Pallidal neuronal activity in myoclonus-dystonia syndrome

A. Gulberti[1], C.K.E Moll[1], A. Sharott[1], W. Hamel[2], A. Muenchau[3], C. Buhmann[3], U. Hidding[3], S. Zittel[3], C. Gerloff[3], M. Westphal[3], D. Mueller[2], A.K. Engel[1]

[1] Department of Neurophysiology and Pathophysiology,
[2] Department of Neurosurgery, [3]Department of Neurology
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Introduction

Pallidal stimulation with high frequencies has proven to be an option in the treatment of therapy-refractory patients with myoclonus-dystonia (MD). Hitherto, there are few reports (see references) on pallidal neuronal activity in this rare movement disorder. The aim of the present study was to further characterize pallidal activity in MD patients. We obtained single-cell activity as well as local field potentials (LFPs) from the external and internal pallidum (GPe and GPi) of two awake MD patients (subjects M+G) and of one generally anesthetized MD patient (subject P) undergoing microelectrode-guided stereotaxy for the implantation of deep brain stimulation electrodes in the GPi.

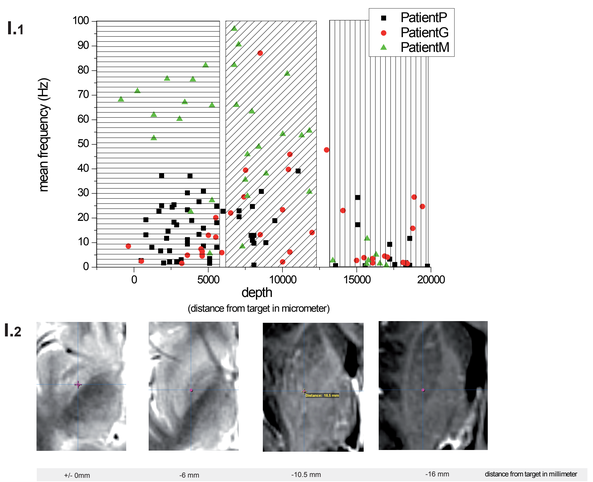
Patients and Methods

Patient	Diagnosis	Disease duration	Age at operation	Preoperative medication	C2-responsive
M	Myoclonus-Dystonia,	30 yrs, progressive	46 yrs	Betablocker ✗ Topamax ✗ Primidon ✗ Carbamazepin ✗ Keppra ✗ L-Dopa ✗	✓
G	Myoclonus-Dystonia, dissasociative m. d., depression	26 yrs Tremor, 3 yrs MD	26 yrs	Rivotril ✓ Botulinumtoxin ✗	not known
P	Myoclonus-Dystonia, depression	31 yrs,	39 yrs	Botulinumtoxin ✓/✗ Rivotril ✗ Betablocker ✗ Primidon ✗ Keppra ✗ Liskantin ✗	✓

