Title

Motor learning of hands with auditory cue in patients with Parkinson's disease.

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Running head

Motor learning with cues

Tables: 2
Figures: 5

Summary:

In the present research, changes in motor cortex function were observed in relation to repetitive, voluntary thumb movement (training) in patients with Parkinson's disease (PD) and normal control subjects. Changes in the direction of thumb movement due to motor evoked potential (MEP) by transcranial magnetic stimulation (TMS), after motor training with and without rhythmic sound, were measured using a strain gauge for 12 patients with PD and 9 normal control subjects. PD patients who experienced the freezing phenomena showed poor change in direction of TMS-induced movement after self-paced movement; however, marked change in direction of TMS-induced movement was observed after training with auditory cue. PD patients who had not experienced the freezing phenomena showed positive effects with the auditory cue, producing similar results as the normal control subjects. Two routes for voluntary movement are available in the nervous system. The decreased function of basal ganglia due to PD impaired the route from the basal ganglia to the supplementary motor cortex. These data suggest that the route from sensory input to cerebellum to premotor cortex could compensate for the decreased function of the route via the basal ganglia to the premotor cortex. Once change in the motor cortex occurred, such change persisted even after the interruption of training. These phenomena suggest that motor memory can be stored in the motor cortex.

Key words: Motor learning; auditory cue; TMS-induced movement direction; Parkinson's disease

Introduction: Patients with Parkinson's disease (PD) face difficulty in initiating and performing complex, sequential movements. PD patients frequently complain of slowness and early fatigue during movements associated with their motor disability. They show deficits in motor learning and in the acquisition of new skills, although the extent of the deficit remains unclear. Therefore, to elucidate the most effective motor learning interventions, it is important to generate basic insights into the learning capabilities of PD patients.

The involvement of the motor cortex in learning movements has recently attracted much attention. Transcranial magnetic stimulation (TMS) has proven to be a valuable and non-invasive tool for investigation of the central motor system (Barker et al., 1985; Rothwell et al., 1991; Berardelli, 1991). Imaging studies using positron emission tomography (PET) have provided evidence that the motor cortex is more active during the process of motor learning (Grafton et al., 1992; Kawashima et al., 1994; Honda et al., 1998). Brain mapping using functional magnetic resonance imaging (fMRI) (Karni et al., 1995) and transcranial magnetic stimulation (Pascuel-Leone et al., 1995) has also shown changes in the motor cortex during the acquisition of motor skills. Change in the motor cortex of healthy individuals during thumb movement exercise has been observed in studies similar to the present research. However, similarities between motor cortex function in healthy patients and in patients with PD are unknown. It appears that the same learning-related changes in the motor cortex of healthy individuals also occur in patients with PD. The present study used a metronome as an external auditory cue to determine whether external triggers are a factor in skill acquisition. As human cortical movement representation can undergo rapid plasticity (Classen et al., 1998), the aim of this study was to evaluate the differences in motor control reorganization between PD patients and

normal controls during thumb exercise with and without rhythmic sound as assessed by the directional change of TMS-induced thumb movements.

Methods:

Subjects: Twelve Parkinson's disease patients aged 52-77 years (65.1±7.5 years, 8 males and 4 females) and nine normal age-matched volunteers aged 45-75 years (64.3± 8.5 years, 8 males and one female) with no history of neurological disorder participated in this study. The mental condition of Parkinson's patients was normal and in Hoehn and Yahr stages II or III. The freezing phenomena was assessed by the activities of daily living (ADL) section of the Unified Parkinson's Disease Rating Scale (UPDRS) and was considered to be present if the score was 1 or > 1 on the 'freezing when walking' question. Parkinson's patients were divided in two groups according to presence or absence of the freezing phenomena. Type I patients (n = 7; 6 males and 1 female; mean age 68.1±6.3 years) had experienced the freezing phenomena, while Type II patients (n = 5; 2 males and 3 females; mean age 61.0±7.7 years) had not experienced the freezing phenomena. All subjects were right handed and provided informed written consent to participate in this study. Clinical characteristics and demographic data of the patients and normal volunteers are shown in Table 1. None of the patients displayed severe "on-off" fluctuations and all were tested while they were in their "on"-stage.

Subjects were seated comfortably in a chair with their right fore arm flexed at the elbow and positioned on the board of a strain gauge. In order to perform unidirectional thumb movement, the thumb was fixed to the strain gauge by a splint. The training movement was performed against a one dimensional rubber expander, which enabled the thumb to return passively to the starting point of movement. The strain gauge moved with TMS-

evoked thumb movements either in extension or flexion. The thumb was fixed to the strain gauge plate during both exercise and TMS trials while the investigator continuously monitored the correct performance of thumb movement. This particular model is a modification from Classen et al., who used two accelerometers fixed to the thumb to record movement directions; one accelerometer measured abduction or adduction movements and the other measured flexion or extension movements. However, in the present study, a strain gauge was used to record the unidirectional flexion or extension movements of the thumb.

