



Intermuscular coherence as biomarker for pallidal deep brain stimulation efficacy in dystonia



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HIGHLIGHTS

- Intermuscular coherence can function as a biomarker for Globus Pallidus interna Deep Brain Stimulation (GPI-DBS) efficacy in dystonia.
- GPI-DBS decreases intermuscular coherence in the low frequency band and beta band.
- Intermuscular coherence correlates with dystonia symptom severity.

ABSTRACT

Objective: Finding a non-invasive biomarker for Globus Pallidus interna Deep Brain Stimulation (GPI-DBS) efficacy. Dystonia heterogeneity leads to a wide variety of clinical response to GPI-DBS, making it hard to predict GPI-DBS efficacy for individual patients.

Methods: EEG-EMG recordings of twelve dystonia patients who received bilateral GPI-DBS took place pre- and 1 year post-surgery ON and OFF stimulation, during a rest, pinch, and flexion task. Dystonia severity was assessed using the BFMDRS and TWSTRS (pre- and post-surgery ON stimulation). Intermuscular coherence (IMC) and motorcortex corticomuscular coherence (CMC) were calculated. Low frequency (4–12 Hz) and beta band (13–30 Hz) peak coherences were studied.

Results: Dystonia severity improved after 1 year GPI-DBS therapy (BFMDRS: 30%, median 7.8 (IQR 3–10), TWSTRS: 22%, median 6.8 (IQR 4–9)). 86% of IMC were above the 95% confidence limit. The highest IMC peak decreased significantly with GPI-DBS in the low frequency and beta band. Low frequency and beta band IMC correlated partly with dystonia severity and severity improvement. CMC generally were below the 95% confidence limit.

Conclusions: Peak low frequency IMC functioned as biomarker for GPI-DBS efficacy, and partly correlated with dystonia severity.

Significance: IMC can function as biomarker. Confirmation in a larger study is needed for use in clinical practice.

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Abbreviations: GPI-DBS, Globus pallidus interna deep brain stimulation; CBTC-loop, Basal ganglia-thalamo-cortical loop; IMC, Intermuscular coherence; CMC, Corticomuscular coherence; LFP, Local field potential; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

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1. Introduction

Dystonia is defined by “sustained or intermittent muscle contractions that lead to abnormal movements, postures, or both” (Albanese et al., 2013). Deep Brain Stimulation of the globus pallidus interna (GPI-DBS) is considered effective and safe in medically refractory dystonia (Vidailhet et al., 2013). However, there are still challenges for DBS. For instance, GPI-DBS in dystonia is

limited by the time required to observe the stimulation effect. Although the mobile component of dystonia tends to respond quickly, the static part may take weeks or even months to improve (Chung and Huh, 2016). Deciding whether or not to change the patient's stimulation settings if no response is observed may be difficult (Picillo et al., 2016). This time consuming titration of optimal stimulation settings is a burden for patients and caregivers. Another challenge is the wide heterogeneity in dystonia with a variety of DBS effects (Vidailhet et al., 2013). To optimize therapy and select suitable candidates for DBS treatment, a biomarker to indicate the expected response in individual patients is yet to be defined. Converging evidence shows an abnormal excessive low frequency (4–12 Hz) oscillatory neural activity in the cortico-basal ganglia-thalamo-cortical loop (CBGTC) (Foncke et al., 2007a; Lehericy et al., 2013; Sharott et al., 2008; Tijssen et al., 2000; Tsang et al., 2012a). Increased coherence of this frequency band has been described between two dystonic muscles (intermuscular coherence, IMC) (Foncke et al., 2007b; Grosse et al., 2004; Tijssen et al., 2000), but also between local field potentials (LFP) of the GPi and the electromyography (EMG) of dystonic muscles (Foncke et al., 2007a; Neumann et al., 2017; Sharott et al., 2008), and between GPi LFP and electrocorticography (ECoG) of the sensorimotor cortex of dystonia patients (Wang et al., 2018). Coherence is a method that depends on the phase synchrony of two or more signals (Windhorst and Johansson, 1999; Engel et al., 2001). Significant coherence supports a common drive in two signals. In dystonia, coherence has also been obtained between electroencephalography (EEG) and LFP of the GPi (Barow et al., 2014). Furthermore, abnormal connectivity has been measured between different parts of the cerebral cortex of dystonia patients via EEG (Jin et al., 2011). Abnormal corticomuscular coherence (CMC) has been established in Parkinson's Disease (PD) (Airaksinen et al., 2015), but not much has been published on CMC in dystonia patients.

