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The placebo effect on resting tremor in Parkinson's disease: an electrophysiological study

Gaetano Barbagallo [a, 1], Rita Nisticò [b, 1], Basilio Vescio [c], Antonio Cerasa [b, d], Giuseppe Olivadese [b], Salvatore Nigro [b], Marianna Crasà [b], Andrea Quattrone [a], Maria Giovanna Bianco [b], Maurizio Morelli [a], Antonio Augimeri [c], Maria Salsone [b], Fabiana Novellino [b], Giuseppe Nicoletti [b], Gennarina Arabia [a], Aldo Quattrone [b, e, *]

[a] Institute of Neurology, University "Magna Graecia", Catanzaro, Italy
[b] Neuroimaging Unit, IBFM, National Research Council, Catanzaro, Italy
[c] Biotecnomed, S.C.aR.L, Catanzaro, Italy
[d] S. Anna Institute and Research in Advanced Neurorehabilitation (RAN) Crotone, Italy
[e] Neuroscience Research Centre, University "Magna Graecia", Catanzaro, Italy

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ABSTRACT

Introduction: The aim of our study was to investigate the effect of apomorphine and placebo on resting tremor in tremor-dominant Parkinson's disease (tPD) patients.
Methods: Fifteen tPD patients were enrolled. Each patient underwent two treatments on two consecutive days: on day one the patients received a subcutaneous injection of placebo, while on day two they received apomorphine. On each day, the patients underwent three electrophysiological recording sessions: T0, T1, and T2: before, 30 min, and 60 min after the treatment respectively. Electrophysiological changes in tremor amplitude were evaluated using a triaxial accelerometer.
Results: Placebo was effective in improving resting tremor in all tPD patients ($p = 0.009$) at T1, but not at T2. Eight out of 15 tPD patients (53.3%) responded to placebo with an at least 70% reduction in tremor amplitude compared to the basal condition (responders). By contrast, seven out of 15 tPD patients (46.7%) did not show any variation in tremor amplitude after placebo administration (non-responders). Apomorphine induced a marked reduction in tremor amplitude at 30 min and 60 min in all investigated tPD patients. Of note, the decrease in tremor amplitude in placebo responders was similar to that achieved with dopaminergic stimulation induced by apomorphine.
Conclusions: Our study demonstrates that placebo was very effective in reducing resting tremor in about half of patients with tPD. The decrease in tremor amplitude in placebo responders was similar to that induced by apomorphine. The cerebral mechanisms underlying the placebo effect on resting tremor need further investigations.

1. Introduction

In the last fifteen years, a plethora of evidence from clinical trials has switched the focus, highlighting the potential application of placebo effects in medical care [1]. Parkinson's disease (PD) is one of the main clinical disorders for which placebo response rates are high. In fact, in PD up to 50% of patients have shown placebo responses characterized by significant improvements in motor symptoms [2]. In particular, all domains of parkinsonian disability seem to be subject to placebo-associated improvements, with a trend toward more effects on bradykinesia and rigidity than on tremor [3].

* Corresponding author. Neuroscience Research Centre, University "Magna Graecia" of Catanzaro, Viale Europa, 88100 Catanzaro, Italy.
E-mail addresses: gaebarbagallo@gmail.com (G. Barbagallo), r.nistico@unicz.it (R. Nisticò), basilio.vescio@biotecnomed.it (B. Vescio), a.cerasa@unicz.it (A. Cerasa), olivadese.giuseppe@gmail.com (G. Olivadese), salvatoreangelo.nigro@gmail.com (S. Nigro), mariannacrasa@yahoo.it (M. Crasà), an.quattrone@hotmail.it (A. Quattrone), maria.giovanna.bianco@gmail.com (M.G. Bianco), m.morelli@unicz.it (M. Morelli), antonio.augimeri@biotecnomed.it (A. Augimeri), salsonemaria@gmail.com (M. Salsone), fabiananovellino@gmail.com (F. Novellino), g.nicoletti@unicz.it (G. Nicoletti), g.arabia@unicz.it (G. Arabia), quattrone@unicz.it (A. Quattrone).
[1] These authors contributed equally to this work.

