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A case series and systematic review of rapid eye movement sleep behavior disorder outcome after deep brain stimulation in Parkinson's disease

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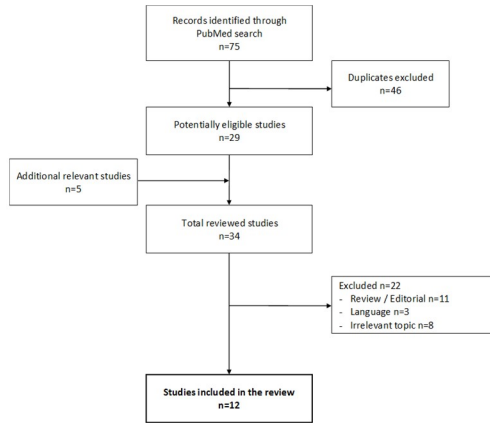
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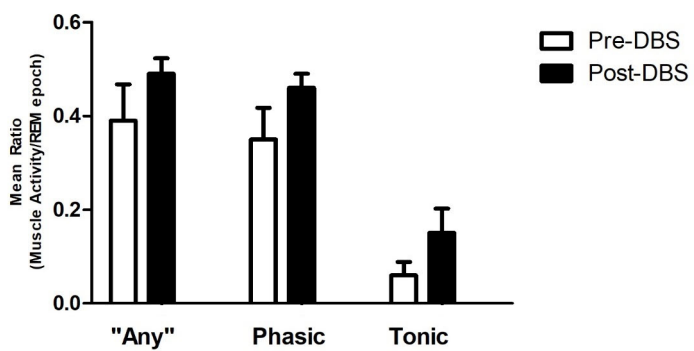
Table 1 DBS Studies that reported on RBD, in order of patient population size or alphabetical

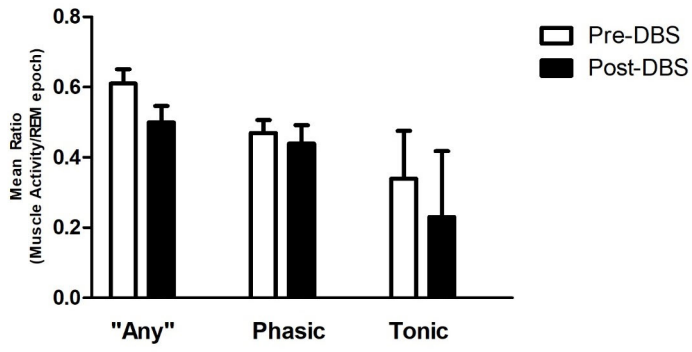
Author, Number of Patients and Stimulation Target	Mean disease duration at baseline \pm SD [years]	pre / post DBS LEDD [mg], mean	Antidepressants / Benzodiazepines during observation	Motor improvement after DBS in % or absolute values in UPDRS III (medication on/off)	Effect of DBS on RBD
Studies that used polysomnography for the diagnosis of RBD					
Arnulf et al. [25] 10 patients (STN)	not stated	- / 372 only post-DBS LEDD (w/o dopamine agonists) values were reported	Yes / Yes	-66% in UPDRS-III (on)	Increased phasic EMG activity in REM sleep
Bargiotas et al. [9] 50 patients (STN)	RBD-group: 11.9 ± 3.9 nonRBD-group: 11.7 ± 4.4	RBD-group: 1172 / 384 nonRBD-group: 1242 / 357	not stated	RBD-group: -35% in UPDRS-III (on) nonRBD-group: -21% in UPDRS-III (on)	RBD assessed only pre-DBS
Baumann-Vogel et al. [24] 50 patients (STN)	12 ± 5	1025 / 369	Yes / Yes	-35% in UPDRS-III (on)	No impact on the prevalence of RBD and on RSWA
Cicolin et al. [20] 5 patients (STN)	13.8 ± 4.9	1010 / 116	Yes / Yes	-45% in UPDRS-III (off)	No difference in RSWA
Dulski et al. [19] 36 patients (STN) evaluated by RBD1Q (36 patients) and PSG (24 patients)	11.4 ± 4.3	1653 / 1142	not stated	-2 points in UPDRS-III (on)	Decrease of RBD symptoms in questionnaires, but no RBD recorded on PSG
Iranzo et al. [18] 11 patients (STN)	17.3 ± 9.1	No absolute values indicated	Yes / Yes	-64% in UPDRS-III (off)	No difference in phasic EMG activity in REM sleep
Monaca et al. [21] 10 patients (STN)	12.1 ± 2.6	1078 / 562	Yes / Yes	-36% in UPDRS-III (off)	No RBD detected

