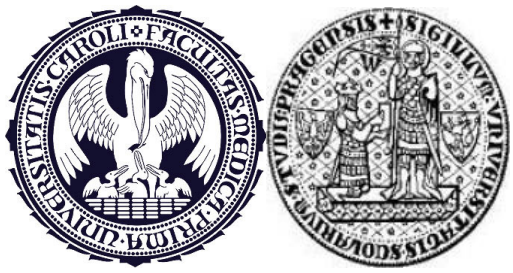
Univerzita Karlova v Praze
1. lékařská fakulta

Charles University in Prague

Studijní program: Neurovědy



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Eye Movement Metrics in the Differentiation of Parkinsonian Syndromes

A digest of thesis submitted for the degree of Ph.D.

"AUTOREFERÁT"

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Prague, Czech Republic

2017

Summary

In this thesis we investigated conjugate and dis-conjugate eye movements (EM) in Parkinson's disease (PD) and other parkinsonian syndromes aiming to characterize and differentiate some aspects of their oculomotricity using infrared video-oculography.

First of all we published a practical review for medical students and clinicians describing clinical examination of eye movements, and interpretation of principal findings. Then we examined principal saccadic eye movements and smooth pursuit in the horizontal and vertical directions with video-oculography in a large group of healthy subjects, aiming to help new oculomotor laboratories in the constitution of their own norms. We conclude that age influence EM metrics but not gender or education level. The latency of saccades and the error rate of antisaccaes increases, while the velocity and gain diminishes with age. Saccades should be investigated in the horizontal and vertical plane because they are influenced by the direction of the target, resulting in a right/left and up/down asymmetry.

In a third project we focused on a frequent complain of PD patients, namely blurred near vision and visual discomfort during reading. We objectively assess for the first time vergence eye movements (VEM) in PD patients using VOG. Patients show increased latency of VEM and the divergence is slow and hypometric. In an unpublished part of this study, we additionally provided evidence in favour of disrupted VEM in Ephedrone parkinsonism (EP), Multisystem atrophy (MSA) and Progressive supranuclear palsy (PSP). EP patients had longer latencies, slower velocity and reduced gain of VEM. MSA and PSP patients had also longer latencies, but the velocity, similar to PD patients, was only decreased for divergence. MSA patients exhibited reduced gain of VEM, while this was not observed in PSP.

Rapid eye movement sleep behaviour disorder (RBD) is by far the strongest clinical marker of prodromal PD. We investigate EM a group of patients diagnosed as idiopathic RBD (iRBD), aiming to detect prodromal PD. We found two groups of patients: i) iRBD composed of patients, free from any parkinsonian sign with EM similar to controls; and ii) RBD with possible PD, composed of patients with disrupted EM. We concluded that EM abnormalities could be considered as an additional early diagnostic marker of PD.

Intraoperative microelectrode recording of single neuronal activity at the basal ganglia, in PD patients, was used to identify neurons participating in scanning eye movements based on specific electrophysiological pattern. We found that twenty percent of the neurons of the subthalamic nucleus, substantia nigra pars reticulata and globus pallidus showed eye movement related activity. Neurons

related to scanning eye movements differ from neurons related to saccades, suggesting a functional specialization and segregation of both systems of eye movement control.

A recently described secondary toxic parkinsonian syndrome due to Ephedrone abuse draws the attention of the eye movement disorders community, because of its particular rapid onset and severe evolution. Horizontal and vertical eye movements were recorded in EP patients. We found slow and hypometric horizontal saccades, an increased occurrence of square wave jerks, long latencies of vertical antisaccades and high error rate in the antisaccade task. Patients make more errors than controls when pro- and antisaccades are mixed. Based on oculomotor performance, a direct differentiation between EP and PD was possible, EP patients presenting extensive oculomotor disturbances probably due to the manganese induced damage to the basal ganglia.

Finally we were interested in the improvement of some symptoms of PSP patients to benzodiazepines, which are gamma-aminobutyric acid (GABA) analogues. GABA levels were measured with spectroscopy and correlated to an eye movement paradigm, the remote distractor effect (RDE). Thus we did not find any significant difference in GABA level at the frontal cortex, or an increased RDE in our patients compared to controls.

In this thesis we provide additional evidence about the importance and clinical utility of EM examination in the differentiation of PD and other parkisnonian syndromes, gaining insights into the physiology of the basal ganglia.

