Motocontrol and Movement Satbility of the Arm; Rules in the Parkinsonian and Healthy Control

Abstract of PhD thesis

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INTRODUCTION

In my thesis I deal with the biomechanical and control characteristics of the movement disturbances caused by a frequent neurological disease: the Parkinson's disease (PD). There are various clinical methods to examine the physical state of the PD patients, which are based on the examination of the behavior of the patients regarding the medical scale. In these cases the developed methods are subjective. On the contrary, biomechanical measurements, e.g. kinematic and dynamic measurements, give the possibility to measure patients in an objective way, through which there is a possibility to examine the development of the symptoms and the efficacy of the medication and treatment like the effect of Deep Brain Stimulation (DBS) what is discussed in my dissertation.

The three- dimensional movement analysis allows not only the determination of the movement's motor output in a timeframe, but also at the level of the joint movements while completing a movement task or during a coordinated movement of effector systems. Because in cases of patients suffering in neuro-motoric diseases such as stroke, Parkinson's disease, sclerosis multiplex, hemiplegia, the multijoint movements are often affected, that is why the movements measured both at the end of the limbs and at the joints are of high importance. The deeper understanding of human movement control means partly a scientific benefit regarding the introduction of the main principles; on the other hand the research of the movement regulation and its objective characterization modernizes the PD patients' diagnosis and therapy through the information technology to a great extent as a daily benefit.

Considering diseases of the motor system an important question is, if the variance of the joint rotations and the variance of the end-effector movements of a multijoint limb are the same in patients suffering under movement disturbances and in healthy people or if there is a difference between them.

In my study I performed two different series of examinations to study how motor control is affected by the disease.

In the first examination PD patients participated, who previously had a serious operation. During the operation a neurostimulator was implanted in the midbrain, to electrically stimulate certain nucleus located in this area of the brain (Deep Brain Stimulation - DBS). This treatment greatly reduced symptoms, which cannot be impacted through medicines.

We have examined our patients by the help of the protocol based on a movement test, which was used in a daily medical practice. We chose two cyclical movements, which are part of the UPDRS scale: the movement named thumb-index tapping (TIT) and the cyclical repeated pronation, or supination.

The patients executed the movements with the stimulator switched on with the stimulator switched off. We recorded kinematic variables of the movements and computed the amplitude, the velocity and the frequency of the repetitive movements. We compared the data received in the two different conditions.
We investigated the time span within which bradykinesia re-occurs immediately after the termination of deep brain stimulation.
DBS is really an effective treatment in advanced Parkinson's disease, however, the time course of the immediate wearing-off effect of DBS is unclear. This effect is crucial when positioning the electrode during the operation. The immediate effect of DBS on the main symptoms of PD is used to evaluate the tests performed during positioning the stimulating electrodes.

In the second series of examinations we compared control strategies of PD subjects and healthy controls in means of variances occurred in the joint space (internal space) and in the level of the endpoint of the limb (external work space). Using movement analyzing systems we measured and recorded the coordinates of the joints of the arm and the end of the arm during drawing arm movements. I compare the variances of the endpoint of the limb (hand movement variances) for the two groups of subjects by computing the ratio of the variances observed in the two groups. I compute this ratio for the variances of arm configurations as well.
In the case of healthy motor control the relative high variance in the joint space does not cause instability in the endpoint of the limb because the error compensation between the joints will work and the errors in the individual parts of the system do not cause greater variance at the endpoint level. If this error compensating mechanisms is damaged in the PD subjects, than the ratios of the variances at the endpoint level will be higher than the ratios of the variances of the arm configurations. Thus the comparison of the dimensionless ratios in the joint space and in the external workspace gives information about functioning of the error compensation.

THE AIM OF THE RESEARCH

The studies in connection with DBS had two aims. First of all the study was designed to determine the time course of the immediate wearing-off effect of DBS on upper limb bradykinesia. Secondly, we wanted to compare the wearing-off effect of the stimulation to different movement types studying the differences of the effects on various muscle groups.

The aim of my studies on tracking, drawing arm movements was to measure, evaluate and quantify the variance and stability of arm configurations and hand positions in healthy and PF subjects.

I was searching for parameters that quantitatively characterize the variances or repetitive arm movements. The final aim is to apply the measurements in clinical practice. This would be helpful to assist diagnosis of motor disorders and in monitoring the status of the illness.

