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Effect of exercise on reactivity and motor behavior in patients with Parkinson's disease.

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Abstract

Background

Following cued levodopa (LD) intake, endurance exercise showed a beneficial effect on scored motor performance in patients with Parkinson's disease (PD) in comparison with rest. This may result from an exercise induced increase of endogenous dopamine synthesis. As a result, beneficial effects on movement and reactivity may occur.

Objectives

To measure reactivity and motor performance in a repeated fashion with instrumental tasks after cued administration of soluble 200 mg LD/50 mg benserazide.

Design

PD patients consecutively performed paradigms, which assess reactivity and movement performance, after a standardised period of rest or of age related, heart rate adapted endurance exercise on two consecutive days in random order.

Results

Reactivity and execution of simple and complex motion series were significant better following exercise than after rest.

Discussion

Endurance exercise has a beneficial effect on reactivity and movement behavior in PD patients following cued application of LD probably due to an augmented synthesis of dopamine respectively other catecholamines and release in the prefrontal cortex, the nucleus accumbens and the basal ganglia. Small changes in catecholamine modulation of prefrontal cortex cells can have profound effects on the ability of the prefrontal cortex to

guide behaviour. Previous exercise may also improve pedunculo-pontine nucleus function, which is involved in motor related attention processes.

Introduction

Treated patients with Parkinson's disease (PD) report a reduced exercise capacity due to hypothetical limited effect of dopaminergic drugs or an increased need for them. Clinical trials excluded possible causes like central dopamine deficiency, impaired gastrointestinal absorption and bioavailability of levodopa (LD), mitochondrial muscle dysfunction. But in PD patients, endurance exercise had a beneficial effect on not blinded scored motor symptoms following cued LD intake compared with rest.¹ However even blinded rating is questionable, when comparing an exercise – with a rest condition due to onset of vegetative epiphenomena, i.e. sweating. This observed improved motor performance after endurance exercise may be due to release of endogenous dopamine, which contributes to regulation of reactivity and of movement.^{2;3} Conventional PD rating tools may be not sensitive and specific enough to capture these subtle changes of behavior, which may be determined by simple instrumental tasks. Their execution depends on endogenous dopamine release in nigrostriatal and prefrontal brain structures in healthy humans, whereas an equal cued, dopaminergic stimulation is necessary to enable identical conditions in a cohort of PD patients to investigate whether endogenous dopamine release following exercise improves reaction- and movement behavior.⁴ Various types of movement series exist. There are complex ones like peg insertion which ask for additional involvement of i.e. prefrontal areas. They are similar to performed motion series of simple reaction time tasks, since they require execution of aimed movements. In contrast tapping procedures are simple movement sequences, which are automatic and repetitive. They are more influenced by velocity with involvement of basal ganglia structures only. Objective of this exploratory, pilot trial was to assess reactivity and

motion behaviour after cued dopaminergic stimulation and an interval of rest or of exercise in PD patients.

Subjects and Methods

Subjects

22 treated idiopathic PD patients, diagnosed according to the UK Brain Bank criteria, (age: 61.05 ± 2.08 [mean \pm SD] years; duration of PD: 4.21 ± 0.61 years; UPDRS: 34.19 ± 2.62 ; UPDRS I: 1.91 ± 0.34 ; UPDRS II: 10.33 ± 1.18 ; UPDRS III: 19.29 ± 1.82 ; UPDRS IV: 2.57 ± 0.62 ; HYS: 1.91 ± 1.58 ; Mini Mental State Examination: 28.39 ± 1.97) without unpredictable motor fluctuations were consecutively enrolled. PD patients, who had other medical conditions, which may affect the outcomes of the performed assessments, did not participate. Their concomitant drug treatment consisted of LD/Dopadecarboxylase inhibitor (N = 22, 450 ± 112.5 mg [mean \pm SD]); Entacapone N = 9, 1000 ± 200 mg; bromocriptine N = 2, 30 mg each; cabergoline N = 2, 2 mg, 4 mg; pergolide N = 2, 2.25 mg, 8 mg; pramipexole N = 11, ropinirole N = 2, 9 mg, 15 mg; rotigotine N = 1, 8 mg; rasagiline N = 3, 1 mg each, selegiline N = 3, 7.5 mg each; amantadine N = 1, 300 mg).

