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Research report

Motor and cognitive placebo-/nocebo-responses in Parkinson's disease patients with deep brain stimulation

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HIGHLIGHTS

- Positive motor expectations exert *motor placebo* responses on proximal movements.
- These motor placebo responses resemble the clinically known STN-DBS-effect.
- Shorter disease duration is correlated with a stronger motor placebo response.
- In motor responders positive motor expectations exert *cognitive nocebo* responses.
- These cognitive nocebo responses are likely due to implicit learning mechanisms.

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ABSTRACT

Expectation contributes to placebo and nocebo responses in Parkinson's disease (PD). Subthalamic nucleus (STN) deep brain stimulation (DBS) improves proximal more than distal movements whereas it impairs executive cognitive function such as verbal fluency (VF). We investigated how expectation modulates the pattern of motor improvement in STN-DBS and its interaction with VF.

In a within-subject-design, expectation of 24 hypokinetic-rigid PD patients regarding the impact of STN-DBS on motor symptoms was manipulated by verbal suggestions (positive [placebo], negative [nocebo], neutral [control]). Patients participated with (MedON) and without (MedOFF) antiparkinsonian medication. Motor function was assessed by Unified Parkinson's Disease Rating Scale and quantitative kinematic analysis of proximal alternating hand and distal finger tapping. VF was quantified by lexical and semantic tests.

In MedOFF, expectation significantly affected proximal but not distal movements resulting in better performance in the placebo than in the nocebo condition. Placebo responders with improvement of $\geq$25% were characterized by a trend for impaired lexical VF.

These results indicate that positive motor expectations exert both motor placebo and cognitive nocebo responses by further enhancing the STN-DBS-effect on proximal movements and by impairing VF. The placebo response on motor performance resembles the clinically known STN-DBS-effect with stronger improvement in proximal than distal movements. The nocebo response on VF is likely due to implicit learning mechanisms associated with an expectation-induced placebo response on motor performance.

1. Introduction

Placebo responses represent a complex psychobiological phenomenon. The counterpart of a placebo response is the so called nocebo response, comprising all negative effects such as worsening of symptoms or side effects induced by an inert substance or treatment. Cognitive factors like expectations regarding the effect of a treatment and associative learning processes like classical conditioning, have been identified as main mechanisms mediating placebo responses [for reviews see 1,2].

Abbreviations: BDI, Beck depression inventory; DBS, deep brain stimulation; MedOFF, off antiparkinsonian medication; MedON, on antiparkinsonian medication; MDRS, Mattis dementia rating scale; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; NRS, numeric rating scale; PD, Parkinson's disease; STN, subthalamic nucleus.

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In Parkinson's disease (PD), motor symptoms and physiological processes can be substantially affected by placebo treatments. For example, the administration of placebo drugs induces a significant dopamine release in the dorsal and ventral striatum [3,4] as well as alterations in neuronal firing patterns in the subthalamic nucleus [5] which are both associated with an improvement in motor function. Moreover, in a recent meta-analysis, Goetz et al. [6] conclude that clinical improvement in response to pharmacological placebo treatment is observed in 16% (range: 0–55%) of PD patients. Furthermore, placebo and nocebo responses have also been described in PD patients treated with deep brain stimulation of the subthalamic nucleus (STN-DBS). For instance, bradykinesia is not only affected by the stimulation condition per se (STN-DBS ON vs. OFF) but is additionally modulated by patients' varying expectations induced by awareness vs. non-awareness of the fact that STN-DBS is switched ON vs. OFF [7]. Likewise, motor function can be considerably modulated by means of opposite positive or negative expectations regarding STN-DBS with improved motor performance following positive expectation and impaired motor performance in consequence of negative expectation [8,9].

Dopamine replacement therapy and STN-DBS are well established and effective treatments of motor symptoms in PD [12–14]. Although both treatments generally lead to an improvement in motor function, differential therapeutic effects have been described for fine finger movements representing distal movements and arm movements reflecting proximal movements: While the dopamine precursor levodopa has a more pronounced effect on distal compared to proximal movements, STN-DBS improves proximal more than distal movements [15,16]. Additionally, a side-effect often observed in patients treated with therapeutic STN-DBS is impairment in verbal fluency [17–19].

Being part of a transregional and translational research unit investigating the role of conditioning and expectation as underlying mechanisms of placebo and nocebo responses in different physiological systems, pathophysiological conditions and therapeutic interventions, we set out to study the effect of expectation in PD patients treated with STN-DBS addressing specific issues which have not been investigated so far. Placebo and nocebo responses in PD patients treated with STN-DBS have not been studied regarding: (1) motor functions differentially affected by STN-DBS such as distal and proximal movements, (2) executive cognitive functions affected by STN-DBS, i.e. verbal fluency, (3) the manipulation of the pharmacological status, i.e. with and without antiparkinsonian medication, (4) a PD patient subgroup that is homogenous with respect to the predominant clinical symptoms, i.e. hypokinetic-rigid PD patients. Thus, the effect of expectation regarding STN-DBS should be investigated considering motor and non-motor functions that are specifically affected by therapeutic STN-DBS. Therefore, the aim of the present study was to investigate how differing expectations (positive [placebo], negative [nocebo], neutral [control]) regarding STN-DBS modulate motor function and verbal fluency in hypokinetic-rigid PD patients with and without antiparkinsonian medication. Given evidence that placebo responses mimic the response to the active treatment, we hypothesized that the effect of expectation would be more pronounced on proximal compared to distal movements. Moreover, as typical side-effects of the active treatment can also be induced by placebo treatments [20], a further aim of the study was to analyze whether expectation regarding the impact of STN-DBS on motor function would also affect verbal fluency.