Hypothesis

1. The application of DBS essentially influences kinematical parameters, namely the peek velocity, the amplitude and the frequency of repetitive hand movements.
2. In the case of Parkinson's Disease DBS has a continued effect after switching off the stimulation.
3. The variance of the endpoint movements in drawing arm movements of PD subjects is higher than in arm movements of healthy controls.
4. The variance of the arm configurations in drawing arm movements of PD subjects is higher that that of healthy subjects.
5. We assume that in PD subjects the error in the endpoint movement is caused by the lack of the error compensation between the joints of the arm.

THE METHOD

All of our measurements have been performed with an ultrasound based movement analyzing system developed by the company of Zebris (Medizintechnik GmbH, Isny, Germany). These systems can calculate the spatial position of the speakers based on the evaluation of the transmission times of the emitted ultrasound impulses received by three microphones. These microphones are fixed to the body. The sampling frequency of the system depends on the number of the used microphones. Maximum rate at the first system is 300/n Hz, and 200/n Hz at the second one.

Measurements of the effect of Deep Brain Stimulation

Subjects

Nine patients suffering from advanced stage PD were assessed in the study. All of them had had implanted electrodes. Surgery had been performed at an average of 16.7 months before assessment (range, 5–42) at the Department of Neurology of the Hospital Klinikum Grosshadern in Germany. However, all patients with one exception continued taking additional antiparkinson medication. In order to avoid the interference between medication and DBS, the patients were tested after withdrawal of their medication for at least 12 hours before the experiments. To rule out confounding effect of the DBS controlling the contralateral (not tested) hemibody ipsilateral stimulator was switched off immediately after completing UPDRS-ON testing (approximately 15 minutes before the movement registration begin) and remained off during whole experiment. The UPDRS-OFF assessment was done immediately after completing the first "OFF" trial.

The movement task

Two alternating movements were studied:

1) thumb-index tapping (TIT) that were generated by alternate flexion and extension in the metacarpophalangeal joints of the index and the thumb.

2) alternate forearm pronation-supination (PS) - in literature it is also called diadochokinesis.

Subjects were instructed to perform above listed movements as fast and with the largest amplitude as possible. During all tests the subjects sat at a table in a comfortable position. During the TIT registration, the markers were taped on the distal phalanxes of the thumb and index finger. For the registration of the PS movements the markers were fixed in one line on both ends of a paperboard cylinder which was held by a subject. Pronation and supination then appeared as rotation of the line connecting the two markers.

The most severely affected arm was investigated in all patients. The performance of the patients during TIT and PS was monitored for 5 minutes. A continues movement with high performance lasting for 5 minutes would have been quite tiring especially for the patients with movement disorders, therefore we have divided the test to smaller parts.

The experimental design for both condition of stimulation switched on (DBS-ON test) and stimulation switched off (DBS-OFF test) contained there following conditions:

1) $TIT_{DBS\text{-}OFF}$ 5 min; thereafter resting period of 10 min;
2) $TIT_{DBS\text{-}ON}$ 5 min; thereafter resting period of at least 20 min;
3) $PS_{DBS\text{-}OFF}$ 5 min; thereafter resting period of 10 min;
4) $PS_{DBS\text{-}ON}$ 5 min.

Before recording begun, there were two 1 min lasting practice trials, with a break of 1 min between them. DBS was always switched off during the pause of the second cycle. The half-time of this pause was taken as start for the calculation of the change in the performance (T0). After the end of the DBS-OFF trials, the DBS was again returned to on. The DBS-ON trials were performed in order to determine the impact of fatigue on the tested tasks and the same way of analysis was used as for DBS-OFF trials.

Data processing

Two markers were used in each task. The coordinates of the two markers were sampled with a frequency of 100 Hz each. The positional data of the two markers were continuously recorded for the duration of each 5-min test. Data were analyzed off-line using customized software programmed in MATLAB® (The MathWorks, Inc., Natick, MA). For the TIT-movement the distance between the two markers was calculated, for PS the angle of the line connecting the two markers in respect of its starting position was determined and amplitude, and peak velocity of each individual movement was calculated. These data were averaged (Amp, Vel) for each 4-s long movement epoch and also frequency have been calculated (Fre) and a value corresponding to the time elapsed between T0 and the middle of the movement epoch was assigned to them. For every test the averaged values of the second movement epoch were taken as the baseline (i.e., 100%) and all parameters were normalized and expressed as a percentage of the corresponding baseline value.

