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Post-operative electrode location and clinical efficacy of subthalamic nucleus deep brain stimulation in Meige syndrome

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ABSTRACT

Background: Subthalamic nucleus (STN) deep brain stimulation (DBS) has recently been shown to be an effective treatment for Meige syndrome but efficacy of symptomatic improvement and its relationship to factors in DBS remains to be explored.
Objectives: This study explored the relationship of electrode contact location in bilateral STN-DBS with clinical efficacy in Meige syndrome patients through retrospective analysis.
Methods: Pre- and post-operative magnetic resonance (MR) images of Meige syndrome patients (n = 15) were analysed. Clinical outcomes were evaluated with the Burke–Fahn–Marsden Dystonia Scale (BFMDRS). The location of active contacts in Montreal Neurological Institute (MNI) standard space and volume of activated STN tissue were determined and related to clinical outcomes.
Results: At the last follow up (mean = 14.8 ± 4.0 months; range = 11–24 months), Meige syndrome patients (n = 14) showed improved BFMDRS scores (mean improvement = 70.9%, $p = 0.001$) compared to pre-operative assessment. Active contacts of stimulation given from coordinates in the MNI space (mean left side: x = −12.5 ± 1.2 mm, y = −13.3 ± 1.7 mm, z = −5.5 ± 2.5 mm; mean right side: x = 12.7 ± 1.4 mm, y = −12.7 ± 1.7 mm, z = −6.4 ± 2.4 mm) were found mainly clustered in the dorsolateral STN. While there were no significant differences in patients grouped by their degree of symptomatic improvement (< 30%, 30–70% and > 70%) with their respective coordinates, the volume of activated tissue within the STN of patients was significantly correlated to the BFMDRS improvement (R = 0.6, $p = 0.02$).
Conclusions: These findings further support the stimulation of the dorsolateral STN for effective alleviation of symptoms in Meige syndrome patients and indicate that specific factors of DBS can be considered to predict clinical efficacy.

1. Introduction

Meige syndrome is an adult-onset focal dystonia characterized by blepharospasm, cervical dystonia, and facial oromandibular dystonia [1], occurring more commonly in women than in men (ratio ranged from 1.6:1 to 3.3: 1) [2]. In serious cases, the symptoms of Meige syndrome can lead to functional blindness. With the pathogenesis of Meige syndrome being unclear [3], clinical treatment remains challenging with the disease often being refractory to medication and usually treated with common line therapies such as botulinum toxin [4]. However, despite botulinum toxin being effective for Meige syndrome at early stages, some patients may experience a diminished

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response over time, sometimes due to antibodies that make the patient immune to treatment effects at later stages [5].

In recent years, bilateral deep brain stimulation (DBS) of the internal globus pallidus (GPi) [6] or subthalamic nucleus (STN) [7,8] has been used to treat dystonia. Although STN-DBS for the treatment of Meige syndrome has not been widely reported, previous studies have shown that Meige syndrome patients achieve a substantial improvement when treated with STN-DBS [9]. While certain studies have supported STN-DBS for alleviating dystonia, clinical efficacy varies on a case-by-case basis, highlighting the importance of outcome factors that can predict the clinical benefit following DBS. Previously, optimising stimulation parameters in DBS has been demonstrated as an important factor for improving treatment efficacy. Specifically, the localisation of the stimulating electrode within the target region may be related to the improvement of clinical outcomes [10].

The best clinical improvement (CI) in dystonia is assumed to be achieved by stimulation of specific regions of the STN, such as the dorsolateral functional zone, a key region of the brain motor circuit network [11], and is a common neurosurgical target for Parkinson's disease [12]. The exact anatomical location of the electrode contacts utilized for chronic stimulation in Meige syndrome remains unclear and the relationship between clinical outcome and the location of the electrode contacts in STN remains to be investigated. In this study, long-term clinical outcome in Meige syndrome patients receiving bilateral STN-DBS and the location of active DBS contacts were related in a retrospective fashion.

2. Methods

2.1. Patients

Fifteen consecutive patients with Meige syndrome were studied. All Patients met the diagnostic criteria described by Pakkenberg et al. [13] and underwent bilateral STN-DBS at the Aviation General Hospital of China Medical University between 2014 and 2016. This study (Chinese Clinical Trial Register; ChiCTR; number ChiCTR-ORC-17011398) was approved by the Aviation General Hospital of China Medical University institutional review board and all patients provided written informed consent.

