functions. Still, our work has some limitations: Even though this has been the largest group of primary dystonia to be treated with constant-current GPi-DBS and to be prospectively evaluated with a comprehensive battery of neuropsychological tests, our sample size remains small. Hence, the results should be interpreted with caution. This is aggravated by the phenotypical—and hence potential pathophysiological-heterogeneity of dystonia. Finally, we feel the need to address the problems inherent in every study of neuropsychological functions: Impairments of executive function cannot be easily fractionated; A patient’s performance in one executive function test may have limited predictive value on another test, let alone in real life. [38,39] Moreover, the current conventional executive function tests tend to be crude and unspecific in terms of the cognitive processes they engage and evaluate [38].

## 5. Conclusions

To the best of our knowledge, this study is the first to evaluate in a standardized way the neuropsychological outcome of constant-current

pallidal DBS in generalized dystonia. As more centers switch from constant-voltage to constant-current stimulation, the need to assess the effects of that treatment becomes increasingly important. [40] Overall, our findings suggest that GPi-DBS using constant-current stimulation does not have a discernible negative impact on cognition and mood over a one-year period. Patients even showed improvement of performance in phonetic verbal fluency, Trail Making A and Stroop tests, 6 and 12 months postoperatively. From a neuropsychiatric perspective, mood and anxiety remained stable. Larger sample sizes would increase the power of analysis and also allow for a better correlation between different phenotypes of dystonia and potential neuropsychologic outcomes. Long-term follow-up would allow to evaluate whether cognitive and neuropsychiatric trends remain stable over time.

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## Declaration of competing interest

None

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