Clinical and functional studies in Myoclonus-Dystonia
Foncke, E.M.J.

Link to publication

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Local field potentials and oscillatory activity of the internal Globus Pallidus in Myoclonus-Dystonia

E.M.J. Foncke, L.J. Bour, J.D. Speelman, J.H.T.M. Koelman, M.A.J. Tijssen

Mov Disord 2007;22(3):369-76
Abstract

The pathophysiology of Myoclonus-Dystonia (M-D), an autosomal dominantly inherited movement disorder characterized by myoclonic jerks and dystonic contractions, is largely unknown. In the present study, local field potential (LFP) activity in the globus pallidus internus (GPI) from two genetically proven M-D patients are investigated. Coherence analysis between GPI LFP activity and electromyographic muscle activity (EMG) and synchronization of GPI neuronal activity using Event Related Spectral Perturbation (ERSP) in a go no-go paradigm were studied. Significant increased coherence in the 3-15 Hz frequency band was detected between GPI LFP activity and several muscles with the LFP leading the muscles. The ERSP analysis revealed synchronization in the 3-15 Hz frequency band within the GPI before the imperative cue of the go no-go task, and desynchronization in the same band after the cue. The LFP recordings of the GPI in M-D show that the low frequency band previously described in dystonia is also involved in the dystonia plus syndrome M-D. The 3-15 Hz synchronization in the go-no go paradigm has not been described previously and may point to the existence of (myoclonus)-dystonia specific oscillatory activity in the GPI.
Introduction

Myoclonus-Dystonia (M-D) is an autosomal dominantly inherited movement disorder with reduced penetrance and variable expression frequently caused by mutations in the epsilon sarcoglycan gene (SGCE, DYT 11). It is characterised by myoclonic jerks and dystonic contractions. M-D usually has a benign course without interfering with daily life, but some individuals are markedly impaired from myoclonus and/or dystonia. The effect of pharmacological treatment, including clonazepam and trihexyphenidyl is often disappointing. Recently, deep brain stimulation (DBS) of the internal globus pallidus (GPI) has been reported to be beneficial and safe in several forms of dystonia. To date 8 genetically proven M-D patients were treated successfully by chronic stimulation of the GPI. The pathophysiology of M-D is largely unknown and neurophysiological studies investigating the involvement of the basal ganglia in M-D are limited. The lack of stimulus-sensitivity of the myoclonus and the absence of giant somato-sensory evoked potentials suggests a subcortical origin of the myoclonus in M-D.

Stereotactic surgery enables us to study local field potential (LFP) activity of different basal ganglia (BG) nuclei, including the subthalamic nucleus (STN), the thalamus and the GPI. Oscillatory drives can be studied between the BG and (in)voluntary muscle activity. In one not genetically proven M-D patient, significant coherence in the 4-10 Hz frequency band has been detected between pallidal LFP activity and EMG activity during spontaneous dystonic and myoclonic movements. In EMG-EMG coherence analysis the same frequency band was described in cervical and generalized dystonia patients.

The LFP recordings also enable us to study changes in power spectra in the BG during rest and related to motor activity. In patients with idiopathic focal or generalized dystonia changes in pallidal LFP spectral power during resting condition showed decreased power in the 11-30 Hz beta band and increased power in the 4-10 Hz alpha band. These spectra differed from untreated Parkinsonian patients. Studies on motor control in patients with stereotactic surgery have been mainly focussed on the 8-30 Hz activity in the STN of Parkinsonian patients. The low frequency oscillatory activity of GPI neurons in dystonic patients can be hypothesized to (de)synchronize during voluntary motor activity and to be involved in the generation of dystonia/and or myoclonus.

In the present study, we investigate the characteristics of LFP activity in the GPI from two genetically proven M-D patients, who underwent bilateral GPI stimulation because of medication refractory motor symptoms. Coherence analysis was performed between LFP and EMG activity during rest and during different motor tasks. In addition, synchronization of GPI neuronal activity using event related spectral perturbation (ERSP) in a go-no go paradigm was studied.
Methods

Patients and surgery

Patients

Two patients with genetically proven M-D were studied. The clinical characteristics are shown in table 1. A detailed description of the motor symptoms using the Burke-Fahn-Marsden Dystonia Rating Scale motor part (BFMDRS-motor) and a modification of the Unified Myoclonus Rating Scale (UMRS) before and six months after surgery is shown.

Three weeks before surgery, patient two was injected with 400 IE of Botulinum Toxin type A (Dysport) in the neck muscles to perform surgery when the patient is awake. Informed consent was obtained according to the declaration of Helsinki. The study was approved by the ethics committee of the Academic Medical Centre of Amsterdam.