2.2. Clinical evaluation

All patients were diagnosed and evaluated by an experienced movement disorder clinician. Dystonic symptoms were assessed in patients pre- and post-operatively [Baseline; FU1: 1 month after surgery; FU2: 3–6 months after surgery; LFU: the last follow up, 11–24 months after surgery] using the BFMDRS scale (including the movement and disability scales) as previously described [14]. The health-related quality of life was assessed with the 36-item Short-Form General Health Survey (SF-36).

2.3. Surgical procedure and DBS programming

The surgical procedure was carried out as previously described [15]. For all patients, an image fusion procedure (3T MRI and 1.5T MRI), routinely carried out by our group. Images from 3T MRI obtained a day before the surgery were fused with 1.5T (with a Leksell stereotactic frame) on the day of surgical procedure. The coordinates of the target and the entrance trajectory were defined on stereotactic MR images by directly visualizing the STN. Quadripolar DBS leads (model L301, PINS Medical), which had 4 contacts (contact height of 1.5 mm, a spacing of 1.5 mm between each contact and a diameter of 1.3 mm), were bilaterally implanted targeting the STN under local anesthesia in one session. Intraoperative macrostimulation was used to determine the voltage threshold for stimulation-induced adverse effects. At the end of the surgical procedure, a neurostimulator (G102 or G102R, PINS Medical) was implanted into the subclavicular region under general anaesthesia.

Approximately 1 month after implantation, DBS programming was initiated. Monopolar screening was performed for the contacts on each electrode as previously described [16,17]. The optimal parameters were selected when patients achieved satisfactory improvement with minimal side effects. Thereafter, additional adjustments of parameters were made by telemedicine if necessary. The DBS system offered video communication, remote programming and postoperative follow-up, allowing doctors to adjust stimulation parameters for patients with network connection [18].

2.4. DBS electrode localisation and volume of activated tissue estimation

All patients underwent postoperative MRI to exclude surgical complications and for evaluation of electrode contact localisation. Pre- and post-operative MRI were used to calculate the DBS electrode contact location. For subsequent normalisation and electrode localisation, electrode contacts were confirmed on the post-operative MRI. The center of the electrode contact was determined as the center of its artefact visible on the MRI image as described previously [10,19]. SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and LEAD-DBS software (www.lead-dbs.org; [20]) were used to evaluate contact locations and nonlinearly transfer them into standard stereotactic (MNI ICBM2009b NLIN, Asym) space. Volume of the STN in standard space was defined by the DISTAL atlas [21,22]. After verification of electrode locations, the volume of tissue activated (VAT) was calculated as described previously described in Ref. [10]. The overlap between the VAT and the STN was calculated and expressed in mm^3. The sum of the two overlapping VTA/STN volumes from both hemispheres was correlated with the percent change in BFMDRS scores across patients at the last follow up.

2.5. Statistical analyses

All statistical analyses were performed using SPSS 20.0 (IBM Corp., USA). All raw data are reported as mean ± standard deviation (SD). Scores of BFMDRS, quality of life scales, and coordinates of active contacts were analyzed using the Wilcoxon signed-rank or Kruskal–Wallis tests for non-parametric variables. Correlations between the latest improvement in the BFMDRS scores and overlap between VAT and STN were analyzed by using Pearson's correlation given non-Gaussian distributions. Statistical significance level was set at $p < 0.05$.

3. Results

3.1. Patient population

The patients (14 females; 1 male; mean age = 53.3 years; age range = 33–71 years) had a mean disease duration of 3.3 years (range = 0.5–8 years). For the last follow-up, the mean follow-up duration was 14.8 ± 4.0 months (range, 11–24 months) and one patient did not complete the study. The clinical characteristics and demographics of these patients are shown in Table 1.

3.2. Clinical outcomes

At the short term follow up, rapid improvement was observed in most patients, patients had greatly benefited from DBS therapy, with BFMDRS scores significantly reduced compared to pre-operative scores (68.2%; $p < 0.001$). For patient No. 2, however, there was no initial satisfactory outcome at the first clinical visit, but symptoms were seen to improve gradually, whereby a favourable outcome was achieved at the last follow up. Following the chronic high frequency stimulation settings, eight patients showed an improvement of ≥70% and four patients showed an improvement between 30% and 70%.

