Possibilities of applying the quantitative assessment in monitoring the development of Huntington's disease

Możliwe aplikacje pomiarów ilościowych w monitorowaniu postępów choroby Huntingtona

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Choroba Huntingtona jest nielicznie występującą chorobą genetyczną, której progresja oceniana jest przy użyciu specjalnie do tego celu skonstruowanej skali – UHDRS. Narzędzie to składa się z siedmiu elementów – w tym również ze skali motorycznej. Pomimo szerokiego jej stosowania w praktyce klinicznej, jej słabą stroną jest subiektywność oceny, lekarz bowiem ocenia poszczególne funkcje motoryczne bazując jedynie na obserwacji. Artykuł zawiera opis metod, które uzupełniły by ocenę funkcji motorycznych o obiektywny pomiar ilościowy. Autorzy przytaczają przykłady znanych z literatury potencjalnych „biomarkerów" choroby Huntingtona oraz prezentują propozycje metod i urządzeń umożliwiających ich pomiar w warunkach ambulatoryjnych. Taka ilościowa ocena dostarczając danych liczbowych, pozwoliłaby na przeprowadzanie analiz statystycznych zmian jakie zachodzą wraz z postępem choroby, już na najwcześniejszym etapie jej rozwoju, potencjalnie umożliwiając wykrycie nawet bardzo subtelnego pogarszania się stanu pacjenta, jakie nie jest jeszcze uchwytne dla wyłącznie subiektywnej, nieoprzyrządowanej obserwacji.

Słowa kluczowe: *choroba Huntingtona, sakkady, śledzenie nadążne, sprawność manualna, zaburzenia okoruchowe, niepokój ruchowy języka*

Huntington's disease is a rare genetic illness, the progression of which is evaluated using a specially developed scale – UHDRS. Such a tool consists of seven parts – inter alia the motor assessment scale. Although widely used, it is not free from some disadvantages. The motor subscale relays purely on the qualitative assessment – the doctor evaluates the particular motor function only by observation. The article contains the description of methods which could be potentially used to enrich the motor assessment, making it an objective and quantitative measurement. The authors quote the examples of potential "biomarkers" of HD disease known from the literature and present the methods and instrumentation allowing its measurement in a clinical or ambulatory setup. Such quantitative assessment would allow to acquire the numerical data and conduct the statistical analysis of changes, which accompany the disease progression, and would potentially allow to monitor even subtle deteriorations of the motor performance, which are not detectable by subjective observation.

Key words: *Huntington's disease, saccades, smooth pursuit tracking, tapping, oculomotor disorder, tongue protrusion*

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Introduction

Huntington's disease (HD) is a neurodegenerative disorder, characterized by cognitive, behavioral and motor dysfunctions [1]. A comprehensive and widely accepted instrument to asses the clinical status of HD is the Unified Huntington's Disease Rating Scale (UHDRS). It was developed by the Huntington Disease Study Group and allows testing of seven different functions (Motor Assessment; Cognitive Assessment, Behavioral Assessment, Independence Scale, Functional Assessment, Total Functional Capacity) [1]. The HD motor rating scale includes inter alia the assessment of ocular pursuit, initiation and velocity of saccades, finger tapping as well as tongue protrusion [1]. All these functions are evaluated by the doctor through the patient observation, however, its score carries the weight of subjective judgment. Evaluation and rating of the eye movement function, without the

instrumentation is known to be difficult and unreliable. Due to high dynamics of eye movements, (the average reaction time 200 ms [2]; average duration of 10 degrees saccade 38-45 ms [3]), for their adequate evaluation there is a necessity to use the instrumentation with high temporal (1 ms) resolution. Limitations of our visual system (low temporal resolution – 200 ms sampling rate), the clinical observation, allow only to notice the extreme disturbances of eye movement control, which accompany the later phase of HD progression. The subtle changes which are already present in the presymptomatic stadium of HD development are hidden from the 'naked eye' observation. It is why it seems to be important to complement the subjective assessment with the objective and quantitative measures. This article contains examples of the known "biomarkers" of early HD development and describes the methods and required instrumentation, which can be used outside the eye movement laboratory. Lack of appropriate instrumentation was the main obstacle of its introduction into the clinical practice.