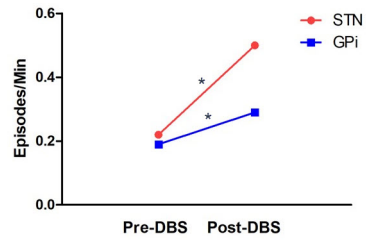
Nishida et al. [26] 10 patients (STN)	12.3	663.2 / 335.5 (w/o dopamine agonists)	Yes / Yes	-38% in UPDRS-III (off)	Decrease in tonic EMG activity in REM sleep, resolution of RBD-related symptoms
Piette et al. [23] 1 patient (STN)	12	LEDD not calculated	not stated	Only pre-DBS score indicated UPDRS-III: 60 (off)	Single episode of RBD (EMG and behavioral) directly after electrode implantation
Tolleson et al. [27] 5 patients (GPi)	9.8 ± 4.0	1537 / 1129	not stated	change after DBS not stated	No RBD detected
Studies that used questionnaires for the diagnosis of RBD					
Kim et al. [17] 90 patients (STN) evaluated by a clinical interview	14.8 ± 4.5	1033 / 370	Yes / not stated	RBD-group: -22 points in UPDRS-III (off) nonRBD-group: -18 points in UPDRS-III (off)	Increase in clinical RBD
Zibetti et al. [22] 42 patients (STN) evaluated by a semi-structured clinical interview	16.7 ± 5.1	RBD-group: 1091 nonRBD-group: 935 / (no post DBS values were reported)	Yes / Yes	RBD-group: -21 points in UPDRS-III (off) nonRBD-group: -29 points in UPDRS-III (off)	RBD assessed only pre-DBS

SD, standard deviation; LEDD, levodopa equivalent daily dose; DBS, deep brain stimulation; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; RBD, rapid eye movement sleep behavior disorder; STN, subthalamic nucleus; GPi, globus pallidus internus; PSG, polysomnography, RBD1Q, rapid eye movement single question scale; EMG, electromyography









Study Highlights

- A systematic review of the literature reveals that, increasing number of studies, report on rapid eye movement sleep behavior disorder outcome after deep brain stimulation, however, results are inconsistent.

Our findings suggest the followings:

- REM sleep without atonia is not significantly affected by deep brain stimulation
- Complex behavior in REM sleep increases after deep brain stimulation independent of the stimulation target
- Complex behavior in REM sleep and REM sleep without atonia might represent two distinct elements in rapid eye movement sleep behavior disorder and should be assessed separately, especially in studies that report on rapid eye movement sleep behavior disorder outcome after treatment interventions.

A case series and systematic review of rapid eye movement sleep behavior disorder outcome after deep brain stimulation in Parkinson's disease

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KEYWORDS

rapid eye movement sleep without atonia; REM sleep behavior disorder; Parkinson's disease; deep brain stimulation; complex behavior; dream enactment; tonic activity; phasic activity

ABSTRACT

REM-sleep behavior disorder (RBD) is a parasomnia and a common sleep disorder in Parkinson's disease (PD). While deep brain stimulation (DBS) is an established treatment for advanced PD with beneficial effects on cardinal PD motor symptoms, the data on the impact of DBS on RBD are limited and often controversial.

We reviewed published articles that reported on RBD in the context of DBS surgery via systematic PubMed search. We identified 75 studies and included 12 studies, involving a total of 320 subjects, in our review. Results in respect to EMG activity outcome after subthalamic stimulation are inconsistent. We found no study that reported on RBD outcome after pallidal DBS and no DBS study quantified complex behavior during REM sleep.