<table>
<thead>
<tr>
<th>Table 1: Clinical characteristics of the M-D patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT 1</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Age at surgery</td>
</tr>
<tr>
<td>39</td>
</tr>
<tr>
<td>SGCE-mutation</td>
</tr>
<tr>
<td>exon 5 (IVS7+2C&gt;T)</td>
</tr>
<tr>
<td>Medication at surgery</td>
</tr>
<tr>
<td>Citalopram</td>
</tr>
<tr>
<td>Motor scores</td>
</tr>
<tr>
<td>Pre-</td>
</tr>
<tr>
<td>Post (6 mo)</td>
</tr>
<tr>
<td>UMRS-rest</td>
</tr>
<tr>
<td>42</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>UMRS-action</td>
</tr>
<tr>
<td>38</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>BFMDRS-motor</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Total motor score</td>
</tr>
<tr>
<td>102</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>58</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

Surgery

The procedure for DBS is a one stage bilateral stereotactic approach using microrecording and macrostimulation. The intended coordinates at the tip of contact 0 were 21 mm lateral to the midplane of the third ventricle, 2 mm anterior to the midcommissural point and 5 mm below the AC-PC (anterior-posterior commissure) line. The macroelectrode used was model 3387 (Medtronic Neurological Division, Minneapolis, MN, USA) with four platinum–iridium cylindrical surfaces (1.3 mm diameter and 1.5 mm length) and with an intercontact separation of 1.5 mm. Contact 0 was the most distal and contact 3 was the most proximal. Fusion of the postoperative CT-scan and the preoperative MRI-scan confirmed that the deepest electrode contact pair was in the GPi and the highest contact pair was in the GPe/putamen. Figure 1 shows the postoperative imaging of the electrode positions in patient two.
Recordings (LFP and EMG)

Surface EMG was recorded with 9 mm diameter Ag/AgCl electrodes from eight muscles, i.e., sternocleidomastoid (SCM), splenius capitis (SPL), deltoid (DEL), biceps (BIC), extensor carpi radialis (ECR), flexor carpi radialis (FCR), abductor pollucis brevis (APB) and tibialis anterior (TIB). EMG electrodes were placed 2-3 cm apart on the muscle belly (except for intrinsic hand muscles where one electrode was sited over the metacarpo-phalangeal joint) with impedance lower than 5 kOhm. Bipolar deep brain activity was recorded from the adjacent four contacts of each macroelectrode (0–1, 2–3), yielding four local field potential (LFP) derivations, i.e., two at the right side LFP01R, LFP23R and two at the left side LFP01L, LFP23L. Contact 0 and 1 are the deepest contacts and assumed to be at the GPi. Contact 2 and 3 are the highest contacts and assumed to be at the GPe and/or putamen. For the purpose of this study, the highest contacts were disregarded. All EEG and EMG signals were continuously sampled at 1000 Hz, analog filtered at 0.5 to 500 Hz (12 dB/oct) and monitored on line using a Schwartzer 34 EEG amplifier system (Schwartzer, GmbH, Medical Diagnostic Equipment, Munich, Germany) and Brainlab software (OSG bvba, Rumst, Belgium). In addition, four DC channels (DC-500 Hz; 12 dB/oct) were sampled (1000 Hz) for the LED trigger, the flash stimulator trigger, the ergometer and the accelerometer output. Off-line EMG signals were digitally highpass-filtered at 30 to 250 Hz (24 dB/oct) and subsequently full-wave rectified to determine the
amplitude modulation of the discharge rate and to remove movement artefacts. LFP and EEG signals were digitally bandpass-filtered off-line at 0.5 to 100 Hz (12 dB/oct).

Paradigms

Motor tasks
Patients were recorded at rest and while maintaining extension of the wrist (WE). The degree of posturing was standardised by instructing the patient to exert 25% of maximal voluntary contraction. An ergometer was used to monitor whether the contraction level of 25% of maximum force was maintained. Record lengths were 3 minutes per condition.

Go-No-go task
Subjects performed a visual choice reaction task, while seated in front of and watching a green LED (diameter 0.5 degree) and a flash stimulator placed next to each other. The warning cue consisted of turning the green LED on. There was a fixed interval of 5000 ms between the warning cue and the imperative cue. The warning cue was not informative of the subsequent imperative cue. In the go-condition the LED was turned off, indicating the patient to make a short lasting extension movement of the right wrist. In the no-go condition, a flash light appeared simultaneous with turning the LED off, to indicate the patient not to move. The 30 go or no-go trials were pseudo-randomized, with an equal amount of go and no-go trials and the inter-trial durations varied between 10 and 15 s to avoid anticipation and adaptation. Subjects were allowed a practice run of a few trials and understood the protocol prior to start.