Saccades

Saccades are rapid, conjugate eye movements which place the image of interest in the central region of retina [2, 4, 5]. Those eye movements are highly stereotyped, which makes them so interesting for a researcher [4]. Deviations of saccadic profiles may be of immense neurological significance and the technical innovations made them relatively easy to evaluate. Two aspects of saccadic movements, its trajectory and the latency (reaction time) can be measured in laboratory conditions. There are several different parameters of saccadic trajectory (duration, amplitude, peak velocity), which are closely related one to another [4]. The stereotypic trajectory of saccades depends on the highly specific temporal firing pattern of the burst cells in paramedian pontine reticular formation (in the brainstem) [4]. Meanwhile the saccadic reaction time is determined by the high level (mostly cortical) decision process. Saccade latency (intersaccadic interval), in opposition to a stereotypic saccade movement and its nearly constant duration (saccade with equal amplitude), is characterized by a large variability [2, 4] For this reason its analysis should focus not only on mean/median latency values but also on the latency distributions [6].

Saccadic eye movements can be divided largely into two groups: the visually guided and the volitional saccades [2, 5]. The first group includes saccades which are generated as the response to the new, suddenly appearing visual stimuli, the so called 'reflexive saccades'. On the other hand the volitional saccades are internally generated, for example when saccading between two simultaneously present targets or between its remembered locations. Two parallel active systems are responsible for the generation of these two different types of saccadic eye movements [2, 5].

Posterior parietal cortex and parietal eye filed participate in generation of "reflexive" saccades. Those areas are directly connected with superior colliculus – the structure that transfers the saccade commands to the brainstem [5]. Superior colliculus receives also a connection from the frontal eye fields and supplementary eye fields. The structure V1 and other areas of visual cortex send the projections to those fields [2]. Such a wide cortical network and its interactions with the dorsolateral prefrontal cortex participate in the generation of the volitional saccades [5].

Patients with HD usually demonstrate the difficulties in initiation of saccade, mainly voluntary. The dysfunction of maintaining fixation is manifested by unwanted saccadic intrusions and general saccade slowing [4, 5, 7]. The problems with voluntary saccade initiation affects more the vertical than horizontal saccades [7]. There was a hypothesis about undershooting the target by HD patients. Hypometric saccades, followed by the increased number of corrective saccades, were found in HD patients also by Winograd-Gurvich et al. [5]. The hypometria was not significantly different between the reflexive and voluntary saccades, what may suggest that in HD patients such a dysfunction can be connected with some subcortical pathology. Meanwhile saccade slowing in HD is frequently attributed to the development of brainstem dysfunction [5].

In many studies dedicated to Huntington disease, different kinds of voluntary saccade were evaluated: antysaccades, memory guided saccades and self-paced saccades. In the antisaccade task the participant is asked to inhibit the "reflexive" response on the suddenly appearing target and to generate the saccade toward the opposite direction [2, 5]. In a memory guided saccadic task the subject is holding the gaze on the central fixation point and the peripheral target is only briefly flashed, resulting in cueing the location for the subsequent saccade. The response is generated when the "go" signal is given [2, 5]. In both kinds of tasks, HD patients have shown the increase of saccadic reaction time, what may suggest that HD affects initially the structures within the basal ganglia and frontal regions, which are participating in the decision processes connected with the volitional saccade initiation. In the self-paced saccade test, the participants are asked to move their gaze between two constantly projected points. In the limited time HD patients can make fewer self-paced saccades than the controls in the same time [5]. However not only the latency of

volitional saccade is affected by HD, there are also reports about the increased number of direction errors in the antisaccade task. It was even suggested that more than 20% of errors in this task may possibly be the most sensitive indication of oculomotor dysfunction in HD [5]. The antisaccade error rate correlates also with the UHDRS motor score and the total chorea score [8]. Despite the fact that many reports suggested that the abnormalities in the visually guided saccades are more subtle than those in the volitional saccades, there were studies showing a greater usability of "reflexive" saccade in the evaluation of oculomotor abnormalities in HD. Ali et al. showed that basing on the measurement of visually guided saccades it was possible to successfully predict the HD status. They performed an multivariate analysis of the mean saccadic latencies including the parameters of its distributions, that allowed to correctly diagnose 75% of HD patients and 95% of control subjects [4].