Introduction

Eye movement examination is an essential tool, which places few cognitive demands on subjects and provides a lot of information about brain anatomy and physiology. It also gives information about cognition, memory, adaptation and learning representing a large span of brain functions that may be probed, thus explaining why they have been and remain extensively used in both research and clinical practice.

It has been particularly used in movement disorders clinics providing key contributions for the diagnosis of some neurodegenerative (e.g. parkinsonian syndromes), hereditary (e.g. spino-cerebellar ataxias) or metabolic (e.g. Nieman-Pick disease) disorders and in neurophysiological departments to explore sensory, motor, and cognitive neural systems.

A large choice of video based infrared eye trackers is now available allowing to easily and non-invasively record saccades and smooth pursuit. Hence, an increasing number of neurophysiological departments tend to include eye movements (EM) setups in their equipment for the investigation of the central nervous system.

The movement disorders department of the Neurological Clinic of the first faculty of medicine, in Prague, created an eye movement laboratory for clinical diagnosis and research in 2010.

We began by publishing a paper describing how eye movements should be assessed in clinical practice. This first paper was oriented to students, residents, ambulant and hospital neurologists and was published in Cesk and Slov Neurol in 2011. As a first step for a rational diagnostic approach, the accurate and detailed clinical examination of a patient is crucial. Physicians should be comfortable with neurological examination of eye movements and physical diagnosis. We proposed a detailed description of the clinical examination at the bedside, an algorithm for interpretation of the findings and the anatomy and physiology of eye movements.

A second step was to create our own laboratory norms. We examined 145 control healthy subjects and published our experience giving some clues for researchers who aim to create their own laboratory for research in EM. This paper was published in an important neurophysiological journal in 2013 and remains one of the Top Ten most downloaded papers on this field.

As a national expert centre on movement disorders, we were interested to enlarge the clinical utility of eye movement study in the differentiation between Parkinson disease (PD) and atypical or secondary parkinsonian syndromes.

Although the motor symptoms of PD have long been documented, the non-motor aspects do not seem to be as well recognized in clinical practice. Conjugate EM in Parkinson disease were widely studied in the past, however despite the frequent viewing complain of PD patients, no studies about convergent eye movements were performed. No objective characterization of EM was available at that time. We conducted with Jaromir Hanuska, former student of medicine, an important VOG study of vergence eye movements (VM) study in 18 PD patients (published in 2015). We additionally described VEM in EP, MSA and PSP and compared these results with our PD patients and a matched control group.

The Ephedrone project was an international collaboration between Czech Republic, Republic of Georgia and France. Our VOG device was exported, four of our researchers collaborated with seven other neurologist and residents, and examined 27 patients with EP in Tbilisi. Our team published two papers in 2014 that enlarge the knowledge on EP and the pathophysiology of the basal ganglia.

It has been shown that the STN contains neurons activated during voluntary saccades or pursuit EM. We analyze the relation between EM and the activity of neurons in the STN, the substantia nigra pars reticulata (SNr) and the internal pallidum (GPi) in PD patients. During the exploration phase of DBS surgery, alert PD patients were shown a series of photographs and some of them underwent a visually guided saccade task. Extracellular neuronal activity and electrooculography were recorded during the task. Action potentials of individual neurons were identified and the relation between the activity of individual neurons and the EM was assessed.

We have investigated a group of PSP patients with VOG and with spectroscopy to measure the correlation between low GABA levels and the remote distractor effect. The paper is submitted to the Revue Neurologique on 2016.

In collaboration with the sleep department we examined patients with idiopathic REM sleep behaviour disorders (RBD) aiming to explore a possible early diagnostic marker for PD. This paper was never published, but it serves as pilot study for an on-going study on the field.

We believe that VOG as a not invasive tool is an interesting method for diagnostic, follow up, and research of several movement disorders and other pathologies.

Objectives

We aimed to investigate conjugate and dis-conjugate eye movements (EM) in Parkinson's disease (PD) and other parkinsonian syndromes lo enlarge knowledge about their pathophysiology and differential diagnosis.