Design

PD patients were put off their regular PD drug therapy for 12 hours over night. They had a standardised breakfast (300 kcal) in the morning at 7 am. Soluble LD/benserazide (200mg/50mg, Madopar LT®) was applied after prior domperidone (Motilium®, 40 mg) intake to avoid nausea 30 minutes later. A simple reaction time paradigm (SRT) was

performed 30 minutes before (point I) and 60, 90, 120 150 minutes after LD application (moments II – V). Conditions were identical except rest or exercise, both of which were performed in random order (randomization to condition sequence with sealed envelopes: Tanja Steiner) between moments I and II on two consecutive days in each participant (Figure 1). The patient did not know in advance, whether they would perform the exercise or the rest session on day 1, when performing the baseline investigation. One patient was tested at each session only. PD patients were trained with the use of the cycle ergo meter on the day before start of the trial. The patients took their remaining drug regime after the study interval to reduce a bias of prior long-term dopamine substitution.

Exercise condition

Cycle ergo meter exercise for the lower extremities was employed using a heart rate adaptive training program (Cateye Ergociser Modell EC-1600). By pedalling on the bike ergo meter, the target heart rate was set in correlation to the age. The heart frequency was measured by ear-clip every 30 seconds and automatically relayed to the cycle workload. After reaching the age adjusted, required heart rate (formula: $200 - \text{age}$) in the 15 minutes lasting warm up period, a steady state of endurance exercise within totally one hour lasting interval of exercise between moments I and II was performed with continuous, automatic adaptation of the bike pedal resistance.

Rest session

The patients were in a lying position.

Simple reaction time paradigm (SRT)

The response to a visual SRT task (manufactured by Schuhfried Ges.m.b.H., Austria) was measured. The apparatus consisted of a 31 cm x 42 cm rectangular surface with two stimulus lights (red and yellow), each coupled to the reaction button electrode 1 cm in diameter 15 cm equidistant from a central start button electrode. SRT performance did not depend on the red light, which was not presented and employed during the whole test procedure. The subject pressed with the index finger of the dominant (right-: N = 19, left-: N = 1, both-handed: N = 2) hand the central start button. After the appearance of the yellow stimulus light the subject had to switch off the light as quickly as possible by moving his finger from the central start button to the reaction button. Reaction time (RT) was considered as elapsed interval between onset of the yellow stimulus light and release of the start button. Movement time (MT) was the period between release of the start button and the pressing of the reaction button. Thus this paradigm only asks the subject to detect one stimulus and to produce the same response on every trial.⁵ Since the more affected hand of PD patients presents slower SRT performance than the other less affected one, PD patients were asked only to use the right dominant hand for this within-subjects comparison.⁶ RT and MT were assessed by a computer to millisecond accuracy. 28 RT trials were run. We used out of 26 right answers a truncated mean of values, which excludes measures greater than or less than 2 standard deviations (SD) of the mean value, for statistical analysis. In this trial, no participant fell within the 2 SD cut off.

Peg insertion

In order to execute the peg insertion procedure (manufactured by Schuhfried Ges.m.b.H., Austria) subjects were asked to transfer 25 pegs (diameter 2.5 mm, length 5 cm) from a rack into one of 25 holes (diameter 2.8 mm) in a computer-based contact board individually and as quickly as possible. The distance between rack and appropriate holes was exactly 32 cm. The board was positioned in the middle and the task was carried out on each side. When transferring each peg from rack to hole, elbows were allowed to be in contact with the table. The interval between inserting of the first and the last pin initially with the right - and then the left hand was assessed. Then the data for the right and left hand were averaged to reduce the amount of data. The period for this task was measured by a computer in seconds with an accuracy below 100 ms.⁷

Tapping

In order to execute the tapping test (manufactured by Schuhfried Ges. m. b. H., Mödling Austria), we instructed the individuals to tap as quickly as possible on a computer based contact board (3 cm x 3 cm) with a contact pencil for a period of 32 seconds after the initial flash of a yellow stimulus light. We did not control for peak height reached by the pencil. The board was positioned in the middle. When performing the task, elbows were allowed to be in contact with the table. We registered the number of contacts by means of a computerized device. First we measured the tapping rate with the right hand and then with the left.⁷

All participants were asked to familiarize with the applied instrumental tests for an interval of 1 minute to reduce or avoid learning and training effects on test performance on the day before.

Statistics

T-tests for comparisons between rest and exercise, respectively ANCOVA (covariates: age, body weight, UPDRS) with repeated measures design within one condition were employed for this statistical exploratory analysis. The Least Significant Difference t-test was used for post hoc comparisons. The level of significance was $p < 0.05$. To minimise the effect of various baseline values, the differences (formula: value [moment I] minus value [II, III, IV, V each] during the rest- and within the exercise session were calculated.

Ethics

All participants gave written informed consent. The study was approved by the local ethic committee of the university.