Visually guided saccades were also used to monitor the progression of the disease in the premanifest and manifest HD patients over a three-year period [6]. In both HD groups it allowed to observe the systematic changes from year to year in all parameters of saccadic latency distribution. In controls those parameters stayed unchanged. It is worth to mention that the latency of visually guided saccades can correlate with total chorea score in HD patients [8].

All those reports suggest that the measurement of saccadic parameters, relatively simple to conduct in laboratory conditions, may be used as a biomarker of the cortical and sub-cortical abnormalities in HD. It can be useful in the monitoring of disease progression and serve also as the evaluation tool of novel therapies. Motor scale of UHDRS includes the assessment of the saccadic velocity and latency, that is performed by the doctor based on visual observation of patient's eye movements. The human eye samples the visual environment only [1] about two or three times per second, resulting in 300 ms of the sampling period [2]. Therefore the subjective visual evaluation of the saccadic latency, which is in the range of 200 ms [2]) as well as of saccadic durations, which for 10 degree last around 45 ms [3] is simply impossible. Moreover due to a high physiological variability of saccadic latency, its assessment requires gathering the large population of saccades, and the analysis of not only the mean latencies but also its distribution parameters. To perform such an experiment outside the eye movement laboratory requires use of specialized measurement systems, dedicated to recording and analyzing saccadic eye movements. One of such system the Saccadometer [9] Advanced (Fig. 1) was applied in the Track-HD multicenter study [10].

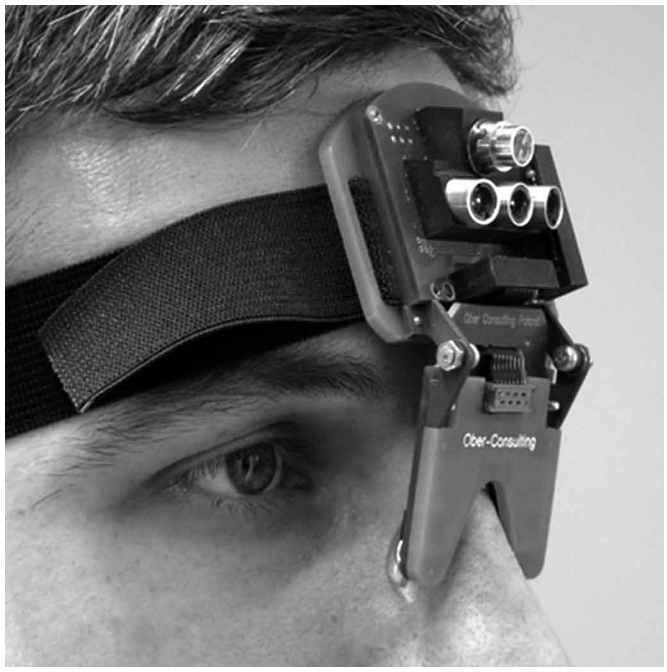

Fig. 1. Saccadometer Advanced, the forehead plate caries the laser stimulator assembly (one green and three red) and provides the conditions for effective cancelation of vestibulo-ocular responses, improving the stability of eye fixation on the displayed targets, necessary for high temporal resolution detection of saccades onset and landing

Smooth pursuit tracking

Another oculomotor disorder accompanying the development of Huntington disease is the impairment of smooth pursuit [11, 12]. It is reported to be characterized by the low gain and the saccadic intrusions, with pronounced manifestation in pursuit along the vertical axis [13]. Saccadic intrusions occur in both directions, without lateral preference. The UHDRS scale rates the horizontal and vertical ocular pursuit as a part of Motor Assessment, using a four-point scale. The scale can reflect only the rough function assessment, rating it from "normal", through "jerky", reflecting large saccadic intrusions which may be perceived by the examiner as a small disturbance in movement smoothness, to "incomplete range" and "cannot pursue" [1]. Regardless of the examiner's skill and experience, without the eye movement instrumentation this method barely allows to notice only large saccadic intrusions, and fails to detect gain impairment. Complementing the smooth pursuit subjective examination with eye movement measurement system such as the multisensor Jazz [14], allows to complete objective evaluation of the smooth pursuit trajectory and quantification of its correctness in terms of amplitude and gain (Fig. 2).