The low frequency dystonic drive has been reported in different types of dystonia (Foncke et al., 2007a; Sharott et al., 2008; Tijssen et al., 2000; Tsang et al., 2012a) and appears to be a promising biomarker that can be measured non-invasively by EMG and EEG recordings. In addition to the low frequency 'dystonic drive', changes in the beta band frequency (13–30 Hz) have been described in the GPi of dystonia patients (Miocinovic et al., 2015; Neumann et al., 2015). The beta band activity was even further diminished than in Parkinsonian patients (Silberstein et al., 2003), supporting the concept of altered oscillatory activities in the CBGTC-loop in dystonia.

In the present study, we aimed to find a biomarker for GPi-DBS in dystonia by exploring different parameters of IMC and CMC analysis before and one year after DBS surgery. We hypothesized that strong IMC and/or CMC in the low frequency band pre-surgery, and a significant decrease in IMC and/or CMC post-surgery would indicate a good response to DBS. We also hypothesized that DBS would increase beta band activity in dystonia.

2. Method

2.1. Study design and participants

Between March 2015 and December 2016, twelve patients undergoing bilateral DBS surgery of the GPi in the University Medical Center Groningen (UMCG) were included. Inclusion criteria for the study were age of 18 years or more and a life expectancy of at least 1 year after surgery. The indication for DBS therapy was made by the DBS team of the UMCG. All patients were implanted with 3387 Medtronic quadripolar electrodes (Medtronic, Minneapolis, United States of America). The localization of the DBS leads in

the GPi were confirmed for every patient with BrainLAB software (Munich, Germany) using 3-Tesla pre-surgery MRI and post-surgery CT fused images. The study was approved by the local medical ethical committee. Before patients were included, they provided written informed consent.

Scalp EEG and surface EMG measurements were performed one day prior to the DBS surgery and approximately one year after surgery. Post-surgery, recordings were performed both ON and OFF DBS.

2.2. Clinical assessment

Clinical assessment of dystonia severity was performed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS, range 0–120) in all patients. Additionally, patients with cervical dystonia were assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS, range 0–35). The motor examinations were videoed, and subsequently assessed by two movement disorders experts who were blinded for treatment status. For both the BFMDRS and the TWSTRS, only motor-score assessments were performed.

For every patient, the pre-surgery clinical assessment took place within six months prior to surgery (average 4.4 ± 3.1 months pre-surgery). The post-surgery assessment was performed approximately one year after the surgery when the patient was ON stimulation. All patients were assessed on the day of the post-surgery neurophysiological measurements, except for one patient who had 2 days between the measurements and the clinical assessment, and one patient who had 7 days between the measurements and assessment. The average time the clinical assessment was performed post-surgery was 12.2 ± 1.4 months. No clinical assessment OFF stimulation was performed.

Differences in clinical scores measured with the BFMDRS and the TWSTRS pre- and post-surgery were examined. Furthermore, a sub-score of the BFMDRS comprising the neck and either the left or right arm, was examined. Differences in clinical scores were assessed with the Wilcoxon Signed Rank Test. The relation between the dystonia severity and the coherences pre- and post-surgery was assessed in both the low frequency band and the beta band. Secondly, we assessed if the effect of DBS on the coherences in the low frequency band and beta band correlated with the clinical effect of DBS measured with the BFMDRS, BFMDRS sub-score, and the TWSTRS. To assess if the coherences can predict the clinical effect of DBS, we also evaluated if the pre-surgery coherences in both the low frequency and beta band correlated with the clinical effect of DBS measured with the BFMDRS, BFMDRS sub-score, and TWSTRS. We assessed the clinical effect both in terms of absolute changes in dystonia severity and changes in terms of percentages.

