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Verbal communication about drug dosage balances drug reduction in Parkinson's disease: Behavioral and electrophysiological evidences

Elisa Carlino[a,*,1], Alessandro Piedimonte[a,1], Alberto Romagnolo[a], Giulia Guerra[a], Elisa Frisaldi[a], Sergio Vighetti[a,b], Leonardo Lopiano[a], Fabrizio Benedetti[a,b]

[a] Dept of Neuroscience, University of Turin Medical School, Turin, Italy
[b] Medicine & Physiology of Hypoxia, Plateau Rosà, Italy

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ABSTRACT

Introduction: Changing drug dosage is common in clinical practice. Recent evidence showed that psychological factors may affect the therapeutic outcome. The aim of this study is to test whether verbal communication about drug dosage changes motor performance and fatigue in Parkinson's Disease (PD) patients.

Methods: We performed clinical (Unified PD Rating Scale), motor (number of finger flexions and perceived fatigue), and electrophysiological measurements (readiness potential, RP) in PD patients during medication-off and medication-on conditions in three groups. The first group got a full dose of L-dopa and was told it was a full dose. The second group got half dose and was told it was half dose. The third group got half dose, but it was told it was a full standard dose.

Results: We found that overt half dose was less effective than the full dose for clinical improvement, motor performance, and readiness potential. However, if half dose was given along with verbal instructions that it was a full dose, clinical improvement, motor performance and readiness potential were not significantly different from the full dose.

Conclusions: Our findings indicate that verbal communication about dose reduction is as effective as the 50% dose reduction itself, demonstrating that deceptive information about the dose may have an important impact on the therapeutic outcome. Moreover, the supplementary motor area, source of the RP, seems to be involved in this psychological effect.

1. Introduction

Chronic use of L-dopa for treatment of Parkinson's Disease (PD) may lead to motor complications which can worsen the quality of life of PD patients and undermine the L-dopa therapy itself [1]. As changing drug dosage is common in clinical practice [2,3], one strategy may imply a L-dopa dose reduction, albeit it could be sometimes limited by patients' propensity for dopaminergic overtreatment [4].

Recent research uncovered the important role of psychological factors in drug response for PD patients and clarified some of the biological underpinnings. Both placebo and nocebo effects, respectively mediated by patient's positive and negative expectations, have been found to play a central role in the therapeutic outcome of these patients [5,6]. Furthermore, bradykinesia, rigidity, and resting tremor have shown to be particularly susceptible to placebo effect compared to other domains of PD impairment [7–9].

Supporting the crucial role of psychological factors in PD treatment are also the open-hidden studies, where the hidden administration of a drug has been found to be less or not at all effective compared to its administration in full view of the patient [10]. Interestingly, it has been recently showed that verbal communication about the cost of a treatment can affect PD patients' expectations [11].

This study aims to understand the contribution of verbal instructions on the L-dopa response, specifically on motor performance and fatigue perception, in a cohort of PD patients. The L-dopa dose was thus halved, while manipulating patients' expectations about drug dosage.

2. Materials and methods

2.1. Patients and group assignment

A total of 45 PD patients participated in the study. They were told

* Corresponding author.
E-mail address: elisa.carlino@unito.it (E. Carlino).
[1] These authors equally contributed to the work.

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that they would participate in a study aimed at better understanding the efficacy and mechanisms of action of L-dopa, including the influence of psychological factors. In particular, they were asked to perform a motor task, consisting in lifting a weight with the right index finger until exhaustion in both medication-off and medication-on conditions. The experimental procedures were conducted according to the policies and ethical principles of the Declaration of Helsinki. The study was approved by the local Ethics Committee.