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Most studies have focused on the placebo-induced improvements in the hypokinetic symptoms of PD, such as rigidity [4–6] and bradykinesia [7–9]. The placebo-induced improvement of these hypokinetic symptoms in PD seems to be mediated by endogenous dopamine release in the striatum [10,11]. Resting tremor is one of the cardinal motor signs of PD, along with rigidity and bradykinesia [12], which occurs at a frequency of 4–6 Hz and mainly involves the distal limbs. Whether resting tremor can also be influenced by placebo treatment is still unknown.

In the current study, we investigated the effects of placebo administration on resting tremor in patients with tremor-dominant Parkinson disease (tPD). To quantitatively assess tremor modifications, we used a triaxial accelerometer comparing the subcutaneous injection of apomorphine with the subcutaneous injection of placebo in patients with tPD.

2. Methods

2.1. Subjects

We enrolled fifteen patients with a diagnosis of idiopathic tPD according to established clinical criteria [13]. Inclusion criteria consisted of: a history of resting tremor, a resting tremor score of $\geq$2 on the Unified Parkinson Disease Rating Scale (UPDRS) for at least one hand during physical examination [14], and damage to the nigrostriatal dopaminergic system on DATscan images [15,16]. Each patient underwent an accurate clinical history and a neurological examination. Exclusion criteria were: (1) cognitive impairment (MMSE score<24); (2) neurological, cerebrovascular or thyroid comorbidities; (3) moderate to severe dyskinesias; (4) normal dopamine transporter single-photon emission computed tomography (DAT-SPECT); (5) evidence of brain tumor, marked atrophy, and/or diffuse white matter hyperintensities on magnetic resonance imaging (MRI); and (6) treatment with deep brain stimulation and general exclusion criteria for MRI scanning. Imaging studies, including MRI and DAT-SPECT, were assessed in all patients, as described extensively elsewhere [15]. Basal motor evaluation was calculated in the “practically off” condition (at least 12 h after the last dose) according to the motor portion of the UPDRS (UPDRS-III). A levodopa equivalent daily dose was calculated for each patient under anti-parkinsonian therapy.

All patients were recruited after providing written informed consent which included authorized deception. All the experimental procedures were conducted according to the policies and ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the University “Magna Graecia” of Catanzaro.

2.2. Electrophysiological examination

The upper limb with the dominant rest tremor was recorded. Rest measurements were performed with the patient's arm flexed at 90°, fully supported against gravity. A triaxial accelerometer (3D Acceleration Sensor MR, Brain Products, Gilching, Germany), was placed on the dorsal side of the patient's hand. Amplitude and frequency of resting tremor were analyzed. For each patient, the changes in the tremor amplitude at the frequency characteristic of PD (3–5 Hz) during T1-and T2 sessions were normalized to values recorded at the basal condition (T0), and expressed in percentage units (%). The placebo response was defined as a decrease in tremor amplitude at T1 or T2 of at least 70% compared to the basal condition (T0) recorded on two out of 3 axes (x, z, and y) of the accelerometer. An additional measure was obtained by calculating the amplitude tremor decrease in relation to the most involved axis (MIA).

To calculate amplitude tremor, the signal peak-to-peak amplitude (A_{pp}) on each axis was measured as $A_{pp} = M/(4^{*}N_{samples})$, where M was the amplitude peak in principal tremor frequency in the signal amplitude spectrum (Fig. 1).

All acceleration signals were recorded at a 5 KHz sampling frequency using a BrainAmp MR acquisition system and filtered in the 1–12 Hz frequency band before being processed. Digital Signal Processing was performed using the GNU/Octave computing environment, version 3.8.2.

Twelve hours prior to experimental sessions, all medications except domperidone were withdrawn. Electrophysiological examination was performed by an investigator who was blind to the patient's diagnosis.