2.3. Neurophysiological measurements

19-channel EEG recordings were obtained with the electrodes placed according to the international 10–20 system. The EMGs of the patients were bilaterally placed on the sternocleidomastoid muscle (SCM), biceps muscle, triceps muscle, wrist flexors, and wrist extensors. To ensure correct EMG electrode (Red Dot, 3 M Health Care, St. Paul, Canada) placement, patients were asked to contract the respective muscles.

During the recordings, three different tasks were performed (two minute recordings per task) with the patient in supine position. All tasks were filmed during the neurophysiological recordings. First, a rest recording was conducted. Thereafter, the maximum voluntary contraction was determined, and two contraction tasks at 25% of the maximum voluntary contraction were performed for each body side (Foncke et al., 2007a; Foncke et al., 2007b). The tasks consisted of (1) an isometric contraction task

and (2) a posturing task, in which patients had to pinch a dynamometer with their hand or to flex their arm against the dynamometer, respectively. The pinch task tested the muscles in the lower arm, while the flexion task tested the muscles in the upper arm.

The acquired data were analyzed using Brain-RT software (OSG BVBA, Rumst, Belgium). Neurophysiological data was visually inspected for artefacts and removed if present. The artefact free segments of a task were concatenated for further analyses.

IMC and CMC were obtained per patient per task using custom written software build in LabVIEW software (National Instruments, Austin, United States of America) with a frequency resolution of one Hertz.

Several options were explored to find the IMC characteristic that could function as biomarker. We explored the peak IMC in both the low frequency band (4–12 Hz) and beta band (13–30 Hz). First, the highest peak IMC per body side was used. Both clinically dystonic muscles and clinically non-dystonic muscle were used in this approach. Secondly, the IMC between the left and right SCM was taken, as the SCM was clinically affected most in the majority of the patients. Thirdly, the IMC in the active muscle pair per task was taken: the left and right SCM during rest, the wrist flexors-extensors for the pinch task, and the biceps-triceps pair for the flexion task. Lastly, the IMC between the upper arm muscles and the lower arm muscles was performed.

For CMC, the contralateral muscles and, separately, the bipolar EEG between the motor cortex (C3/C4) and the central midline (Cz), and the motor cortex with Hjorth montage were used. In both the low frequency band and the beta band, the highest peak CMC per body side, SCM peak CMC, average peak CMC per body side, and the peak CMC of the most active muscle per task (SCM in rest, wrist extensors for the pinch task, and biceps for the flexion task) were explored. For the highest peak CMC, both clinically dystonic and non-dystonic muscles were used.

Before statistical analyses were performed, all IMC and CMC were checked on significance by using a 95% confidence limit. The confidence limit was calculated as $1-(0.05)^{1/(L-1)}$, with L being the amount of seconds in the segment that was analyzed (Halliday et al., 1995). Coherences were considered significant if at least two successive frequency bins had coherences above the 95% confidence limit. We counted the number of measurements that contained significant coherences, and, per frequency band, expressed this as percentages of the total measurements per task.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, United States of America). For all

tests, a significance level of 0.05 was set. For all data, normality was assessed using the Shapiro-Wilk test.

For all analyses, peak coherences were analyzed using the Friedman test to assess differences per task between the pre-surgery, post-surgery ON stimulation, and post-surgery OFF stimulation measurements. Post-hoc analyses were used to check which conditions differed significantly. The post-hoc analyses used the Bonferroni correction for multiple comparisons. To assess differences in the dystonia severity pre- and post-surgery, a Wilcoxon signed rank test was performed. Coherences were correlated to the dystonia severity using Spearman's rho.

3. Results

3.1. Study participants

Twelve patients (seven women, five men) were included in the study. Six patients had cervical dystonia, one segmental dystonia in the neck and arms, one oromandibular dystonia, and four generalized dystonia (Table 1). The median age of the patients was 58 years (interquartile range (IQR) 48–64). The median disease duration since diagnosis was 8 years (IQR 4–12). The stimulation settings used during the post-surgery measurements are listed in Supplementary Table 1.