All patients suffered from idiopathic Parkinson's disease, meeting UK PD Brain Bank criteria [12]. All patients had a stable dosage of dopaminergic medications for at least 4 weeks prior to the assessment and showed no signs of atypical parkinsonism. A blinded neurologist, specialized in movement disorders (A.R.), performed all clinical assessments. Patients' characteristics and neuropsychological assessments are reported in Supplementary Tables 1 and 2

Before the experimental session, the neurologist neutrally informed all patients that they would receive either their full usual dose or half dose. Moreover, patients were informed that treatment effects would be measured using both clinical and behavioral techniques. Patients were randomly subdivided into three groups and received different information about the drug dosage by the researchers (E.C. and A.P.). The first group (N = 15) received the full usual morning dose of L-dopa and was told the truth, i.e. that they were given the full usual morning dose of L-dopa (Full group). The second group (N = 15) received half dose and, likewise, was told the truth, namely that the dose was halved (Half group). By contrast, the third group (N = 15) received half dose of morning L-dopa but the patients were told that they were given the full morning dose (Deceit group). After the experimental session, participants were fully debriefed.

2.2. Experimental design and measurements

All the experimental procedures (Fig. 1) were assessed in the early morning.

First, the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was assessed in the medication-off condition (i.e., at least 12 h after the last L-dopa dose).

For the motor task, a finger flexor device was used (Fig. 1) [13]. The movement consisted in the flexion of the right index finger while lifting a weight. The amount of weight to be lifted was identified as follows: after familiarization with the experimental set-up, all patients were assessed for the “one-repetition maximum” (1-RM). To do this, they performed a single flexion with 0.5 kg progressive increments, starting from 1 kg, until the weight was too heavy to be lifted. The last successfully lifted weight was considered the “one-repetition maximum”. Then, patients rested for 30 min. The weight to be lifted during the experimental task was individually set at 30% of the 1-RM. After the identification of the weight amount, patients were informed that they had to repeat the flexions until exhaustion. Movements were self-paced (inter-movement interval: 10 s) by means of a clock on a computer screen positioned just in front of the patient. Patients were instructed to flex their index finger to lift the weight, and then to relax immediately (Fig. 1). The rate of perceived exertion (RPE) was verbally reported every five movements, according to a numerical rating scale from 0 (no fatigue) to 10 (maximal fatigue). Thus, motor performance was assessed by means of number of flexions and RPE.

During the resting period, the electroencephalogram (EEG) set-up (Galileo; EBNeuro, Firenze, Italy) was assembled in order to record the Readiness Potential (RP), a slow negative potential related to fatigue. EEG recordings were acquired through 19 scalp locations in accordance to the 10–20 international system, with linked common ears reference. Impedance was < 5 KΩ in each active lead. Data were collected and digitized at a sampling rate of 512 Hz.

After completing the motor task in the medication-off condition, they were asked to rest for other 45 min. During this interval, a dose of L-dopa/benserazide dispersible formulation (either full or half) was administered according to the group assignment (Fig. 1). A second clinical assessment was thus performed in order to measure the clinical motor response in the medication-on condition. After this assessment, patients were asked to repeat the motor task for the second time.

2.3. RPE analysis

RPE was reported verbally by the patients every 5 flexions, i.e. every 50 s, for the whole duration of the motor task, both in the medication-off and in the medication–on conditions. Thus, for each subject in each condition we obtained two curves representing the increase of fatigue over time. We calculated the area under the curve (AUC) by means of the Riemann sum method [14]: the larger the area under the curve, the more intense the experienced fatigue.

2.4. Electrophysiological analysis

EEG continuous data were pre-processed and analyzed using Matlab (Mathworks Inc., Natick, MA, USA) and EEGLAB [15]. Since RP amplitude is influenced by fatigue and its final part shows substantial changes [13], EEG data were extracted from the last 33% of the total flexions performed by the patient, and were segmented into epochs of 3000 ms each (from 2500 ms before the movement to 500 ms after the movement). Epochs were then averaged together, time-locked to the