Table 1
Clinical features of Meige syndrome patients and effective stimulation parameter settings.

Patient No.	Sex	Age at onset, y	Duration of illness, y	Baseline distribution of dystonia	Botulinum toxin treatment	Stimulation parameters at the last follow up [Amplitude (volts)/ Frequency (Hz)/Pulse-width (μsecs)]	Adverse effects	Postoperative follow up time (Months)
1	F	38	3	Eyes	None	NA	None	NA
2	F	64	2.5	Eyes, neck, axial	Accepted	Left: 2.8/130/60; Case(+) 1 (−) Right: 2.8/130/60; Case(+) 5 (−)	None	20
3	F	49	0.5	Eyes, mouth	None	Left: 2.0/130/60; Case(+) 3 (−) Right: 1.3/130/60; Case(+) 6 (−)	None	24
4	F	33	2	Eyes	Accepted	Left: 3.3/130/60; Case(+) 3 (−) Right: 3.3/130/70; Case(+) 7 (−)	None	20
5	F	49	6	Eyes, mouth	Accepted	Left: 3.3/130/60; Case(+) 4 (−) Right: 3.3/130/60; Case(+) 8 (−)	None	16
6	F	48	3.5	Eyes	Accepted	Left: 2.5/130/60; Case(+) 3 (−) Right: 1.0/130/60; Case(+) 8 (−)	None	16
7	F	66	8	Eyes	Accepted	Left: 2.5/130/120; Case(+) 4 (−) Right: 2.0/130/80; Case(+) 8 (−)	None	13
8	F	66	5	Eyes, mouth	Accepted	Left: 2.6/130/60; Case(+) 7 (−) Right: 2.6/130/60; Case(+) 3 (−)	None	12
9	F	56	4	Eyes, mouth	None	Left: 1.7/130/60; Case(+) 7 (−) Right: 1.5/130/60; Case(+) 3 (−)	None	12
10	F	71	2	Eyes	Accepted	Left: 2.8/130/60; Case(+) 7 (−) Right: 2.8/130/60; Case(+) 3 (−)	None	12
11	F	42	5	Eyes, mouth	Accepted	Left: 2.3/130/60; Case(+) 1 (−) Right: 2.3/130/60; Case(+) 5 (−)	None	15
12	M	54	3	Eyes	Accepted	Left: 2.5/135/90; Case(+) 2 (−) Right: 2.5/135/90; Case(+) 6 (−)	None	12
13	F	59	1.5	Eyes, neck, axial	Accepted	Left: 2.65/130/70; Case(+) 4 (−) Right: 2.65/130/60; Case(+) 8 (−)	None	11
14	F	51	1.5	Eyes, mouth	Accepted	Left: 3.05/150/60; Case(+) 3 (−) Right: 2.9/150/60; Case(+) 6 (−)	None	11
15	F	53	2	Eyes	Accepted	Left: 1.8/130/50; Case(+) 6 (−) Right: 1.8/130/50; Case(+) 4 (−)	None	13

Improvements persisted at subsequent evaluations with a mean decrease of 70.9% found at the last follow up ($p < 0.001$). Patients also showed a statistically significant improvement in quality of life, as measured by the SF-36 at the last follow up compared to baseline ($p < 0.05$). This was found in categories for physical functioning ($p < 0.01$), role-physical functioning ($p < 0.01$), bodily pain ($p > 0.05$), vitality ($p < 0.01$), social functioning ($p < 0.01$), role-emotional functional ($p < 0.05$), and mental health ($p < 0.05$; Supplementary Table 1).

3.3. DBS programming and active contact locations

All leads were programmed to monopolar configurations in all patients (mean amplitude = 2.03 ± 0.58 V, range = 0.8–3.0 V; mean pulse width = 63 ± 10 μs, range = 50–90 μs; mean frequency = 133 ± 13, range = 110–170 Hz). At the last follow up, monopolar configuration was used in all patients (mean amplitude = 2.45 ± 0.62 V, range = 1.0–3.3 V; mean pulse width 65 ± 14 μs, range = 50–120 μs; mean frequency = 132 ± 5 Hz, range = 130–150 Hz), as shown in Table 1.