The BFMDRS was scored for all patients, with a median BFMDRS score before surgery of 22.5 (IQR 16–43), and 15.3 (IQR 10–38) after surgery ON stimulation. The TWSTRS was scored in seven patients. The median TWSTRS score before surgery was 22.0 (IQR 17–23), and 13.5 (IQR 9–19) after surgery ON stimulation (Table 1).

Significant decreases of BFMDRS ($Z = -2.551$, $p = 0.011$) and TWSTRS ($Z = -2.207$, $p = 0.027$) scores were observed. The median dystonia severity improvement was 30% (IQR 12–44) and 7.8 points (IQR 3–10) on the BFMDRS. The median dystonia severity improvement was 22% (IQR 16–48) and 6.75 points (IQR 4–9) on the TWSTRS.

3.2. Intermuscular coherence

86 percent of the highest IMC peaks were observed above the 95% confidence limit (Tables 2 and 3), which was more robust compared to the other approaches. Median highest peak IMC per condition are shown in Tables 4 and 5. As an example, the highest IMC of one patient and its characteristics are shown in Fig. 1. The results of the other approaches (i.e. IMC between left and right SCM muscles, IMC between the active muscle pair, and IMC between the upper and lower arm) are depicted in the Supplementary Tables.

Table 1
Patient characteristics.

Patient	Sex	Age (years)	Years after diagnosis	Type of dystonia	BFMDRS before surgery	BFMDRS after surgery	TWSTRS before surgery	TWSTRS after surgery
1	M	47	11	Generalized	49	53		
2	M	52	3	Cervical	23	14.25		
3	F	65	12	Cervical	15.25	8	22	13
4	F	49	21	Generalized	63.75	44.75		
5	F	64	5	Oromandibular	17	18.25		
6	M	63	22	Cervical	19.5	11.25	16.5	13.5
7	F	64	9	Cervical	9	10	22	19
8	F	52	2	Cervical	25.25	12	22.5	17.5
9	M	48	12	Generalized	62.25	47.75		
10	F	21	6	Generalized	23.25	16.25	15.5	7
11	F	64	2	Segmental	22	18	23.5	23.5
12	M	63	5	Cervical	13.75	5	20	8.5
Median (IQR)		58 (48–64)	8 (4–12)		22.5 (16–43)	15.3 (10–38)	22.0 (17–23)	13.5 (9–19)

BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale, maximal score is 120; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale, maximal score is 35. IQR = interquartile range.

Table 2
Percentages of highest peak IMC in the low frequency band above the 95% confidence limit.

	Pre-surgery	Post-surgery ON stimulation	Post-surgery OFF stimulation
Rest	92	58	71
Pinch	88	54	77
Flexion	100	78	95

IMC = intermuscular coherence.

Table 3
Percentages of highest peak IMC in the beta band above the 95% confidence limit.

	Pre-surgery	Post-surgery ON stimulation	Post-surgery OFF stimulation
Rest	92	54	71
Pinch	92	67	73
Flexion	100	70	86

IMC = intermuscular coherence.

Table 4
Highest low frequency band peak intermuscular coherence per body side.

	Pre-surgery median (IQR)	Post-surgery ON DBS median (IQR)	Post-surgery OFF DBS median (IQR)
Rest	0.345 (0.208–0.537)	0.051 (0.015–0.137)	0.133 (0.049–0.334)
Pinch	0.226 (0.111–0.366)	0.058 (0.025–0.229)	0.126 (0.065–0.246)
Flexion	0.375 (0.277–0.469)	0.216 (0.047–0.299)	0.315 (0.271–0.379)

Table 5
Highest beta band peak intermuscular coherence per body side.

