Stimulation of the pedunculopontine and cuneiform nuclei for freezing of gait and falls in Parkinson disease: Cross-over single-blinded study and long-term follow-up

Julie Bourilhon, Yannick Mullie, Claire Olivier, Saoussen Cherif, Hayat Belaid, David Grabli, Virginie Czernecki, Carine Karachi, Marie-Laure Welter

Stimulation of the pedunculopontine and cuneiform nuclei for freezing of gait and falls in Parkinson disease: cross-over single-blinded study and long-term follow-up.

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Highlights: 3-5

- Gait and balance disorders were clinically aggravated 2 years after PPN- or CuN-DBS
- Gait parameters were also aggravated with a less degradation with PPN- *vs* CuN-DBS
- Non-axial motor signs were not aggravated after two years with PPN-DBS

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Disclosure

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Abstract

Introduction Deep brain stimulation (DBS) of the mesencephalic locomotor region, composed of the pedunculopontine (PPN) and cuneiform (CuN) nuclei, has been proposed to treat dopa-resistant gait and balance disorders in Parkinson's disease (PD). Here, we report the long-term effects of PPN- or CuN-DBS on these axial disorders.

Methods In 6 PD patients operated for mesencephalic locomotor region DBS and prospectively followed for more than 2 years, we assessed the effects of both PPN- and CuN-DBS (On-dopa) in a cross-over single-blind study by using clinical scales and recording gait parameters. Patients were also examined Off-DBS.

Results More than 2 years after surgery, axial and Tinetti scores were significantly aggravated with both PPN- or CuN-DBS relative to before and one year after surgery. Gait recordings revealed an increased double-stance duration with both PPN- or CuN-DBS, higher swing phase duration with CuN-DBS and step width with PPN-DBS. With PPN- *versus* CuN-DBS, the step length, velocity and cadence were significantly higher; and the double-stance and turn durations significantly lower. Irrespective the target, we found no significant change in clinical scores Off-DBS compared to On-DBS. The duration of anticipatory postural adjustments as well as step length were lower with *versus* without PPN-DBS. We found no other significant changes in motor, cognitive or psychiatric scores, except an increased anxiety severity.

Conclusion In this long-term follow-up study with controlled assessments, PPN- or CuN-DBS did not improve dopa-resistant gait and balance disorders with a worsening of these axial motor signs with time, thus indicating no significant clinical effect.

1. Introduction

Deep brain stimulation (DBS) of the mesencephalic locomotor region, composed by the pedunculopontine (PPN) and cuneiform (CuN) nuclei, has been proposed to treat dopa-resistant freezing of gait (FOG) and/or falls in advanced Parkinson's disease (PD)[1]. Whereas double-blind controlled studies mainly failed to demonstrate that mesencephalic locomotor region DBS is effective to treat these axial signs, a subjective improvement has been reported in about half of the 5 to 11 patients included in previous long-term follow-up studies (24 to 48 months)[2–4], with heterogeneous results among patients[5,6]. Correlation analyses suggested that good responders have active contacts located within the PPN area[1,5]. However, some experimental and clinical data suggested that DBS applied more dorsally within the CuN could provide beneficial effects on gait and balance [7,8], with higher walking speed and length after short DBS duration[9]. Finally, the long-term effects on parkinsonian gait and balance disorders of PPN- and CuN-DBS applied in the same patients have never been reported.

The current study aims to examine the effects of DBS of the PPN or CuN in 6 PD patients with dopa-resistant FOG and/or falls, 24 to 36 months after surgery, with a cross-over single-blind design assessment using both clinical scales and gait recordings to specifically assess gait and balance control.

2. Methods

2.1 Subjects

Six patients with PD were operated for DBS of the mesencephalic locomotor region and prospectively followed for a mean of 30.7 months (SD 5.4). Details on inclusion and exclusion

criteria have been reported previously [9]. Patients had an advanced form of PD with a mean disease duration of 11 years (SD 6) at the time of surgery with dopa-resistant FOG and/or falls (Table). Patients had bilateral mesencephalic locomotor region DBS with two 8 in-line contacts electrodes to target the PPN, located at the level the pontomesencephalic junction, and the CuN dorsally located along the same trajectory (Figure-A). The study was approved by the local ethics committee (CPPRB Ile-de-France Paris 6). All subjects gave an informed written consent before enrolment (ClinicalTrial.gov registration NCT02931097).

2.2 Procedures

Patients were assessed at the time of inclusion one month before surgery, and 12 months after surgery with PPN-DBS, both Off and On-dopa treatment[9]. At the first long-term follow-up visit, patients were assessed with their usual chronic DBS settings, i.e. with PPN-DBS (patients P02, P03, P04, P05 and P06) or CuN-DBS (P01), and after switching off the DBS for 1 hour. For the patients with PPN-DBS, CuN-DBS was then applied for the following 3-4 months, and for the patient with CuN-DBS, we applied PPN-DBS. For this, we chose bipolar DBS with confirmed location within the PPN and CuN areas (for details see [9], Figure-A), with low frequency of stimulation (20-30 Hz) and pulse width (60 us), with amplitude chosen below the occurrence of side effects. Patients were then re-assessed first On-DBS, and after switching off the DBS for 1 hour. These two long-term assessments were performed after the intake of their usual antiparkinsonian treatment (On-dopa, Table). Clinical scales and spatiotemporal parameters of gait initiation recordings were assessed at each visit.

The clinical scales were: the MDS-UPDRS part 1: mental status, part 2: ADL, part 4: levodopa-related motor complications, and part 3: motor disability score, comprising the 'axial' score; the gait and balance scale (GABS); the Tinetti scale; the freezing of gait questionnaire (FOG-Q); the Activities-Balance Confidence (ABC) scale; the Parkinson's

Disease Questionnaire (PDQ-39); the Mattis Dementia Rating Scale (MDRS); the Comprehensive Psychopathological Rating Scale; which includes the Montgomery and Asberg Depression rating Scale (MADRS); and Brief Anxiety Scale (BAS); and the Hospital Anxiety and Depression Scale (HAD).