Statistical analysis

To test whether systematic changes over time occurred for each condition the normalized values of Amp, Vel and Fre were analyzed using Friedmann´s ANOVA for repeated measures. If significance level reached values below 0.05, the systematic changes were approximated by an exponential decay model, characterized by the time constant (τ) and the % decay (D). These coefficients were computed for each subject and for each parameter (Amp, Fre, Vel) by minimizing the mean squared error between the experimental data and the model fit. The fitted coefficients were used to describe the patients´ performance decline.

Measurement of drawing arm movements

Subjects

Twenty-four subjects volunteered for the experiment. In the studied group there were twelve Parkinsonian patients and the control group consisted of twelve age matched healthy subjects.

The movement task

Each subject sat on a chair having both shoulders strapped to the back of the chair. A table was positioned horizontally in front of the subject's chest such that by laying the upper and the forearm on it he/she was constrained to execute a planar movement. A cast was wrapped around the wrist and around the last three fingers while with the index finger and thumb the subject was holding an inkless pen. The task was to trace two figures, a circle and a square and to perform it with both hands separately. Subjects were asked to track the figure as precisely as possible and to perform the motion at a comfortable speed.

Four conditions were set: two for the figure (circle and square) and two for the hands (dominant and non-dominant). Each subject executed seven trials per condition with a total of twenty-eight trials for the entire experiment. Also three practice trials were allowed before each experimental condition.

Data processing

A T shaped device containing three speakers 1cm in diameter was placed on the surface of the subject's forearm and upper arm. The sampling frequency was set at 25 Hz. A hypothetical arm model was used to identify six anatomical points with the device pointer: 1st humerus-tuberculum majus; 2nd and 3rd - epicondylus medialis at lateralis humeri; 4th and 5th processi styloidei ulnae at radii, 6th hand. The coordinates of the elbow and the wrist joints were computed as averages of coordinate to get the individual position of the center of rotation, the longitudinal axes and the lengths of the segments. The shoulder and elbow joint angels were calculated using approximations of longitudinal axes of segments as straight lines connecting pairs of center of rotations. Rotations of these segments were approximated by rotation of the marker triplets. The joint angles were defined as: 1. horizontal shoulder abduction-adduction, 2. inward - outward rotation of the upper arm, 3. flexion-extension in the elbow, 4. hand supination and pronation. The angular configuration of the arm is represented by these four joint angles (4 dimensional vector) at each time point.

The length of the path, the velocity and the time of the drawings was calculated from the changes of the position of the 6th marker. The definition of the movement initiation and termination was assessed by considering velocity profile of the endpoint using threshold of 10 % of its maximal value. Data were normalized for 1000 data points in the time.

Statistical analysis

For statistics we performed a repeated measurements analysis, ANOVA, having a main effect for the two groups Parkinsonian (P) and Control (C), with two factors for Hands (dominant and non-dominant) and two factors for Figures (circle and square).

RESULTS

Results for DBS tests

THESIS:

- **Effect of deep brain stimulation is still present for a short period after breaking off the stimulation and supports the movement control of the PD patients.**

- **When positioning the electrode during the operation it is necessary to wait at least 1 min. between certain clinical testing trials performed after the stimulation switched off. After this time it is safe to assume the effect of stimulation has completely vanished.**

In each patient, there was a significant deterioration in overall motor performance (total UPDRS motor score) after switching the DBS off in comparison with DBS on (Wilcoxon test: $p<0.008$).

The first step of our experimental data analysis – Friedmann´s ANOVA – revealed the following results. The parameters amplitude (Amp) and peak velocity (Vel) showed significant changes over time for all conditions except the continuous stimulation in the thumb-index tapping task ($TIT_{DBS\text{-}ON}$). This indicates that amplitude and peak velocity were subject to fatigue in the PS-movement task but not in the TIT-movement task. In contrast, the parameter frequency (Fre) did not show any consequent changes. Significant temporal changes of the Fre were observed for $TIT_{DBS\text{-}ON}$ and $PS_{DBS\text{-}OFF}$, while changes did not reach significance for $TIT_{DBS\text{-}OFF}$ and $PS_{DBS\text{-}ON}$.

Based on these results, we fitted the coefficients D and τ of an exponential time course of Amp, Vel and Fre only in trials with significant temporal changes. The % decay of

performance was in the range of 60-80% for amplitude and velocity values in OFF-trials. The corresponding time constants in the OFF-trials were app. 30 s for TIT and 15-18 s for PS tests.