Figure legends of Results I+II

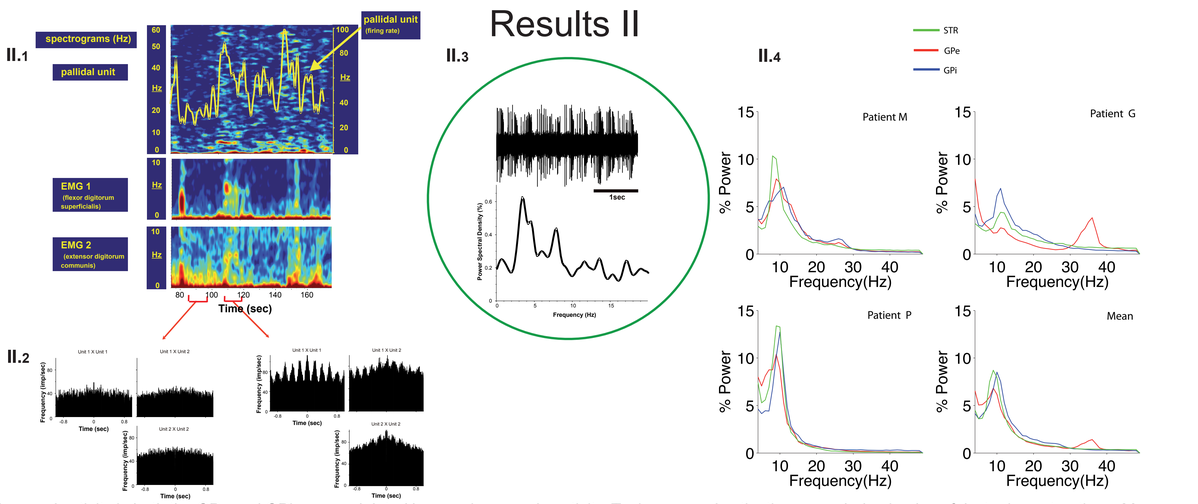
I.1) Summary of mean frequencies of all neurons recorded from striatum, GPe and GPi. The individual data points are plotted as a function of distance from target (i.e., GPi).
I.2) Representative magnetic resonance images, taken from subject P. Reconstruction of the trajectory as probe view (“surgeon´s view“) to show the internuclear boundaries (medullary laminae) as visible on the MRI.
I.3) The coefficient of variation of the interspike intervals (CV (ISI)) can be taken as a measure of (ir-)regularity of neuronal firing. Large values indicate irregular activity, whereas low CV values point at regular spiking activity. The data points of all three patients are plotted as a function of depth.
I.4) and I.5) contain the same information as the synoptic graphs I.1) and I.3), respectively. Mean frequencies (I.4) and coefficients of variation of the interspike intervals (I.5) are plotted individually for each patient and separated for each structure (striatum, GPe, GPi) to demonstrate the heterogeneity of the present sample. Note the remarkably low firing rates of neurons in the GPi of subject G. In contrast to the two patients operated under local anesthesia, firing rates of GPe and GPi are virtually identical in patient P (operation in general anesthesia). Note the low CV (ISI) values and low firing rates for most of the striatal units, indicating the recording of a subpopulation of regularly and slowly discharging neurons, most likely corresponding to cholinergic interneurons, which are known to be tonically active (see abstract of Moll et al.).
II.1) and II.2) show the relationship of myoclonic muscle activity and modulated pallidal discharges in subject M. During episodes of myoclonic jerks, the firing rate of the pallidal neuron (recorded from the GPi) increases. Moreover, the right auto-correlogram as well as a cross-correlation with a simultaneously recorded pallidal neuron from a different electrode show a modulation in the frequency range of myoclonic jerks (i.e., around 4-6 Hz), indicating a synchronized oscillatory activity within this period. The left correlation-matrix in II.2) demonstrates the absence of synchronized or oscillatory pallidal cell firing in a different period, in the absence of myoclonic activity.
Figure II.3) demonstrates the presence of rhythmic bursting in a pallidal neuron recorded from the GPi of patient G. The power spectral analysis of the spike train allows the identification of oscillatory activity at around 4-5 Hz, interestingly even in the absence of noticeable myoclonic activity in the limbs (as evidenced by multiple EMG-recordings).

Results I



The firing rate analysis revealed some distinct patterns of activity-levels for these three patients. GPi neurons of patient G fired significantly less than external pallidal neurons (GPi: 8,8±1,8Hz, mean±SEM, n=13; GPe: 31,6±7,3Hz, n=11). The firing rates of cells in the GPi of patient M were statistically not different from those obtained in the GPe (GPi: 61,9±8Hz, n=14; GPe: 54,8±6Hz, n=16) and matched the high pallidal firing rates reported for dystonic patients in previous studies. The interpretations of firing rates and -patterns of pallidal units in subject P is difficult due to the effects of general anesthesia on the whole central nervous system. However, GPi neurons in patient G fire even slower than those recorded under general anesthesia - thus indicating a abnormally low pallidal output.