Hypothesis

- Blurred vision in PD patients is due to disrupted VM and this could be objectively demonstrated.
- If idiopathic REM sleep behaviour disorder (RBD) is a pre-clinical non-motor sign of PD, patients with RBD should have similar EM as PD patients, in order to identify occulomotricity as possible marker for pre or sub-clinical pathology of meso-pontine structures.
- Eye movements in EP should be different from PD due to large brain dysfunction.
- Basal ganglia structures are involved in scanning eye movements, and intraoperative microelectrode recordings could demonstrate this.
- Patients with progressive supranuclear palsy (PSP) are more distractible, should have a bigger remote distractor effect (RDE) and lower Gamma-aminobutyric acid (GABA) levels.

2.1 From the beginning: How to examine eye movements as clinician:

Eye Movement Examination in Neurological Practice [1]

A neurologist must be able to perform in a few minutes a systematic examination and to interpret the results driving the diagnostic approach. The test of integrity of the extra ocular eye muscles and their innervation is followed by the exploration of the different functional classes of eye movements. We provide practical information on the clinical examination of eye movements and the interpretation of these findings. The examination of eye movements should place few cognitive demands on subjects. It provides a lot of information about function of the central and peripheral nervous system, eye muscles and orbit.

We published an algorithm of eye movement exam with a video example, which was published online and the first faculty of medicine. This paper gave a general overview of the classification of eye movements, anatomy and neurophysiological description of the function of the EM system. We highlighted on the interest of the patient history, the accurate examination about

position and movement during saccades and pursuit EM. At last, we described how to name principal patient symptoms as diplopia, oscillopsia, vertigo and the principal signs as strabismus, nystagmus, skew deviation, ocular tilt, square wave jerks, flutter, opsoclonus, eye muscles palsies, and disorders of saccades and pursuit. Finally our paper broadly describes the most commonly used technique, videooculography.

2.2 The normative study: How to examine eye movements as eye movement specialist: *Horizontal and Vertical Eye Movement Metrics: What´s Important?* [2]

We provide a detailed description of EM metrics of a large group of healthy subjects, using video based infrared videooculography, a photoelectric method that reflect an infrared light into the pupil, allowing rapid, reliable, and non-invasive recording of horizontal and vertical EM.

We concluded that there is no difference between females and males, neither between the different educational levels of the subjects. Age is relevant for the analysis of EM. In fact, the EM system ages with the rest of all cognitive functions of the brain. We also concluded that EM should be investigated in the horizontal and vertical plane, due to the anatomical segregation of both kinds of EM. The eye movement paradigm should be simple and feasible to perform in a short time. We conclude that with aging the reaction time of pro and antisaccades becomes longer. The velocity decreases, saccades became less accurate and the error rate for antisaccades increased. Metrics as velocity and accuracy did not change with aging, indicating probable preservation of brainstem and cerebellum.

Another interesting finding of our study was the high error rate of elderly healthy subjects, with preserved capacity to monitor their mistakes.

We finally propose an index to be used in the clinical practice, comparing the SRT of horizontal pro- and antisaccades. This index should be > 1 and it may be useful to analyse diseases with prolongation of the SRT as the Corticobasal syndrome.

The paper has been downloaded and cited several times and helping clinicians in the creation of their own norms.

2.3 Exploring a non-negligible non-motor symptom: Vergence eye movements in Parkinson's disease and other parkinsonian syndromes:

Fast vergence eye movements are disrupted in Parkinson's disease: A video-oculography study. [3]

Convergence insufficiency may cause important difficulties in every-day life and is a frequent cause of visual discomfort in patients with Parkinson's disease (PD).[4-6] Until now characterization of VEM has been limited to clinical reports or to small patient series and to the best of our knowledge, never been characterized in PD.

In progressive supranuclear palsy (PSP) one study has shown decreased amplitude/velocity ratio of VEM,[7] and in multiple system atrophy (MSA) diplopia due to convergence insufficiency has been reported in two patients.[8] A recently described parkinsonian syndrome, the Ephedrone-induced parkinsonian syndrome (EP) secondary to ephedrone abuse, is characterized by severe, rapid progressive, irreversible Parkinsonism and dystonia.[9-16] Patients with EP, in the large majority young ephedrone abusers, complain often about visual discomfort during reading (Bonnet, personal communication), while VEM have also never been characterized. Moreover in PD and other parkinsonian syndromes convergent and divergent VEM have not been studied separately.