	Pre-surgery median (IQR)	Post-surgery ON DBS median (IQR)	Post-surgery OFF DBS median (IQR)
Rest	0.153 (0.106–0.310)	0.039 (0.016–0.165)	0.075 (0.057–0.217)
Pinch	0.139 (0.072–0.201)	0.081 (0.024–0.195)	0.121 (0.078–0.216)
Flexion	0.266 (0.101–0.365)	0.089 (0.026–0.173)	0.206 (0.135–0.370)

For the *low frequency band*, a significant ($\text{Chi}^2(2) = 22.333$, $p < 0.001$) difference between the pre-surgery, post-surgery ON stimulation, and post-surgery OFF stimulation conditions was found during the rest condition. In this, the post-surgery ON stimulation low frequency coherence decreased significantly compared to pre-surgery ($\text{Chi}^2 = 1.333$, $p < 0.001$) and also compared to the post-surgery OFF stimulation low frequency coherence ($\text{Chi}^2 = -0.917$, $p = 0.004$). For the pinch condition, a significant ($\text{Chi}^2(2) = 10.636$, $p = 0.005$) difference between the clinical

conditions was also observed in the low frequency band. The post-surgery ON stimulation coherence decreased significantly compared to the pre-surgery coherence ($\text{Chi}^2 = 0.955$, $p = 0.005$), but not compared to the post-surgery OFF stimulation measurement ($p > 0.05$). Also in the third task, the flexion task, a significant ($\text{Chi}^2(2) = 11.446$, $p = 0.003$) difference was measured in the low frequency band, with the post-surgery ON stimulation low frequency coherence significantly decreased compared to the pre-surgery low frequency coherence ($\text{Chi}^2 = 0.833$, $p = 0.021$) and post-surgery OFF stimulation low frequency coherence ($\text{Chi}^2 = -0.952$, $p = 0.006$) (Table 4 and Fig. 2).

In the *beta band*, during the rest condition, a significant ($\text{Chi}^2(2) = 12.000$, $p = 0.002$) difference was seen between the three clinical conditions. Post-hoc testing showed that the post-surgery ON stimulation beta band coherence was significantly decreased compared to pre-surgery beta band coherence ($\text{Chi}^2 = 1.000$, $p = 0.002$). No significant differences were observed in the pinch task ($p > 0.05$). For the flexion task, the three conditions also differed significantly ($\text{Chi}^2(2) = 8.667$, $p = 0.013$). Beta IMC decreased significantly post-surgery ON stimulation compared to pre-surgery ($\text{Chi}^2 = 0.762$, $p = 0.041$) and post-surgery OFF stimulation ($\text{Chi}^2 = -0.810$, $p = 0.026$) (Table 5 and Fig. 2).

3.3. Intermuscular coherence in relation with dystonia severity

Using both pre-surgery and post-surgery ON stimulation data, for the *low frequency band*, the BMFDRS motor score correlated significantly with IMC peak in the flexion condition ($\rho = 0.488$, $p = 0.016$), but not for the rest and pinch condition. The BMFDRS sub-score (neck and arm) correlated significantly with the low frequency IMC peak in all three conditions: the rest ($\rho = 0.368$, $p = 0.010$), pinch ($\rho = 0.484$, $p < 0.001$), and the flexion condition ($\rho = 0.490$, $p = 0.001$). The TWSTRS score only correlated significantly with the peak IMC in the pinch condition ($\rho = 0.584$, $p = 0.028$). Using both pre-surgery and post-surgery ON stimulation data in the *beta band*, the IMC peak only correlated significantly with the BMFDRS sub-score in the pinch condition ($\rho = 0.303$, $p = 0.036$).

Studying the correlation between the effect of DBS on IMC and the clinical effect of DBS on symptom severity, no significant results were found for the low frequency band. For the *beta band*, only an improvement in the dystonia severity measured by the TWSTRS score in terms of percentages correlated significantly with an increase in beta IMC peak in the rest condition ($\rho = -0.594$, $p = 0.025$).