Stimulation and procedure:

TMS was performed using a MagStim 200 (UK) connected to a figure-of-eight coil held with the handle pointed backwards and laterally at a 45° angle to the sagittal plane. The optimal coil position was defined as the scalp position at which small thumb movements in a constant direction (flexion) could be evoked. After marking the coil position on the scalp with a pen, a stimulation intensity of 120% of resting movement threshold was used. This intensity evoked consistent isolated thumb movements in all subjects. The movement threshold was defined as a displacement of the splint on the strain gauge ≥ 50 gm in three of five trials. Motor training, namely thumb movement exercise, was executed on the strain gauge, which was connected to a highly sensitive amplifier (WGA-710 A), which in turn was connected to an evoked-potential, electromyography measuring system (Neuropack Σ). The amplifier was zeroed while the thumb rested on the strain gauge to counteract the weight of the thumb. Minimum movement of the thumb, either TMS-evoked or self-induced, accelerated the amplifier marker +.01 for flexion, which in turn showed a downward deflection of movement trace, and −.01 for extension,

which show an upward deflection of movement trace on the monitor. Movement signals were recorded by Neuropack Σ using 50 Hz and .01 Hz as high and low cut filters, respectively. A baseline (pre-training) TMS-evoked thumb movement in a specific direction (flexion) was established during rest. Subjects were asked to voluntarily extend their thumb slowly and continuously for 15 minutes without external sound (self-paced) in the opposite direction of the baseline movement (flexion) at a rate of 60 movements per minute. Five-minute intervals of TMS-evoked movement were recorded to examine changes in the direction of thumb movement. After the first 15 minutes of training, subjects were allowed to rest for another 15 minutes. Every additional 5 minutes, TMS-evoked movement was recorded to examine whether the change of direction returned to the baseline (pre-training). During the TMS study, subjects were required to suspend thumb extension exercise for 15 seconds for three stimulation trials. In the first sitting, TMS-evoked movement of direction was recorded during the 15-minute thumb extension exercise without cue followed by 15 minutes rest. In the next session (not in the same day), the technique was repeated and TMS-evoked movement of direction after the 15 minutes thumb extension exercise was recorded with a metronome beat of 1 Hz as an auditory cue, followed by 15 minutes rest.

Change of direction in TMS-induced movement indicates motor reorganization. In addition, changes in amplitude from the baseline of TMS-induced movement with sound (metronome-paced) and without sound (self-paced) were compared across the three groups of normal participants, freezing PD patients, and non-freezing PD patients (normal, freezing, non-freezing groups, respectively) to evaluate the effect of sensory cues on motor reorganization.

TMS-induced movement differs from motor evoked potentials (MEP). MEP is the electrical activity of muscles evoked from cortical motor neuron stimulation and is recorded by electrodes. In contrast, TMS-induced movement is recorded by the displacement of a strain gauge following pressure from contracted muscles evoked by cortical stimulation (Fig 1).

Results:

Effect of pre- and post-training thumb movement exercise: Data concerning TMS-evoked change in direction of movement is shown in Fig 2. Figure 2 (A) shows the downward pre-exercise movement direction caused by flexion of the thumb during TMS at the representative cortical motor area defined by pre-exercise movement. Following thumb extensions at a rate of 1 Hz without external sound (self-paced), TMS-induced movement direction changed to the direction of exercise during TMS at the same representative cortical motor area and at the same intensity. Before exercise, the strain faced the downward direction, but after 5 minutes of exercise, the direction of strain began to move toward the direction of exercise. At rest, the movement returned to the original, pre-exercise direction. This pattern was observed in 5 of 9 controls and in 9 of 12 PD patients (5 freezing PD patients and 4 non-freezing PD patients) during both self-paced and metronome-paced thumb exercise. Figure 3 shows that the directional change of TMS-evoked movement after 15 minutes of thumb extensions in PD patients remained as a memory trace 5 minutes after stopping the exercise. Three control subjects and one freezing PD patient who did not produce a directional change in the TMS-induced movement demonstrated a slight reduction in amplitude (Fig 2) (B).

Following self-paced thumb training, one freezing PD patient did not show a change in TMS-induced movement direction; however, the movement direction did change to the metronome-paced rhythm after 10 minutes of exercise (Fig 4) (A). One control subject and one non-freezing PD patient showed a change to the practice direction after 15 minutes of thumb exercise (Fig 4) (B) and were excluded from the statistical analyses.

Effect of sensory cue on motor learning: The influence of auditory cue was examined by measuring the peak amplitude of strain in all subjects who demonstrated a change in the amplitude of TMS-evoked movement every 5 minutes during 15 minutes of continuous exercise. These measurements were compared between the self-paced and metronome-paced training of each group. Mean difference values between the baseline amplitude (pre-exercise) and the amplitude following the three pulses of TMS are plotted in Table 2. Mean strain amplitude of the three groups (normal, non-freezing and freezing) were compared between the self-paced and metronome-paced rhythms at three time points by analysis of variance (ANOVA), and post hoc comparisons with Bonferroni corrections were applied. The level of significance was set at $p<0.05$.