The eye movement infrared reflectometry, used in this case, features high temporal and spatial resolution (1 kHz, 5 angular minutes), and allows automatic detection of saccadic intrusions as small as 1-2 degrees,

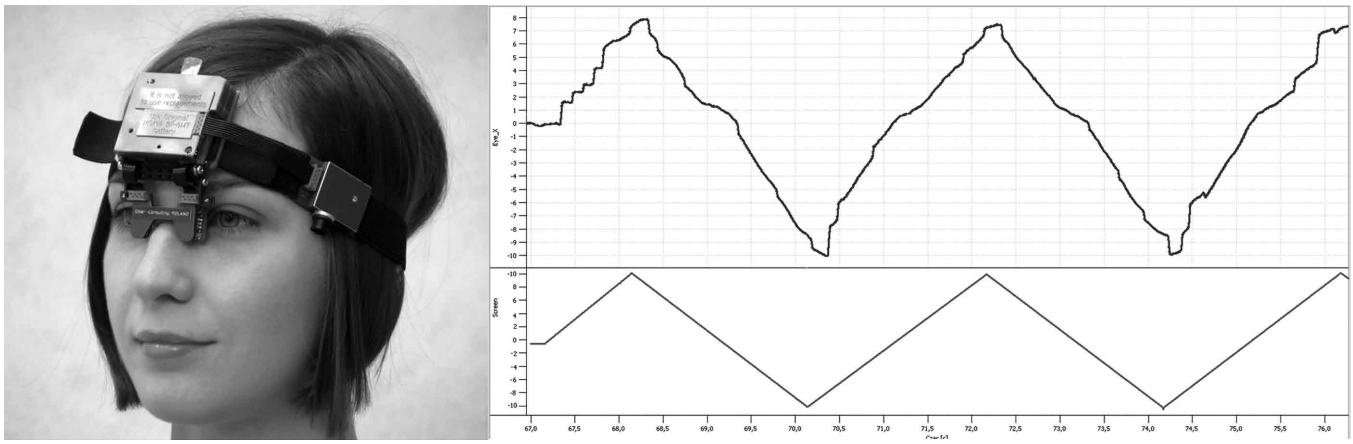

Fig. 2. On the left the EM system Jazz-Integra used for recording of eye movements of HD patient (presented on the right side), when carrying the smooth pursuit of the constant velocity-ramp experiment. The target was moving horizontally across the computer screen with velocity of 10 degrees per second, within the range of ±10 degrees. On the diagram the horizontal axis represents time – one division 500 ms. Along the vertical the amplitude of the eye movement and target excursion, one division equals one degree, the target starts its movement in the center of the screen. The first two complete tracking cycles are presented, it can be noticed that at the beginning of the tracking response, the constant velocity target displacement is approximated with the sequence of five saccades with the zero velocity fixations between the saccades. Only after the fifth saccade the following fixation has adjusted its velocity according the target velocity. Usually in physiological condition it is enough for only one saccade to program the adequate tracking velocity [11]. The number of initial saccadic approximation, with zero velocity of inter-saccadic fixations, as well as the total number of saccadic intrusions in the later part of the tracking trajectory, reflects the degree of smooth pursuit dysfunction. The saccadic intrusions in the later cycles of tracking, evidence inadequate eye velocity, which is leading to the departure of the target from the fovea area, where the target usually should be kept during smooth pursuit tracking

without the necessity to restrain the head movement. Quick sensor installation (less than 1 minute), small size and capability for immediate automatic SP assessment, fits the requirements of on-the-spot examination. Aside of the sensor itself, the method requires computer screen for stimuli presentation. Optional calibration procedure (takes about 1 minute), may be necessary to accurately quantify gain and saccadic intrusion amplitudes and can be embedded within the stimuli presentation. The SP range and the number of intrusions can be assessed without calibration.

While smooth pursuit function is often preserved in early HD development, there are reports [15] that saccadic intrusions in SP, may be easier to induce by the presence of additional distracting stimuli and become a more sensitive marker, with a linear relation to the disease clinical stage. This may result from the progressing cell loss in the basal ganglia, which is involved in preferential selection and inhibitory control.