Studying the correlation between the pre-surgery IMC and the clinical effect of DBS on dystonia severity to assess if pre-surgery IMC can predict the clinical effect, the *low frequency* IMC peak

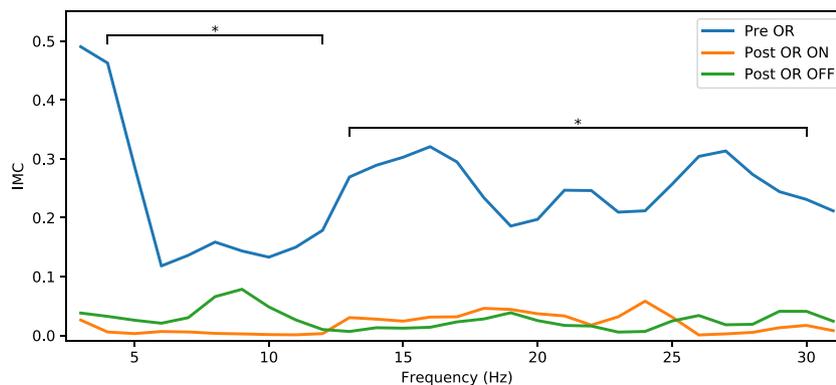


Fig. 1. Highest intermuscular coherence per body side of one patient during the rest condition. IMC = intermuscular coherence, * = $p < 0.05$. Both the low frequency band ($p < 0.001$) and beta band ($p < 0.001$) showed significant differences between the three clinical conditions.