Scores were found to be higher in metronome-paced training than self-paced training in all three groups (Table 2). Additionally, the main effect of both self-paced [$F(2, 15)$, $p= .000$] and metronome-paced [$F(2, 15)$, $p=.006$] rhythm were seen after 5 minutes of exercise in each group. Post hoc comparison revealed that non-freezing and freezing PD patients showed significantly ($p=.000$ in both non-freezing and freezing groups) reduced amplitude compared to normal participants at self-paced rhythm, and also at metronome-paced rhythm but at a reduced level of significance ($p=.027$ in non-freezing group, $p=.012$ in freezing group). After 10 minutes of exercise, an increase in strain scores were observed, but no significant main effect was observed for both cue and non-cue rhythm.

After 15 minutes of exercise, a significant main effect was observed in non-cue rhythm [F (2, 15), p=.048]. Post hoc comparison revealed that freezing PD patients showed a near significant (p=.059) effect compared to normal participants, whereas during metronome-paced exercise, the effect was not significant (p=.534) compared to normal participants.

Kinematical traces during thumb exercise (Fig 5) with rhythmic sound and without rhythmic sound clearly indicate the effect of auditory cue on motor training. The wave without sound is irregular and not parallel, indicating a deficit in the execution of simultaneous and sequential movements. Conversely, waves recorded with rhythmic sound are regular, parallel to the baseline and flat for a short period. Rhythmic movements resulted from the external stimuli, which suggest that Parkinson's subjects are able to use sensory cues to overcome difficulties in initiation or continuation of movement.

Discussion:

Improved motor learning with auditory cue was observed in the normal participants, freezing PD patients, and non-freezing PD patients. However, the main finding of the present research is that after 15 minutes of exercise with non-cue rhythm, the difference in TMS-evoked movement amplitude was marked in freezing patients when compared to normal participants, whereas after exercise with auditory cue, the TMS-evoked movement amplitude increased in freezing PD patients and showed no significant difference compared to normal participants. After 15 minutes of exercise, the increase in TMS-evoked movements from self-paced to metronome-paced in normal participants, non-freezing and freezing PD patients were 10.8%, 10.6% and 13.0%, respectively. This

indicates that the motor learning of non-freezing PD patients is similar to that of normal participants.

Observation of change in movement direction required 5 minutes of thumb extension exercise for most subjects (14 of 21 subjects). For 2 subjects, 10 or 15 minutes of continuous training was required to initiate a change in TMS-evoked movement. Four subjects (3 normal participants and one PD patient) did not produce a directional change in TMS-induced movement but a trend of reduced amplitude was seen in those subjects, likely due to the training duration of 15 minutes. We expect that an increased duration of exercise would have resulted in a change in movement direction.

A period of 15 minutes exercise was chosen to maintain equal time duration and to avoid considerable fatigue in all subjects. After beginning the thumb extension exercise, a slight trend of whole upper limb movement during extension exercise was observed in some PD patients. However, in spite of this limitation, and in accordance with other studies (Classen et al., 1998; Karin et al., 2000), short training of a unidirectional thumb movement was found to exert a change in TMS-evoked movement direction, thus suggesting a transient change in the representing cortical area. This type of change, either morphological or functional, has been described as brain plasticity. Evidence of motor cortex reorganization has also been observed in subjects with chronic neurological disorders including cerebral tumor, amyotrophic lateral sclerosis (Seitz et al., 1995), after hemispherectomy (Cohen et al., 1991), after anastomosis of the musculocutaneous nerve and intercostals nerves following cervical root avulsion (Mano et al., 1995), and after limb amputation (Brasil-Neto et al., 1993). The findings of the present study further support the notion that the primary motor cortex can be reorganized by motor practice

even in a single training period (Muellbacher et al., 2001). As a result of voluntary activation, a shift in the cortical motor map for the hand muscles was demonstrated in healthy subjects under the physiological condition (Wilson et al., 1993). The results of the present study of thumb training showed similar abilities of healthy subjects and Parkinson's disease patients to represent encoded kinematic details of the practiced movement (Classen et al., 1998). Cortical reorganization, as observed in the present study, is likely due to functional synaptic mechanisms of corticocortical connections, which include the removal of local inhibition and changes in synaptic efficacy (Karin et al., 2000).

Plasticity has been clearly demonstrated using TMS in humans during motor learning, and in response to brain injury. To enhance plasticity so as to recover damaged brain function, several techniques have been used for rehabilitation. In addition to neuromuscular electrical stimulation, sensory stimulation, robot-enhanced training, and administration of pharmacological agents such as amphetamine, constraint-induced movement therapy plays a vital role in enhancing plasticity for skill acquisition even in intact humans (athletes) and in the rehabilitation of individuals with brain damage (Butefisch et al., 1995). Neural plasticity is associated with the acquisition of motor skills (Cohen et al., 2002). These experiments have also shown that Parkinson's disease patients are able to change their performance as a result of practice, and that performance improves when supported by external stimuli. Studies of patients with Parkinson's disease and even in patients with normal pressure hydrocephalus indicated that rhythmic auditory stimulation, visual cue on gait velocity, cadence, and stride length were attributed to improvements in performance (Macintosh et al., 1997; Stolze et al., 2001).