Spatiotemporal parameters of gait initiation, straight forward gait and turn were recorded using a force platform (0.9X1.8m, Advanced Mechanical Technology Inc. LG6-4-1) and the VICON system with Plug-In-Gait model with markers positioned on the arm and leg joints. The patients, barefoot, initiated gait on the force platform and walked for 5-6 m at a self-paced speed, making a half-turn and returning to the initial position (n=15-20 trials). The following parameters were calculated during: 1) gait initiation with anticipatory postural adjustments (APAs) phase including the posterior and lateral displacements of the center of foot pressure, and APAs duration, first step length, width and velocity; 2) straight-forward gait with cadence, stride-length, stride time variability, velocity, double-stance duration, and duration of freezing episodes; 3) turn amplitude and duration[9].

Safety was also assessed and we classified any new symptoms as adverse events.

2.3 Statistical analysis

Here, we aim to assess the effects of long-term PPN-DBS or CuN-DBS relative to baseline assessment obtained before and one year after surgery. We also compared the changes in clinical and gait parameters between PPN-DBS and CuN-DBS, and also between On and Off-DBS conditions. For this purpose, we modelled each outcome using a linear mixed-model. We included treatment condition (baseline, Month 12, Month 24-28) and a period effect as fixed effects, and patient intercepts as random effects. We used R (version 3.3.1, R Core Development Team) for the statistical analysis, with the *LmerTest* package for the linear

mixed-effect model testing using the Satterthwaite approximation for degrees of freedom. We used a significance threshold of 0.05. Post-hoc comparisons were FDR-corrected.

3. Results

Among the 6 patients included, PPN-DBS was chronically applied in 5 patients and CuN-DBS in one patient. For the long-term cross-over assessments, 5 patients performed the full assessments for both PPN- and CuN-DBS. One patient (P04) only performed the first assessment with PPN-DBS, the second assessment being cancelled with a premature drop-out due to recurrent falls leading to hip fracture (Table).

3.1 Effects of long-term mesencephalic locomotor region DBS on parkinsonian disability and gait and balance disorders

At the long-term cross-over assessments, we found a significant increase in the axial score and a significant decrease in the Tinetti static score compared to before surgery and one year after surgery with both PPN- or CuN-DBS (Figure-B). We found no other significant changes in motor (UPDRS part 3, non-axial motor, Tinetti dynamic, GABS, FOG-Q, ABC-scale scores, Table, Figure-B), cognitive (MDRS) or psychiatric (MADRS, BAS scores) scores, except an increase in the HAD score (not shown).

For gait parameters, we found that the double stance phase duration was significantly higher with PPN- or CuN-DBS relative to before surgery and one year after surgery. The step width was also higher with PPN-DBS (Figure-C). With CuN-DBS, the swing phase duration was significantly higher, and the lateral CoP APAs significantly lower ((p=0.001 and p=0.037, respectively).

3.2 Effects of CuN-DBS relative to PPN-DBS on gait and balance disorders

We found no significant difference for clinical scores between PPN- and CuN-DBS (Table, Figure-B). For gait parameters, we found that with PPN- *versus* to CuN-DBS, the mean step length, cadence and walking velocity were significantly higher; and the step width, double stance and turn durations (Figure-C and D), and number of FOG episodes during straight-forward walking (not shown) significantly lower with no other significant differences.

3.3 Changes in gait and balance disorders Off relative to On-DBS

Comparing Off versus On-DBS, we found no significant change in any clinical scores, whatever the target. For gait parameters, APAs duration and step length were lower On- vs Off-PPN-DBS (Figure-C), and the step width was lower On- vs Off-CuN-DBS (Figure-C), with no other significant differences.

3.4 Antiparkinsonian treatment, contact locations and deep brain stimulation parameters

During the follow-up period relative to inclusion, the antiparkinsonian treatment was slightly decreased in 4 patients or increased in 2 patients (Table).

For PPN-DBS contacts, the mean (SD) X-laterality, Y-anteroposteriority and Z-depth coordinates relative to the 4th ventricle floor and pontomesencephalic junction were 6.1 (1.1), 8.5 (3.6) and -1.9 (1.0) mm, respectively and for CuN-DBS contacts, 8.4 (2.6), 10.8 (3.9) and 4.4 (2.7) mm. Stimulation parameters were 20 or 30 Hz frequency, with a pulse width of 30 or 60µs, using bipolar stimulation with an amplitude ranging from 1.8 to 3.6V.

3.5 Adverse events

Six adverse events were reported during the follow-up period consisting mainly of persistent FOG with recurrent falls. Due to recurrent falls, one patient (P04) had a hip fracture that needed surgical intervention and hospitalization considered to be a serious adverse event, that prevented to perform the final assessment. One patient (P03) had an unexpected arrest of their neurostimulator due to full discharge that occurred between two visits.

4. Discussion

We report for the first time the long-term effects of PPN- and CuN-DBS with clinical and physiological assessments of gait and balance disorders in a small homogeneous cohort of advanced PD patients. We found that gait and balance disorders On-dopa were aggravated two years after surgery and were not alleviated with either PPN- or CuN-DBS. We observed no significant effects or aggravation of other parkinsonian signs.

In line with the effects obtained one year after surgery in the same cohort of patients [9], we observed that 2 to 3 years after surgery, On-dopa mesencephalic locomotor region DBS did not improve gait and balance disorders compared to before surgery or without DBS. This lack of objective improvement of mesencephalic locomotor region DBS applied for more than 2 years was also previously reported in a study with blinded assessment performed in 8 patients[4]. No significant changes in objective clinical scores were also demonstrated in open-label studies with long-term assessments[2]. Moreover, in other long-term follow-up studies, data in about 25-30% of cases are also missing due to either death or inability to perform the tests, further suggesting no significant long-term positive effects. However, some authors reported a subjective improvement of FOG and falls two years after surgery in about 1/3 of patients with decreased FOG or falls items of the UPDRS part II [2–4,8]. However, in our patients, only one (P07) reported a subjective improvement in FOG severity (FOG-Q), and none a subjective improvement in the feeling of postural instability (ABC scale). This apparent discrepancy could be due to a different location of DBS electrodes in our patients in comparison to other teams[5]. However, the comparison of our PPN-DBS coordinates with another study does not favor this hypothesis, since their coordinates (mean laterality, anteroposteriority and depth of 5.3, 8.4 and -0.8 mm, respectively)[5] should correspond to

the highest density of remaining PPN cholinergic neurons. We hypothesize that in our severe and advanced PD patients, the lack of benefit could be due to the profound loss of cholinergic neurons, with insufficient stimulation of the remaining cells[1]. When applied within the CuN, located more dorsally, we also observed no positive clinical effects on axial motor signs, with even poorer gait performance relative to PPN-DBS. The CuN contains non-cholinergic neurons and has been shown to promote high speed running in mice when stimulated optogenetically[10,11] and evoked locomotion in decerebrated cats[12]. In monkeys, lesions of the CuN induce increased forelimb and neck tone as well as increased step speed[13]. Thus, the CuN could be more involved in initiation of high-speed gait and tonus control of the upper body parts, with therefore less influence on self-paced gait.