2.3. Experimental design

Using a repeated-measures design, each patient was tested on two consecutive days. The patient underwent three electrophysiological recording sessions on each day, using a triaxial accelerometer: at baseline (T0), just before treatment administration, at T1-and a T2 sessions, 30 min and 60 min after drug or placebo administration, respectively. Each recording session lasted about 1 min. On the first day, the patients received the placebo (subcutaneous injection of 1 mL saline solution), whereas on the second day they received a subcutaneous injection of 1 mg apomorphine. In both conditions patients were informed that they had received an active treatment for their tremor, but the patients did not know when they were receiving a placebo or apomorphine (all patients received both treatments). As apomorphine could induce vegetative symptoms, placebo and apomorphine conditions were not applied in a counterbalanced order. In fact, patients were not randomly assigned to one of two possible orders, in order to prevent possible side effects induced by apomorphine that might reduce expectations in the placebo condition.

Drug and placebo injections were performed by a nurse. Motor evaluation before and after drug/placebo administration was performed by a blinded neurologist who did not know anything about the purpose of the study, the nature and the sequence of the subcutaneous injections. Moreover, patients were asked to abstain from reporting any side effects to the blinded neurologist that performed the motor evaluation.

All patients had never received apomorphine subcutaneous injections before this experiment and they were given domperidone (60 mg/daily) for 48 h before the experimental sessions, in order to prevent vomiting and/or nausea [10]. The apomorphine-induced side effects were also minimized using a low-dose apomorphine. Previous studies [17] have shown that a 1 mg subcutaneous injection of apomorphine induced a significant improvement in tremor without side effects. Furthermore, all patients underwent routine electrocardiography in order to exclude the presence of domperidone-induced QT prolongation.

2.4. Statistical analysis

To compare sex distributions among tPD subgroups, we used the χ^2 test, whereas differences in demographic, clinical, and DAT-SPECT data between tPD subgroups were assessed using the unpaired t-test or the Mann-Whitney U test, for normally or non-normally distributed variables, respectively.

Differences between apomorphine and placebo T0 measurements were assessed by the Wilcoxon rank sum test, while the one-sample t-test was used to assess differences in amplitude percentage change at a tremor frequency between T0 and T1, between T0 and T2 and between treatments, in tPD total group and in tPD subgroups.

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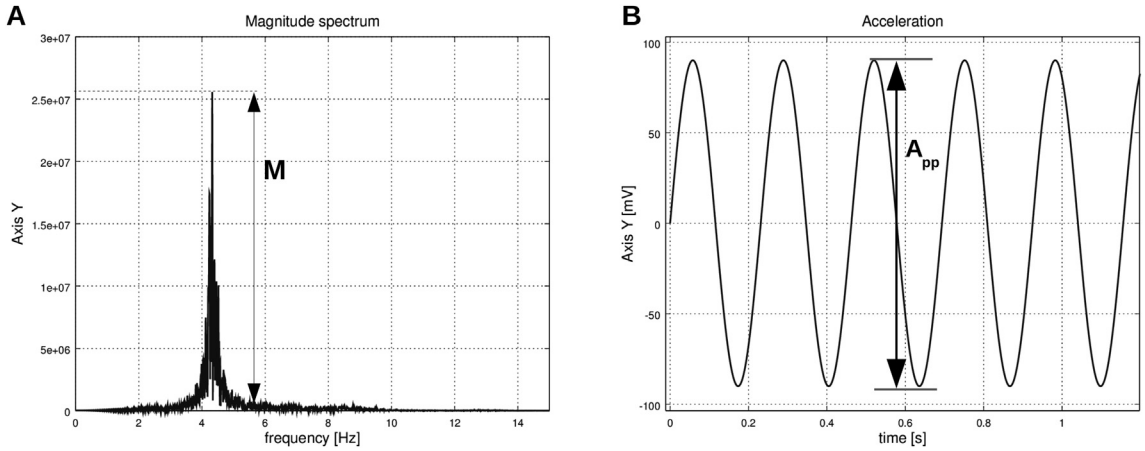

Fig. 1. Evaluation of accelerometric tremor amplitude in one representative subject, y axis.
(**A**) Amplitude of the spectrum at tremor frequency; (**B**) peak-to-peak amplitude of acceleration signal.