Analysis

Coherence analysis
Coherence analysis was performed off-line with MATLAB 7.1 (The Mathworks Inc, Natick, MA, USA) using the Neurospec scripts from DM Halliday (Division of Neuroscience and Biomathematical Systems, University of Glasgow, UK) and based on methods outlined by Halliday and colleagues. The coherence was calculated between one of the LFP recordings and one of the high-pass filtered and rectified EMG recordings. Since recordings were made during the condition of rest or isometric contraction, LFP and EMG signals were assumed to be realisations of stationary zero mean time series. To avoid fatigue the total record of 180 sec duration was acquired in three sessions of 60 sec. The statistical tool used for data analysis was the discrete Fourier transform (DFT). DFT coefficients were estimated by dividing the record of 180 sec duration into 90 non-overlapping disjoint segments of equal duration of 2.048 seconds (segment power of 11, frequency resolution of 0.49 Hz). Spectra variance was estimated by averaging across these DFT segments. In the frequency domain estimates of the autospectrum of the LFP, $f_{xx}(\lambda)$ and EMG, $f_{11}(\lambda)$ and their cross-spectrum, $f_{x1}(\lambda)$ were constructed. The coherence $|R_{x1}(\lambda)|^2$, the phase and cumulant density with 95% confidence limits between LFP and EMG activity were estimated. Phase was formally assessed only where coherence was
significant and extended over at least five data points. The constant time lag between the LFP and EMG is calculated from the slope of the phase estimate after a line had been fitted by linear regression, but only if a linear relationship accounted for >80% of the variance. In addition to the data points, at zero frequency either the point with 0, $\pi$, or $2\pi$, etc., is included in the linear fit. This is based on the consideration that a constant delay in the frequency domain is associated with a linear phase increase as a function of frequency. Whether 0, $\pi$, or $2\pi$, etc., at 0 Hz is included in the linear fit through the phase data, depends on the amount of delay and therefore with the amount of $2\pi$ phase jumps. The time lag between two signals is also determined from the time value of the highest peak in the cumulative density plots.

ERSP Analysis

To visualize mean event-related changes in spectral power over time in a broad frequency range, baseline-normalized spectrograms or event related spectral perturbations (ERSP) were calculated using EEGLAB. 17,18 For this purpose the LFP and EMG signals were down-sampled to 250 Hz. Subsequently, the ERSP was calculated by computation of the power spectrum over a sliding window of 1024 ms (256 samples) applied every 35 ms and then averaging across data trials. Short-time Fourier transforms was used. To visualize power changes across the frequency range from 0.2 to 79.8 Hz, the mean baseline log power spectrum was subtracted from each spectral estimate. Significance of deviations from baseline power was assessed using a bootstrap method. 17 Finally, after normalization of the signal amplitude by the mean absolute power of all trials for each patient, the ERSP’s of the patients were averaged. The envelope of the mean ERSP, indicating the low and high mean dB values, relative to baseline at each time in the epoch, were calculated and displayed in the figures.

Results

Clinical results

The improvement of motor symptoms six months postoperatively are summarized in table 1. A mean motor improvement of 81% of the sum of the BFMDRS-motor and the UMRS 6 months postoperatively was noticed in both patients.

Coherence analysis between LFP and EMG activity

In the resting condition, the full-wave rectified SCM EMG shows an ‘irregular’ rhythmic activity as reflected by the high power in the 3-10 frequency band in the autospectrum of the SCM muscle. This rhythm is less pronounced in the EMG activity of the TIB.
The autospectrum of the bilateral LFP activity shows a similar high power in the 3-15 Hz frequency band compared to the power in other frequency bands in the resting condition (Fig. 2).

Patient 1
A strong significant coherence between LFP01_L and SPL_R, SCM_L, ECR_R and TIB_R EMG activity in the 3-15 Hz frequency band with three peaks at approximately 4.5, 7 and 13 Hz in the resting condition was seen. Significant coherence in the 3-15 Hz frequency band has also been observed between LFP01_L and SPL_R, SCM_L, ECR_R and TIB_R EMG activity during the WE motor task. (Fig. 3) Comparable results of coherence have been obtained between the LFP01_R activity and SPL_L, SCM_L, ECR_R and TIB_R EMG activity. The time lag between LFP and the EMG activity of four different muscles in the condition of rest and wrist extension was estimated from the phase and cumulant density plots and are listed in Fig. 3. Except for the ECR muscle, the time lags calculated from the phase and cumulative density plots are with a 95% confidence limit within the same range.