Finally, we observed no significant aggravation of non-axial motor PD disability during the follow-up period, with mesencephalic locomotor region DBS, with also a mild decrease in the antiparkinsonian treatment in 4/6 patients. This suggests that DBS applied within the mesencephalic locomotor region could decrease parkinsonian motor disability, as reported in primates rendered parkinsonian showing increased movements after low frequency PPN-DBS[14].

Our study has some limitations. First, the number of patients was limited. Second, we tested first PPN-DBS in 5 out of 6 patients, without randomization of the DBS conditions, and with different duration of chronic DBS between PPN and CuN-DBS assessments. This could have influenced the effects obtained. However, we observed no significant changes in clinical scores between PPN- and CuN-DBS conditions, as well as relative to before surgery and no significant changes in clinical or gait parameters after switching off the DBS.

Our results do not support PPN- or CuN-DBS to treat doparesistant gait and balance disorders in advanced PD. Further research is needed to elucidate the role of this brainstem region in locomotion and balance in humans and dysfunction in FOG or falls of PD patients.

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Figure. Active contacts locations and effects of CuN and PPN-DBS on parkinsonian motor disability and gait and balance disorders.

A) Location of the contacts used for DBS and reported on right and left sagittal 3D-views after fusion with the 3D MRI image. The pink and light-blue outline the cholinergic PPN an GABAergic CuN neurons, respectively. The active contacts used for PPN-DBS are represented in green and those for CuN-DBS in yellow. Graphs represent B) the non-axial and axial parkinsonian motor and Tinetti static scores (On-dopa) and C) gait initiation parameters obtained before surgery, 12 months after surgery with PPN-DBS (M12), and during the long-term follow-up period with CuN-DBS or PPN-DBS On-dopa. D) Cadence and velocity during straight-forward walking and turn duration with CuN-DBS or PPN-DBS (On-dopa) obtained during the long-term follow-up period.

Each color point represents an individual patient, and light and dark grey boxes parameters obtained in the Off-DBS and On-DBS conditions, respectively. Horizontal black lines represent the estimated marginal mean for each condition, and the upper and lower bound of the grey rectangles the corresponding 95% confidence intervals.

APAs= anticipatory postural adjustments, M=month, PPN=pedunculopontine nucleus, CuN= cuneiform nucleus, *p< 0.05.

Table. Baseline demographic characteristics and effects of PPN-DBS and CuN-DBS in 6 PD patients

	P01	P02	P03	P04	P05	P06	Mean (SD)
Age/sex	65/M	68/M	67/F	68/M	67/M	54/M	64.8 (5.4)
Disease duration (years)	6	12	10	17	12	12	11.5 (3.6)
UPDRS 3 (On-dopa)							
Inclusion	17	19	28	28	40	12	24.0 (10.1)
Month 12	36	28	23	25	43	14	28.2 (10.2)
PPN-DBS	22	24	27	28	24	22	24.5 (2.5)
CuN-DBS	46	28	28	ND	26	19	29.4 (10.0)
GABS (On-dopa)							
Inclusion	12	24	25	30	19	4	19.0 (9.6)
Month 12	29	23	11	24	18	7	18.7 (8.3)
PPN-DBS	22	24	21	18	24	10	19.8 (5.3)
CuN-DBS	46	28	27	ND	26	10	27.4 (12.7)
FOG-Q							
Inclusion	29	36	36	40	44	22	36.3 (5.2)
Month 12	43	34	46	37	42	38	40.0 (4.4)
PPN-DBS	40	32	36	36	33	37	35.7 (2.9)
CuN-DBS	38	35	35	ND	29	39	35.2 (3.9)
ABC scale							
Inclusion	78	68	46	42	43	79	59.5 (17.4)
Month 12	65	69	31	49	35	65	52.3 (16.5)
PPN-DBS	62	62.5	37	63	34	74	55.6 (16.3)
CuN-DBS	30	73	37	ND	34.5	57	50.3 (15.7)
LEDD (mg/d)							
Inclusion	650	2200	1060	1650	2175	1200	1456 (660)
Month 12	650	2085	780	1550	2275	1300	1440 (664)
PPN-DBS	550	1880	900	1450	1690	1350	1303 (497)
CuN-DBS	750	1880	900	ND	1690	1350	1314 (488)

ABC scale= activities balance confidence; CuN= cuneiform nucleus; DBS= deep brain stimulation ; FOG-Q= freezing of gait questionnaire; GABS= gait and balance scale; LEDD= levodopa-equivalent dosage; PPN= pedunculopontine nucleus; UPDRS= Unified Parkinson's disease rating scale.

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Disclosure

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Conclusion In this long-term follow-up study with controlled assessments, PPN- or CuN-DBS did not improve dopa-resistant gait and balance disorders with a worsening of these axial motor signs with time, thus indicating no significant clinical effect.

1. Introduction

Deep brain stimulation (DBS) of the mesencephalic locomotor region, composed by the pedunculopontine (PPN) and cuneiform (CuN) nuclei, has been proposed to treat dopa-resistant freezing of gait (FOG) and/or falls in advanced Parkinson's disease (PD)[1]. Whereas double-blind controlled studies mainly failed to demonstrate that mesencephalic locomotor region DBS is effective to treat these axial signs, a subjective improvement has been reported in about half of the 5 to 11 patients included in previous long-term follow-up studies (24 to 48 months)[2–4], with heterogeneous results among patients[5,6]. Correlation analyses suggested that good responders have active contacts located within the PPN area [1,5]. However, some experimental and clinical data suggested that DBS applied more dorsally within the CuN could provide beneficial effects on gait and balance[7,8], with higher walking speed and length after short DBS duration[9]. Finally, the long-term effects on parkinsonian gait and balance disorders of PPN- and CuN-DBS applied in the same patients have never been reported.

The current study aims to examine the effects of DBS of the PPN or CuN in 6 PD patients with dopa-resistant FOG and/or falls, 24 to 36 months after surgery, with a cross-over single-blind design assessment using both clinical scales and gait recordings to specifically assess gait and balance control.