Statistical analysis was performed with R Statistical Software (R for Unix/Linux, version 3.1.1).

3. Results

Demographic, clinical, and DAT-SPECT features of the study subjects are listed in Table 1. All patients showed normal conventional imaging results on the MRI together with bilateral presynaptic nigrostriatal damage, more marked on the side contralateral to the most clinically affected side. In addition, eight out of 15 tPD patients (53.3%) responded to placebo with a reduction in tremor amplitude of at least 70% compared to the basal condition (placebo responders). By contrast, the remaining seven of 15 tPD patients (46.7%) did not show any variation in tremor amplitude after placebo administration (placebo non-responders). Apomorphine induced a marked reduction in tremor amplitude in all investigated tPD patients. No demographic or clinical or DAT-SPECT differences were found between placebo responders and placebo non-responders, except for the post-placebo resting tremor subscore ($p = 0.004$). Almost all of the tPD patients were treated with anti-parkinsonian drugs. Only four patients did not receive dopamine replacement therapy (tPD de-novo): of these, two patients were in the placebo responders subgroup and two patients were in the placebo non-responders subgroup.

Fig. 2A shows the main accelerometric results regarding the tremor amplitude changes (%) induced by apomorphine and placebo administrations in the tPD total group. In the tPD total group apomorphine administration induced a significant decrease in the tremor amplitude both at T1 and T2 ($p < 0.001$); whereas placebo administration induced a significant decrease in the tremor amplitude at T1 ($p = 0.009$), but not at T2 ($p = 0.06$). When we compared the apomorphine and placebo responses, we found that the tremor amplitude decrease was more marked with apomorphine than placebo at T1 ($p = 0.01$), but not at T2 ($p = 0.06$).

Table 1
Demographic, clinical, and DAT-SPECT features of the study subjects[a]

	tPD total group (n° = 15)	tPD subgroups		p value[b]
		Placebo responders (n° = 8)	Placebo non-responders (n° = 7)	
Sex, M/F	11/4	6/2	5/2	ns[c]
Age, y	65.6 ± 7.2	63.6 ± 7.8	67.9 ± 6.1	ns[d]
MMSE	27.1 ± 1.6	27.4 ± 1.2	26.7 ± 2.2	ns[d]
Age at onset, y	60.6 ± 7.7	58.3 ± 7.2	63.3 ± 8.0	ns[d]
Disease duration, y	5.0 ± 3.2	5.4 ± 2.8	4.6 ± 3.8	ns[d]
LEDD, mg/die	326.4 ± 258.7	267.6 ± 231.1	393.6 ± 289.8	ns[d]
Pre-treatment UPDRS-ME	24.3 ± 8.5	23.6 ± 11.7	25.0 ± 3.0	ns[d]
Pre-treatment resting tremor subscore	4.9 ± 1.8	5.0 ± 2.3	4.9 ± 1.3	ns[d]
Post-apomorphine UPDRS-ME	18.2 ± 6.5	17.0 ± 8.3	19.6 ± 3.8	ns[d]
Post-apomorphine resting tremor subscore	2.1 ± 1.0	1.8 ± 1.0	2.4 ± 0.8	ns[e]
Post-placebo UPDRS-ME	21.2 ± 6.7	18.3 ± 7.7	24.8 ± 3.5	ns[d]
Post-placebo resting tremor subscore	3.3 ± 1.8	2.1 ± 1.4	4.7 ± 1.1	0.004[e]
DAT-SPECT features				
Contralateral putamen	2,3 ± 0.5	2.4 ± 0.6	2.0 ± 0.3	ns[d]
Ipsilateral putamen	2,6 ± 0.5	2.8 ± 0.6	2.3 ± 0.2	ns[e]

Abbreviations – tPD = tremor-dominant Parkinson's disease. M = male; F = female. MMSE = Mini Mental State Examination. LEDD = levodopa equivalent daily dose. UPDRS-ME = Unified Parkinson's Disease Rating Scale-Motor Examination. Resting tremor subscore = UPDRS item 21. DAT-SPECT = dopamine transporter single-photon emission computed tomography (the DAT-SPECT value was determined using the ratio of specific [putamen ipsi- and contralateral to the more clinically affected side] to non-specific [occipital area] radioligand binding).