The average coordinates of active contacts in MNI on the left and right were: x = −12.5 ± 1.2 mm, y = −13.3 ± 1.7 mm, z = −5.5 ± 2.5 mm; and x = 12.7 ± 1.4 mm, y = −12.7 ± 1.7 mm, z = −6.4 ± 2.4 mm; respectively (Table 2). The mean coordinates of the active contacts relative to the anterior-posterior commissure were: x = 11.8 ± 1.6 mm, y = −2.0 ± 1.8 mm, and z = −3.0 ± 2.2 mm on the right side and x = −11.2 ± 1.4 mm, y = −2.5 ± 1.8 mm, and z = −2.3 ± 2.5 mm on the left side (Supplementary Table 2).

To characterise whether electrode location was related to clinical efficacy we separated patients into sub-groups in further analysis. Group I, group II and group III comprised of patients with improvement rates < 30%, between 30 and 70%, and improvement rates > 70%, respectively. The active contacts of the electrode locations in the postoperative MRIs according to the improvement rate groups are shown in Fig. 1.

There were no significant differences between the respective coordinates on x-/y- and z-axes among the improvement rates in subgroups, from analysis of the BFMDRS scores ($p > 0.05$; Supplementary Table 3). However, the patients whose electrodes were located within or near the dorsolateral STN showed significantly greater improvement (Fig. 1).

Table 2
Localization of active electrode contacts in Montreal Neurological Institute (MNI) standard space.

Patient No.	Left Side			Right Side		
	X	Y	Z	X	Y	Z
1	−10.1	−13.5	−11.5	10.1	−11.9	−13.1
2	−13.3	−16.3	−6.6	12.5	−14.8	−5.4
3	−12.8	−11.2	−4.2	13.1	−13.4	−7.7
4	−14.4	−11.5	−3.3	12.7	−11.9	−4.0
5	−14.0	−13.7	−4.0	14.7	−10.4	−3.8
6	−11.7	−13.5	−5.6	14.7	−14.0	−6.4
7	−12.1	−11.5	−3.7	11.9	−9.9	−5.0
8	−12.6	−13.0	−4.1	11.6	−13.4	−6.7
9	−12.3	−11.9	−4.4	14.4	−11.7	−5.1
10	−13.1	−12.7	−3.6	12.2	−12.4	−6.3
11	−12.0	−13.2	−5.9	12.7	−13.0	−5.5
12	−10.2	−17.5	−10.6	10.5	−16.5	−8.3
13	−12.3	−13.0	−3.8	12.2	−12.9	−6.0
14	−12.8	−13.7	−7.0	12.2	−13.1	−8.5
15	−13.1	−12.6	−3.9	14.6	−11.6	−3.5
Mean	−12.5	−13.3	−5.5	12.7	−12.7	−6.4