The aim of this study was to refine the description of vergence movements in PD and parkinsonian syndromes. Eighteen PD patients, four patients with probable MSA, six patients with probable PSP and 27 EP patients were examined. We have additionally examined 42 control subjects age- and gender-matched to the different patients.

We compare PD/EP patients and MSA/PSP with their respective control group and show that several VEM metrics were differently distorted for convergence and divergence.

The SRT for convergence and divergence was longer in all patient groups. The SRT of VEM is mainly commanded by the frontal eye field (FEF),[17-19] the posterior parietal,[20] extra striate and primary visual cortices.[21, 22] Longer SRT in all patients reflect longer cortical processing time for target selection and decision making to initiate the movement and point to dysfunctional cortical processing in the before mentioned areas. In PD the degeneration of the dopamine neurons at the substantia nigra pars compacta and their projections to the striatum, result in disrupted functional connectivity and patients may show widespread cortical hypo metabolism specially at the frontal and parietal regions.[23, 24] In MSA the substantia nigra, striatum, locus coeruleus, pontine nuclei, inferior olives, cerebellum and spinal cord are predominantly affected by alpha-Synuclein inclusion pathology.[25] However a significant hypometabolism at the frontoparietal cortex of MSA patients has been shown with

functional imagery.[26] Pathologically, PSP is defined by the accumulation of tau protein and neuropil threads, mainly in the basal ganglia, pontine tegmentum, oculomotor nucleus, medulla, and dentate nucleus and cortex.[27] Manganese (Mn) induces neurotoxicity in EP and lesions in the frontal white matter and cortical structures.[14, 28]

Concerning the velocity of VEM, EP shows the largest abnormalities, despite their young age and short disease duration. They have very slow convergence and divergence. Ephedrone induced parkinsonism affects predominantly the pallidum and substantia nigra pars reticulata, but may damage also the brainstem and cerebellum.[29] Patients with PD, MSA and PSP had decreased velocity of divergence not for convergence. The mesencephalic reticular formation, play an important role in influencing the velocity of VEM. However according to our results it is probable that the control of velocity of convergence and divergence is segregated depending on the VEM.

Parkinson´s disease, EP and MSA patients exhibit reduced gain of VEM, while this was not observed in PSP. The colliculus superior and cerebellum [30, 31] particularly cerebellar flocculus influence the vergence angle and the dorsal vermis ocular alignment with orbital position.[32] Increasing evidence suggests that the cerebellum may have certain roles in the pathophysiology of PD, and in MSA the systems most consistently and severely affected include the olivopontocerebellar (OPC) and striatonigral (StrN) systems.[32] We have also found that almost all patients show skewed shape of the velocity profile of VEM. Several neurophysiological studies have suggested that the skewness of saccades is also related to the cerebellum.[33, 34]

We have objectively characterized for the first time VEM in parkinsonian syndromes opening new ways for further research.

2.4 An early diagnostic marker of Parkinson's disease:

Impairment of ocular saccades as possible early sign of neurodegeneration in REM sleep behaviour disorder (unpublished)

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia and movement disorder characterized by violent movements and behaviours during REM sleep.[35, 36] The main suspected mechanism of RBD is a lesion of the REM sleep atonic system, located at the pontomedullary brain stem.[37] If RBD is not associated with neurological disorders, it is termed idiopathic (iRBD). Increasing evidence show that 50-80% of patients with idiopathic RBD convert to synucleopathies specially Parkinson's disease (PD), but also to dementia with Lewy bodies (DLB) [38]

and multiple system atrophy (MSA).[36] Consequently, RBD have been considered to be a sensitive prodromal marker for PD, which can appear up to 5-15 years before disease onset.[39, 40]

We raised the hypothesis that accordingly to the rostrocaudal progression theory of the synucleopathy in PD proposed by Braak,[41], patients with RBD who will probably develop a PD should present some eye movement abnormalities.

We aimed to characterize eye movements in a series of iRBD patients, in order to identify sub-clinical dysfunction of meso-pontine structures. Thirteen patients, with suspicion of iRBD were enrolled. All patients were asymptomatic for parkinsonian symptoms. Possible PD was diagnosed according to the UK Parkinson's disease society brain bank clinical criteria.[42] None of them had received a diagnosis of PD before and none of them where treated with levodopa. Fourteen healthy controls were enrolled. Three different task were performed in the same order, in one session lasting for 30-min: i) Prosaccades horizontal and vertical GAP 13°; ii) Single antisaccades horizontal and vertical; iii) Mixed horizontal and vertical antisaccades.