However, the present study focused on differences in peak amplitude between self-paced and metronome-paced TMS-induced movements following simple thumb training.

The freezing phenomena and starting hesitation play a vital role in the development of bradykinesia and gait disorder in Parkinson's disease patients. These phenomena may be improved in some patients by the use of motor and sensory "tricks" (Stern et al., 1980; Wolfson et al., 1995), such as alteration of body weight, taking longer strides, and walking sideways. Useful auditory and verbal stimuli include marching like a soldier to commands, walking to music or listening to a metronome ticking (David et al., 2002). Visual stimuli include stepping over objects such as another person's foot or the handle of a walking stick, and imagining colored lines on the floor to step over. In the present study we used the rhythmic sound of a metronome as an auditory stimulus in order to improve motor performance, which enhanced the motor reorganization by acquisition of skills.

Several mechanisms may explain the improved motor performances from an external cue. One previous study stated that different neural mechanisms mediate self-generated (internally triggered) and reaction-time (externally triggered) movements (Horak et al., 1996). As there are two routes in voluntary movement in the nervous system, the decreased function of basal ganglia due to PD impaired the route from the basal ganglia to the supplementary motor cortex. It is suggested that the route of the external circuit (i.e. external sensory stimulus, to cerebellum, via premotor cortex to primary motor cortex to voluntary muscle contraction) could compensate for the decreased function of the route of the internal circuit (i.e. limbic system to basal ganglia, via supplementary motor cortex to primary motor cortex to voluntary muscle contraction) (Marsden and Obeso, 1994). In

the case of insufficient substantia nigra function in PD patients, the external auditory cue was effective in facilitating the performance of strain gauge motor training in the present research. As in previous studies, once the change in TMS-evoked movement direction occurred, it persisted even after the cessation of training (Fig 3) suggesting that motor memory could be stored in the primary motor cortex or in the premotor cortex (Mano et al., 2003).

The kinesiological traces during exercise with and without rhythmic sound clearly showed the effect of rhythmic sound in producing a smooth motor cue for PD patients. The set of waves recorded during exercise without sound are irregular, not parallel to the baseline, and decline sharply during simultaneous and sequential execution of movements. Conversely, with feedback (rhythmic sound) the cue is regular, parallel to the baseline and flat for a short period. Rhythmic movements resulted from the external stimuli that aid in overcoming deficiencies. The rhythmic sound induced rhythmic and forceful movements of the thumb and enabled skilled motor learning that subsequently increased the peak amplitude of TMS-induced movements. Since neuroanatomical evidence suggests a direct connection between Broca's area and the supplementary motor area, the present study indicates that for Parkinsonian patients who have experienced the freezing phenomena, repetitive and rhythmic sound activated the motor area and facilitated the maintenance of the motor set or motor plan that aids the acquisition of motor skills (Albani et al., 2001). We conclude that the process of motor reorganization in patients with Parkinson's disease does not differ from that of normal subjects. In addition, rhythmic sounds may be an effective rehabilitation tool for improving gait disorder (Dibble et al., 2004) and motor performance in PD patients who experience the freezing phenomena.

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Table1. Clinical and demographic data of Parkinson's disease patients and normal participants.

Cases	Age (Years)	M/F	Mentality	Frozen phenomenon	Hoehn & Yahr stage
1	77	M	N	+	3
2	75	M	N	+	3
3	62	F	N	+	3
4	64	M	N	+	3
5	64	M	N	+	3
6	72	M	N	+	3
7	63	M	N	+	2
8	70	F	N	—	2
9	52	M	N	—	3
10	54	F	N	—	2
11	66	F	N	—	2
12	63	M	N	—	2
Normal (n=9)	45-75	8/1	N	-	-

M, male; F, female; N, normal; +, present; —, absent.

Table2. Comparison of TMS-induced movement amplitude of strain (gm) at self-paced and metronome-paced rhythms between time intervals in groups.

	5-minute exercise		10-minute exercise		15-minute exercise	
	Self-paced	Metronome-paced	Self-paced	Metronome-paced	Self-paced	Metronome-paced
Normal (n=8)	192±15.7	197.5±20	186±29.8	199±64.1	220.1±45.9	238±47.4
Non-freezing (n=4)	125±4.5 [a]	141±28.2 [b]	144±46.7	172.5±6.4	175.5±6.6	186.2±8.5
Freezing (n=6)	112.5±10.7 [c]	141.3±42.4 [d]	156±12.2	159±39.5	160.8±48.1[e]	209.1±36.2

[a, b, c, d, e] significantly different from Normal participants (p= .000, p=.027, p=.000, p=.012 and p=.048 respectively).