[a] Data are given as mean values ± standard deviation.
[b] Placebo responders vs placebo non-responders comparison.
[c] χ^2 test.
[d] Unpaired *t*-test.
[e] Mann-Whitney *U* test.

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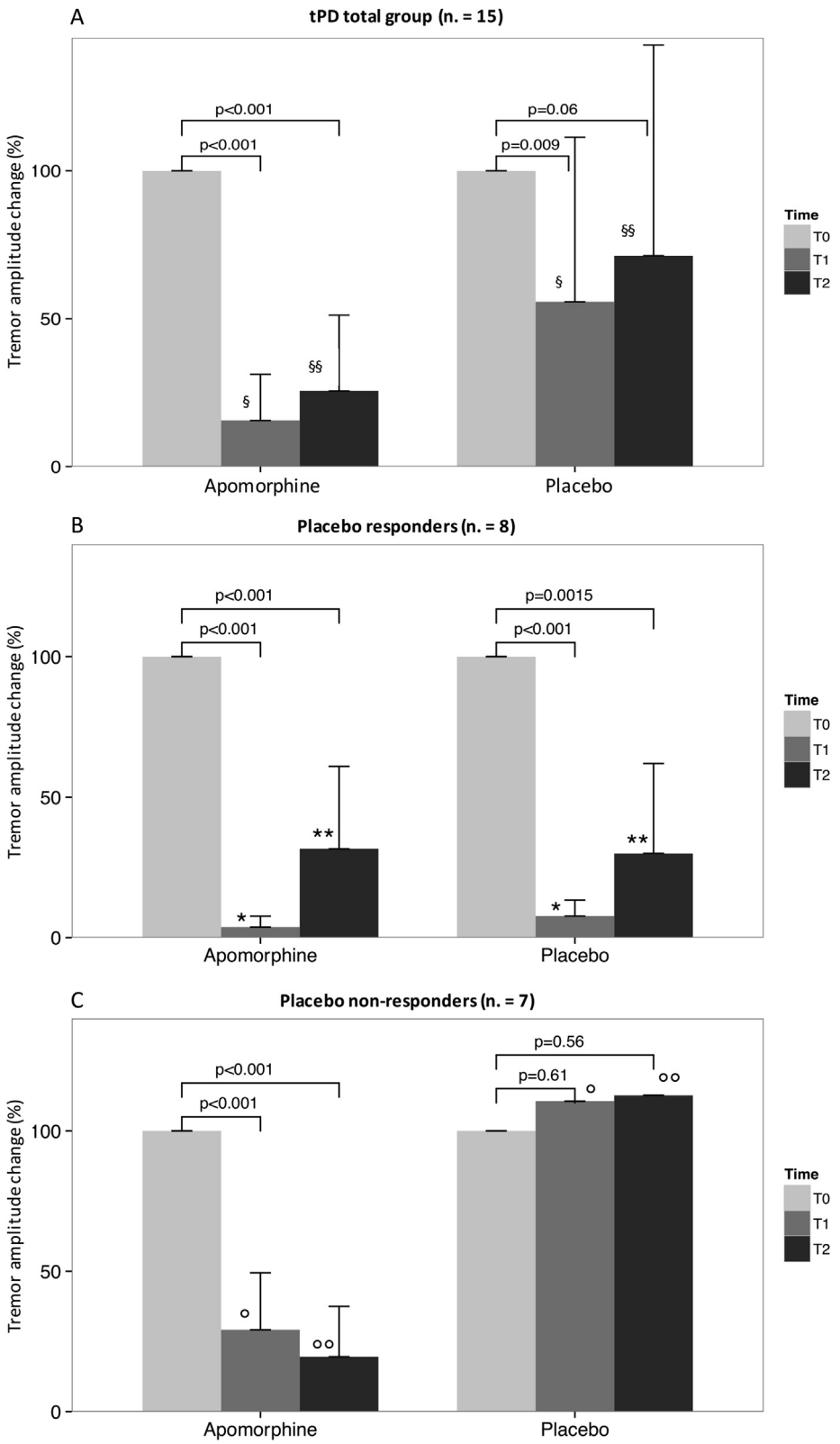