We also added data on RBD outcome after subthalamic (N=4 patients) or pallidal (N=3 patients) DBS from patients with PD with RBD, obtained as part of a prospective DBS study in our centre. Our case series showed an increase of complex behavior during REM (CB-REM) after surgery, independent of DBS target. Conversely, we found a trend towards increasing REM sleep without atonia (RSWA) in subthalamic-stimulated patients and a trend towards decreased RSWA in pallidal stimulated patients.

We conclude that CB-REM and RSWA might represent two distinct elements in RBD and should be assessed separately, especially in studies that report on RBD outcome after treatment interventions. Further, larger, prospective, controlled studies in different DBS targets, reporting separately on the different RBD modalities, are needed.

INTRODUCTION

Rapid eye movement (REM) sleep behavior disorder (RBD) is a REM parasomnia. According to the 3rd International Classification of Sleep Disorders (ICSD-3), diagnosis of RBD is based on the presence of repeated episodes of vocalization or complex motor behaviors during REM sleep in polysomnography (PSG) and on polysomnographic recording of REM sleep without atonia (RSWA). RBD is very common among patients with Parkinson's disease (PD), already from the early PD stages[1] and recent evidence suggest that the presence of RBD is associated with differences in the spectrum of clinical symptoms, in natural history and prognosis of PD which are likely to imply underlying differences in pathophysiology among PD patients with and without RBD.

Deep brain stimulation (DBS) is a well-established treatment for motor disability in advanced PD. Solid evidence regarding improvement of PD motor symptoms is available mainly for stimulation of basal ganglia (BG) structures such as the subthalamic nucleus (STN)[2,3] and the globus pallidus internus (GPi)[4]. In recent years, several studies reported on the impact of DBS on non-motor symptoms of PD such as cognitive, psychiatric, mood and sleep-wake disturbances. In particular, the interest in the impact of STN- and GPi-DBS on RBD is increasing[5], mainly due to the involvement of BG structures a) in REM sleep and REM atonia regulatory networks, via indirect and direct projections to brainstem structures[6] and b) in the processing of information from associative and limbic structures to the cortico-striato-thalamo-cortical pathways, which is an important step for executive functioning and motor behavior[7].

Here we summarize and systematically review published literature on RBD outcome after STN- and GPi-DBS in PD patients. In addition, we added clinical data from seven PD patients with RBD at our center where complex behavior during REM (CB-REM) and different types of EMG activity during REM were separately assessed before and after STN- or GPi-DBS.

METHODS

Review

Extraction of articles was performed by two authors (F.C. and P.B.) and was evaluated by the rest of the authors.

Selection criteria: a systematic review of 1) articles in English 2) published until May 31st, 2020 using PubMed database was performed. 3) We used the search terms “Parkinson’s disease” and “deep brain stimulation” or “pallidal stimulation” or “subthalamic stimulation” in combination with “rapid-eye movement sleep behavior disorder”, “REM sleep behavior disorder”, and “RBD”, in order to identify articles addressing the RBD outcome after DBS in patients with PD. 4) The articles should contain an abstract. 5) Only original articles were included in the study. Review articles were only used to identify further relevant literature.

Case Series

The protocol for this prospective case series was approved by the local ethics committee (KEK Bern 2016-00567). All patients gave their written informed consent.

Patients

This is a preliminary analysis of the first 20 patients included in our prospective single-center study focused on the impact of STN- and GPi-DBS on sleep-wake disturbances and other non-motor symptoms in PD patients. Among 20 recruited patients, 9 patients were diagnosed with RBD based on clinical and PSG criteria for RBD diagnosis. One patient has been excluded from the study due to the lack of REM-sleep in the follow-up examination, another one due to explantation of the DBS-electrodes (recurrent infections). There were no other sensorimotor or life-threatening complications.

Data from 7 patients with PD[8] and confirmed RBD who underwent a sleep-wake assessment prior to bilateral DBS (inclusion and exclusion criteria for DBS as previously published)[9] and 6 months post-DBS at the University Hospital Bern have been analyzed. Among them, 3 patients had GPi and 4 had STN stimulation.