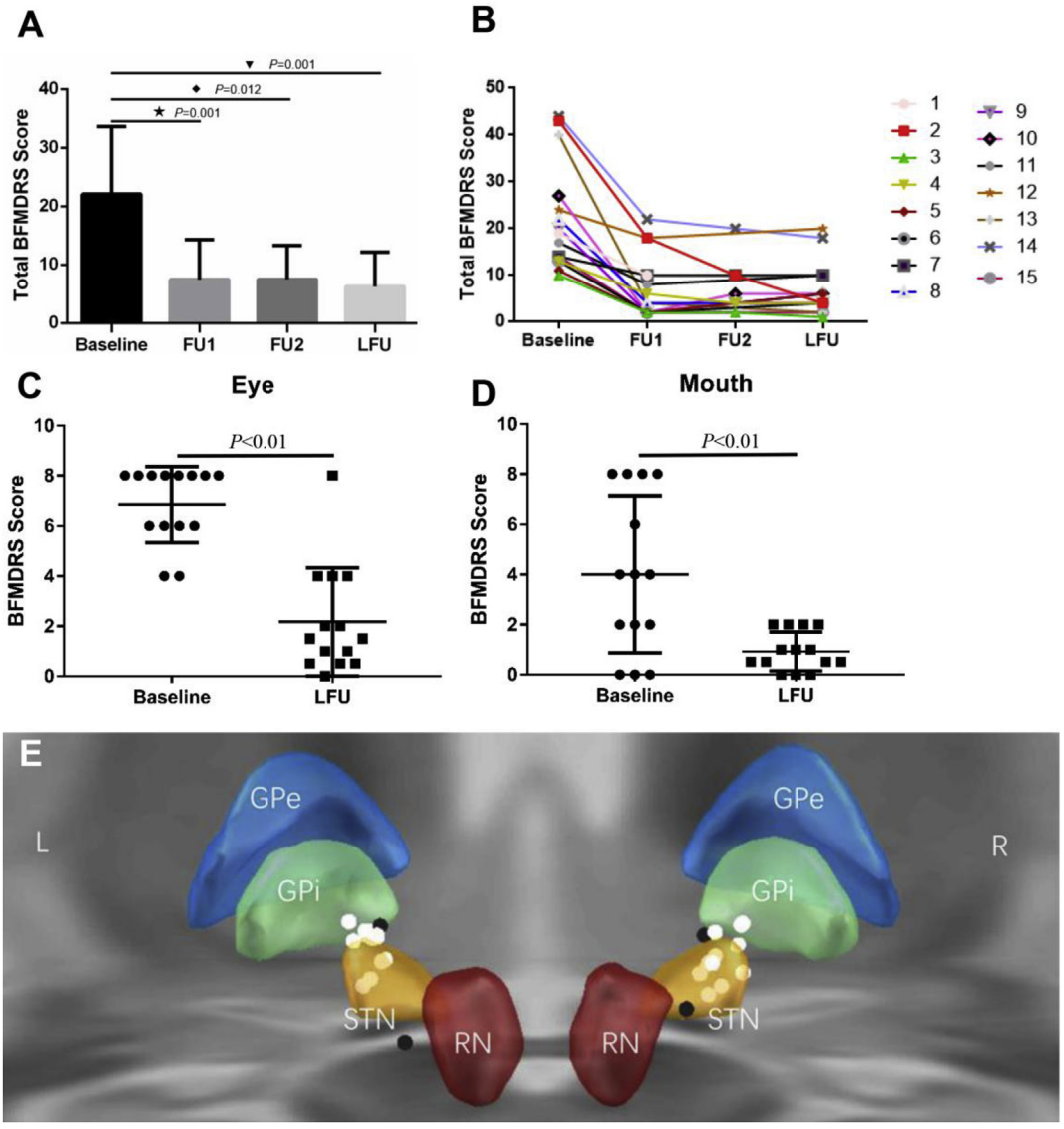

Fig. 1. Localization of electrode contacts in subthalamic nucleus (STN) deep brain stimulation (DBS) and its corresponding clinical improvement in Meige Syndrome patients. (A) Bar graph of the mean + SD scores of the Burke–Fahn–Marsden Dystonia Scale (BFMDRS) total scores pre- and post-operatively [Baseline; FU1: 1 month after surgery; FU2: 3–6 months after surgery; LFU: the last follow up] in Meige syndrome patients (n = 14). *p* values determined by using the Wilcoxon signed-rank test. (B) Line graph showing individual patient BFMDRS scores pre- and post-operatively [Baseline; FU1: 1 month after surgery; FU2: 3–6 months after surgery; LFU: the last follow up]. (C) The individual eye scores at baseline and last follow-up. (D) The individual mouth scores at baseline and last follow-up. (E) 3D illustration of all active electrode contacts (posterior view). The black dots represent group I (improvement rates < 30%) and the white dots represent group II (improvement rates between 30 and 70%) and group III (improvement rates > 70%). STN: subthalamic nucleus. RN: red nucleus. GPi: internal globus pallidus. GPe: external globus pallidus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.4. VAT of electrode active contact and BFMDRS scores

The overlap between VAT and STN was calculated for each patient and summed up to correlate the resulting value with percent BFMDRS improvement. Our hypothesis was that higher portion of stimulated STN would be associated with better clinical improvement. Indeed, this correlation was significant (R = 0.604, p = 0.022; Fig. 2). In one patient (patient No. 12), the stimulation of the ventromedial STN was associated with the worse outcome. Interestingly, in 3 patients (patients No. 5, 6, and 15), where one side of the active contacts was outside the STN, a good clinical response was seen. In another patient (No. 7), however, where the active contact localisation was also outside the STN, there was a poor clinical outcome.