2. Methods

2.1 Subjects

Six patients with PD were operated for DBS of the mesencephalic locomotor region and prospectively followed for a mean of 30.7 months (SD 5.4). Details on inclusion and exclusion

criteria have been reported previously [9]. Patients had an advanced form of PD with a mean disease duration of 11 years (SD 6) at the time of surgery with dopa-resistant FOG and/or falls (Table). Patients had bilateral mesencephalic locomotor region DBS with two 8 in-line contacts electrodes to target the PPN, located at the level the pontomesencephalic junction, and the CuN dorsally located along the same trajectory (Figure-A). The study was approved by the local ethics committee (CPPRB Ile-de-France Paris 6). All subjects gave an informed written consent before enrolment (ClinicalTrial.gov registration NCT02931097).

2.2 Procedures

Patients were assessed at the time of inclusion one month before surgery, and 12 months after surgery with PPN-DBS, both Off and On-dopa treatment[9]. At the first long-term follow-up visit, patients were assessed with their usual chronic DBS settings, i.e. with PPN-DBS (patients P02, P03, P04, P05 and P06) or CuN-DBS (P01), and after switching off the DBS for 1 hour. For the patients with PPN-DBS, CuN-DBS was then applied for the following 3-4 months, and for the patient with CuN-DBS, we applied PPN-DBS. For this, we chose bipolar DBS with confirmed location within the PPN and CuN areas (for details see ref [9], Figure-A), with low frequency of stimulation (20-30 Hz) and pulse width (60 us), with amplitude chosen below the occurrence of side effects. Patients were then re-assessed first On-DBS, and after switching off the DBS for 1 hour. These two long-term assessments were performed after the intake of their usual antiparkinsonian treatment (On-dopa, Table). Clinical scales and spatiotemporal parameters of gait initiation recordings were assessed at each visit.

The clinical scales were: the MDS-UPDRS part 1: mental status, part 2: ADL, part 4: levodopa-related motor complications, and part 3: motor disability score, comprising the 'axial' score; the gait and balance scale (GABS); the Tinetti scale; the freezing of gait questionnaire (FOG-Q); the Activities-Balance Confidence (ABC) scale; the Parkinson's

Disease Questionnaire (PDQ-39); the Mattis Dementia Rating Scale (MDRS); the Comprehensive Psychopathological Rating Scale; which includes the Montgomery and Asberg Depression rating Scale (MADRS); and Brief Anxiety Scale (BAS); and the Hospital Anxiety and Depression Scale (HAD).

Spatiotemporal parameters of gait initiation, straight forward gait and turn were recorded using a force platform (0.9X1.8m, Advanced Mechanical Technology Inc. LG6-4-1) and the VICON system with Plug-In-Gait model with markers positioned on the arm and leg joints. The patients, barefoot, initiated gait on the force platform and walked for 5-6 m at a self-paced speed, making a half-turn and returning to the initial position (n=15-20 trials). The following parameters were calculated during: 1) gait initiation with anticipatory postural adjustments (APAs) phase including the posterior and lateral displacements of the center of foot pressure, and APAs duration, first step length, width and velocity; 2) straight-forward gait with cadence, stride-length, stride time variability, velocity, double-stance duration, and duration of freezing episodes; 3) turn amplitude and duration[9].

Safety was also assessed and we classified any new symptoms as adverse events.

2.3 Statistical analysis

Here, we aim to assess the effects of long-term PPN-DBS or CuN-DBS relative to baseline assessment obtained before and one year after surgery. We also compared the changes in clinical and gait parameters between PPN-DBS and CuN-DBS, and also between On and Off-DBS conditions. For this purpose, we modelled each outcome using a linear mixed-model. We included treatment condition (baseline, Month 12, Month 24-28) and a period effect as fixed effects, and patient intercepts as random effects. We used R (version 3.3.1, R Core Development Team) for the statistical analysis, with the *LmerTest* package for the linear

mixed-effect model testing using the Satterthwaite approximation for degrees of freedom. We used a significance threshold of 0.05. Post-hoc comparisons were FDR-corrected.

3. Results

Among the 6 patients included, PPN-DBS was chronically applied in 5 patients and CuN-DBS in one patient. For the long-term cross-over assessments, 5 patients performed the full assessments for both PPN- and CuN-DBS. One patient (P04) only performed the first assessment with PPN-DBS, the second assessment being cancelled with a premature drop-out due to recurrent falls leading to hip fracture (Table).

3.1 Effects of long-term mesencephalic locomotor region DBS on parkinsonian disability and gait and balance disorders

At the long-term cross-over assessments, we found a significant increase in the axial score and a significant decrease in the Tinetti static score compared to before surgery and one year after surgery with both PPN- or CuN-DBS (On-dopa) (Figure-B). We found no other significant changes in motor (UPDRS part 3, non-axial motor, Tinetti dynamic, GABS, FOG-Q, ABC-scale scores, Table, Figure-B), cognitive (MDRS) or psychiatric (MADRS, BAS scores) scores, except an increase in the HAD score (not shown).

For gait parameters, we found that the double stance phase duration was significantly higher with PPN- or CuN-DBS relative to before surgery and one year after surgery. The step width was also higher with PPN-DBS (Figure-C). With CuN-DBS, the swing phase duration was significantly higher and the lateral CoP APAs significantly lower ($p=0.001$ and $p=0.037$, respectively).

3.2 Effects of CuN-DBS relative to PPN-DBS on gait and balance disorders

We found no significant difference for clinical scores between PPN- and CuN-DBS (Table, Figure-B). For gait parameters, we found that with PPN- *versus* CuN-DBS, the mean step length, cadence and walking velocity were significantly higher; and the step width, double stance and turn durations (Figure-C and D), and number of FOG episodes during straight-forward walking (not shown) significantly lower with no other significant differences.

3.3 Changes in gait and balance disorders Off relative to On-DBS

Comparing Off versus On-DBS, we found no significant change in any clinical scores, whatever the target. For gait parameters, APAs duration and step length were lower On- vs Off-PPN-DBS (Figure-C), and the step width was lower On- vs Off-CuN-DBS (Figure-C), with no other significant differences.

3.4 Antiparkinsonian treatment, contact locations and deep brain stimulation parameters

During the follow-up period relative to inclusion, the antiparkinsonian treatment was slightly decreased in 4 patients or increased in 2 patients (Table).