Motor Assessment

We performed the Unified Parkinson’s Disease Rating Scale (UPDRS part III) to assess motor parkinsonian signs[10]. The UPDRS-III was evaluated at baseline pre-DBS and at 4 to 6 months follow-up post-DBS, both times on dopaminergic medication titrated for best individual clinical response. Levodopa equivalent daily dose (LEDD) was calculated as previously described[11].

Video-Polysomnography

Standard nocturnal video-polysomnography (v-PSG) was performed during hospitalization as previously described[12]. All recordings were performed by Embla RemLogic™ Software. Sleep stages and sleep-associated events were manually scored (high frequency filter was set to 15 Hz in the electroencephalography channels and to 35 Hz in the electromyography channel) according to the AASM criteria[13].

Video Analysis of Complex Behavior

REM-related behaviors in patients with RBD may vary in character, intensity, duration and complexity. They may range from simple movements and vocalizations, such as muscle twitches, jerks, mumbling and shouting, to complex behaviors, like running, punching, kicking, swearing and talking. Despite some efforts (see review by Neikrug et al.[14]), there is no established classification system of the motor events observed during RBD episodes.

According to available literature on the type of motor events based on video/audio/EMG analysis [15], motor events were categorized as following:

Primitive myoclonic events and twitching were defined as isolated, simple or even exaggerated, abrupt, brief, jerky, involuntary, non-purposeful, arrhythmic or rhythmic movements involving extremities, trunk, head, face or the whole body.

As complex events were classified all types of REM-related events with higher duration and complexity than primitive myoclonic events, jerks or twitches. These include semi-purposeful or purposeful movements, often, but not explicitly, involving more than one parts of the body, orofacial events (i.e. grimacing), vocalizations (emission of phonemes, shouting, crying, and intelligible or non-intelligible sleep talking) and dream enactment events, which are complex movements with excessive motor activity and often scenic, violent, forceful or even injurious character.

For the CB-REM analysis of the current study, only events from the second group (complex events) were included. Primitive myoclonic events were not visually quantified. An event was deemed as terminated, when there was no more visually or audibly evident activity of the patient in the video/audio/EMG recording.

Visual EMG Scoring

During PSG, muscle activity was measured at the chin and bilaterally at upper (m. flexor digitorum superficialis) and lower (m. tibialis anterior) extremities; muscle tone scoring was based on chin and upper extremities signals.

Sleep stages were scored in 30-seconds-intervals according to the AASM criteria[13]. We used two previously published EMG-scoring methods to quantify muscle activity only in REM sleep, one using 3-seconds and another using 30-seconds-epochs.

For the analysis of 3-seconds-epochs we used EMG scoring criteria as previously suggested [16]. In the upper extremity muscles, missing atonia was defined only if phasic EMG activity was present. Phasic activity was defined as a burst with an amplitude with at least double the background EMG voltage and with a duration between 0.1 and 5 seconds. The end of such a burst is defined as soon as the potential returns to the baseline or there is an identifiable interval between two bursts of at least 250 milliseconds.

In the mentalis muscle, missing atonia was defined as any EMG activity occurring in a defined 3-sec-epoch during REM-sleep; EMG activity was considered as any potential lasting longer than 0.1 sec and with an amplitude of at least double the EMG background activity or higher than 10 μ V, consisting of the following morphologies:

- Tonic activity, if >50% of the epoch had muscle activity continuously greater than double the background EMG voltage
- Phasic activity as defined above.

For the analysis of 30-seconds-epochs, we examined only the tonic activity of the mentalis muscle, as previously suggested[16]. An epoch was considered positive for tonic activity if >50% of the epoch had muscle activity continuously greater than double the background EMG voltage, or ≥ 10 μ V.

In order to compare RSWA between different patients with varying REM durations, we calculated the ratio between RSWA and total REM-time per patient or episode instead of using absolute values for our analysis.