Results II



Neuronal activity in both the GPe and GPi was modulated by ongoing muscle activity. Tonic neuronal activation preceded episodes of dystonic contractions. Moreover, bursts of oscillatory activity accompanied episodes of rhythmic myoclonic jerks. Cross-correlation analysis of simultaneously recorded neurons revealed transient oscillatory synchrony of pallidal neuronal activity in the 2-5Hz frequency range during myoclonic activity. In contrast, cross-correlograms of unit activity in the absence of muscle activity were flat. Power spectral analysis of LFPs showed a trend towards higher and more coherent oscillatory activity at frequencies around 10Hz in striatum, GPe and GPi. Pronounced beta-oscillatory activity was found in the GPe and GPi of subjects M and G, that underwent stereotactic surgery in local anesthesia. In patient P (general anesthesia), this beta-peak was not observed. In contrast, the 10Hz-peak was sharper than in the other two patients, in line with the effects of propofol/remifentanyl anesthesia on the spectral composition of surface and depth EEGs.

Postoperative course

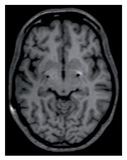
Patient	Stimulus parameters				
	Hemisphere	Polarity	Volt	Microseconds	Hz
M	L	Bipolar: 0-/1-	1.5V	240µs	5Hz
	R	Bipolar: 4-/5-	3.5V	240µs	5Hz
G	L	Bipolar: 0-/1-	3V	150µs	145Hz
	R	Bipolar: 4-/5-	3V	150µs	145Hz
P	L	Monopolar: G+/1-	3V	150µs	145Hz
	R	Monopolar: G+/5-	3V	150µs	145Hz

An immediate improvement of both myoclonic and dystonic symptoms was observed in all patients. Postoperative high-frequency stimulation (130Hz) of the GPi was effective to ameliorate both dystonic and myoclonic symptoms in patients G (with the abnormally low pallidal output) and patient P, whereas it was inefficient in patient M with higher levels of GPi activity. Interestingly, permanent stimulation of the GPi with low frequencies (5Hz) had a clinical effect in the latter case (see table with effective stimulation parameters). Unfortunately, the implanted electrodes had to be explanted in subject M 5 months after the operation, due to an purulent infection of the impulse generator ascending along the subcutaneous wires. Taken together, axial symptoms (e.g. cervical dystonia or myoclonic movements in the head-region) improved more compared to myoclonus and dystonia of the limbs. Therefore, the benefit for the patient is estimated around 50% by both patients and clinical neurologists. A major benefit is the reduction of medication and alcohol-intake now possible without aggravation of the symptoms.

Stereotactic reconstruction

Target structure and stereotactic coordinates: postero-ventro-lateral GPi (20mm lateral, 3mm anterior, 3mm inferior to AC-PC and MCP, respectively.

Patient	Stereotactic reconstruction of the ventralmost electrode contacts (postoperative stereotactic CT scan)			
	Hemisphere	X	Y	Z
M	L	-22.6	+3.1	-4.4
	R	+22.0	+3.0	-2.7
G	L	-19.9	+6.0	-7.9
	R	+21.1	+4.5	-3.8
P	L	-20.1	+2.9	-5.9
	R	+20.9	+4.7	-5.5



Postoperative MRI (horizontal section, T1-weighted) of subject G. The artefact of the implanted DBS electrode is readily discernible. Note the slightly asymmetrical depth position of the ventralmost contact (z-axis).

Conclusions

Taken together, our results indicate that pallidal neuronal activity in MD may differ from patient to patient, including abnormally low pallidal activity levels which are indicative of an abnormally hypoactive output of the basal ganglia. In our patient collective, GPi stimulation leads to significant improvements of the axial features of the disease, whereas improvements of limbs is comparatively poor given the resulting disabilities from the distal affection. Therefore, a different target should be considered in surgery for MD, e.g. thalamic VIM nucleus.

References

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