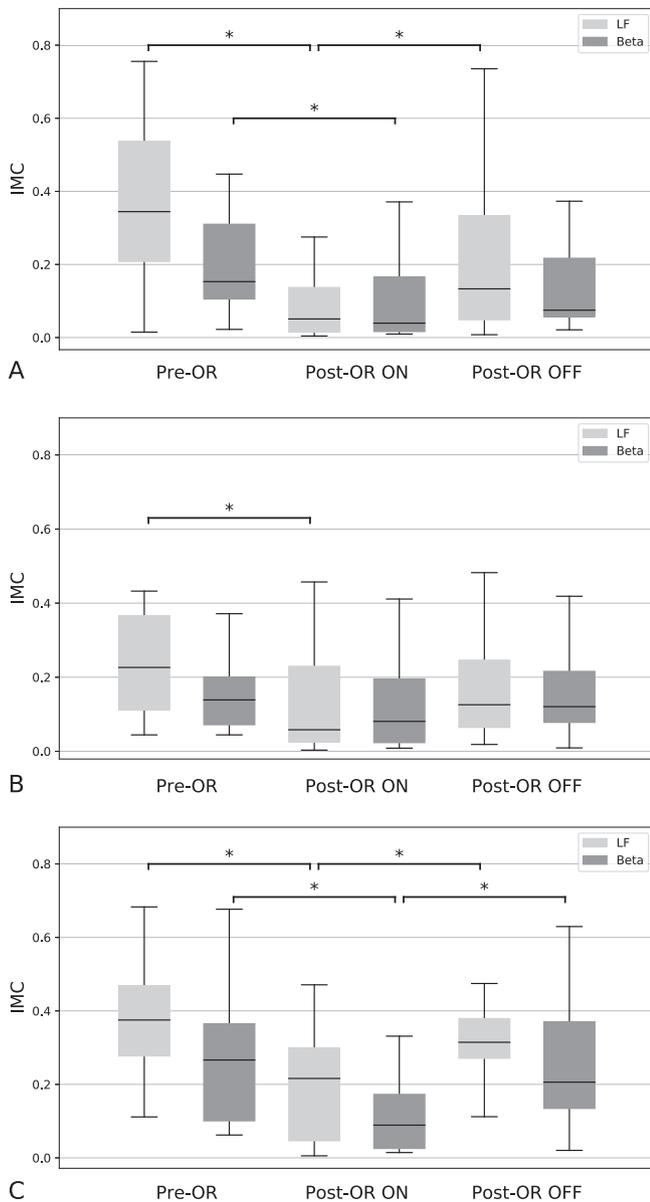


Fig. 2. Median intermuscular coherence per body side. IMC = intermuscular coherence, LF = low frequency band, beta = beta band * = $p < 0.05$. (A) rest condition. In the low frequency band, the post-surgery ON stimulation condition differed significantly from the pre-surgery condition ($\text{Chi}^2 = 1.333$, $p < 0.001$) and the post-surgery OFF stimulation condition ($\text{Chi}^2 = -0.917$, $p = 0.004$). In the beta band, a significant difference was observed between the post-surgery ON stimulation condition and the pre-surgery condition ($\text{Chi}^2 = 1.000$, $p = 0.002$). (B) pinch condition. In the low frequency band, the post-surgery ON stimulation condition decreased significantly compared to the pre-surgery condition ($\text{Chi}^2 = 10.636$, $p = 0.005$). (C) flexion condition. For the low frequency band, the post-surgery ON stimulation condition deviated significantly from the pre-surgery condition ($\text{Chi}^2 = 0.833$, $p = 0.021$) and the post-surgery OFF stimulation condition ($\text{Chi}^2 = -0.952$, $p = 0.006$). In the beta band, the post-surgery ON stimulation condition was significantly smaller than the pre-surgery condition ($\text{Chi}^2 = 0.762$, $p = 0.041$) and the post-surgery OFF stimulation condition ($\text{Chi}^2 = -0.810$, $p = 0.026$).

magnitude pre-surgery correlated only in the flexion condition with an improvement in dystonia severity expressed as difference in BFMDRS sub-score ($\rho = 0.425$, $p = 0.043$). For the *beta band*, lower pre-surgery beta IMC peak correlated significantly with a larger improvement measured by the BFMDRS in terms of percentages ($\rho = -0.457$, $p = 0.025$) in the rest condition and the pinch condition ($\rho = -0.483$, $p = 0.017$), and not the flexion condition. Lower pre-surgery beta IMC peak correlated significantly with a

larger improvement of severity in the TWSTRS score in the rest condition ($\rho = -0.568$, $p = 0.034$) and in the pinch condition ($\rho = -0.541$, $p = 0.046$), but not the flexion condition.

3.4. Corticomuscular coherence

13 percent of CMC were observed above the 95% confidence limit. Given the risk for spurious results, no formal statistical testing was performed. Grand averages of the CMC data are shown in the [Supplementary Tables](#).

3.5. Power spectral density

We have compared IMC with raw EMG spectral amplitude estimates (power spectral densities) and found IMC clearly superior. These results can be found in the [Supplementary data](#).

4. Discussion

The aim of the current study was to find a biomarker for predicting GPi-DBS efficacy in dystonia using EMG and EEG coherence analysis. The IMC showed promising results with a significant decrease in peak coherence in the low frequency band after application of DBS. The IMC in the low frequency band also correlated with dystonia severity. The beta band IMC also responded to GPi-DBS, but contrarily to our hypothesis decreased rather than increased after the application of DBS. CMC was not reliably present neither before nor after DBS.

The highest IMC low frequency peak appeared to function as a biomarker for efficacy of GPi-DBS in our dystonia cohort. Previous studies in dystonia support our findings, but were all based on invasive measures. Barow et al. reported a decrease in low frequency coherence between LFP of the GPi and EEG activity, as well as LFP of the GPi and EMG activity (Barow et al., 2014). Also using GPi LFPs, Neumann and colleagues reported correlation between pre-surgery clinical motor symptom severity assessed by the TWSTRS and low frequency peak power (Neumann et al., 2017). To date, very few studies that aimed to find biomarkers for DBS efficacy in dystonia using non-invasive recordings have been reported in the literature. The most important one is a study by Kroneberg et al. that investigated the effect of GPi-DBS on motor cortical plasticity. The study showed that patients with higher cortical plasticity pre-surgery had more severe dystonia symptoms and benefitted more from DBS (Kroneberg et al., 2018). Furthermore, Miocinovic and colleagues have shown that in the motor cortexes of dystonia patients, interhemispheric coherence was increases compared to healthy controls, and that DBS reduces these coherences (Miocinovic et al., 2017). Our study adds a new possible biomarker for GPi-DBS efficacy.