A repeated measures ANOVA with the two within-subjects factors *condition* ($TIT_{DBS-OFF}$, $PS_{DBS-OFF}$, PS_{DBS-ON}) and *parameter* (Amp, Vel) was used to evaluate their effects on the fitted coefficients. There was a main effect of the condition on the % decay ($p<0.02$) showing that under the PS_{DBS-ON} condition the % decay was smaller than under $PS_{DBS-OFF}$ or $TIT_{DBS-OFF}$ conditions (Scheffe test: $p<0.003$). The % decay tended to be somewhat higher for normalized peak velocity than for normalized amplitude. However this tendency did not reach significance. No interactions between the two factors were observed.

The repeated measures ANOVA of the dependent variable τ did only show a marginal significant effect of the factor *parameter* ($p<0.057$) indicating that the time constant tended to be smaller for the normalized peak velocity than for the normalized amplitude (Scheffe test: $p<0.04$). There was no significant main effect of the factor *condition*. The only difference between conditions indicated by the post-hoc test was a larger time constant for PS_{DBS-ON} than for $PS_{DBS-OFF}$ (Scheffe test: $p<0.035$). No interaction between the two factors was observed.

Results for drawing tests

THESIS:

- **In tracking arm movements Parkinson's disease rather effects the coordination in the time than the coordination in the space.**
- **The variance of the endpoint of the arm and the variance of the angular configurations of the arm is higher in PD patients then in healthy controls.**
- **The higher variance of the endpoint observed in the PD patients is caused directly by the high value of the angular variance. The reason of the higher variance of the position of the hand is not the lack of the synergy of the joints.**

Kinematics

We found that PD group moved with a significantly higher movement time than Control group (main effect $F_{(1,22)}=120.6$, $p<0.01$) and a post-hoc analysis revealed that the difference was present in all the conditions. Figure, considered as a factor, was significant, indicating that for all subjects the time to trace the Square was significantly

longer than to trace the Circle. As the perimeter for the two Figures differed, (which was 72 cm for the Circle and 92 cm for the Square), this result was not surprising.

For the velocity of endpoint movement there was a main effect for Group $F_{(1.22)}=147.2$, $p<0.05$, that is, Control group was significantly faster than PD group. None within subjects effect was significant for velocity. The groups show no differences in the length of path. The within group analysis revealed an effect for Hand $F_{(1.22)}=45.5$, $p<0.05$ that is, the dominant hand showed a smaller path than the non-dominant for both groups. The average absolute deviation of the plotted curve form the reference curve was compared for the two groups. In circle drawings the groups show no differences and in square drawings this average absolute deviation between the reference curve and plotted curve was even smaller in PD group than in Control group with a high standard deviation among subjects in Control group.

Movement stability - the hand position and angular arm configuration variance

The analysis for the end point variance showed a Group main effect $F_{(1.22)}=164.5$, $p<0.01$, namely the variance in Control group was less than in the PD group. A main effect for Figure showed less variability for Circle than for Squares. For the angular variance there was also a Group main effect $F_{(1.22)}=77.9$, $p<0.05$ - Control group was less variable than PD group. Moreover, we found main effect for Figure $F_{(1.22)}=9.5$ $p< 0.01$ and for Hand $F_{(1.22)}=6.7$ $p<0.01$, that is, for both groups, tracing of Circles were less variable than that of Squares as well as tracing with the Dominant Hand was less variable than with the Non-dominant.

We investigated whether the illness has a greater effect on the arm configuration variance or on the hand position variance. For this reason we compared the ratios of arm configuration variances between groups and ratios of endpoint variances between groups. The ratios of the averaged joint angular variances (AVA) in the two groups for each condition and the ratios of the averaged end point variances (AVP) lack significant difference.

DISCUSSION

DBS studies

Our findings demonstrate that the performance of repetitive upper limb and hand movements decreases by 60-80% within the first minute after switching the simulator off. This decrease can be modeled by exponential decay functions with time constants in the range of 15-30s.

Physical fatigue could be excluded as an explanation for the reappearance of bradykinesia, since the decay was much smaller in the ON-conditions than in the OFF-conditions although fatigue should occur similarly in both. For clinical testing, an important consequence of this study is that it is recommended to wait at least 1 min. after the stimulator is switched off, until it is safe to assume that the effect of stimulation has completely vanished.

The two tasks we tested imposed unequal force demands and the engagement of muscles. The thumb-index tapping activates hand and forearm muscles at the metacarpophalangeal joints whereas in the pronation-supination movements are involved more proximal muscle groups. One recent study showed that more proximal arm movements rely more on the effect of DBS compared to finger movements. In our movement tasks we did not observe such difference in spite of the finding that the time constant was smaller in the case of the proximal movements. One possible explanation can be that in our study distal and proximal movements were studied in independent tasks, while in the mentioned study of Wenzelburger both were part of a single coordinated complex movement.