Fig. 2. Intra- and intergroup differences in tremor amplitude changes (%) after apomorphine and placebo administrations.
(**A**) tPD total group (n.: 15): § = T1 apomorphine vs T1 placebo: p = 0.01; §§ = T2 apomorphine vs T2 placebo: p = 0.06 (paired *t*-test, two-tailed). (**B**): placebo responders (n.: 8): ★ = T1 apomorphine vs T1 placebo: p = 0.20; ★★ = T2 apomorphine vs T2 placebo: p = 0.68 (paired *t*-test, two-tailed). (**C**): placebo non-responders (n.: 7): ¢ = T1 apomorphine vs T1 placebo: p = 0.006; ¢¢ = T2 apomorphine vs T2 placebo: p = 0.01 (paired *t*-test, two-tailed).

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Fig. 2B and C shows the main accelerometric results regarding the tremor amplitude changes (%) induced by apomorphine and placebo administrations in the tPD subgroups. In placebo responders (**2B**), both apomorphine and placebo administrations induced a significant decrease in the tremor amplitude both at T1 ($p < 0.001$ for apomorphine and placebo) and at T2 ($p < 0.001$ for apomorphine, and $p = 0.0015$ for placebo). When we compared the apomorphine and placebo responses, we found no significant differences either in T1 ($p = 0.20$) or in T2 ($p = 0.68$).

In placebo non-responders (**2C**), apomorphine administration induced a significant decrease in the tremor amplitude both at T1 and at T2 ($p < 0.001$), whereas the placebo did not induce any tremor improvement.

Regarding the differences in apomorphine-induced responses between placebo responders vs placebo non-responders, we found that placebo responders showed a more marked tremor improvement than placebo non-responders at T1 ($p = 0.016$), but not at T2 ($p = 0.38$).

Table 2 shows the absolute values of the tremor amplitude in the three spatial axes (x, y, and z), the average [$(x + y + z)/3$] and the values detected in the most involved axis (MIA) at T0 condition. No significant differences were found when the tremor amplitude values were compared at T0 and T2 conditions. On the other hand, the tremor amplitude at T1 was significantly lower after apomorphine administration than placebo administration in the tPD total group. In addition, tremor amplitude values were significantly lower after apomorphine or placebo administration in responders than in non-responders.

4. Discussion

The main finding of the current study is that placebo administration induced a marked objective decrease in the tremor amplitude in about 53% of patients with tPD. It is worth noting that the tremor decrease in placebo responders was similar to that achieved with exogenous dopaminergic stimulation induced by apomorphine.

Our data demonstrate the efficacy of placebo in PD-related resting tremor in accordance with previous findings reported on hypokinetic symptoms (i.e. bradykinesia and rigidity). In fact, most of the repeated-measure studies aimed at investigating placebo-associated motor improvement in PD have objectively explored the placebo effect on bradykinesia [7–9] and rigidity [4–6,18,19], rather than on the tremor. Whether tremor also shows a placebo-induced improvement is still debated. Previous results from clinical trials [3] have demonstrated that all domains of parkinsonian disability showed placebo-associated improvement, with a trend toward a higher response in bradykinesia and rigidity than in tremor. By contrast, results from placebo studies on PD tremor are contradictory. One study showed that resting tremor was not influenced by placebo-correlated expectation [19], whereas in another study, the authors demonstrated that tremor decreased after placebo administration by at least 10% [20]. Both these studies were performed in PD patients with chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN), and tremor severity was evaluated when the STN stimulator was switched in ON and OFF. In the first experiment [19], the patients were blind when the STN stimulator was switched OFF-ON or ON-OFF, whereas in the second study [20] the impact of STN stimulation on tremor was manipulated by positive or neutral verbal suggestions, thus creating a targeted expectation (positive suggestions) of a tremor improvement. The influence of the provided verbal suggestions in the second study may explain the positive placebo effect on resting tremor, which was lacking in the first study without modulating benefit expectancy.