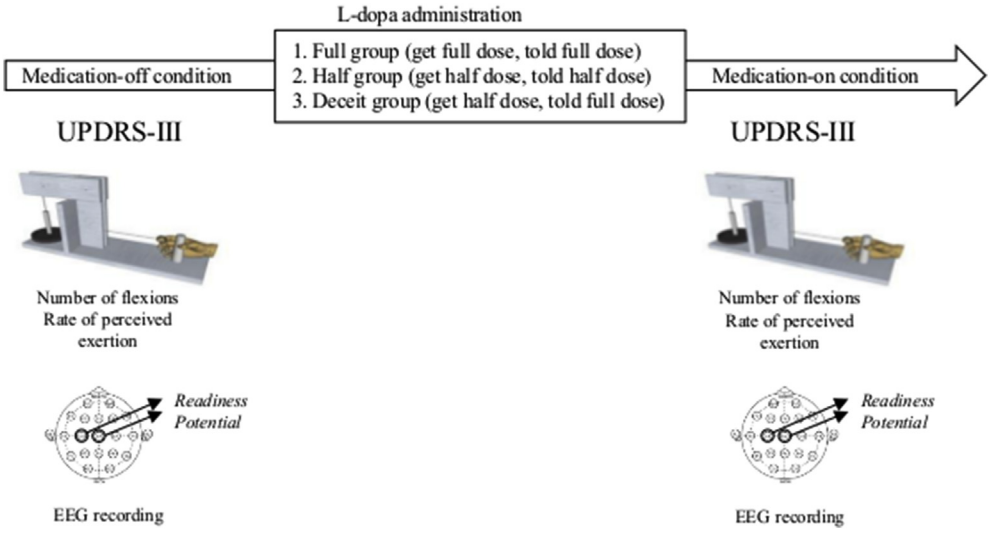

Fig. 1. Experimental design. Clinical evaluation (UPDRS-III), motor performance assessment (number of finger flexions to lift a weight and rate of perceived exertion (RPE)), and readiness potential (RP) recording were performed in the medication-off condition. Then, L-dopa was administered in 3 different groups, at different doses and along with different verbal instructions. Then, the same measurements were performed in the medication-on condition.

onset of the movement. Each epoch was baseline-corrected using the pre-movement interval from 2500 ms to 2000 ms as a reference. EEG epochs were bandpass-filtered from 0 to 30 Hz using Fast Fourier Transformation. Electrooculogram artifacts were subtracted using a validated method based on independent component (IC) analysis [16]. Furthermore, epochs with amplitude values exceeding 75 μV were rejected. Finally, AUC was extracted from −500 ms before the movement under the electrodes Cz and C3, where RP voltage was maximal. For each subject, 2 RP AUC were obtained, one in the medication-off condition and one in the medication-on condition.

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of all the dependent variables. In no case the normality was violated. A first between-groups analysis was performed by means of analysis of variance (ANOVA), followed by the Student–Newman–Keuls (SNK) *post-hoc* test for multiple comparisons to rule out clinical, psychological and/or demographical differences between groups. Fisher's exact test was used to compare the frequency distribution of psychosis episodes, of antidepressant, anxiolytic and antipsychotic drugs intake and of depressed patients. For the clinical/behavioral data, UPDRS-III scores, number of flexions and RPE were used as dependent variables and tested by means of three different 2 × 3 mixed factors ANOVAs with Condition (medication-off vs medication-on) as within-group factor and Group (Full, Half, Deceit) as between-groups factor. UPDRS-III scores, number of flexions and RPE were expressed as the percentage of improvement in the medication-on condition compared to the medication-off condition and used as dependent variables in three one-way ANOVAs to directly compare the improvements between groups. As to the electrophysiological data, RP AUC was used as the dependent variable and tested by means of a 2 × 2 x 3 mixed factors ANOVA, with Condition (medication-off vs medication-on) and Electrode (C3 vs Cz) as within-group factors, and Group (Full, Half, Deceit) as between-group factor. The percentage of RP decrease (i.e. the percentage of improvement) between the medication-off compared to the medication-on conditions was calculated and used as a dependent variable in a 2 × 3 mixed factors ANOVA, with Condition (medication-off vs medication-on) as within-group factor and Group (Full, Half, Deceit) as between-group factor. SNK *post hoc* test was used for all comparisons. The analysis was performed with Statistica, version 9 for Windows. Data are presented as mean ± standard error of the mean (SEM), and the level of significance was set at $P < 0.05$.