For PPN-DBS contacts, the mean (SD) X-laterality, Y-anteroposteriority and Z-depth coordinates relative to the 4th ventricle floor and pontomesencephalic junction were 6.1 (1.1), 8.5 (3.6) and -1.9 (1.0) mm, respectively and for CuN-DBS contacts, 8.4 (2.6), 10.8 (3.9) and 4.4 (2.7) mm. Stimulation parameters were 20 or 30 Hz frequency, with a pulse width of 30 or 60µs, using bipolar stimulation with an amplitude ranging from 1.8 to 3.6V.

3.5 Adverse events

Six adverse events were reported during the follow-up period consisting mainly of persistent FOG with recurrent falls. Due to recurrent falls, one patient (P04) had a hip fracture that needed surgical intervention and hospitalization considered to be a serious adverse event, that prevented to perform the final assessment. One patient (P03) had an unexpected arrest of their neurostimulator due to full discharge that occurred between two visits.

4. Discussion

We report for the first time the long-term effects of PPN- and CuN-DBS with clinical and physiological assessments of gait and balance disorders in a small homogeneous cohort of advanced PD patients. We found that gait and balance disorders On-dopa were aggravated two years after surgery and were not alleviated with either PPN- or CuN-DBS. We observed no significant effects or aggravation of other parkinsonian signs.

In line with the effects obtained one year after surgery in the same cohort of patients[9], we observed that 2 to 3 years after surgery, On-dopa mesencephalic locomotor region DBS did not improve gait and balance disorders compared to before surgery or without DBS. This lack of objective improvement of mesencephalic locomotor region DBS applied for more than 2 years was also previously reported in a study with blinded assessment performed in 8 patients[4]. No significant changes in objective clinical scores were also demonstrated in open-label studies with long-term assessments[2]. Moreover, in other long-term follow-up studies, data in about 25-30% of cases are also missing due to either death or inability to perform the tests, further suggesting no significant long-term positive effects. However, some authors reported a subjective improvement of FOG and falls two years after surgery in about 1/3 of patients with decreased FOG or falls items of the UPDRS part II[2–4,8]. However, in our patients, only one (P07) reported a subjective improvement in FOG severity (FOG-Q), and none a subjective improvement in the feeling of postural instability (ABC scale). This apparent discrepancy could be due to a different location of DBS electrodes in our patients in comparison to other teams[5]. However, the comparison of our PPN-DBS coordinates with another study does not favor this hypothesis, since their coordinates (mean laterality, anteroposteriority and depth of 5.3, 8.4 and -0.8 mm, respectively)[5] should correspond to

the highest density of remaining PPN cholinergic neurons. We hypothesize that in our severe and advanced PD patients, the lack of benefit could be due to the profound loss of cholinergic neurons, with insufficient stimulation of the remaining cells[1]. When applied within the CuN, located more dorsally, we also observed no positive clinical effects on axial motor signs, with even poorer gait performance relative to PPN-DBS. The CuN contains non-cholinergic neurons and has been shown to promote high speed running in mice when stimulated optogenetically[10,11] and evoked locomotion in decerebrated cats[12]. In monkeys, lesions of the CuN induce increased forelimb and neck tone as well as increased step speed[13]. Thus, the CuN could be more involved in initiation of high-speed gait and tonus control of the upper body parts, with therefore less influence on self-paced gait.

Finally, we observed no significant aggravation of non-axial motor PD disability during the follow-up period, with mesencephalic locomotor region DBS, with also a mild decrease in the antiparkinsonian treatment in 4/6 patients. This suggests that DBS applied within the mesencephalic locomotor region could decrease parkinsonian motor disability, as reported in primates rendered parkinsonian showing increased movements after low frequency PPN-DBS[14].

Our study has some limitations. First, the number of patients was limited. Second, we tested first PPN-DBS in 5 out of 6 patients, without randomization of the DBS conditions, and with different duration of chronic DBS between PPN and CuN-DBS assessments. This could have influenced the effects obtained. However, we observed no significant changes in clinical scores between PPN- and CuN-DBS conditions, as well as relative to before surgery and no significant changes in clinical or gait parameters after switching off the DBS.

Our results do not support PPN- or CuN-DBS to treat doparesistant gait and balance disorders in advanced PD. Further research is needed to elucidate the role of this brainstem region in locomotion and balance in humans and dysfunction in FOG or falls of PD patients.

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Figure. Active contacts locations and effects of CuN and PPN-DBS on parkinsonian motor disability and gait and balance disorders.

A) Location of the contacts used for DBS and reported on right and left sagittal 3D-views after fusion with the 3D MRI image. The pink and light-blue outline the cholinergic PPN an GABAergic CuN neurons, respectively. The active contacts used for PPN-DBS are represented in green and those for CuN-DBS in yellow. Graphs represent B) the non-axial and axial parkinsonian motor and Tinetti static scores (On-dopa) and C) gait initiation parameters obtained before surgery, 12 months after surgery with PPN-DBS (M12), and during the long-term follow-up period with CuN-DBS or PPN-DBS On-dopa. D) Cadence and velocity during straight-forward walking and turn duration with CuN-DBS or PPN-DBS (On-dopa) obtained during the long-term follow-up period.

Each color point represents an individual patient, and light and dark grey boxes parameters obtained in the Off-DBS and On-DBS conditions, respectively. Horizontal black lines represent the estimated marginal mean for each condition, and the upper and lower bound of the grey rectangles the corresponding 95% confidence intervals.

APAs= anticipatory postural adjustments, M=month, PPN=pedunculopontine nucleus, CuN= cuneiform nucleus, *p< 0.05.