Two groups of patients were identified after clinical examination: (i) iRBD composed by 5 patients, free from any parkinsonian sign; (ii) RBD with possible PD (RBD PD) composed by 8 patients. Statistically significant differences between the two patient groups and controls were found only in latency for vertical saccades. Furthermore, the increased error rate for horizontal antisaccades in RBD PD patients was also significant. We have found no differences between groups for other metrics. Considering performances of individual patients, 75% of the RBD PD patients showed longer latencies than for vertical prosaccades, whereas such phenomenon was observed only for one iRBD patient, and none of control subjects. Taking into account error metrics, 63% of the RBD PD patients showed increased error rate for horizontal antisaccades. In the iRBD only 40% presented a high error rate for horizontal antisaccades.
Eye movement metrics did not correlate to disease duration, nor to the MDS UPDRS III score. However we found a negative correlation between latency for vertical prosacades and MOCA score as well as positive correlation between the high error rate on antisaccades and MOCA score.

This is the first study investigating eye movement performance in patients with RBD. We show that eye movements in patients with iRBD did not differ from controls, while patients with possible RBD PD present long latencies for vertical prosaccades and a high error rate in the antisaccade task.

We observed that the eye movement abnormalities present in RBD PD patients were correlated with bad performance in the MOCA test. Cognitive impairment has been described in 30% to 40% of

PD patients. Moreover PD patients with cognitive impairment and RBD are affected in similar brainstem structures and their ascending projections to the cerebral cortex, probably preceding involvement of the neocortex.[43]

We believe that saccades may be associated to other early markers of PD as olfaction, RBD, autonomic symptoms, depression, constipation, visual abnormalities and cognitive impairment and presynaptic dopamine depletion.[40]

2.5 A physiological approach, investigating scanning eye movements in PD with microelectrode recording:

Basal ganglia neuronal activity during scanning eye movements in Parkinson's disease.[44]

Stereotactic, microelectrode-guided implantation of deep brain stimulation (DBS) electrodes at the globus pallidus internus (GPi) and the subthalamic nucleus (STN) is part of the routine surgical treatment in Parkinson's disease (PD), when the medication fails and treatment complications appear. During the implantation of the stimulator intraoperative microelectrode single unit recordings (MER) are used to identify the basal ganglia structures based on their electrophysiological response, to localize the target for DBS electrode implantation,[45] and offers researchers a unique opportunity to investigate brain behaviour related to single-unit responses.

The pattern of EM carried out while exploring an image, also called scanning EM, is composed of a succession of saccades and fixations, and results from successive re-allocation of attention from one detail to another.[46, 47] Scanning EM (SEM) involve planning, visuospatial attention, and spatial working memory.[48] Saccades made during scanning EM can be considered as internally triggered, as the subject moves the gaze around a complex visual image actively searching for information relevant to current motivations and goals.

The basal ganglia are considered to drive voluntary movements, and their role in the control of eye movements has been supported by extensive evidence derived from experimental studies in monkeys,[49-51] and in humans through clinical[52-55] and electrophysiological studies.[55, 56] Although most of them have focused on behaviour such as reflexive visually guided, memory guided or predictive saccades and their role in scanning EM have received little attention and is, to our knowledge, not known.

The main goal of our study was to determine whether basal ganglia are involved in SEM through simultaneous intraoperative microelectrode recordings in a homogeneous group of PD patients undergoing implantation of deep brain stimulation electrodes.

Nineteen PD patients, who underwent implantation of deep brain stimulation electrodes, were investigated with simultaneous intraoperative microelectrode recordings and single cannel electrooculography in a scanning eye movement task by viewing a series of colored pictures selected from the International Affective Picture System. Four patients additionally underwent a visually guided saccade task. Microelectrode recordings were analyzed selectively from the subthalamic nucleus, substantia nigra pars reticulata and from the globus pallidus by the WaveClus program which allowed for detection and sorting of individual neurons. The relationship between neuronal firing rate and eye movements was studied by crosscorrelation analysis. Out of 183 neurons that were detected, 130 were found in the subthalamic nucleus, 30 in the substantia nigra and 23 in the globus pallidus. Twenty percent of the neurons in each of these structures showed eye movement-related activity. Neurons related to scanning eye movements were mostly unrelated to the visually guided saccades.