The peak IMC changes in our study were detected during rest and in motor tasks, in both dystonic and non-dystonic arm muscles. In the literature, coherence in dystonia is regularly studied at rest (Jin et al., 2011; Neumann et al., 2015; Sharott et al., 2008), but also during motor tasks (De Bruijn et al., 2015; Nijmeijer et al., 2014; Tsang et al., 2012b; Van Wijk et al., 2017). In a study comparing cervical dystonia patients and controls, it was difficult to reliably discriminate the dystonic muscles based on low frequency coherence analysis (Nijmeijer et al., 2014). Interestingly, in our current study we also detected altered muscle activity in muscles in the arm not clearly affected by dystonia. This has previously been described in cervical dystonia patients (De Vries et al., 2007). The low frequency IMC is a promising biomarker but optimal task and muscle selection are warranted to optimize the prediction of DBS efficacy in dystonia.

Contrarily to our hypothesis, the beta band IMC also decreased after the application of DBS. Similarly, studies in PD have also reported a decrease in beta band activity in the cerebral cortex and the LFP of the GPi after DBS application (Malekmohammadi, 2018; Silberstein et al., 2003). However, based on the thought that DBS functionally restores brain activity (Wichmann and DeLong, 2016), we expected an increase in beta band coherence in dystonia. The decrease in beta band activity might imply a general, not disease specific, effect of GPi-DBS. Since the exact mechanism of DBS is not fully grasped, further studies towards the effect on different coherence bands are required to further improve our knowledge on the pathophysiology of dystonia.

In our study, significant correlations between the low frequency and beta band peak IMC and the dystonia severity were found. Not many studies have been reported to relate symptom severity to coherence in dystonia. How clinical assessment and coherence are related is not completely clear, as one group reported cortico-pallidal coherence being inversely related to symptom severity, but a positive correlation between dystonia severity and GPi LFP-EMG coherence (Liu et al., 2008). Future studies are required to support our findings of a positive correlation between dystonia severity and the strength of IMC.

As the reduction of dystonia severity is the main goal of GPi-DBS surgery, we were positive that the most robust correlations for a biomarker were those between the pre-surgery IMC and the clinical effect of DBS on dystonia severity. In the low frequency band, this improvement was observed for the IMC during the flexion task in relation with the change in BFMDRS sub-score of the neck and arm. We found that the beta band IMC pre-surgery was associated with a good response on the dystonia severity in the rest and pinch condition, but not in the flexion condition.

The CMC were below significance level and therefore not suitable to explore as a future biomarker. Not much has been reported on CMC in dystonia. It can be hypothesized that the pathological brain activity of dystonia is generated in the GPi and thereafter resonates in the CBGTC-loop, but that this activity is too weak to be measured by EEG.

The current study has its limitations. First, the study population was relatively small. Although, similar studies have used same sized patient populations (Foncke et al, 2007a; Neumann et al, 2015), future research needs to be conducted with a larger study population to confirm our findings. The main reason for this is that, albeit differences before and after surgery were found and IMC characteristics significantly correlated with dystonia severity, the differences were relatively modest and no prediction at the individual patient level could be made. Secondly, patients with different types of dystonia were included in this study. As the effect of DBS differs per type of dystonia, a biomarker could also differ per type of dystonia. Thirdly, it should be stated that pre-surgery EMG and EEG measurements took place on another time point than the assessment of the pre-surgery severity of the dystonia symptoms. The video recordings were performed maximally 6 months before DBS implantation. However, most video recordings were performed closer to the operation. Nevertheless, this may have had some influence on the results, although the dystonia severity should not fluctuate too much over time. However, given the busy pre-surgery period for patients, and the fact that the neurophysiological measurements need to be planned long before the surgery, it is not always possible to assess the symptom severity on the same day as the neurophysiological measurements. Lastly, although it may take up to a year before the correct DBS settings are found, future research could also monitor the longitudinal effect of DBS on IMC at intermediate time points, e.g. 3 and 6 months after surgery, instead of waiting for one year to assess IMC as possible biomarker for DBS efficacy.

To conclude, this study has shown that highest peak IMC is a candidate biomarker for GPi-DBS efficacy in dystonia. This IMC showed significant decreases in low frequency band and beta band activity after the application of DBS. Furthermore, the IMC strength correlated with dystonia severity. Therefore, this research contributes to the development of a non-invasive biomarker for DBS efficacy in dystonia patients.

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Appendix A. Supplementary material

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