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Short communication

Placebo effects induced by auditory cues decrease parkinsonian rigidity in patients with subthalamic stimulation

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HIGHLIGHTS

- We analyzed parkinsonian rigidity in patients treated with deep brain stimulation.
- We evaluated conditioned auditory cues as triggers of placebo effects.
- We measured viscoelastic stiffness as an indicator of rigidity.
- The values of viscoelastic stiffness decreased due to placebo effect.
- Simple auditory cues can affect the clinical status due to placebo effect.

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ABSTRACT

Placebo effects are the consequence of an interaction between an organism and its surroundings and may be influenced by cues from the environment. Our study was designed to analyze if conditioned auditory cues could trigger placebo effects and affect parkinsonian rigidity as measured by viscoelastic properties of skeletal muscles in patients treated with subthalamic stimulation. We found that after repeatedly associating with the effect of deep brain stimulation on rigidity, a common dial phone signal itself was able to reduce the mean values of viscoelastic stiffness in the placebo stage ($368.8 \pm 50.4\ N\ m^{-1}$) as compared to the stimulation-off conditions ($383.7 \pm 61.2\ N\ m^{-1}$) ($q = 4.18$; $p < 0.05$) in ten patients with Parkinson's disease. Thus, it appears that due to associative learning processes environmental cues can acquire the capacity to trigger placebo effects affecting the clinical status of the patients.

1. Introduction

The placebo effect is a phenomenon if an inert treatment may induce a therapeutic benefit in patients suffering from variable conditions including pain, anxiety, depression or Parkinson's disease (PD). Placebo effects are the consequence of an interaction between an organism and its environment and involve different mechanisms, such as expectations regarding the effect of a treatment and associative learning processes. Improvements in motor performance after placebo administration have been reported in a considerable proportion of patients with PD [1,2]. The placebo-induced release of dopamine in the striatum [3] and nucleus accumbens [4] has been detected with positron emission tomography proportionally to the anticipated improvement in motor control in patients with PD. Moreover, a decrease of neuronal discharges has been revealed in single neurons in the subthalamic nucleus (STN) of the placebo responsive PD-patients due to placebo treatment [5]. However, there are substantial differences in the occurrence and magnitude of placebo effects, and the mechanisms as well as factors potentially mediating the effects are yet to be elucidated.

Deep brain stimulation (DBS) of the STN is currently considered the most important surgical option in the treatment of patients with advanced PD [6]. DBS improves most of the motor symptoms of PD, reduces motor fluctuations and dyskinesias. Still, evaluation of placebo effects in PD-patients treated with DBS has revealed that improvement of motor deficits from DBS can be considerably modulated by means of positive or negative expectations [7–10] or by awareness *vs.* non-awareness of the fact that DBS is switched-on or not [11].

It is well recognized that placebo effects may be influenced by cues from the environment and environmental stimuli consistently

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predictive of a rewarding drug can acquire value in and of themselves through the process of classical conditioning [12–14]. For instance, classical conditioning can contribute to the modulation of pain sensitivity and diverse types of initially neutral environmental cues (audiovisual, contextual, olfactory, gustatory cues, *etc*.,) can determine the response that is conditioned to them [15]. Recently, Scheuren et al. investigated the influence of Pavlovian conditioning with acoustic stimuli on pain inhibition and found that the functional state of endogenous pain control systems may depend on associative learning processes that may lead to an attenuation of pain perception [16]. Whether treatment-associated contextual cues from the environment could trigger placebo effects in patients with Parkinson's disease, has not been determined.

Effective STN-DBS can induce a sudden decrease in rigidity in patients with PD. The change is usually subjectively quantified by passive flexion/extension movements around the wrist joint according to the Unified Parkinson's disease Rating Scale (UPDRS) item 22 and used for optimal programming of the stimulator settings. Unfortunately, the UPDRS score relies substantially on the clinical experience of the evaluators and the reliability between different raters can be poor [17]. According to recent studies, increased rigidity is associated with increased values of viscoelastic stiffness and myotonometric evaluation of stiffness has been successfully used to measure the effect of therapeutic interventions in patients with PD [18,19]. Therefore, myotonometry has good potential to explore the effect of placebo treatment on parkinsonian rigidity.

Identification of the factors that induce or modify the intensity of placebo effects is of major clinical and fundamental scientific importance. Our study was, therefore, designed to analyze if conditioned environmental cues could trigger placebo effects and affect parkinsonian rigidity as measured by viscoelastic properties of skeletal muscles in STN-DBS treated patients with PD.