We identified for the first time a significant number of neurons related to scanning eye movements in human STN, GP and SNr from awake and alert PD patients. A major finding is that neurons of the STN related to SEM were to a great extent, not related to reflexive prosaccades and vice versa. This allowed us to strongly support the hypothesis of a functional and anatomical segregation between internally and externally generated EM, as it has been suggested at different cortical and subcortical levels over the past years.

The results agree with the role of the basal ganglia in the EM control. Our results suggested that each of the explored structures – STN, SNr and GPi contains a relatively high percentage of neurons involved in the execution and/or control of eye movements.

2.6 Secondary toxic parkinsonian syndrome: One interesting non-invasive tool to differentiate Ephedrone induced Parkinsonism from PD

Eye movements in Ephedrone-Induced Parkinsonism.[57]

Recently, the clinical syndrome of manganese toxicity has been observed in methcathinone addicts using potassium permanganate as the oxidizing agent of ephedrine.[9, 11, 12, 14-16, 58] The reasons for attributing the development of neurological disorders in ephedrone abusers to the toxic effects of manganese include the consistency of the clinical syndrome with the occupational manganism, and the fact that no similar neurological disorders were described in methcathinone addicts using the drug prepared by chromate instead of permanganate oxidation.

The clinical syndrome described in ephedrone abusers is characterized by a rapidly progressive, irreversible, and non-levodopa responsive atypical parkinsonian syndrome. Principal

symptoms include early gait impairment and postural instability with falls, limb dystonia, facial dystonia and hypomimia, speech disorders and eye movement abnormalities. Most case reports of ephedrone abusers noticed eye movement abnormalities, especially slowing and mild restriction of vertical saccadic eye movements, slow horizontal saccades and impaired vertical optokinetic nystagmus.[9, 15] In addition, apraxia of eyelid opening has been described.

The exact mechanism of manganese toxicity is unknown but a participation of oxidative stress is highly probable. The available evidence suggests that excessive levels of the toxic form of manganese (Mn^{3+}) accumulate in the brain leading to neurodegenerative changes reflected in numeric atrophy of neurons and gliosis in susceptible parts of the brain (mainly GPi and SNr).

In this project we aimed to characterize eye movement abnormalities in EP with videooculography (VOG).

We additionally investigated the function of the autonomic nervous system through Pupillometry. A imbalance of parasympathetic-sympathetic has been shown in welders with Mn-induced toxicity in form of lower heart rate variation following deep breathing, immediate standing up and Valsalva manoeuvre.[59] Patients with EP may present autonomic features as impotence, hyper salivation and soborrehea.[9] The pupillometry provides a simple and non-invasive tool to study the autonomic system resulting in a dynamic equilibrium that is expressed in pupil diameter. The pupillary light reflex is driven primarily by increased parasympathetic activity, while the resting size of the pupil diameter in darkness and in response is determined primarily by changes in sympathetic activity.

We did not show any abnormalities of the pupillometric analysis of EP. Besides, patients had no changes on heart rate and blood pressure after immediate and 2 minutes standing. Patients did not report any symptom of orthostatism nor urinary dysfunction. Further specific symptom oriented diagnostic studies may be necessary to gain insights about the function of the autonomic system in this disease.

Horizontal and vertical eye movements were recorded in 28 EP and compared to 21Parkinson's disease (PD) patients, and 27 age- and gender-matched healthy subjects using standardized oculomotor tasks with infrared videooculography. EP patients showed slow and hypometric horizontal saccades, an increased occurrence of square wave jerks, long latencies of vertical antisaccades, a high error rate in the horizontal antisaccade task, and made more errors than controls when pro- and antisaccades were mixed. Based on oculomotor performance, a direct differentiation between EP and PD was possible only by the velocity of horizontal saccades. All remaining metrics were similar between both patient groups.

EP patients present extensive oculomotor disturbances probably due to manganese induced dammage to the basal ganglia, reflecting their role in oculomotor system.