3. Results

Psychological and demographical data showed no significant differences between groups in duration of PD (P = 0.18), UPDRS-III scores in medication-off condition (P = 0.31), L-Dopa morning dose (P = 0.73), LEDD (P = 0.90), 1-RM (P = 0.429), MMSE scores (P = 0.378), BDI scores (P = 0.273), percentage of psychosis (P = 0.999), percentage of antidepressant, anxiolytic or antipsychotic drugs intake (P = 0.859, P = 0.879, and P = 0.999 respectively), percentage of depressed patients (P = 0.910) and age (P = 0.22) (Supplementary Tables 1 and 2).

No significant dyskinesia or other involuntary movements biased the clinical or instrumental assessments. Considering UPDRS item 33 ("Disability related to dyskinesia"), no significant differences between groups occurred (Kruskal-Wallis Test: P = 0.633).

3.1. Clinical assessment

Clinical data are reported in Fig. 2A (mean UPDRS-III scores) and Fig. 2B (UPDRS-III percentage of improvement). ANOVA showed a significant interaction of Condition x Group [$F(2,42) = 11.81$, $P < 0.0001$], with a *post hoc* analysis showing a significant improvement of UPDRS-III in the medication-on compared to the medication-off condition in all groups (Full, $P < 0.001$; Half, $P < 0.001$; Deceit, $P < 0.001$) (Fig. 2A). ANOVA of the percentage of improvement in the medication-on condition showed a significant effect of Group [$F(2,42) = 9.38$, $P < 0.001$], with a *post hoc* analysis showing a larger improvement of the Full group compared to the Half group ($P < 0.01$) and a larger improvement of the Deceit group compared to the Half group ($P < 0.001$). Most interesting, no significant differences between the Full and Deceit group were present (Fig. 2B).