2. Material and methods

Ten patients in an advanced stage of PD (seven male and three female) participated in the study. The mean age of the patients was 65 years (range 52–74) and mean disease duration 14.4 years (range 6–30). Eight patients had akinetic-rigid and two patients tremor-dominant subtype of the disease. In the preoperative period the patients were evaluated with the UPDRS: the average score in the UPDRS part III (motor evaluation) was 26.2 in the Levodopa-on condition and 53.7 in the Levodopa-off condition. The average total equivalent dose of antiparkinsonian medications in the presurgical period was 925.5 mg/day (range 0–1816.5 mg/day) (Table 1). Our surgical technique has been described in detail elsewhere [18]. Before the study, the patients had been treated with STN DBS for an average of 3.4 years (range 1–8). DBS parameters had a pulse width of 60 μs and a pulse rate of 130 Hz bilaterally in all patients. The mean amplitude of the stimulation was 2.8 V (range 2.0–4.5 V). Six patients received monopolar, two patients mono- and bipolar, and two bipolar stimulation (Table 1).

Ten healthy persons (seven male and three female, mean age 64.4 years, range 55–73) and five patients with PD (four male and one female, mean age 64.2 years, range 55–74, arm rigidity value 2–4 according to UPDRS (mean 2.5)) also participated in the study as a control group. None of the healthy controls had a history of movement disorders or was taking any drugs that could interfere with skeletal muscle properties.

The patients, as well as the control persons, gave their informed consent to the study and the project was approved by the Ethics Committee at the University of Tartu.

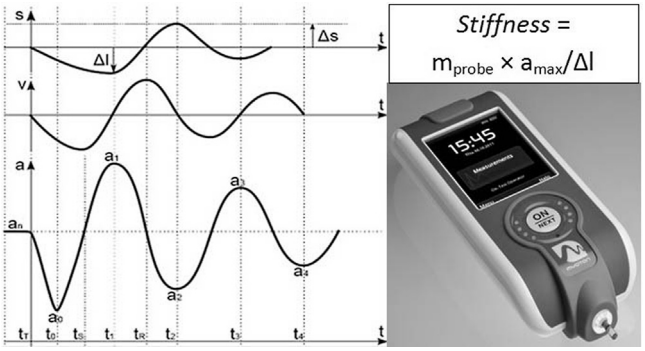

Fig. 1. Myoton myotonometer is a handheld device for measuring viscoelastic properties of muscles. The schematic graph depicts waveforms of acceleration (a), velocity (v), and displacement of the tissue (s), acquired in the process of damped natural oscillations in myotonometry. The direct impact of the testing end on the tissue (t'_d) is considered terminated when the tissue deformation is the deepest (Δl—graph S), and the speed of the testing end is zero (graph V). Viscoelastic stiffness reflects the resistance of the tissue to the force that changes its shape.

2.1. Myotonometry

Myoton myotonometer (Müomeetria Ltd., Tallinn, Estonia) is a simple handheld device for measuring viscoelastic properties of muscles by recording the damped mechanical oscillations. Myoton enables to examine the oscillations of skeletal muscles provoked by a constant mechanical impact made by the testing-end of the machine. The impact causes the tissue under the probe to be deformed and after that the mechanical oscillations of the tissue occur governed by the viscoelastic properties of the tissue. The determined values are calculated from the acceleration of the testing end during the measurements (Fig. 1, full details of the method are given elsewhere [20,21]). Viscoelastic stiffness, as measured by myotonometry, reflects the resistance of the tissue to the force that changes its shape ($C = m \times a_{max}/\Delta l$). The higher this value is, the more energy is needed to modify the shape of the tissue. During contraction in normal muscle the stiffness usually increases proportionally with the increase in the contraction force.

In our study, the myotonometer was used to measure viscoelastic stiffness in patients as well as in control persons. The measurements were performed by two examiners. During the tests, the subjects were sitting relaxed on an examination chair with the upper extremity bended at elbow joint at 30–45 degrees from the longitudinal axis of the upper arm, palm downwards. First, one examiner flexed and extended the joint as in a regular clinical examination for ten times and after that myotonometric measurements were performed by the second examiner on musculus extensor digitorum. The location of the measuring point on the muscle was defined at the line of proximal one-third of the upper arm, ±10 mm more proximally or distally, in the middle of the muscle belly. The muscle belly was identified by manual palpation. The myotonometer's impact mechanism was started by slowly lowering the case of the device while the testing end of the myotonometer was kept perpendicularly with the muscle's surface. The examiners were blinded for the recorded values of viscoelastic stiffness.

2.2. Experimental design

The study took place in an off-medication condition after one night of drug withdrawal. The neurostimulator was switched off for a half an hour before the measurements. At the beginning, three consecutive measurements were performed in DBS-off conditions (pre-conditioning phase). Before further measurements, the patients were informed that the neurostimulator is going to be switched on periodically and at the same time an auditory signal is