2. Materials and methods

2.1. Participants

Twenty-four Parkinson's disease patients of the hypokinetic-rigid subtype (12 men and 12 women, mean age: 62.83 ± 1.9 [SEM] years, range: 39–77) with chronic bilateral STN-DBS participated in the study. Patients were recruited from the Movement Disorder Centre of the University hospital of Duesseldorf. In order to rule out possible cognitive impairment and clinically relevant depressive symptoms all patients were tested with the Mattis Dementia Rating Scale (MDRS) [21] with a cut-off score of <130 and filled in the Beck Depression Inventory (BDI) [22] with a cut-off score for clinically relevant depression of ≥18 before study participation. For patients' characteristics and stimulation parameters, see supplementary Tables 1 and 2.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2013.04.051

2.2. Experimental design and procedure

Three expectation conditions (positive [placebo], negative [nocebo], neutral [control]) were applied in a counterbalanced order using a repeated-measures design. Patients were randomly assigned to one of six possible orders.

Each patient participated twice on two consecutive days, 1 day on pharmacological treatment, i.e. patients took their usual antiparkinsonian medication (MedON) and 1 day when patients had withdrawn from any antiparkinsonian medication for at least 12 h (MedOFF) prior to study participation. Whether patients were on or off medication on the first day was counterbalanced across patients, i.e. half of them were without medication on the first day and on medication on the second day and vice versa. The six orders of the expectation conditions were randomly combined between MedON and MedOFF.

The experimental sessions were performed at the Department of Neurology of the University hospital of Duesseldorf. First, at the start of the experimental session STN-DBS was turned off (Stim OFF). After a time interval of ten minutes patients were informed that STN-DBS would be turned on again. However, before STN-DBS was switched on, patients' expectations regarding the effect of the subsequent stimulation on motor symptoms were manipulated through verbal suggestions by an experienced movement disorders physician (L.W., C.H. or S.F.). The physician who induced expectations was held constant for each patient. Positive expectations were induced by informing the patient that the stimulator will be turned on with parameter settings which will strongly improve motor function (placebo condition). Negative expectations were induced by telling the patients that the stimulator will be turned on with parameter settings which will strongly impair motor function (nocebo condition). To induce a neutral expectation regarding the effect of the upcoming stimulation, patients were told that the parameter settings of the subsequent stimulation will not have any impact on motor function (control condition). Immediately after expectations were verbally induced, patients rated the extent to which they expected an improvement or impairment or no change of their current motor function by the upcoming stimulation (see Section 2.2.1). Thereafter, the stimulator was turned on (Stim ON) according to the patient's individual therapeutic settings. Note that the stimulation parameters (intensity, frequency and pulse width) were identical under all three conditions (placebo, nocebo and control). After each condition the stimulator was switched off for 10 min. STN-DBS usually improves symptoms such as rigidity and tremor in less than a minute and improvement in bradykinesia is gradually achieved within a couple of minutes [23]. Therefore, in each condition dependent variables were assessed after the stimulator had been turned on for 15 min. The experimental session lasted about 120 min per day. For an overview of the experimental procedure, see Fig. 1.

The experimenter who assessed the dependent variables was blinded regarding the expectation condition whereas patients were blinded with respect to the fact that in each condition the identical therapeutic stimulation parameters were applied. Hence, to ensure the successful manipulation of expectation it was necessary that patients were naïve concerning the exact aim of the study. Accordingly, the written patient information included a cover story regarding the aim of the study, i.e. that the study was designed to systematically investigate different settings of STN-DBS stimulation parameters and their effect on motor function. In addition, it gave note that three stimulator settings would be randomly chosen and that patients would be informed about the subsequent effect on motor function which would be induced by the chosen parameter settings. This approach was approved by the local ethics committee (see Section 2.3). Furthermore, the patient information comprised details about possible transient unpleasant but unharmful side effects resulting from changes of stimulation parameters like prickling or dizziness.

2.2.1. Expectation rating

Immediately after expectations regarding the stimulation effect of STN-DBS on motor symptoms were verbally induced, patients rated to what extent they expected an improvement, impairment or no change of their current motor state. Therefore, patients' expectation was assessed by means of a numeric rating scale (NRS) ranging from +5 indicating expectation of strong improvement to -5 indicating expectation of strong impairment of motor function while 0 represented expectation of no change of motor function.

2.2.2. Movement parameters

2.2.2.1. Distal and proximal movements: finger tapping and diadochokinesia. A finger tapping task was chosen to reflect distal movements and diadochokinesia was used to determine proximal hand movements. Finger tapping and diadochokinesia were objectively assessed by means of a 3D ultrasound motion detection system (CMS 70P