Figure legends:

Fig 1. Upper trace of thumb movement on strain gauge induced by transcranial magnetic stimulation (TMS) and lower trace of motor evoked potential by TMS recorded by electrode from thenar eminence of right thumb.

Fig 2. Example of TMS-induced movement during 15 minutes exercise and 15 minutes rest from two normal representative controls during self-paced exercise. Pre-exercise movement direction derived from TMS-induced thumb flexion movement. After exercise in the opposite direction (extension) of the thumb, the direction of TMS-induced thumb movement changed from the pre-exercise direction to the exercised direction (A). The changes appeared after 5 minutes of exercise (arrow head). After 5 minutes of rest the direction of movement began to return to its original or pre-exercise position (4^{th} arrow head). TMS trials were given at 5-minute intervals. Fig B shows representative data from one control (two responses are superimposed), indicating a decrease in amplitude rather than no change in the TMS-induced movement direction after 15 minutes thumb extension exercise.

Fig 3. Example of TMS-induced movement during 15 minutes exercise without cue and 15 minutes rest from one representative freezing PD patient. The change of direction was initiated after 5 minutes of training (arrow head), note that the change in direction of TMS-evoked movement after thumb exercise for 15 minutes remained as a memory trace for 5 minutes after cessation of the exercise and the change occurred to the pre-exercise direction after 10 minutes of rest (5th arrow head).

Fig 4. Change in TMS-induced movement direction initiated after 10 minutes (arrow head) of thumb extension exercise with auditory cue in a freezing PD patient (A) (the wave in the trace is due to tremor) while the direction changed after 15 minutes of exercise with auditory cue in a normal participant (B).

Fig 5. Strain gauge recordings during motor training. Kinemetically the shape of the wave during exercise with auditory cue (B) is smooth, regular, rhythmic and flat, in comparison to the wave of exercise without sound (A).

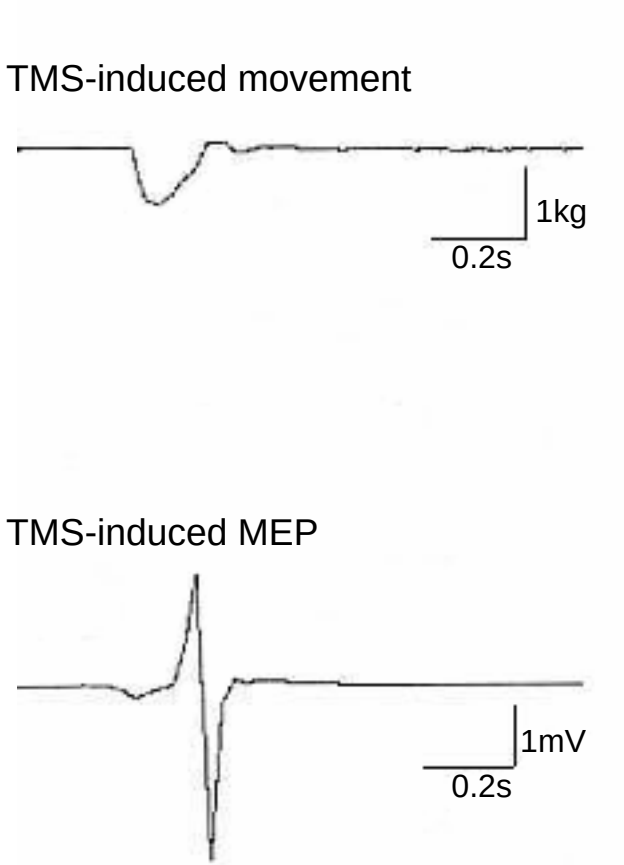
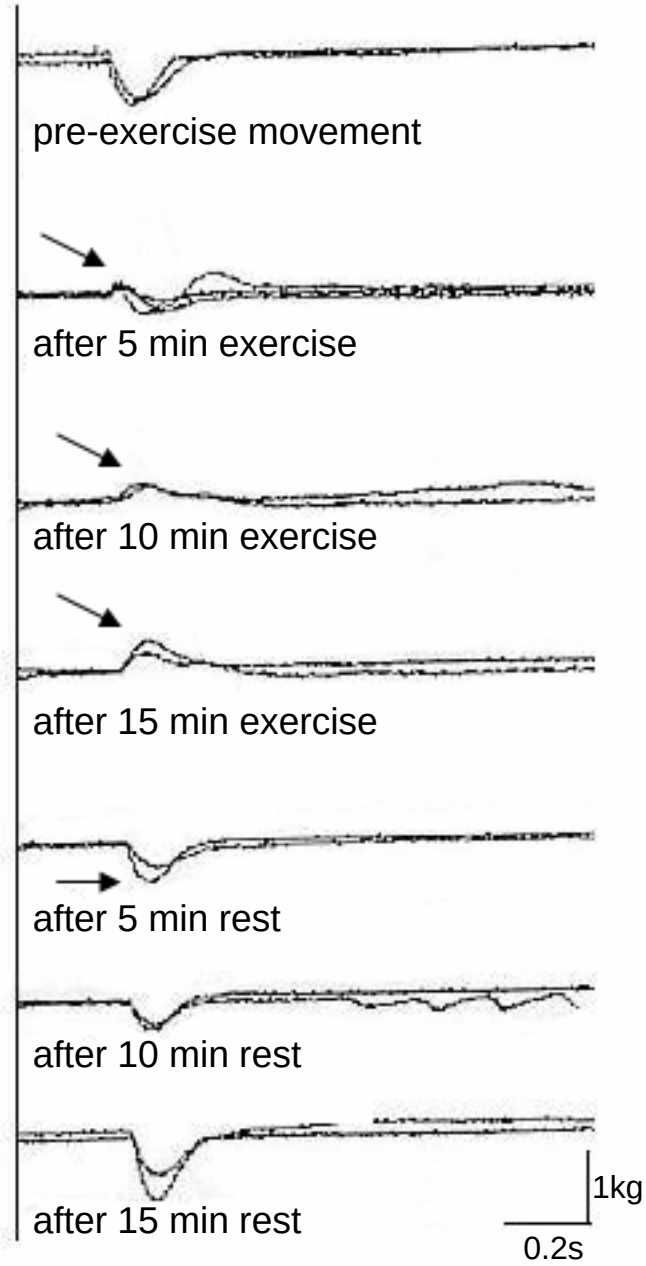