To further illustrate this analysis, two index patients (#12 and 13) were selected and visualized (Fig. 2). In patient #12, the bilateral overlap between STN and VAT was a mere 43 mm^3 and the patient demonstrated the lowest symptom improvement of the cohort (16.7%). Active coordinates in this patient were x = −10.2 mm, y = −17.5 mm, z = −10.6 mm (left hemisphere); and x = 10.5 mm, y = −16.5 mm, z = −8.3 mm (right hemisphere). In contrast, overlap between VAT and STN of patient 13 was 256 mm^3 and the patient showed the highest symptom improvement (95%).

4. Discussion

Three conclusions may be drawn from the current study. First, the study accumulates further evidence that STN-DBS constitutes a highly efficacious treatment for patients suffering from Meige Syndrome. Second, significantly higher clinical improvements were achieved if active contacts resided inside the subthalamic nucleus (compared to outside). Finally, the overlap between the volume of activated tissue and the subthalamic nucleus could explain ≈36% of the variance in

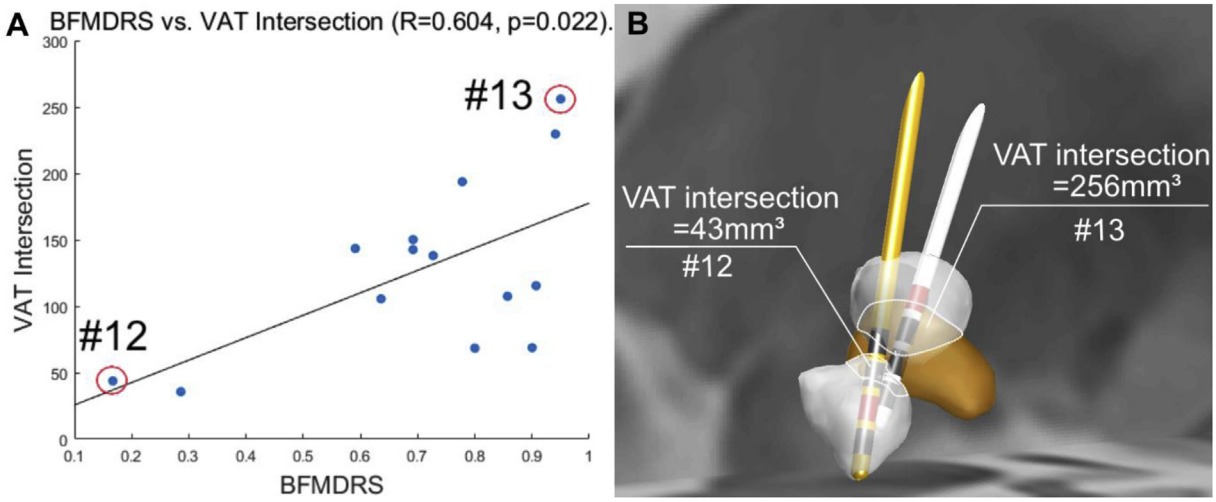

Fig. 2. A correlation analysis between the volume of tissue activated (VAT) within subthalamic nucleus (STN) and clinical outcomes in Meige Syndrome patients receiving STN deep brain stimulation (DBS). (A) Correlation analysis of VAT with BFMRDS scores of individual patients (n = 14; R = 0.604, p = 0.022; Pearson's correlation analysis). (B) The VAT within the STN of an individual patient (No. 12) with lowest symptom improvement (16.7%); VAT within the STN of an individual patient (No. 13) with highest symptom improvement (9.

clinical improvement of the group. The latter two points demonstrate a clear relationship between location of the stimulation site and clinical outcome and further the evidence for the dorsolateral subthalamic nucleus as an optimal target to treat Meige Syndrome.

4.1. Methodological considerations

Although follow up assessments ranged from 11 to 24 months in our retrospective analysis, symptomatic improvements were found to be sustained following STN-DBS in Meige syndrome patients. The VAT analysis of active contacts indicated efficacy of clinical improvement but other factors such as comorbidities or difference in dystonic symptoms were not captured in the present analysis and could be sources of additional variance in the cohort. In order to characterize the level of efficacy by the degree of improvement, the patients were divided into three subgroups. As improvements below 30% is deemed as a failure of DBS for dystonia [23], so we set this as the first cut-off. Given the mean long-term patient improvement of DBS in Meige syndrome is about 70% [9]. It is reasonable to use this as a marker for distinguishing between high-level responders and moderate responders. Despite a relatively large sample size given a rare movement disorder, we found no significant differences in sub-group analyses for determining electrode location and its relation to clinical improvements. A more detailed simulation of each patient that included modeling a VAT, however, showed that a large amount of variance in clinical outcome may be explained by DBS targeting alone.