2.7. The atypical Parkinson syndrome progressive supranuclear palsy: The study of eye movements correlating a symptom with a brain neurotransmitter:

GABA Spectra and Remote Distractor Effect in Progressive Supranuclear Palsy: A pilot study (Submitted 2016)

Loss of interneurons containing benzodiazepine receptors has been suggested to be related to the pathophysiology of progressive supranuclear palsy (PSP)[60] and patients may improve fine motor skills, dexterity, and voluntary saccadic eye movements after administration of GABA receptor agonists. [61, 62] GABA levels are inversely correlated with people's susceptibility to distraction, which can be examined with an eye movement paradigm, the remote distractor effect (RDE).[63] This effect consists of the delay of saccades to simple visual targets, when an irrelevant stimulus appears elsewhere in the visual field.[64] The RDE involves cell populations coding for visually guided saccades and for inhibition of distractors, either at the level of the superior colliculus or within the cortical eye fields.[65] In healthy subjects, it was shown that higher GABA levels in the region around frontal eye field (FEF) predicted smaller RDE.[63] We thus hypothesized that in comparison with healthy controls, PSP patients will show higher RDE and lower GABA spectra at defined volume of interest (VOI) placed at the right FEF measured with magnetic resonance spectroscopy (MRS).

To address this issue we examined seven right-handed patients with probable PSP, age range 59-76 yrs, disease duration 2-10 yrs. Two patients were treated with levodopa and one with amantadine, while five patients were not taking any drugs. In addition, eight right handed, healthy subjects, age range 56-74 yrs, were examined as a control group. All participants signed the informed consent. The study was approved by the ethics committee of the Faculty of Medicine and General University Hospital, Prague, Czech Republic and was in compliance with the Declaration of Helsinki. The eye movement paradigm RDE, acquisition of GABA spectra with MRS and statistics of this study are described in supplementary material.

The RDE did not demonstrate any significant differences between patients and controls. However, when pooling the results of distractor trials, we found a significantly increased number of errors in PSP compared to controls. The GABA concentrations ranged from 0.18 to 2.10 mM (median 0.82) in the PSP group and from 0.55 to 2.40 mM (median 1.02) in the control group (p=0.61).

In this pilot study we found higher error rates in the RDE task in PSP patients compared to controls. As saccadic inhibition appears to produce the major component of the RDE [64], our results are in line with the known loss of saccade inhibition reflecting prefrontal dysfunction in PSP patients.[66] Contrary to our expectations, we did not find any statistically significant differences in frontal GABA levels between PSP patients and controls. The low number of investigated subjects might explain this negative result. Further studies are thus needed to elucidate the relationship between GABA levels and saccadic inhibition in PSP, to sustain the idea of specific therapeutic mechanism of GABA agonists in PSP.

Conclusion

Eye movements reflect function of sensory, motor, and cognitive neural systems in healthy subjects but also differentiate different pathologies between them. We focused our interest in movement disorders, particularly in Parkinson's disease and other parkinsonian symptoms.

We provide a detailed description of EM metrics of a large group of healthy subjects, using video based infrared videooculography, helping researchers to create their own laboratory. We demonstrate that age, direction of target presentation should be taken into account during eye movement examination, while sex and education level are not important. [2]

We show for the first time that patients with PD [3] and other parkinsonian symptoms have large vergence eye movement abnormalities and that these movements may differentiate between them. The SRT for convergence and divergence was longer in PD, PSP, MSA and EP reflecting cortical involvement. Divergence is mostly affected in PD and degenerative parkinsonian syndromes, while the EP patients have altered convergence and divergence.

In RBD we show that eye movements in patients with iRBD did not differ from controls, while patients with possible RBD PD have similar eye movements as patients with a firm diagnosis of PD. If our results may be confirmed with larger studies, EM abnormalities may be associated to other early markers of PD.

A significant number of neurons related to scanning eye movements, not related to reflexive prosaccades and vice versa, were identified at the basal ganglia from awake and alert PD patients. This finding suggests a functional and anatomical segregation between reflexive saccades and voluntary

scanning EM. [44]

In patients with EP we characterize for the first time EM, showing slow and hypometric horizontal EM, long SRT and high error rate of antisaccades. And finally we failed to demonstrate that the RDE correlates with low GABA levels in patients with PSP.

This thesis builds the first milestone of the constitution of a Videooculography laboratory in our faculty. This interesting method should continue to be used in research and clinical practice, incorporating fMRI, TMS and pharmacological approaches, for example.

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