Figure 1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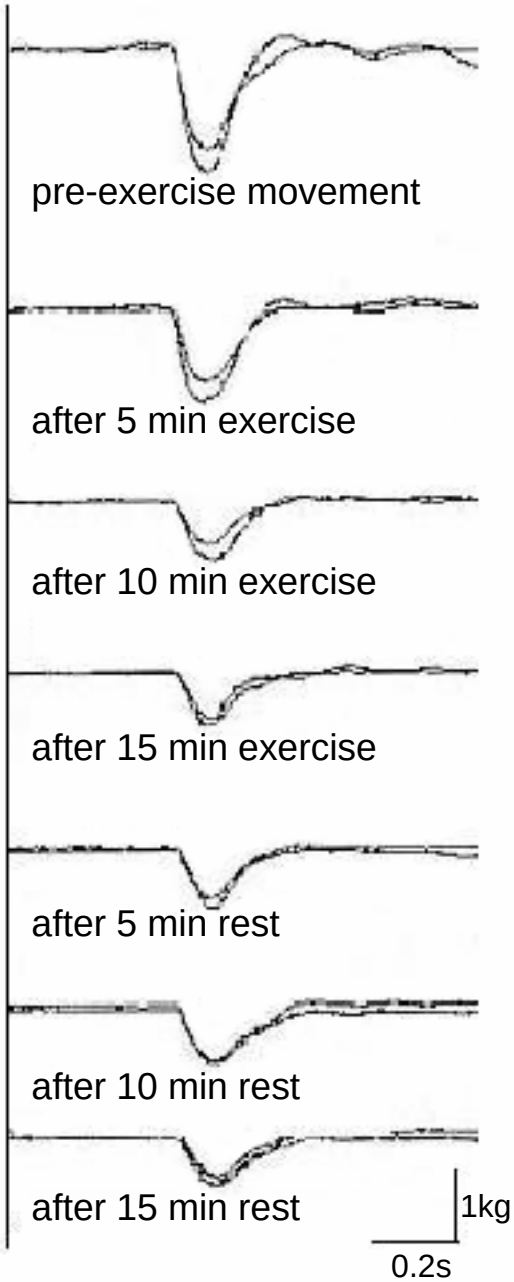
after 5 min exercise
after 10 min exercise
after 15 min exercise
after 5 min rest
after 10 min rest
after 15 min rest
1kg
0.2s

(A)


pre-exercise movement
after 5 min exercise
after 10 min exercise
after 15 min exercise
after 5 min rest
after 10 min rest
after 15 min rest
1kg
0.2s

(B)