Table. Baseline demographic characteristics and effects of PPN-DBS and CuN-DBS in 6 PD patients

	P01	P02	P03	P04	P05	P06	Mean (SD)
Age/sex	65/M	68/M	67/F	68/M	67/M	54/M	64.8 (5.4)
Disease duration (years)	6	12	10	17	12	12	11.5 (3.6)
UPDRS 3 (On-dopa)							
Inclusion	17	19	28	28	40	12	24.0 (10.1)
Month 12	36	28	23	25	43	14	28.2 (10.2)
PPN-DBS	22	24	27	28	24	22	24.5 (2.5)
CuN-DBS	46	28	28	ND	26	19	29.4 (10.0)
GABS (On-dopa)							
Inclusion	12	24	25	30	19	4	19.0 (9.6)
Month 12	29	23	11	24	18	7	18.7 (8.3)
PPN-DBS	22	24	21	18	24	10	19.8 (5.3)
CuN-DBS	46	28	27	ND	26	10	27.4 (12.7)
FOG-Q							
Inclusion	29	36	36	40	44	22	36.3 (5.2)
Month 12	43	34	46	37	42	38	40.0 (4.4)
PPN-DBS	40	32	36	36	33	37	35.7 (2.9)
CuN-DBS	38	35	35	ND	29	39	35.2 (3.9)
ABC scale							
Inclusion	78	68	46	42	43	79	59.5 (17.4)
Month 12	65	69	31	49	35	65	52.3 (16.5)
PPN-DBS	62	62.5	37	63	34	74	55.6 (16.3)
CuN-DBS	30	73	37	ND	34.5	57	50.3 (15.7)
LEDD (mg/d)							
Inclusion	650	2200	1060	1650	2175	1200	1456 (660)
Month 12	650	2085	780	1550	2275	1300	1440 (664)
PPN-DBS	550	1880	900	1450	1690	1350	1303 (497)
CuN-DBS	750	1880	900	ND	1690	1350	1314 (488)

ABC scale= activities balance confidence; CuN= cuneiform nucleus; DBS= deep brain stimulation ; FOG-Q= freezing of gait questionnaire; GABS= gait and balance scale; LEDD= levodopa-equivalent dosage; PPN= pedunculopontine nucleus; UPDRS= Unified Parkinson's disease rating scale.

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Stimulation of the pedunculopontine and cuneiform nuclei for freezing of gait and falls in Parkinson disease: cross-over single-blinded study and long-term follow-up.

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Highlights: 3-5

- Gait and balance disorders were clinically aggravated 2 years after PPN- or CuN-DBS
- Gait parameters were also aggravated with a less degradation with PPN- *vs* CuN-DBS
- Non-axial motor signs were not aggravated after two years with PPN-DBS

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Disclosure

The authors declare to have no conflict of interest relative to the research

Julie Bourilhon, Yannick Mullie, Claire Olivier, Saoussen Cherif and Virginie Czernecki have nothing to disclose.

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Abstract

Introduction Deep brain stimulation (DBS) of the mesencephalic locomotor region, composed of the pedunculopontine (PPN) and cuneiform (CuN) nuclei, has been proposed to treat dopa-resistant gait and balance disorders in Parkinson's disease (PD). Here, we report the long-term effects of PPN- or CuN-DBS on these axial disorders.

Methods In 6 PD patients operated for mesencephalic locomotor region DBS and prospectively followed for more than 2 years, we assessed the effects of both PPN- and CuN-DBS (On-dopa) in a cross-over single-blind study by using clinical scales and recording gait parameters. Patients were also examined Off-DBS.

Results More than 2 years after surgery, axial and Tinetti scores were significantly aggravated with both PPN- or CuN-DBS relative to before and one year after surgery. Gait recordings revealed an increased double-stance duration with both PPN- or CuN-DBS, higher swing phase duration with CuN-DBS and step width with PPN-DBS. With PPN- *versus* CuN-DBS, the step length, velocity and cadence were significantly higher; and the double-stance and turn durations significantly lower. Irrespective the target, we found no significant change in clinical scores Off-DBS compared to On-DBS. The duration of anticipatory postural adjustments as well as step length were lower with *versus* without PPN-DBS. We found no other significant changes in motor, cognitive or psychiatric scores, except an increased anxiety severity.

Conclusion In this long-term follow-up study with controlled assessments, PPN- or CuN-DBS did not improve dopa-resistant gait and balance disorders with a worsening of these axial motor signs with time, thus indicating no significant clinical effect.

1. Introduction

Deep brain stimulation (DBS) of the mesencephalic locomotor region, composed by the pedunculopontine (PPN) and cuneiform (CuN) nuclei, has been proposed to treat dopa-resistant freezing of gait (FOG) and/or falls in advanced Parkinson's disease (PD)[1]. Whereas double-blind controlled studies mainly failed to demonstrate that mesencephalic locomotor region DBS is effective to treat these axial signs, a subjective improvement has been reported in about half of the 5 to 11 patients included in previous long-term follow-up studies (24 to 48 months)[2–4], with heterogeneous results among patients[5,6]. Correlation analyses suggested that good responders have active contacts located within the PPN area[1,5]. However, some experimental and clinical data suggested that DBS applied more dorsally within the CuN could provide beneficial effects on gait and balance [7,8], with higher walking speed and length after short DBS duration[9]. Finally, the long-term effects on parkinsonian gait and balance disorders of PPN- and CuN-DBS applied in the same patients have never been reported.

The current study aims to examine the effects of DBS of the PPN or CuN in 6 PD patients with dopa-resistant FOG and/or falls, 24 to 36 months after surgery, with a cross-over single-blind design assessment using both clinical scales and gait recordings to specifically assess gait and balance control.

2. Methods

2.1 Subjects

Six patients with PD were operated for DBS of the mesencephalic locomotor region and prospectively followed for a mean of 30.7 months (SD 5.4). Details on inclusion and exclusion

criteria have been reported previously [9]. Patients had an advanced form of PD with a mean disease duration of 11 years (SD 6) at the time of surgery with dopa-resistant FOG and/or falls (Table). Patients had bilateral mesencephalic locomotor region DBS with two 8 in-line contacts electrodes to target the PPN, located at the level the pontomesencephalic junction, and the CuN dorsally located along the same trajectory (Figure-A). The study was approved by the local ethics committee (CPPRB Ile-de-France Paris 6). All subjects gave an informed written consent before enrolment (ClinicalTrial.gov registration NCT02931097).

2.2 Procedures

Patients were assessed at the time of inclusion one month before surgery, and 12 months after surgery with PPN-DBS, both Off and On-dopa treatment[9]. At the first long-term follow-up visit, patients were assessed with their usual chronic DBS settings, i.e. with PPN-DBS (patients P02, P03, P04, P05 and P06) or CuN-DBS (P01), and after switching off the DBS for 1 hour. For the patients with PPN-DBS, CuN-DBS was then applied for the following 3-4 months, and for the patient with CuN-DBS, we applied PPN-DBS. For this, we chose bipolar DBS with confirmed location within the PPN and CuN areas (for details see [9], Figure-A), with low frequency of stimulation (20-30 Hz) and pulse width (60 us), with amplitude chosen below the occurrence of side effects. Patients were then re-assessed first On-DBS, and after switching off the DBS for 1 hour. These two long-term assessments were performed after the intake of their usual antiparkinsonian treatment (On-dopa, Table). Clinical scales and spatiotemporal parameters of gait initiation recordings were assessed at each visit.