Patient 2
Similar results were found in patient 2. During the WE motor task a significant but weaker coherence compared to patient 1 was found between LFP01_L and SPL_R (0.1 between 3-7 Hz) activity and LFP01_L and SPL_L (0.1 between 3-8 Hz) activity. During resting condition, no significant coherence was detected. Due to a large variance, time lags could not be reliably estimated from the phase and cumulative density plots.
Figure 3: LFP-EMG Coherence  Coherence plots of patient one (upper panel) between pallidal LFP01 activity and the SCM, SPL, ECR, TIB muscles during rest (REST) and voluntary isometric contraction at 25% of maximum dorsiflexion of the right wrist (WE). The horizontal dashed lines indicate the 95% confidence limit.

Phase plots (middle panels) and cumulative density plots (lower panels) between the pallidal LFP01 activity and the SCM, SPL, ECR, TIB muscles during the two different conditions. The linear regression fits are shown in the phase plots and the listed time lags (and standard error of mean) are derived from the slope. In the cumulative density plots the horizontal dashed lines at the right side indicate the 95% confidence limit; the vertical bars indicate the largest peak of the curve. The time lags (and standard error of mean) of the peaks are listed.

Note the significant coherence between LFP01 and SPL, SCM, ECR, and TIB EMG activity in the 3-15 Hz frequency band with three peaks at approximately 4.5, 7 and 13 Hz in rest and during the WE motor task. The time lags suggest that GPI leads all muscles.
Event Related Spectral Perturbation

Figure 4 shows the average of go trials in patient 1 and demonstrates that there is no increased EMG activity in the neck muscles prior to the imperative cue, which is also visible in the accelerometer signal. The results of the ERSP analysis are shown in figure 5. In order to enhance the statistical power the average of all trials from both patients are presented. Separate analysis of the patients revealed similar results.

Go trials

There is an increase of power in the low frequency band ranging from 3 to 15 Hz of the LFP about 2000 ms before the go cue in the LFP01. The increase of power in the 3-15 Hz band is maximal 300 ms before the mean RT and is more pronounced at the contralateral LFP01 (LFP01\(_L\)) compared to the ipsilateral LFP01 (LFP01\(_R\)) activity. A decrease of power in the 3-15 Hz band starts approximately at the same time of the mean RT (400 ms) and reaches a minimum at 900 ms after the go cue. This decrease lasts up to 3000-4000 ms after the go cue. In addition, a significant increase of power in the 25-35 Hz band is observed at about 1.5 seconds after the go cue at the LFP01\(_L\). Furthermore, in the 50-70 Hz frequency band a small significant increase of power only in LFP01\(_L\) activity at the time of the mean RT is visible.
**No Go trials**

The same ERSP pattern in the 3-15 Hz band of the LFP01 activity is noticed during the no go trials, except that the decrease of power in the 3-15 Hz band after the no go cue is less pronounced. After the no go cue the increase of power in the 50-70 Hz is not recorded.

---

**Figure 5: Event related spectral perturbation**

Event related spectral perturbation (ERSP) of the left pallidal LFP01, (left panels) and right pallidal LFP01, (right panels) activity with a correct response to the go cue (GO) and a correct response to the no go cue (NOGO). Trials of both patients are pooled. The vertical black bar indicates the moment of the imperative cue. The colored vertical bar next to the ERSP indicates the spectral power increase/decrease in dB (10log).

The horizontal green and blue traces under the ERSP panel shows the envelope of the mean ERSP, indicating the low and high mean dB values, relative to baseline at each time in the epoch. The 95% confidence limits are at +/- 2 dB.

Note the increase of power in the 3 to 15 Hz frequency band of the LFP about 2000 msec before the go cue most pronounced in LFP01 with a maximal 300 msec before the mean RT. A decrease of power in the 3-15 Hz band starts approximately at the same time of the mean RT (400 msec) and reaches a minimum at 900 ms after the go cue. This decrease lasts up to 3000-4000 ms after the go cue. Note a similar but less pronounced decrease of power in the 3-15 Hz band after the no go cue.
Discussion

The main findings of this GPi LFP study in two genetically proven M-D patients with improvement of motor symptoms six months postoperatively include increased coherence between GPi LFP activity and muscles in the 3-15 Hz frequency band and synchronization of GPi neuronal activity in the 3-15 Hz frequency band before and desynchronization after the imperative cue in a go no-go motor paradigm.