Results

SRT

RT ($F_{(4,84)} = 2.5$, $p < 0.05$; Figure 2A [see Figure for post hoc analysis]) reduced after exercise and increased after rest ($F_{(4,84)} = 2.55$, $p < 0.05$; Figure 2B). There were no significant differences of the baseline values (RT: exercise versus [vs] rest: $p = 0.1$).

Figure 2C compares the computed differences of baseline and each assessment point

(formula see statistics section) between both conditions. Its outcomes support the observed RT reduction after exercise and the RT increase following rest. MT only significantly (exercise: $F_{(4,84)} = 3.17, p < 0.02$ [Figure 3A]; rest: $F_{(4,84)} = 1.86, n.s.$ [Figure 3B]) reduced following exercise. Baseline values between the rest and exercise session were not significant different (MT: exercise vs rest [$p = 0.8$]). Figure 3C describes the computed MT differences of baseline and each assessment point between both conditions. The number of right answers did not significantly change after exercise ($F_{(4,84)} = 0.12, ns$) (data not shown), but decreased after rest ($F_{(4,84)} = 6.89, p < 0.001$; post hoc analysis: I [27.9 ± 0.29 ; mean \pm SD] vs II [27.59 ± 0.59] $p < 0.001$; I vs III; ns.; I vs IV; ns.; I vs V ns.).

Peg insertion

The interval for the peg insertion task significantly reduced after exercise (right: $F_{(4,84)} = 16.04, p < 0.001$; Figure 4A; left: $F_{(4,84)} = 13.91, p < 0.001$; Figure 4B) and rest (right: $F_{(4,84)} = 4.90, p = 0.0013$; Figure 4C; left: $F_{(4,84)} = 6.85, p < 0.001$; Figure 4D). Baseline values were not significant different (peg insertion interval: exercise vs rest [right: $p = 0.16$; left: $p = 0.38$]). Figures 4E and 4F compare the computed differences of baseline and each assessment point between both conditions. Their results demonstrate the significant better improvement of peg insertion performance after exercise in particular with the right hand (Figure 4E), but not with the left one (Figure 4F).

Tapping

The tapping rate significantly increased after exercise (right: $F_{(4,84)} = 5.70$, $p < 0.001$; Figure 5A; left: $F_{(4,84)} = 5.48$, $p < 0.001$; Figure 5B), but not after rest (right: $F_{(4,84)} = 0.73$, ns; Figure 5C; left: $F_{(4,84)} = 2.48$, ns; Figure 5D). Baseline values did not significantly differ (right: $p = 0.35$; left: $p = 0.46$). Analogue to the previous analyses, significant differences between rest and exercise were found following moments IV and V (right hand, Figure 5 E), respectively moment V (left hand, Figure 5 F). This supports the finding of an improved tapping rate after exercise.

There was no impact of the set covariates in the whole analysis and no complaints of PD patients before and after exercise.

Discussion

Exercise and reactivity

The improved SRT performance following exercise may result from an augmented endogenous dopamine synthesis and release in various brain structures.⁵ Dopamine improves the nucleus accumbens function, which represents an interface between limbic and motor structures. The nucleus accumbens plays a major role in control of goal-directed actions and receives a dopaminergic input from the ventral tegmental area. Behavioural studies consistently showed that the nucleus accumbens supports instrumental behaviours elicited by cues associated with drugs. Indirect stimulation of dopamine receptors in the nucleus accumbens by d-amphetamine shortened reaction times. Thus stimulation of the nucleus accumbens with dopamine is involved in guiding the speed of instrumental responding.^{8;9} The impaired SRT execution after rest confirms

previous outcomes on reactivity in PD patients with an exact timing of both LD intake and test performance.¹⁰ An animal study also showed an impaired RT after cued dopaminergic stimulation in a particular species of fast reacting rats.¹¹ Sedative effects of LD may play a role and release of fatigue counteracting brain norepinephrine is lower during rest than exercise.¹² Therefore the number of correct answers also worsened in the SRT paradigm after rest.

Exercise and motor performance

Execution of the peg insertion task was better after exercise than rest in particular with the right dominant hand. This outcome confirms the prior observed behavioural pattern with the SRT paradigm with better test execution after exercise and that instrumental determination of disturbed movement performance is more valuable on the dominant side in PD patients.¹³ The peg insertion paradigm asks for execution of complex movement sequences with a complex interplay of additional need for visual and spatial cognition, self-elaboration of internal strategies, sorting and planning. All these processes are influenced by the modulating role of striatal dopamine levels on association areas of the prefrontal cortex and the basal ganglia.^{4;14} Prior exercise supported endogenous dopamine synthesis and release in these brain areas.^{2;15} It is known, that small changes in catecholamine modulation of prefrontal cortex cells can have profound effects on the ability of the prefrontal cortex to guide behaviour. We assume that these hypothetical higher prefrontal catecholamine levels following exercise supported the better peg insertion performance as they also improved the execution of the attention related components of this task.¹⁶ The tapping procedure only asks for performance of an

automated, repetitive motion series without need of attention and concentration related cognition load. Therefore it depends more on dopamine dependent basal ganglia function alone. Thus tapping outcomes also improved due to an exercise increased endogenous striatal dopamine release. Generally, one may also hypothesize, that prior exercise additionally resulted in a better pedunculo-pontine nucleus function, which is involved in motor related attention processes.¹⁷