The clinical scales were: the MDS-UPDRS part 1: mental status, part 2: ADL, part 4: levodopa-related motor complications, and part 3: motor disability score, comprising the 'axial' score; the gait and balance scale (GABS); the Tinetti scale; the freezing of gait questionnaire (FOG-Q); the Activities-Balance Confidence (ABC) scale; the Parkinson's

Disease Questionnaire (PDQ-39); the Mattis Dementia Rating Scale (MDRS); the Comprehensive Psychopathological Rating Scale; which includes the Montgomery and Asberg Depression rating Scale (MADRS); and Brief Anxiety Scale (BAS); and the Hospital Anxiety and Depression Scale (HAD).

Spatiotemporal parameters of gait initiation, straight forward gait and turn were recorded using a force platform (0.9X1.8m, Advanced Mechanical Technology Inc. LG6-4-1) and the VICON system with Plug-In-Gait model with markers positioned on the arm and leg joints. The patients, barefoot, initiated gait on the force platform and walked for 5-6 m at a self-paced speed, making a half-turn and returning to the initial position (n=15-20 trials). The following parameters were calculated during: 1) gait initiation with anticipatory postural adjustments (APAs) phase including the posterior and lateral displacements of the center of foot pressure, and APAs duration, first step length, width and velocity; 2) straight-forward gait with cadence, stride-length, stride time variability, velocity, double-stance duration, and duration of freezing episodes; 3) turn amplitude and duration[9].

Safety was also assessed and we classified any new symptoms as adverse events.

2.3 Statistical analysis

Here, we aim to assess the effects of long-term PPN-DBS or CuN-DBS relative to baseline assessment obtained before and one year after surgery. We also compared the changes in clinical and gait parameters between PPN-DBS and CuN-DBS, and also between On and Off-DBS conditions. For this purpose, we modelled each outcome using a linear mixed-model. We included treatment condition (baseline, Month 12, Month 24-28) and a period effect as fixed effects, and patient intercepts as random effects. We used R (version 3.3.1, R Core Development Team) for the statistical analysis, with the *LmerTest* package for the linear

mixed-effect model testing using the Satterthwaite approximation for degrees of freedom. We used a significance threshold of 0.05. Post-hoc comparisons were FDR-corrected.

3. Results

Among the 6 patients included, PPN-DBS was chronically applied in 5 patients and CuN-DBS in one patient. For the long-term cross-over assessments, 5 patients performed the full assessments for both PPN- and CuN-DBS. One patient (P04) only performed the first assessment with PPN-DBS, the second assessment being cancelled with a premature drop-out due to recurrent falls leading to hip fracture (Table).

3.1 Effects of long-term mesencephalic locomotor region DBS on parkinsonian disability and gait and balance disorders

At the long-term cross-over assessments, we found a significant increase in the axial score and a significant decrease in the Tinetti static score compared to before surgery and one year after surgery with both PPN- or CuN-DBS (Figure-B). We found no other significant changes in motor (UPDRS part 3, non-axial motor, Tinetti dynamic, GABS, FOG-Q, ABC-scale scores, Table, Figure-B), cognitive (MDRS) or psychiatric (MADRS, BAS scores) scores, except an increase in the HAD score (not shown).

For gait parameters, we found that the double stance phase duration was significantly higher with PPN- or CuN-DBS relative to before surgery and one year after surgery. The step width was also higher with PPN-DBS (Figure-C). With CuN-DBS, the swing phase duration was significantly higher, and the lateral CoP APAs significantly lower ((p=0.001 and p=0.037, respectively).

3.2 Effects of CuN-DBS relative to PPN-DBS on gait and balance disorders

We found no significant difference for clinical scores between PPN- and CuN-DBS (Table, Figure-B). For gait parameters, we found that with PPN- *versus* to CuN-DBS, the mean step length, cadence and walking velocity were significantly higher; and the step width, double stance and turn durations (Figure-C and D), and number of FOG episodes during straight-forward walking (not shown) significantly lower with no other significant differences.

3.3 Changes in gait and balance disorders Off relative to On-DBS

Comparing Off versus On-DBS, we found no significant change in any clinical scores, whatever the target. For gait parameters, APAs duration and step length were lower On- vs Off-PPN-DBS (Figure-C), and the step width was lower On- vs Off-CuN-DBS (Figure-C), with no other significant differences.

3.4 Antiparkinsonian treatment, contact locations and deep brain stimulation parameters

During the follow-up period relative to inclusion, the antiparkinsonian treatment was slightly decreased in 4 patients or increased in 2 patients (Table).

For PPN-DBS contacts, the mean (SD) X-laterality, Y-anteroposteriority and Z-depth coordinates relative to the 4th ventricle floor and pontomesencephalic junction were 6.1 (1.1), 8.5 (3.6) and -1.9 (1.0) mm, respectively and for CuN-DBS contacts, 8.4 (2.6), 10.8 (3.9) and 4.4 (2.7) mm. Stimulation parameters were 20 or 30 Hz frequency, with a pulse width of 30 or 60µs, using bipolar stimulation with an amplitude ranging from 1.8 to 3.6V.

3.5 Adverse events

Six adverse events were reported during the follow-up period consisting mainly of persistent FOG with recurrent falls. Due to recurrent falls, one patient (P04) had a hip fracture that needed surgical intervention and hospitalization considered to be a serious adverse event, that prevented to perform the final assessment. One patient (P03) had an unexpected arrest of their neurostimulator due to full discharge that occurred between two visits.

4. Discussion

We report for the first time the long-term effects of PPN- and CuN-DBS with clinical and physiological assessments of gait and balance disorders in a small homogeneous cohort of advanced PD patients. We found that gait and balance disorders On-dopa were aggravated two years after surgery and were not alleviated with either PPN- or CuN-DBS. We observed no significant effects or aggravation of other parkinsonian signs.