Tongue motor performance

Tongue force protrusion is one of the motor symptoms assessed by Unified Huntington's Disease Rating Scale-Total Motor Score. The measurement of tongue protrusion is based on the five-point scale. The ability to maintain an extended tongue stable during 10s, is considered as a normal healthy condition (level 0). The end of the scale, the level four characterizes the person who cannot protrude the tongue from beyond the lips [1]. Rating of the next levels is based on the naked-eye visual inspection of the tongue tip movements. The discrete five-point scale has not an adequate resolution to document the fine changes of the tongue quietness loss. The quantitative approach can be complementary to such an observational assessment, applying direct measurement of the tongue force exerted on the transducer, first introduced by Reillman [16]. The measurement procedure requires the patient to push the tongue against the force transducer, with the required particular stable force levels (0,25-2 N) for certain time (20 s).

The measured signal should be immune against the upper body and head movements, e.g. chorea movements. They may interfere with the tongue force measurement, when the force to be measured is applied against the external reference base (transducer attached to the table). This can be prevented by anchoring the transducer reference base inside the head, by holding the transducer housing between the front teeth [17] (Fig. 3). Allowing the tested person to observe the actual tongue force on the screen, opens the possibility to design more complex experiments. Switching off and seeing the actual force level displayed (establishing the force visual feedback), allows to learn how fast and accurately the tested person can stabilise the force at the required level.

The variability of tongue protrusion force can discriminate between the control, premanifest and symptomatic HD [16]. Sensitivity to motor deficits in the premanifest patients is the highest at the lowest target force level 0.25 N. Tongue force measurement

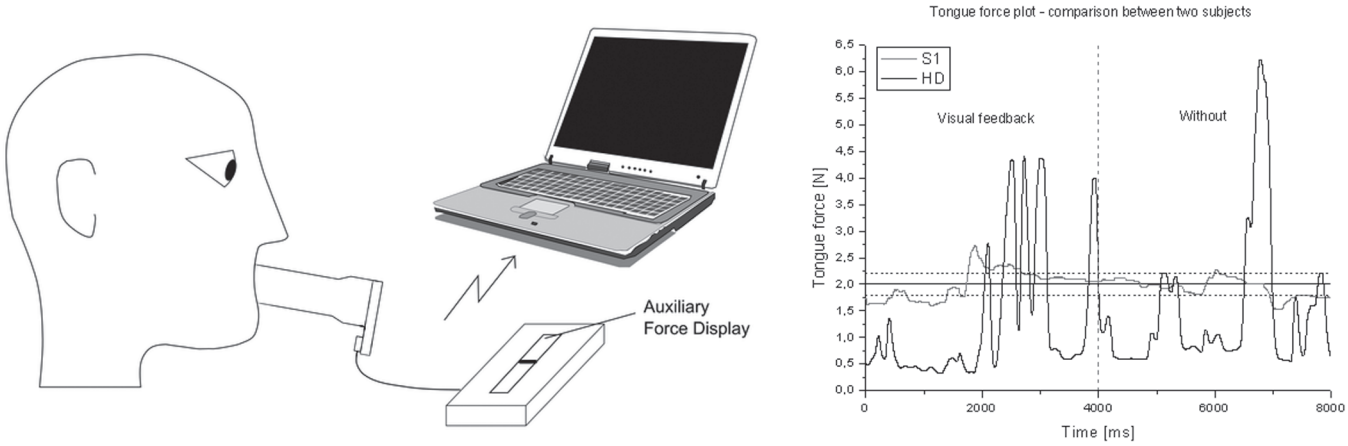

Fig. 3. On the left the schematically presented GlossoTonometer, held by the subject between the front teeth. Subject exerts the pushing force on the plunger which transfers it on the force transducer mounted at the tip of the modified syringe. The actual force value is displayed on the auxiliary bar-graph display on the front of the miniature data acquisition system, which transmits by Bluetooth the force value to the computer controlling the experiment. The subject can view the computer screen which provides the visual feedback of the instantaneous force in comparison to the required value. On the right the screenshot of the computer display, as it will be seen by the tested person, when the visual feedback is continuously available. In the real experiment, after the first four seconds the force trace disappears for another four seconds and after that appears again (repeated several times). Two results are presented for comparison, the data of HD patient (black trace) and the healthy person in red. It is possible to notice that the variability of the patient trace is much larger than of the healthy person, as well as the disappearance of the visual feedback has nearly no effect on sustaining the desired tongue force only in case of a healthy control.