Figure 2

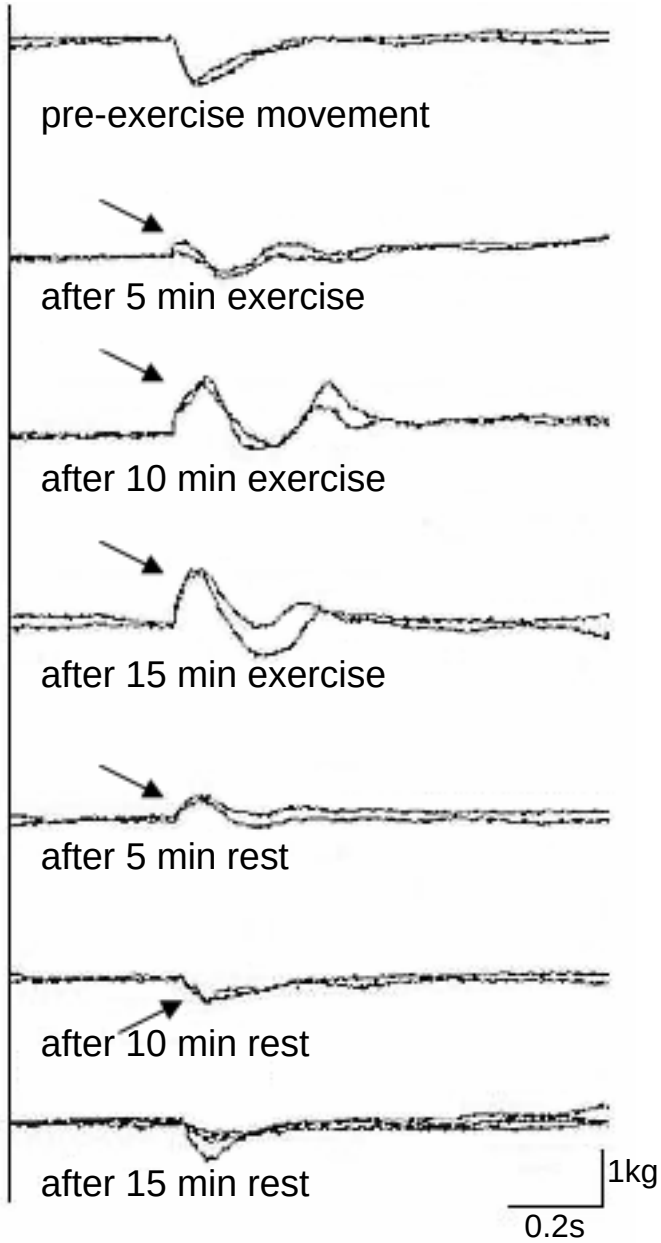
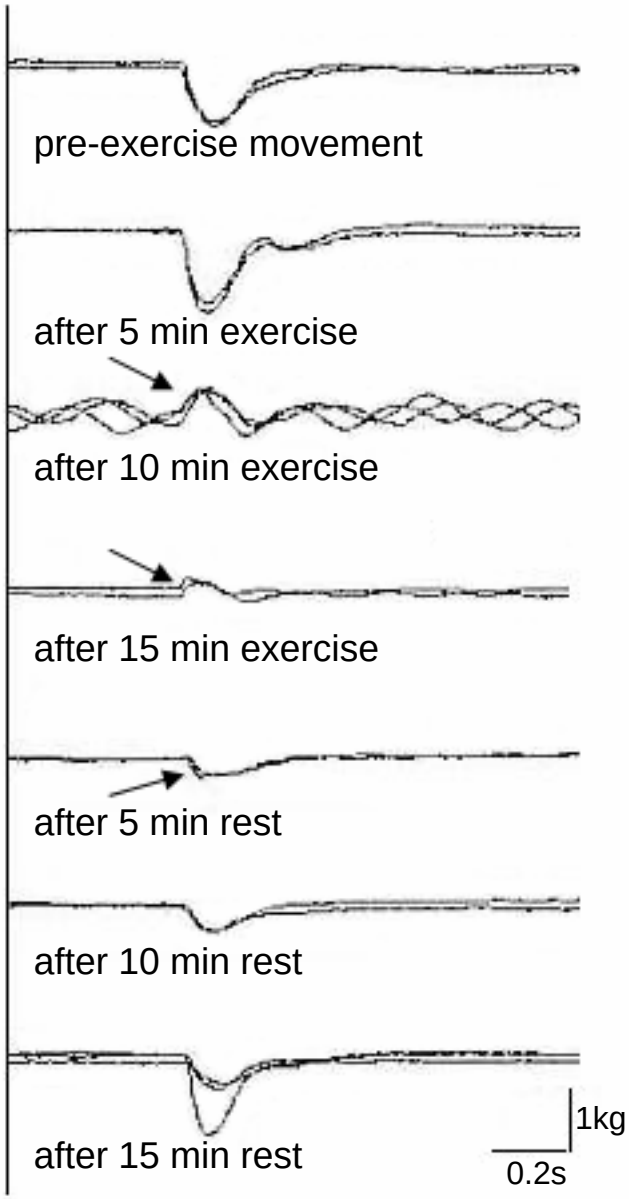
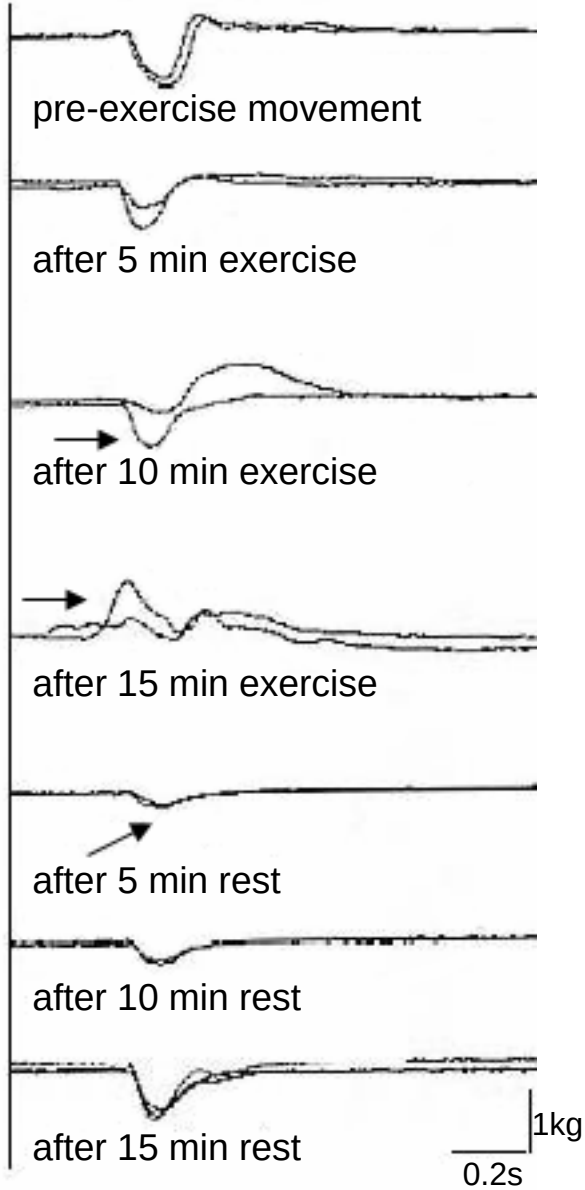