Several limitations apply for this study. First, it is a retrospective and single-center analysis of a small sample of 15 patients. However, world-wide, few centers operate with target STN in patients suffering from dystonia [7] or Meige Syndrome [9]. Thus, despite our small sample, we argue that the study may serve to formulate the two hypotheses that i) STN-DBS is effective for treating Meige Syndrome and ii) that surgical electrode placement directly affects clinical outcome. Second, with an average follow-up period of 1 year, it is unclear if therapeutic effects would sustain over time. To address this, follow-up data is being collected and a long-term outcome study is planned.

4.2. Effect of STN-DBS for Meige syndrome

To date, clinical studies have demonstrated that DBS of STN or of GPi are similarly effective for dystonia GPi [7,24]. However, GPi DBS is associated with higher stimulation parameters resulting in shorter battery life compared with STN DBS. Moreover, many patients experience persistent problems with gait and fine motor activities [7]. Meanwhile, there are several advantages of STN DBS for dystonia: 1. The stimulation parameters of STN usually lower which leads to less battery-drainage. From a surgical perspective, STN targeting may be seen as more straight-forward given the conspicuous appearance of the iron-dense structure on T2-weighted imaging. Finally, in our own experience, stimulation induced symptom improvements seem to happen more promptly in case of the STN, making DBS programming more efficient in our center.

Here, we demonstrated that chronic STN-DBS at 130–150 Hz can achieve long-term (approx. 1 year) symptomatic benefit for Meige syndrome patients with 70.9% improvement in BFMDRS scores in all the conducted clinical follow-ups. Previous studies have shown a similar range of clinical efficacy as reported here when targeting the GPi (53%–72% improvement) [16,25] or STN (74% improvement) [9]. While the pathophysiology of Meige syndrome remains to be characterised, it could be speculated that disruption of abnormal thalamic activity and sensorimotor integration seen in blepharospasm [26,27] remains key to remarkable symptomatic improvement with DBS at the level of the STN or GPi.

4.3. Characterising clinical efficacy - active contact localisation

To the best of our knowledge, the present study is the first to investigate the relationship between active contact localisation in STN-DBS and clinical outcome in Meige syndrome patients. The active contact localisation in STN-DBS patients were found mainly distributed within the dorsolateral region. However, our additional sub-group analyses of clinical efficacy did not further discriminate the patient post-operative outcomes. It is well-known that the dorsolateral STN has been utilised as a DBS target for patients with dystonia [7,17] and PD [28], given the involvement of the dorsolateral STN in motor function. Being considered as a crucial relay station within the basal-ganglia thalamocortical loops, targeting specific areas of the STN, which can be divided into motor, limbic and associative functional sub-regions [21], each contributing to motor, limbic and associative loops, respectively [11]. Stimulating the dorsolateral STN (as its sensorimotor functional zone) would be expected to disrupt pathologic neuronal motor activity or afferent fibres and result in the improvement clinical symptoms.

Given the variability in DBS clinical studies and inter-patient differences [17], we utilised VAT calculations for assessing clinical

efficacy of STN-DBS in Meige syndrome patients and found that there was a significant correlation in improved symptoms with the degree of overlap between VAT and STN. The variability in these results suggest that besides active contact localisation, VAT calculated from stimulation parameters indicates the modulation of the STN and surrounding white matter fibres that may play a much more important role in the mechanism of action of STN-DBS [29]. While active contact localisation remains important, our results suggest that the clinical response may not be derived from a single point but if anything rather from the surrounding VAT that is additionally determined by the amplitude of the electric current. These data emphasise the importance of developing patient-specific VAT models and associated stimulation settings to achieve maximal clinical response in therapies for neurological disorders.

5. Conclusions

This study further supports the use of STN-DBS for the treatment of Meige Syndrome to achieve long-term symptomatic relief and indicates the highest clinical efficacy is related a stimulation voltage inside the subthalamic nucleus.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.05.014.

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