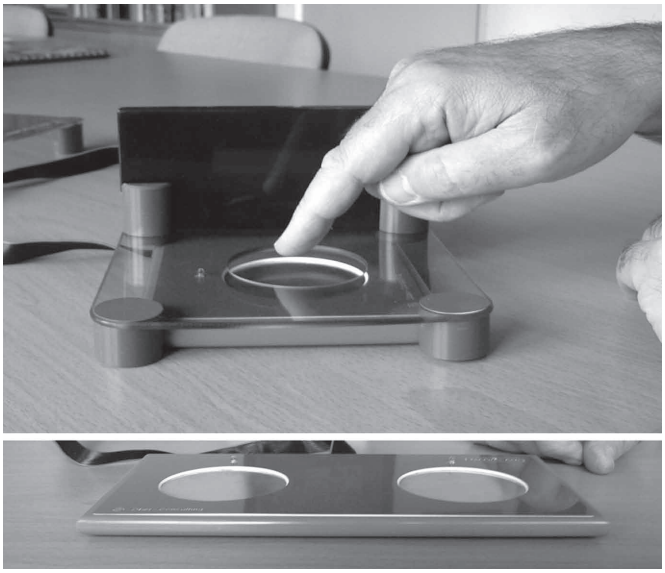

Fig. 4. Tapping Pad, at the bottom the low profile sensor plate, provides the possibility to rest the forearm on the table. At the top – the tapping pad with an attached transparent overlay with the vertically oriented obstacle, separating two sensor surfaces. The obstacle not only physically extends the path of the lateral hand movements, but also make it more complex to control (involving vertical component).

can be applied not only for monitoring the HD progression, but potentially can be useful for quantitative evaluation of other neurodegenerative diseases at their presymptomatic stage of development.

Manual function

Motor Assessment scale of the UHDRS includes also the visual evaluation of finger tapping and the speed of pronation and supination of the hand [1]. The visual assessment could be complemented by performing the UHDRS test on the computerized tapping devices, equipped with a pair of sensor touching plates, which do not require to exert the force to activate the switch (zero force and zero displacement). Such a system allows to measure not only the number of taps or pronation-supination cycles during the given period of time, but also the duration of finger-hand contact with the sensor surface, as well as the time when the finger or hand was moving (rotating). Such a quantitative measurement opens the possibility to know more about the tested movement [1] and also analyze the distribution of all measured movement parameters (counting the number of finger taps in five second gives only one number). This feature was used in two studies dedicated to HD by Antoniades at al. [6, 18]. The Tapping Pad system monitors the touching of both sensor pads independently. It allows to study the synchronicity of the left and right hand tapping, during the accelerating of tapping speed. Under such condition usually one of the hands cannot follow the increase and falls out of bimanual synchronous continuation, identifying in this way the non-dominant hand. The computerized device is portable and adjusted for ambulatory use. Due to its low mechanical profile it requires to raise the hand less than two centimeters above the table surface, so the forearm can rest on the table during the examination. It normalizes the upper extremity (whole arm biomechanical chain) position in relation to the tapping surface and facilitates inter- subject comparison of the acquired data.

Conclusions

Complementing the observational assessment of the UHDRS motor scale by the objective measurement seems to be the only way allowing to capture even the most subtle changes that accompany the HD development, which are normally impossible to notice by the naked eye visual inspection.

There is hope that the quantitative approach being so effectively applied on the motor dimension of HD, can be also implemented in the cognitive as well as behavioral dimensions. Especially the quantification of severity of apathy and depression may have a potential impact on the evaluation of patients' response to the prescribed treatment.

The quantitative data, with its low gradient of changes, which are specific for the slowly progressing diseases such as HD, allows continuous monitoring of patient's functional status and can be used for strictly quantitative clinical studies, easy to normalize and implement on a large scale, aimed at evaluation of the new emerging therapies.

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