pre-exercise movement
after 5 min exercise
after 10 min exercise
after 15 min exercise
after 5 min rest
after 10 min rest
after 15 min rest
1kg
0.2s

Figure 3


pre-exercise movement
after 5 min exercise
after 10 min exercise
after 15 min exercise
after 5 min rest
after 10 min rest
after 15 min rest
1kg
0.2s

(A)


pre-exercise movement
after 5 min exercise
after 10 min exercise
after 15 min exercise
after 5 min rest
after 10 min rest
after 15 min rest
1kg
0.2s

(B)

Figure 4

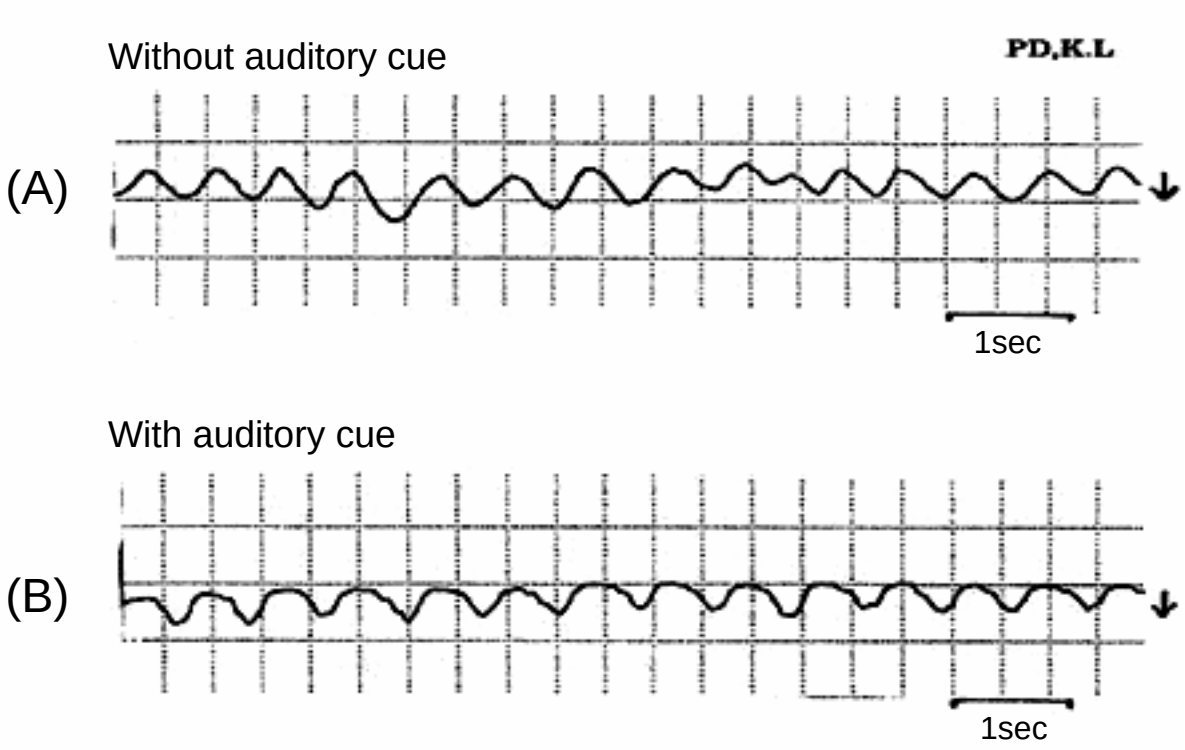


Figure 5