Considering the parameters used for evaluation, we found that amplitude and velocity of repetitive movements are reliable values, whereas frequency is not. Frequency decays less and slower than the other two parameters. However, in the clinical setting, movement frequency is easy to determine whereas amplitude and velocity measurements necessitate some technical devices. This problem could be avoided by means of a task where the distance (amplitude) between sequential movements is fixed; for example, in hand tapping test assessed through a device with two manual counters or a finger-tapping using keyboard of the computer. It seems useful to develop recording devices, which can determine amplitude and velocity of simpler repetitive limb movements on-line.

Drawing arm movements

The main aim of this measurement and examination was to compare the differences in angular configuration and hand position variances, movement time, velocity and length of path in tracking geometrical figures of patients with PD and healthy subjects. In general, PD subjects used a longer movement time and performed slower movements when compared to the healthy control group. In contrast, we found no differences in the length of path of hand trajectories between the two groups suggesting that patients tended to be as accurate as healthy people by lowering the speed of movement and by increasing the movement time. The average absolute deviation of the endpoint position

from the reference figure was even smaller for PD subjects than for controls. The patients tend to draw close to the reference figure in each trial and this is reflected in the relatively small deviation from the reference curve, but they deviation from their own drawings were more different in consecutive trials and this is reflected in the higher variances of movement execution. We assumed that healthy human motor control yields less variance than the one applied by patients with neurological based movement disorders. This hypothesis has been supported for PD by our study since either the angular configurations as well as the working point variances were higher for PD patients than for healthy subjects. The redundant number of available biomechanical degrees of freedom in the arm movements that were studied was "restricted" by healthy motor control to form well-coordinated joint synergies. The question is whether the synergy of joint rotations helps the movement coordination in the patients or the synergy is damaged and this is manifested in an even higher relative variance of the most distal arm segment. We quantitatively characterized joint synergies by computing the variances of angular configurations, and we found that patients used more variable joint combinations by drawing different curves in individual or separate trials than controls. A remaining question is if this difference between the two groups is more emphasized in the variances of hand position. If the joint synergy is disturbed than hand position variances are differing at a greater rate between the two groups. We compared dimensionless ratios for variances in the two groups, both at the endpoint and at the joint's configuration level and found that they were not significantly different. This latter finding supports the hypothesis that the reason for the higher variances of the patient's drawings is not the insufficiency of inter-segmental compensation of joint rotations. Thus the ill-coordinated hand movement is caused by the error in the movements of the individual body parts rather than by the lack of inter-segmental coordination. This may explain the result that the higher variances caused by the illness is not more emphasized in the most distal segment of the arm than in the entire arm configuration.

It is difficult to separate the time and space in spatial-temporal coordination. However, our results support the findings that the two groups (PD and healthy) differ more significantly in controlling time than in controlling spatial coordination. In voluntary Parkinsonian arm movements that apparently perform tremor primarily, timing seems to be disturbed.

CONCLUSIONS

Similarly to previous studies our findings confirm that DBS significantly improve the control of arm and hand movements. We demonstrated that the amplitude and velocity of repetitive upper limb movements significantly improve under stimulation. Verifying the second hypothesis we have sown that the effect of DBS had not disappeared completely during the first minute after switching off the stimulation. This result has very high clinical relevance since the possible interactions between the particular tests can take an effect to the output of the tests. It is substantial for the right interpretation of the results of the tests performed during the time of the operation and also important for the later set up of the electrodes. The result can help to apply a simple but important correction in the used protocol.

The third hypothesis suggested that the variance of the hand movements was higher at the PD patients. The presented method is capable to show the differences in movement stabilities of tracking movements objectively. Our results show that the variance of the endpoint of the arm movement is significantly higher for PD patients than healthy controls and confirms our third hypothesis.

The fourth hypothesis has been also confirmed. It means that PD patients can hardly solve the problem of redundancy of the multijoint system and use more combinations of arm configurations than healthy controls.

The fifth hypothesis has been disproved. It suggests that the higher variance of the endpoint observed in the PD patients is caused directly by the high value of the angular variance. The reason of the higher variance of the position of the hand is not the lack of the synergy of the joints. The central control of the inter-segmental coordination is well organized but due to the error in the coordination of the individual joints it will still cause an error at the movements of body segments and their endpoints.

Publications

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