Motor improvement

The improvement of the motor symptoms in two genetically proven M-D patients six months postoperatively with 81% confirms previous GPi stimulation results in severe forms of M-D. 2,7

Coherence analysis

A significant increased coherence in the 3 to 15 Hz frequency band between the LFP’s of the internal pallidum and the muscles affected by myoclonus and dystonia during resting condition and extension of the right wrist was identified, where the LFP activity led the EMG activity. The overall coherence in patient two was weaker probably due to the botulinum toxin treatment three weeks before surgery. The coherence in the 3-15 Hz band between pallidal LFP and EMG activity has been previously described by Liu et al. in a patient with the M-D phenotype during spontaneous dystonic and myoclonic movements. 3 The same pathological drive in the 4-7 Hz band was described in the muscle to muscle coherence in cervical dystonia and symptomatic DYT1 patients and indicates that these findings are a reflection of the pathological process occurring in dystonia. 8,9

Event Related Spectral Perturbation

Study of the ERSP during the go-no go paradigm shows an increased synchronization in the 3-15 Hz band which is clearly visible at the time of the imperative cue and prior to movement. A desynchronization is seen after the onset of movement in the same 3-15 Hz band which last several seconds. Mechanistic effects evoked by the increase of dystonic and myoclonic movements in the neck after the non predictive warning cue are unlikely to be responsible for the observed synchronizations since no EMG activity was observed in the neck muscles. In contrast to what previously has been described in the GPi (Cassidy) and STN (Kuhn) of PD patients, 11,19 no significant desynchronization of the beta-power after the warning cue or prior to movement could be demonstrated in our M-D patients. A reduced beta-power described in PD patients is not necessarily related to the parkinsonian state as the same movement-related suppression was also manifest in the striatum of healthy monkeys and in the putamen of candidates for epileptic surgery. 20,21 Although there are no normal control studies in human, one could hypothesize that the absent desynchronization of the beta power in M-D may be considered abnormal.
and that the 3-15 Hz frequency GPi oscillations are involved in the pathophysiology of (myoclonus)-dystonia. Several observations support this hypothesis. Coherence analysis between the GPi and muscles showed strong coherence in our M-D patients in this 3-15 Hz frequency band. Furthermore, the relative increase in ‘resting’ pallidal LFP spectral power and the synchronization and desynchronization in the go no-go task were in the same frequency range. As a consequence, the improvement of motor symptoms after bilateral GPi stimulation in M-D could be induced by suppression of the abnormally increased 3-15 Hz oscillatory synchrony. Suppression of synchronized oscillatory activity in GPi has been recently suggested as the therapeutic mechanism of GPi DBS in dystonia.

Limitations of the study
First, the number of M-D patients (N=2) that were able to participate in the study is limited because of the low prevalence of the movement disorder and the usually benign course of the disease making the indication for stereotactic surgery rare. The amount of trials is limited because the recordings are made in recently operated patients. Secondly, although surgical coordinates, clinical improvement and postoperative imaging were consistent with the placement of the deepest electrode contact in the GPi and the highest contact in the GPe/putamen, one cannot be completely certain that one or more contacts lie in nearby structures as reported by others. Thirdly, because of the lack of a control group, it is unclear whether the observed changes of LFP activity in the GPi reflect the pathophysiology of M-D. The observations that have been made in the GPi of humans with dystonia and in healthy Rhesus macaque supports the idea of looking to pathophysiological and not to physiological processes in the GPi of these two M-D patients.

Conclusion
The interpretation of the changes in the 3-15 Hz frequency band in relation to the original neuronal models of movement disorders is unclear. These models propose decreased discharge rates in the GPi of patients with hyperkinetic movement disorders. However, the therapeutic mechanism of DBS is hypothesized to inhibit BG neuronal activity. Therefore, these models contradict the benefits from pallidotomy and pallidal DBS in pure dystonic as well as in M-D patients. Moreover, pallidal LFP activity in our M-D patients is increased rather than decreased in the 3-15 Hz frequency band. It appears that our observations are more in line with the current functional models in movement disorders incorporating changes in patterns of activation and the degree of synchronization of neuronal activity of the BG network. Further studies of synchronized neuronal activity in the basal ganglia and coherence with muscle activity across different frequency bands in hypo- and hyperkinetic movement disorders are required to obtain a better
understanding of the nature and pathophysiology of M-D and movement disorders in general.

Acknowledgements
This study was supported by NWO VIDI (project 016.056.333) (to EF and MT)
References