In line with the effects obtained one year after surgery in the same cohort of patients [9], we observed that 2 to 3 years after surgery, On-dopa mesencephalic locomotor region DBS did not improve gait and balance disorders compared to before surgery or without DBS. This lack of objective improvement of mesencephalic locomotor region DBS applied for more than 2 years was also previously reported in a study with blinded assessment performed in 8 patients[4]. No significant changes in objective clinical scores were also demonstrated in open-label studies with long-term assessments[2]. Moreover, in other long-term follow-up studies, data in about 25-30% of cases are also missing due to either death or inability to perform the tests, further suggesting no significant long-term positive effects. However, some authors reported a subjective improvement of FOG and falls two years after surgery in about 1/3 of patients with decreased FOG or falls items of the UPDRS part II [2–4,8]. However, in our patients, only one (P07) reported a subjective improvement in FOG severity (FOG-Q), and none a subjective improvement in the feeling of postural instability (ABC scale). This apparent discrepancy could be due to a different location of DBS electrodes in our patients in comparison to other teams[5]. However, the comparison of our PPN-DBS coordinates with another study does not favor this hypothesis, since their coordinates (mean laterality, anteroposteriority and depth of 5.3, 8.4 and -0.8 mm, respectively)[5] should correspond to

the highest density of remaining PPN cholinergic neurons. We hypothesize that in our severe and advanced PD patients, the lack of benefit could be due to the profound loss of cholinergic neurons, with insufficient stimulation of the remaining cells[1]. When applied within the CuN, located more dorsally, we also observed no positive clinical effects on axial motor signs, with even poorer gait performance relative to PPN-DBS. The CuN contains non-cholinergic neurons and has been shown to promote high speed running in mice when stimulated optogenetically[10,11] and evoked locomotion in decerebrated cats[12]. In monkeys, lesions of the CuN induce increased forelimb and neck tone as well as increased step speed[13]. Thus, the CuN could be more involved in initiation of high-speed gait and tonus control of the upper body parts, with therefore less influence on self-paced gait.

Finally, we observed no significant aggravation of non-axial motor PD disability during the follow-up period, with mesencephalic locomotor region DBS, with also a mild decrease in the antiparkinsonian treatment in 4/6 patients. This suggests that DBS applied within the mesencephalic locomotor region could decrease parkinsonian motor disability, as reported in primates rendered parkinsonian showing increased movements after low frequency PPN-DBS[14].

Our study has some limitations. First, the number of patients was limited. Second, we tested first PPN-DBS in 5 out of 6 patients, without randomization of the DBS conditions, and with different duration of chronic DBS between PPN and CuN-DBS assessments. This could have influenced the effects obtained. However, we observed no significant changes in clinical scores between PPN- and CuN-DBS conditions, as well as relative to before surgery and no significant changes in clinical or gait parameters after switching off the DBS.

Our results do not support PPN- or CuN-DBS to treat doparesistant gait and balance disorders in advanced PD. Further research is needed to elucidate the role of this brainstem region in locomotion and balance in humans and dysfunction in FOG or falls of PD patients.

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Figure. Active contacts locations and effects of CuN and PPN-DBS on parkinsonian motor disability and gait and balance disorders.

A) Location of the contacts used for DBS and reported on right and left sagittal 3D-views after fusion with the 3D MRI image. The pink and light-blue outline the cholinergic PPN an GABAergic CuN neurons, respectively. The active contacts used for PPN-DBS are represented in green and those for CuN-DBS in yellow. Graphs represent B) the non-axial and axial parkinsonian motor and Tinetti static scores (On-dopa) and C) gait initiation parameters obtained before surgery, 12 months after surgery with PPN-DBS (M12), and during the long-term follow-up period with CuN-DBS or PPN-DBS On-dopa. D) Cadence and velocity during straight-forward walking and turn duration with CuN-DBS or PPN-DBS (On-dopa) obtained during the long-term follow-up period.

Each color point represents an individual patient, and light and dark grey boxes parameters obtained in the Off-DBS and On-DBS conditions, respectively. Horizontal black lines represent the estimated marginal mean for each condition, and the upper and lower bound of the grey rectangles the corresponding 95% confidence intervals.

APAs= anticipatory postural adjustments, M=month, PPN=pedunculopontine nucleus, CuN= cuneiform nucleus, *p< 0.05.

Table. Baseline demographic characteristics and effects of PPN-DBS and CuN-DBS in 6 PD patients

	P01	P02	P03	P04	P05	P06	Mean (SD)
Age/sex	65/M	68/M	67/F	68/M	67/M	54/M	64.8 (5.4)
Disease duration (years)	6	12	10	17	12	12	11.5 (3.6)
UPDRS 3 (On-dopa)							
Inclusion	17	19	28	28	40	12	24.0 (10.1)
Month 12	36	28	23	25	43	14	28.2 (10.2)
PPN-DBS	22	24	27	28	24	22	24.5 (2.5)
CuN-DBS	46	28	28	ND	26	19	29.4 (10.0)
GABS (On-dopa)							
Inclusion	12	24	25	30	19	4	19.0 (9.6)
Month 12	29	23	11	24	18	7	18.7 (8.3)
PPN-DBS	22	24	21	18	24	10	19.8 (5.3)
CuN-DBS	46	28	27	ND	26	10	27.4 (12.7)
FOG-Q							
Inclusion	29	36	36	40	44	22	36.3 (5.2)
Month 12	43	34	46	37	42	38	40.0 (4.4)
PPN-DBS	40	32	36	36	33	37	35.7 (2.9)
CuN-DBS	38	35	35	ND	29	39	35.2 (3.9)
ABC scale							
Inclusion	78	68	46	42	43	79	59.5 (17.4)
Month 12	65	69	31	49	35	65	52.3 (16.5)
PPN-DBS	62	62.5	37	63	34	74	55.6 (16.3)
CuN-DBS	30	73	37	ND	34.5	57	50.3 (15.7)
LEDD (mg/d)							
Inclusion	650	2200	1060	1650	2175	1200	1456 (660)
Month 12	650	2085	780	1550	2275	1300	1440 (664)
PPN-DBS	550	1880	900	1450	1690	1350	1303 (497)
CuN-DBS	750	1880	900	ND	1690	1350	1314 (488)

ABC scale= activities balance confidence; CuN= cuneiform nucleus; DBS= deep brain stimulation ; FOG-Q= freezing of gait questionnaire; GABS= gait and balance scale; LEDD= levodopa-equivalent dosage; PPN= pedunculopontine nucleus; UPDRS= Unified Parkinson's disease rating scale.

Figure(s)

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