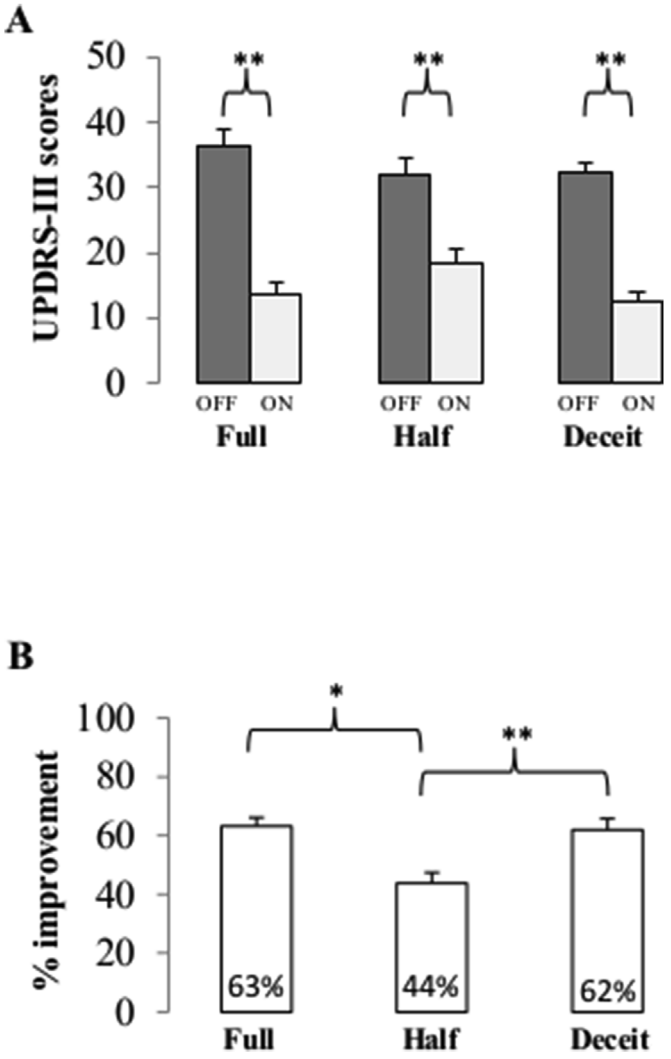

Fig. 2. Clinical assessment. A) UPDRS-III scores in the medication-off and medication-on condition in the 3 groups. B) Percentage of improvement in the 3 groups. *P < 0.01; **P < 0.001.

3.2. Motor performance

Mean number of flexions and percentage of improvement are reported in Fig. 3A and Fig. 3B, respectively. Mean RPE AUC (RPE*seconds) and percentage of RPE improvement are reported in Fig. 3C and D, respectively. As to the number of flexions, ANOVA showed a significant interaction of Condition x Group [$F(2,42) = 11.13$, $P < 0.0001$], with a *post hoc* analysis showing a significant increase in the number of flexions in the medication-on condition compared to the medication-off condition in the Full group ($P < 0.01$) and Deceit group ($P < 0.05$), but not in the Half group (Fig. 3A). ANOVA of the percentage of improvement in the medication-on condition showed a