Potentials in any EMG-lead occurring during phases of respiratory distress or constantly and simultaneously recurring with ECG-activity, as well as activity due to other causes of arousal, were considered as artefacts and weren't taken into consideration for the analysis. Presence of

RBD was confirmed when the total of epochs in which EMG activity, as defined above, occurs in at least one of the examined muscles, exceeded 32% of total REM-sleep time[16].

Statistical Analysis

All comparisons were performed by means of the Student's t-test for unpaired datasets or the factorial ANOVA when more than one grouping variable was needed. A multiple regression model analysis was performed to evaluate the correlation between the value of atonia index (dependent variable) and different parameters identified in the study.

A difference in the results between two groups was deemed significant if the calculated p-value was lower than 0.05. Values are given as means \pm standard deviation. All statistical operations were conducted using SPSS[®] and GraphPad Prism[®] software.

RESULTS

After the initial search and the application of exclusion criteria, 12 studies with a cumulative total of 320 patients, met all selection criteria and were included in the systematic review (Figure 1). The largest study included 90 subjects. Among these studies, 11 reported exclusively on STN-DBS and 1 exclusively on GPi-DBS. Ten studies used polysomnography for the assessment of RBD and 2 studies used RBD questionnaires but no PSG for the diagnosis of RBD.

RBD Prevalence after DBS

Kim et al. reported an overall increase in RBD incidence after STN-DBS in a large PD population (N=90). The prevalence of RBD prior to DBS was 52% (N=47). After implantation, almost all RBD patients (N=46) reported that RBD symptoms persisted, in 13 of them (27.6%) the severity of symptoms decreased. Sixteen patients (17.7%) reported new-onset RBD symptoms[17]. However, most of the studies reported no marked changes in the prevalence of RBD after DBS. In the early study by Iranzo et al., eight among eleven PD patients had polysomnographic confirmed RBD and history of vigorous movements during sleep. After STN-DBS, the prevalence of RBD was re-assessed by polysomnography and found unchanged compared to pre-DBS baseline. However, the study did not report in detail

on EMG activity or complex behavior data[18]. In a more recent study by Dulski et al. with 36 patients, REM atonia was surprisingly preserved in all 24 PD patients undergoing PSG before and after STN-DBS. After surgery, fewer patients reported RBD symptoms in RBD questionnaires[19]. In the study by Cicolin[20] one among five PD patients had RSWA which remained unaffected by STN-DBS. Monaca et al.[21] assessed ten patients via polysomnography, but no patient was diagnosed with RBD before and after STN-DBS. Our previous study[9] and the study by Zibetti et al.[22] investigated whether the presence of RBD before DBS has an impact on motor and non-motor outcome after STN-DBS but both studies did not report on post-DBS RBD outcome. Piette et al. reported a PD patient without RBD, who had immediately after the implantation of the definitive electrode for left subthalamic stimulation multiple RBD episodes of behavioral agitation and confirmed RSWA in polysomnography. The patient never presented any similar episodes again during the 3-year postoperative period[23].

Outcome of RSWA after DBS

The largest DBS study that reported both on RBD and RSWA outcome was published recently by Baumann-Vogel et al.[24]. Authors assessed 50 PD patients with polysomnography before and after STN-DBS and found no impact of DBS on RBD prevalence and on RSWA (SINBAR criteria cut-off pre-DBS: 65.9% and post-DBS: 64.4%)[24].

The first study to report on EMG activity outcome after DBS was the study by Arnulf et al.[25]. In this study, RBD was diagnosed in 5 of 10 patients with PD and the prevalence of RBD remained unchanged after STN-DBS. In these five patients, EMG activity (only phasic activity was reported) was not alleviated by STN-DBS, in contrary it increased in 4 out of 5 patients. Interestingly, in the same study, the authors reported that in the very same patients nocturnal shouting and agitation persisted and were even slightly worsened under stimulation, without however presenting quantification data in polysomnography[25]. Another study by Nishida et al. assessed post-DBS EMG activity in 10 PD patients after STN-DBS[26]. In all four patients, tonic chin EMG density before DBS was present in more than 30% of total REM sleep time and two among four patients reported dream-enacting behaviors as well. In 3 of the 4 patients RBD features improved after DBS. Specifically, tonic chin EMG density was reduced in 3 patients, nocturnal vocalization resolved in one patient and in another patient, EMG activity and nocturnal behaviors remained unchanged. Finally, Tolleson et al.

assessed REM sleep without atonia before and after pallidal stimulation in five PD patient, but no REM sleep without atonia was observed[27].