No studies, however, have been conducted in surgically naïve tPD patients aimed at objectively assessing placebo-induced tremor modifications, and comparing these modifications with those induced by exogenous dopaminergic stimulation.

Our study is the first to assess the placebo-effect on resting tremor in comparison with apomorphine response in tPD patients using a triaxial accelerometer, an electrophysiological tool independent of rater bias, thus avoiding that even unconsciously examiners could have influenced the results [21]. As expected, we

Table 2
Tremor amplitude (mV) before and after apomorphine and placebo administration in tPD total group (n: 15) and in tPD subgroups (placebo responders [n: 8] and placebo non-responders [n: 7])[a]

<!–Col Count:8–>Time	Axis	Apomorphine (n = 15)	Placebo			Placebo vs Apomorphine	Responders vs Non-responders
			N = 15	Reponders (n = 8)	Non-responders (n = 7)	P	P
T0	X	165 ± 240	119 ± 134	112 ± 99	128 ± 175	0.38[b]	1[c]
	Y	148 ± 134	158 ± 147	168 ± 167	148 ± 134	0.98[b]	1[c]
	Z	210 ± 304	176 ± 197	181 ± 186	171 ± 225	1[b]	1[c]
	Average	175 ± 192	151 ± 122	153 ± 118	149 ± 135	1[b]	1[c]
	MIA	231 ± 303	243 ± 204	253 ± 210	231 ± 212	0.16[b]	1[c]
T1	X	32 ± 76	81 ± 135	12 ± 18	159 ± 170	<0.001[b]	0.004[d]
	Y	16 ± 24	60 ± 96	13 ± 16	114 ± 121	<0.001[b]	0.004[d]
	Z	54 ± 113	103 ± 164	17 ± 30	201 ± 201	<0.001[b]	0.01[d]
	Average	34 ± 69	81 ± 124	14 ± 21	158 ± 149	<0.001[b]	0.002[d]
	MIA	38 ± 97	89 ± 147	18 ± 29	170 ± 188	<0.001[b]	0.004[d]
T2	X	22 ± 34	132 ± 186	31 ± 42	200 ± 215	1[b]	0.26[c]
	Y	46 ± 77	68 ± 79	34 ± 41	102 ± 97	1[b]	0.18[c]
	Z	29 ± 55	188 ± 275	48 ± 57	329 ± 340	0.26[b]	0.26[c]
	Average	32 ± 55	124 ± 161	38 ± 39	210 ± 193	0.30[b]	0.26[c]
	MIA	39 ± 61	114 ± 170	51 ± 56	178 ± 225	1[b]	0.36[c]

Abbreviations – T0: basal condition; T1: 30 min after T0; T2: 60 min after T0. MIA = more involved axis, as measured by accelerometer (for ten of 15 tPD patients the MIA was y axis, for 4 tPD patients it was z axis, and for 1 was x axis).
All p values are corrected according to Bonferroni.
[a] Data are given as mean values ± standard deviation.
[b] Wilcoxon signed rank test, two-tailed.
[c] Wilcoxon rank sum test, two-tailed.
[d] Wilcoxon rank sum test, single-tailed.

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found that in the whole group of tPD patients, the objective improvement in resting tremor induced by the placebo administration was less marked than that induced by apomorphine, without differences between placebo and apomorphine baseline accelerometric values. However, when the patients were divided according to the placebo effect into responders and non-responders, we found that the placebo responders showed a similar clinical improvement to that induced by apomorphine. On the other hand, the placebo non-responders did not show any improvement in tremor amplitude compared to baseline values, thus confirming previous studies on hypokinetic symptoms in PD patients showing that the placebo response was detectable in about half of the patients [4,18].