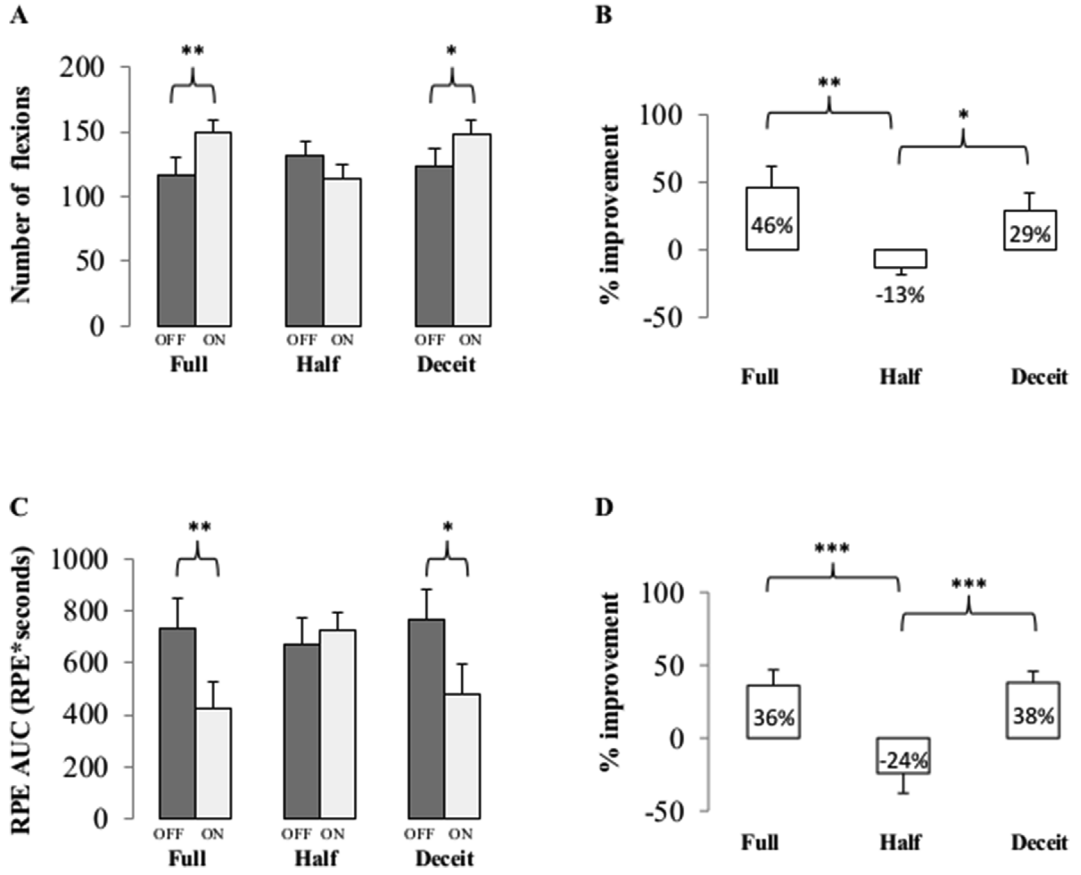

Fig. 3. Motor performance assessment. A) Number of flexions in the medication-off and medication-on condition in the 3 groups. B) Number of flexion percentage of improvement in the 3 groups. C) Area under the curve (AUC) of the rate of perceived exertion (RPE) in the medication-off and medication-on condition in the 3 groups. D) RPE percentage of improvement in the 3 groups. *P < 0.05; **P < 0.01; ***P < 0.001.

significant effect of Group [F(2,42) = 6.13, P < 0.01], with a p*ost hoc* analysis showing a larger improvement of the Full group compared to the Half group (P < 0.01) and a larger improvement of the Deceit group compared to the Half group (P < 0.05). Again, no difference between the Full and Deceit groups was observed (Fig. 3B).

Regarding the RPE AUC, ANOVA showed a significant interaction of Condition x Group [F(2,42) = 5.26, P < 0.01], with a p*ost hoc* analysis showing a decrease of fatigue in the medication-on condition in the Full group (P < 0.01) and Deceit group (P < 0.05), but not in the Half group (Fig. 3C). ANOVA of the percentage of improvement in the medication-on condition showed a significant effect of Group [F (2,42) = 10.36, P < 0.001], with a *post hoc* analysis showing a larger improvement of the Full group compared to the Half group (P < 0.001) and a larger improvement of the Deceit group compared to the Half group (P < 0.001), whereas no difference between the Full and Deceit groups was found (Fig. 3D).

3.3. Electrophysiology

Electrophysiological data are reported in Fig. 4. The averaged RPs in C3 and Cz across all subjects are shown in Fig. 4A for each group in the medication-off (bold RP) and medication-on condition (light RP). In the Full group, the RP was reduced in the medication-on condition compared to the medication-off condition, which suggests a reduction in the central elaboration of fatigue. The same reduction in the medication-on condition was observed in the Deceit group, but not in the Half group.

Mean RP AUC and percentage of RP decrease are reported in Fig. 4B and C, respectively, for both electrode C3 and Cz. ANOVA showed a significant effect of the interaction Condition x Group [F(2,42) = 4.38, P < 0.05] and a significant main effect of the Electrode [F(1,42) = 9.7, P < 0.001]. *Post hoc* analysis showed a significant decrease of RP in both electrodes in the medication-on condition compared to the medication-off condition in the Full group (P < 0.01) and Deceit group (P < 0.01), but not in the Half group. In addition, RP amplitude was larger in C3, which corresponds to the contralateral finger movement, than in Cz (P < 0.01) (Fig. 4B).

For both electrodes, RP percentage decrease in the medication-on condition was significant across Groups [F(2,42) = 4.33, P < 0.05], with *post hoc* analysis showing a larger decrease in both electrodes in the Full group compared to the Half group (P < 0.05) and in the Deceit group compared to the Half group (P < 0.05), without significant differences between the Full and Deceit groups (Fig. 4C).

4. Discussion

The main findings of our study can be summarized as follows. Halving the dose of L-dopa deceptively, i.e. along with the verbal instructions that it is the full standard dose, produces significant global motor performance (UPDRS), fatigue (number of flexions and RPE), and electrophysiological improvements undistinguishable from the full standard dose, as demonstrated by the lack of a significant differences between groups. By contrast, halving L-dopa along with the information about its reduction (Half group), leads to a smaller clinical improvement together with no electrophysiological improvements and the worsening of motor performance, as shown in Figs. 3 (−13% of the number of flexions and −24% of RPE).