Case Series

At baseline, the mean age of patients, the mean levodopa equivalent daily dose (LEDD) and mean UPDRS III were 67.7 ± 2.9 years, 820 ± 669 mg, 12.5 ± 4.2 for STN-group and 70.7 ± 2.0 years, 602 ± 388 mg, 12.0 ± 4.6 for GPi-group respectively.

In the STN-group, the total number of REM-phases, the total REM duration and the mean REM sleep duration per patient were $n=15$, 169 min and 42.6 ± 42.3 min pre-DBS and $n=16$, 171.5 min and 42.9 ± 12.2 min post-DBS.

In the GPi-group, the total number of REM-phases, the total REM duration and the mean REM sleep duration per patient were $n=17$, 169 min and 56.3 ± 23.2 min pre-DBS and $n=12$, 85.5 min and 28.5 ± 14.8 min post-DBS.

In respect to RBD prevalence, after surgery, RBD was still present in all seven subjects as polysomnography continued to detect excessive EMG activity combined with complex behavior.

In the STN-group, pre-DBS, in 15 REM phases the mean ratio number of epochs with RSWA per number of REM epochs for “any” muscle activity was 0.39 ± 0.30 , for phasic muscle activity was 0.35 ± 0.26 and for tonic muscle activity was 0.06 ± 0.11 . Post-DBS, in 16 REM phases the mean ratio for all types of muscle activity was higher compared to pre-DBS, but did not reach significance (for “any” muscle activity 0.49 ± 0.13 , $p=0.25$, for phasic muscle activity 0.46 ± 0.12 , $p=0.16$ and for tonic muscle activity 0.15 ± 0.21 , $p=0.13$) (Figure 2). In the STN-group, after DBS compared to baseline, “any” and phasic muscle activity increased in 3 out of 4 patients (patients 2,3,4) and decreased in patient 1. Tonic muscle activity increased in 2 out of 4 patients (patients 1,4), decreased in patient 2 and remained unchanged in patient 3 (Table 2).

In the GPi-group, pre-DBS, in 17 REM phases the mean ratio number of epochs with RSWA per number of REM epochs for “any” muscle activity was 0.61 ± 0.17 , for phasic muscle activity was 0.47 ± 0.15 and for tonic muscle activity was 0.34 ± 0.56 . Post-DBS, in 12 REM phases the mean ratio for all types of muscle activity was lower compared to pre-DBS but did not reach significance (for “any” muscle activity 0.50 ± 0.16 , $p=0.11$, for phasic muscle

activity 0.44 ± 0.18 , $p=0.60$ and for tonic muscle activity 0.23 ± 0.65 , $p=0.60$) (Figure 3). In the GPi-group after DBS, compared to baseline, “any” and phasic muscle activity decreased in all three patients (patients 5,6,7). Tonic muscle activity decreased in 2 out of 3 patients (patients 5, 6) and increased in patient 7 (Table 2).

Based on the video analysis, in the STN-group, pre-DBS, we identified 38 episodes with CB-REM in 169 minutes of REM (0.22 episodes/min), while post-DBS we identified 87 episodes with CB-REM in 171.5 minutes of REM (0.50 episodes/min). In the GPi-group, pre-DBS, we identified 33 episodes with CB-REM in 169 minutes of REM (0.19 episodes/min), while post-DBS we identified 25 episodes with CB-REM in 85.5 minutes of REM (0.29 episodes/min) (Figure 4).

There was no significant correlation between values of muscle activity (all types; “any”, phasic, tonic) and CB-REM pre-DBS, post-DBS and regarding the observed changes (Δ) with LEDD or UPDRS III (data not shown).