Because our experimental protocol was designed to maximize the placebo response rather than active drug effect, in this preliminary study we preferred to administer the placebo always before the apomorphine, in order to avoid any potential interference of the latter on the placebo effect. Moreover, we used an invasive procedure (placebo was injected, rather than taken orally like a pill), because previous studies concerning pain suggested that invasive treatments may show a higher degree of placebo effect than non-invasive treatments [22–25]. When the patients received the placebo, they were informed that the subsequent injection would strongly improve the tremor. This simple verbal suggestion could have played a central role in determining the placebo effect on resting tremor, by providing a great expectation of a clinical benefit. In fact, it is well known that the magnitude of placebo-induced effects is modulated by the expectancy of improvement [11]. The mechanism by which placebo may improve motor symptoms in patients with PD may be dependent on the activation of the entire nigrostriatal pathway, induced by endogenous dopamine release in the dorsal striatum [10,11,26]. On the other hand, recent studies have suggested that the expectancy of improvement seems to be related to the release of endogenous dopamine within the ventral striatum [11,27]. Thus, a link between dorsal and ventral striatum may be hypothesized as the neuroanatomical basis for the placebo effect in PD. The expectation of a clinical benefit induced by the targeted verbal suggestions, however, cannot be the only factor involved in the placebo response, as placebo was effective in reducing resting tremor in about 53% of tPD patients, but not in the remaining 47%. Other factors, such as individual personality [28] and genetic predisposition [29], may influence clinical outcomes and explain the different placebo responsiveness observed in our tPD patients.

It remains to be clarified how the exogenous dopaminergic stimulation induced by the apomorphine administration could be useful in reducing the tremor severity, as this motor sign does not seem to be directly correlated with the striatal dopaminergic depletion [15], and appears to involve different neural mechanisms other than bradykinesia and rigidity. However, previous studies have demonstrated that both levodopa [30] and apomorphine [17] may be able to improve resting tremor in PD. A possible explanation of the placebo effect on resting tremor may lie in the restorative effect played by dopaminergic drugs in the brain structures involved in the pathophysiology of resting tremor, such as the striatum, globus pallidus, and thalamus [14–16]. In fact, recent studies have suggested that parkinsonian tremor may result from increased interactions between the basal ganglia and the cerebello-thalamo-cortical circuit [14].

The present study has some limitations. The first issue to be highlighted is the lack of randomization between the placebo and drug conditions. In line with previous studies [10], our experimental protocol was designed to maximize the tolerability of the procedure, and to maintain the level of expectation throughout the study, which was crucial to our experiment. Indeed, the occurrence of apomorphine-induced side effects could have “unblinded” the study. Our study design also minimized the potential carry-over effects from the apomorphine. In the patients with no or only minor placebo effect of the first application (placebo non-responders), the sequence of events established in our study (first placebo and after apomorphine) may have enhanced the anticipation of a better effect of the second application, thus adding a placebo component to the apomorphine application (“two pills in one pill”). However, when we compared the apomorphine-induced responses between placebo responders vs placebo non-responders, we found that placebo responders showed a higher tremor improvement than placebo non-responders, suggesting a “predisposition” to placebo and drug responses. Studies with a randomized design are warranted in order to clarify these findings.

Second, almost of all patients assumed dopaminergic replacement therapy. As recent studies investigating bradykinesia [9] and rigidity [5] in PD patients have demonstrated, placebo-associated clinical improvement may be positively modulated by the previous dopaminergic exposure of patients to dopaminergic drugs, suggesting that such an experience may induce some conditioning possibly enhancing the placebo effect [22]. In our study, only four out of 15 patients were de-novo PD, and were equally distributed between the two subgroups. Further investigations are needed to evaluate the effects of placebo on resting tremor in de-novo PD patients in comparison with treated PD patients in order to clarify the role of conditioning in placebo response on resting tremor.

Third, given the preliminary small sample, larger studies with multiple measurements are warranted to explore the potential biomarkers of placebo responsiveness on resting tremor in PD.

Overall, these results suggest that the placebo response is an objectively measurable phenomenon in PD patients with resting tremor, and that the placebo effect may be modulated by the benefit expectation.

Conflicts of interest

None declared.

Disclosure

None reported.

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