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The effect of expectancy and personality on cortical excitability in Parkinson's disease

Jau-Shin Lou, MD, PhD^{1,*}, Diana M. Dimitrova, PhD¹, Richard Hammerschlag, PhD², John Nutt, MD¹, Elizabeth A. Hunt, MPH¹, Ryan W. Eaton, BS¹, Sarah C. Johnson, MPAS, PA-C¹, Melanie D. Davis, MSN, FNP¹, Grace C. Arnold, MPH¹, Sarah B. Andrea, BS¹, and Barry S. Oken, MD¹

¹Department of Neurology, Oregon Health & Science University, Portland, OR

²Oregon College of Oriental Medicine, Portland, OR

Abstract

Background—Our previous studies in PD have shown that both levodopa and expectancy of receiving levodopa reduce cortical excitability. We designed this study to evaluate how degree of expectancy and other individual factors modulate placebo response in Parkinson's patients.

Methods—Twenty-six Parkinson's patients were randomized to one of three groups: 0%, 50% and 100% expectancy of receiving levodopa. All subjects received placebo regardless of expectancy group. Subjects completed the NEO-Five Factor Inventory, General Perceived Self-Efficacy Scale, and Perceived Stress Scale. Cortical excitability was measured by the amplitude of motor evoked potential (MEP) evoked by transcranial magnetic stimulation. Objective physical fatigue of *Extensor carpi radialis* before and after placebo levodopa was also measured. Responders were defined as subjects who responded to the placebo levodopa with a decrease in MEP.

Results—Degree of expectancy had a significant effect on MEP response ($p < 0.05$). Subjects in the 50% and 100% expectancy groups responded with a decrease in MEP, while those in the 0% expectancy group responded with an increase in MEP ($p < 0.05$). Responders tended to be more open to experience than non-responders. There were no significant changes in objective physical fatigue between the expectancy groups, or between responders and non-responders.

Conclusions—Expectancy is associated with changes in cortical excitability. Further studies are needed to examine the relationship between personality and placebo effect in Parkinson's patients.

Keywords

Parkinson's disease; Levodopa; Expectancy; Cortical Excitability; Transcranial Magnetic Stimulation (TMS)

*Correspondence to: Oregon Health and Science University, Department of Neurology, 3181 SW Sam Jackson Park Rd, CR-120, Portland, OR, 97239-3098; louja@ohsu.edu.

Author Roles:

Jau-Shin Lou, MD, PhD; Richard Hammerschlag, PhD: Research project conception, design & organization, execution, and manuscript composition.

John Nutt, MD; Barry Oken, MD: Research project design & organization and manuscript composition Diana Dimitrova, PhD: Research project organization and oversight, and statistical analysis design and execution.

Sarah Andrea, BS: Statistical analysis and Manuscript composition.

Elizabeth Olszewski, MPH; Ryan Eaton, BA; Sara Johnson, MPAS, PA-C; Melanie Davis, FNP; Grace Arnold, BA: Research project execution

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INTRODUCTION

The placebo effect in Parkinson's disease (PD) is prominent in numerous clinical trials, many of which used motor function as a primary outcome measure.^{1,2,3} The physiological mechanisms mediating the placebo effect are poorly understood, however, dopamine may play a significant role.⁴⁻⁶ Expectancy, defined as a subject's anticipation that they know which treatment they will receive, may play a role in the placebo effect. The degree of expectancy depends on the individual's previous experience with a particular treatment.⁷ Furthermore, personality may contribute to the placebo effect; placebo responders score higher on extraversion, openness to experience, and agreeableness, although this effect is inconsistent.⁸ The role of personality on the placebo effect in PD has not been well studied.

Fatigue is more common in patients with PD when compared to normal controls.⁹ Objective physical fatigue in PD, measured by an intermittent force generation paradigm, is associated with abnormally increased cortical excitability.^{10, 11} The objective physical fatigue is different from the subjective physical fatigue measured by questionnaire.¹⁰ Cortical excitability is measured by motor-evoked potentials (MEP) induced by transcranial magnetic stimulation (TMS). Levodopa reduces MEP amplitude and cortical excitability in patients with PD.¹¹ Furthermore, in a double-blind placebo-controlled study levodopa significantly decreased objective physical fatigue.¹² Most interestingly, up to 40% of the subjects receiving placebo also showed a decrease in objective physical fatigue.¹²

We designed this study to test the hypotheses that a higher degree of expectancy would induce larger changes in cortical excitability and that personality, self-efficacy and stress would modulate the cortical excitability.

METHODS

Subjects

We recruited patients for this randomized, double-blind study from the Movement Disorders Clinic at Oregon Health & Science University. All patients provided written informed consent approved by our institution review board.

Eligible patients had a clinical diagnosis of PD meeting at least two of the following diagnostic criteria: tremor, rigidity, bradykinesia, and postural instability. In addition, eligible patients were Hoehn and Yahr stage II to IV with Mini Mental Status Examination (MMSE) >25. Patients were ineligible for inclusion if they had any clinically unstable diseases.