DISCUSSION

In this prospective case series, we analysed clinical and polysomnographic data from PD-patients with RBD prior to and following STN- and GPi-DBS. Our aim was to assess DBS outcome in respect to several types (any, phasic, tonic) of EMG activity and in respect to complex behavior during REM sleep.

RSWA Outcome after DBS

In our cases, REM atonia index is not significantly affected by DBS. In the literature, the results in respect to post-DBS REM atonia outcome are contradictory. Baumann-Vogel et al. reported no change in REM atonia index after STN-DBS[24]. This contradicts with a previous study showing an increased phasic EMG activity in 4 out of 5 patients after STN-DBS[25], but also with the results by Nishida et al.[26] showing a decrease in EMG activity and partial restoration of RSWA, thus a significant positive effect of STN-DBS on RBD. The discrepancy might be due to differences in the scoring methods. Indeed, the EMG-protocol in the study by Nishida was limited to submental muscle leads and REM atonia was not evaluated as index related to REM duration.

To our knowledge, our case series is the first report on EMG activity outcome after GPi-DBS. Previous GPi-DBS studies either did not assess RBD features at all [28], or the included patients had no RBD[27]. Similar to STN-DBS, our findings suggest that GPi-DBS does not have an effect on EMG activity.

Interestingly, although differences in our case series were not significant, we were able to observe a non-significant trend showing an overall increase in all scored types of EMG activities in STN- in opposite to GPi-stimulated patients, where the non-significant trend was towards decrease in all scored types of EMG activity. This might be suggestive that post-DBS RSWA outcome might depend on the stimulated target, however, the very low numbers of the current report do not allow to extract any conclusions. It would be a very interesting future direction for research to investigate, in a larger cohort, whether the stimulation of different DBS targets (STN vs GPi) has a different impact on the several types of EMG activity.

CB-REM Outcome after DBS

This is the first DBS report that includes a quantification of CB-REM based on video-polysomnography to report on the behavioral RBD outcome. We found a significant increase in CB-REM after DBS-implantation, which was independent of dopaminergic medication and motor score outcomes. In addition, CB-REM increased independent of the DBS target, most prominently being the increase in the STN-treated patients. The increased behavioral activity under subthalamic stimulation is in line with previous studies reporting slightly increased nocturnal vocalization[25] or even de-novo occurrence of nocturnal behaviors[17]. However, previously no quantification has been used. It is important to notice that motor events in RBD can be minor movements or twitches, and not all lead to complex or scenic behaviors. In addition, questionnaires may, besides false-negative results, also lead to false-positive findings, often due to the lack of episodes' perception or even due to episodes-mimicking RBD, such as non-REM parasomnias, which are also frequent in Parkinson's disease.

Our findings suggest that BG stimulation impacts the nocturnal REM sleep behavior. On one side this is surprising, since the observed CB-REM in PD, often fluid and with less-parkinsonian kinetic patterns, suggest that during REM sleep, BG may not be the core player for the execution of movements. On the other side, behavioral effects during wakefulness,

including the emergence of impulsive-aggressive behavior, mania, and hypomania[29][30][31] have been previously reported, in particular after STN-DBS. Nevertheless, the role of human BG during REM sleep in PD needs further investigation. Intracranial recordings from basal ganglia during RBD episodes might provide very important evidence towards this direction.

CONCLUSIONS

In the literature, there are discrepant reports in respect to RBD outcome after DBS. This might be due to the used methodology for assessment of RBD outcome. We were able to show that both STN- and GPi-DBS lead to an increase of complex-behavior during REM sleep in PD patients with RBD, which might be perceived from patients and bedpartners as worsening of RBD. However, this increase in nocturnal behavior might not be clearly associated with an increase of EMG activity, which is typically the outcome measure used by polysomnography studies. These findings underline the importance of using video polysomnography to properly diagnose RBD, considering and evaluating separately its modalities (different types of EMG activity and quantification of complex behavior during REM), in particular when reporting therapeutic outcomes. Larger, controlled studies should investigate the role of BG in RBD, especially whether the post-DBS outcome of EMG activity depends on the DBS target.

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