Our study results also confirm findings that exercise provides benefit in PD patients in terms of overall motor function, in particular bradykinesia.¹⁸ This was also found with improvement of UPDRS scores and of the control respectively coordination of grasping forces during the performance of a functional bimanual dexterity task. In particular, when PD patients were forced to perform exercise with a certain pedal rate and resistance 30 % above their preferred voluntary one, a better motor performance and control was observed.¹⁹ In our trial, pedal rate and resistance was also continuously adapted to the heart rate. Therefore we assume that the exercise condition within our trial was more similar to a more forced exercise paradigm and to an aerobic exercise condition.²⁰ Forced exercise may lead to a shift in motor control strategy, from feedback to a greater reliance on feed forward processes. This even suggests that forced exercise may alter central motor control processes.¹⁹ This in line with trial outcomes, which describe dose-dependent benefits of exercise in early PD patients and suggest that even high-intensity exercise can normalize corticomotor excitability.²¹ Our results with a significant better performance of instrumental motor tests following exercise support this hypothesis to a certain extent. We asked our participants to perform exercise above the voluntary level but however not with high intensity.

Limitations

Our explorative pilot trial did not investigate, whether PD patients without any dopamine substitution show the same behavior, i.e. turn out to react different after a period of rest or exercise. Generally, test outcomes were better at baseline of the exercise condition. We cannot explain this phenomenon with dopamine related reward- or expectation mechanisms related to exercise,²² since we performed a crossover design with 11 patients starting with exercise on day 1 and the remaining ones on day 2. However all participants knew the test condition to be performed on the second day. This may reduce expectation and accordingly cause less release of endogenous dopamine and other catecholamines, since the participants were more adapted to the whole situation. Therefore one may also hypothesize, that the more dopamine related motor tests may be more sensitive to this hypothetical phenomenon than the reaction time paradigm. This was not the case, when the right and left handed execution of the motor tests were analyzed separately and accordingly no significant differences appeared concerning the SRT outcomes at baseline.

In conclusion, endurance exercise has a beneficial effect on reactivity and movement behavior in PD patients following cued application of LD probably due to an augmented synthesis and release of endogenous dopamine in various brain structures.

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Competing Interest: None declared.

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Figure 1 – 5 sent as extrafiles

Legends to the Figures

Figure 1

Study flow chart

Figure 2

Head:

RT following exercise (A) and rest (B) at moments I – V and (C) the computed differences of RT outcomes (I - II, I - III, I - IV, I – V) during the exercise– and the rest condition (bold, checkered).

Legend:

RT = reaction time; ms = milliseconds; * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ of the post hoc test; I (baseline), II - V (after the intervention exercise or rest) = assessment moments; SEM = standard error of means

Figure 3

Head:

MT after exercise (A) and rest (B) at moments I – V and (C) the computed differences of MT outcomes (I - II, I - III, I - IV, I – V) during the exercise– and the rest condition (bold, checkered).

Legend:

ms = milliseconds; * = $p < 0.05$, ** = $p < 0.01$ of the post hoc test, *** = $p < 0.001$ of the post hoc test; I (baseline), II - V (after the intervention exercise or rest) = assessment moments; SEM = standard error of means

Figure 4

Head:

Interval for the peg insertion task after exercise (right-: A; left hand: B) and rest (right-: C; left hand: D) at moments I - V and computed differences (I - II, I - III, I - IV, I - V) during the exercise – and the rest condition (right-: E; left hand: F) (bold, checkered).

Legend:

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ of the post hoc test; I (baseline), II - V (after the intervention exercise or rest) = assessment moments; SEM = standard error of means

Figure 5

Head:

Tapping rate following exercise (right-: A; left hand: B) and rest (right-: C; left hand: D) during moments I - V respectively computed differences (I - II, I - III, I - IV, I - V) during the exercise – and the rest condition (right-: E; left hand: F) (bold, checkered).

Legend:

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ of the post hoc test; I (baseline), II - V (after the intervention exercise or rest) = assessment moments; SEM = standard error of means

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