Previous studies have shown the key role of verbal instructions in the modulation of drug action. The balanced placebo design, for example, orthogonally manipulates instructions (“told drug” versus “told placebo”) and drug administration (“received drug” versus “received

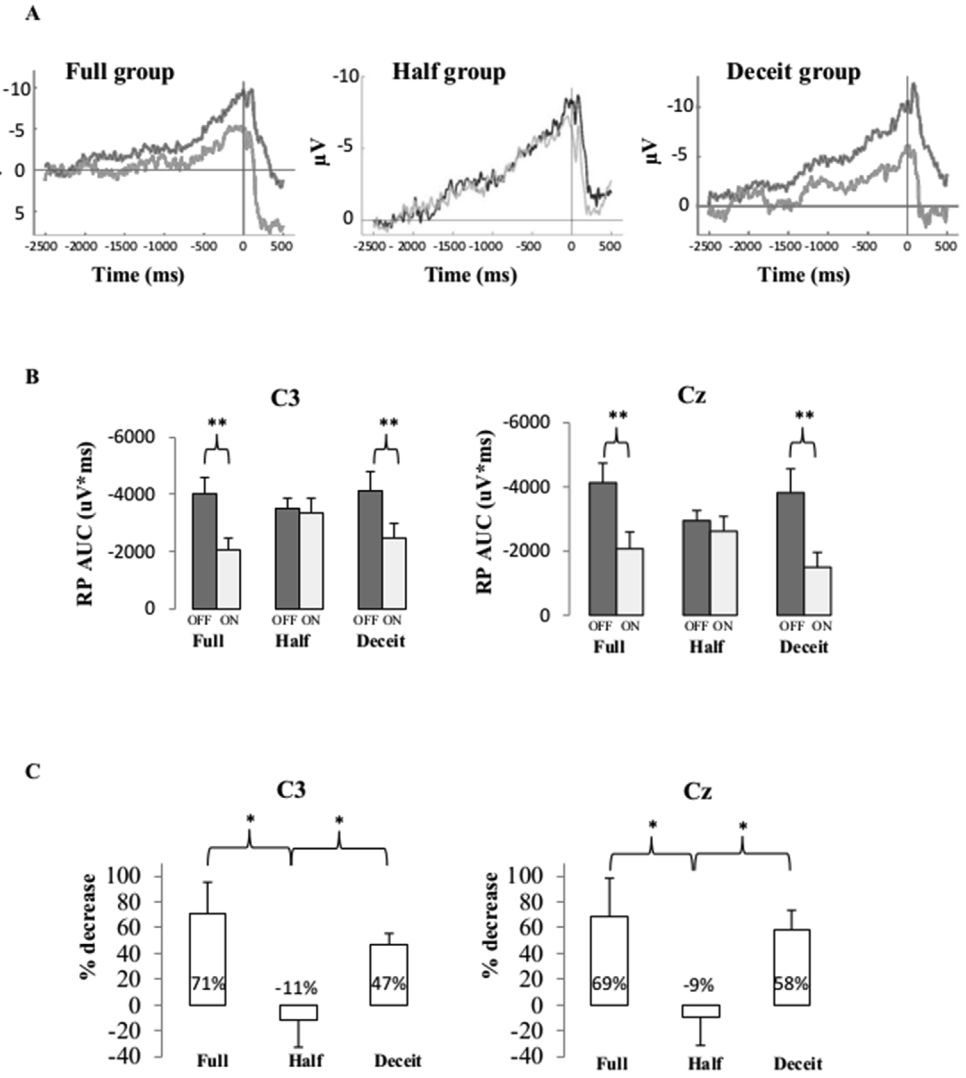

Fig. 4. Electrophysiological data. A) Grand average of the readiness potential (RP) in C3 and Cz across all patients in each group in the medication-off condition (dark grey line) and in the medication-on condition (light grey line). B) Area under the curve (AUC) of the readiness potential (RP), extracted from −500 ms before movement, in the medication-off and medication-on condition in the 3 groups. C) Percentage of RP decrease in the 3 groups. *P < 0.05; **P < 0.01.

placebo") [10,18,19]. Also, experimental studies clearly show that if patients are completely unaware that a treatment is being given (hidden administration), then they do not expect any therapeutic benefit with the consequent reduction in treatment efficacy [7,16,17].

PD symptoms are sensitive to verbal manipulations and conditioning procedures [7–9], and are associated with endogenous dopamine release [20–23]. In particular, the release of dopamine in the motor striatum seems to be greater in PD patients who report clinical improvement [20,21].

Our conclusions should be tempered by some limitations. First, while recent literature shows that prior drug conditioning enhances placebo effects in PD [7–9], we only considered the acute response to a single L-dopa reduction. However, since PD required chronic drug administration, future studies should investigate the duration of these effects by alternating, for instance, full and half doses during the day. Third, since all patients were evaluated during the supposed L-dopa peak-of-dose, potential differences in the duration of L-dopa effect cannot be ruled out. Furthermore, a fourth group of patients expecting to receive the half L-dopa dose, but actually receiving the full dose, should be investigated according to the knowledge of nocebo effect. Moreover, a systematically assessment of patient's expectations toward the treatment, before and after the experimental session, would add important information about the impact of verbal communication. Furthermore, it has to be considered that EEG has a low spatial resolution leading to difficulties in identifying areas involved in specific evoked potentials and, thus, the involvement of pre-motor areas, such as the supplementary motor area (SMA), in our task has been postulated based on previous literature on RP [24,25]. Finally, in order to avoid deception and ethical issues, an open-label group could be investigated, where patients receive the half dose while being told of the positive effects of this dose reduction.

Understanding what happens also beyond the limit of a 50% L-dopa dose reduction is crucial for future research. Indeed, the current paradigm could represent an excellent approach to better identify the minimal dose required to induce an effect in PD patients, and be expanded to other clinical conditions. Furthermore, verbal instructions could be individually tailored taking into account each participant's expectations and his/her capability to respond to placebos.

The involvement of SMA also emerges from our results. In fact, RP is a movement-related negative potential that is recorded over the human scalp about 2 s before a self-paced motor act [24]. This slow potential is mainly generated by areas linked to motor preparation, such as SMA, and motor execution [24,25]. In the absence of fatigue, its amplitude is related to the amount of voluntary force and perceived effort. In the

presence of fatigue, its amplitude increases along with increasing fatigue [26].

This paradigm of cross-manipulation of drug doses and verbal instructions may have profound implications. First, the role of the SMA in both PD pathophysiology and management could be clarified by detecting RP changes. Second, this study opens up new strategies in routine clinical practice, where manipulation of drug dosage is the rule. Third, an ethical discussion on these procedures is certainly desirable in order to understand whether this deceptive administration can be used to patient's advantage.

Author contributions

Study concept and design: Elisa Carlino, Alessandro Piedimonte, Alberto Romagnolo, Leonardo Lopiano, Fabrizio Benedetti.

Data acquisition: Elisa Carlino, Alessandro Piedimonte, Alberto Romagnolo, Giulia Guerra.

Elisa Frisaldi, Sergio Vighetti.

Analysis and interpretation of data: Elisa Carlino, Alessandro Piedimonte, Giulia Guerra.

Drafting of the manuscript or revising it critically for important.

Intellectual content: All authors.

Final approval of the version to be submitted: All authors.

Conflicts of interest

The authors report no conflicts of interest relevant to this study.

Role of funding source

The above mentioned funding sources supported the present research, but were not involved in study design and collection, analysis and interpretation of data, writing of the manuscript, and decision to submit it for publication.

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Appendix A. Supplementary data

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