Participants were told that the study was an evaluation of the effects of levodopa on brain response to TMS and fatigue. We did not initially inform the participants that the purpose was to study the expectancy effect. At the end of last visit, there was a debriefing session where we disclosed to the participants that they did not really receive levodopa. We adhered to guidelines concerning deception in human subjects research.^{13, 14} The study was considered minimal risk. A significant psychological symptom at the debriefing would be considered an adverse event and reported to the IRB. Participants had the option of withholding their data from inclusion in the study if they so desired. No subjects reported being disappointed, displeased, or upset by the deception nature of the study after the debriefing. There were no adverse events due to deception.

Objective physical fatigue and cortical excitability

We assessed objective physical fatigue by measuring the objective fatigue index (FI) in an intermittent exercise paradigm as previously described.¹² Higher FI values indicated more

objective physical fatigue. Cortical excitability was evaluated using MEPs induced by transcranial magnetic stimulation (TMS). Ten MEPs were collected before the intermittent MVC exercise with extensor carpi radialis muscle relaxed using a 9-cm figure-of-eight coil (Magstim 200, Magstim Co., Dyfed, UK) on the motor cortex contralateral to the more affected arm. The stimulation intensity was 10% above the resting motor threshold.¹¹

Subjects were randomly assigned to one of three expectancy groups. The groups represented varying degrees of expectancy regarding whether the subject would receive real or placebo levodopa: 1) 100% expectancy: subjects were told they had 100% chance of receiving levodopa dissolved in Kool-Aid; 2) 50% expectancy: subjects were told they would have 50% chance of receiving real or placebo levodopa dissolved in Kool-Aid; and 3) 0% expectancy: subjects were told they would receive Kool-Aid only without levodopa. None of the groups received any real levodopa. The investigator responsible for conducting the subject assessments was blinded to each subject's randomized group assignment.

The subjects were tested after being off their anti-parkinsonian medicine for at least 12 hours at two separate visits in random sequence: a "Test-Retest" visit and an "Expectancy" visit. During the "Test-Retest" visit, subjects received TMS and performed the intermittent exercise before and after a 30-minute break. At the "Expectancy" visit, the subjects received TMS and performed the intermittent exercise before and after taking Kool-Aid.

Questionnaires

Subjects filled out three questionnaires to evaluate personality:

1. *NEO-Five Factor Inventory* (NEO-FFI): NEO-FFI measures five personality domains: neuroticism, extraversion, openness, agreeableness, and conscientiousness with scores ranging from 0 to 48 for each domain.¹⁵
2. *General Perceived Self-Efficacy Scale* (GPSES): GPSES assesses the presence of optimistic self-beliefs to cope with a variety of difficult demands in life with a maximum score of 40 points.¹⁶
3. *Perceived Stress Scale* (PSS): PSS evaluates the degree to which situations in one's life are appraised as stressful with a maximum score of 50 points (more stressed).¹⁷

Statistical analysis

Internal test consistency was established by calculating Intraclass Correlation Coefficient (ICC) for the outcome measures before placebo levodopa on the "Expectancy" visit and the "Test-Retest" visit. Based on previous data showing that real levodopa decreased MEP,⁹ subjects who responded to the placebo levodopa with a decrease in MEP in the 50% and 100% expectancy groups were further classified as "responders". The placebo effect on MEP amplitude and FI in the responders was examined with a mixed analysis of variance (ANOVA) model with expectancy as a between group factor and the data before and after levodopa as repeated measures. The involvement of individual factors in the placebo effect was explored by comparing responders and non-responders in the 50% and 100% expectancy groups with one-way ANOVA. P-values < 0.05 were considered significant. The data for the more exploratory analyses comparing the responders to non-responders is given with a p-value without any correction for multiple comparisons.

RESULTS

A. Demographic data

Twenty-six patients were randomized (Table 1). UPDRS scores and Hoehn & Yahr stages did not differ among the three groups with different expectancy level. However, the 100% expectancy group was significantly younger than the other two groups ($p<0.05$).

B. Cortical motor evoked potentials (MEPs)

The MEP amplitudes measured at the first test session on the “Expectancy” visit and at the “Test-Retest” visit were consistent ($ICC=0.32$, $p<0.01$).

When data from all 26 subjects were analyzed, the mean MEP amplitude in the 0% expectancy group increased significantly from baseline ($t= 2.77$; $p=0.028$, Figure 1A). While both 50% and 100% expectancy groups exhibited reduced mean MEP amplitudes from baseline, neither was statistically significant ($p=0.2$ and 0.99 respectively; Figure 1A).

Because there was no significant difference in MEP reduction in the 100% and 50% groups, we pooled the data in these groups for post-hoc analysis. A 2-group ANOVA was performed in which a significant difference in mean amplitude change between the 0% expectancy and pooled expectancy groups was observed ($p=0.046$).

We also performed exploratory analysis to compare the MEP changes between responders and non-responders. Assessment of individual subject data revealed that MEP amplitude did not decrease for any of the nine subjects within the 0% expectancy group (Figure 2A). Decreased MEP amplitudes were observed in seven of the nine subjects assigned to the 50% group (Figure 2B, subjects H1-7 in Table 1) and four of the eight subjects assigned to the 100% group (Figure 2C, subjects E1-4 in Table 1). There was no difference in age, disease severity, or duration between responders and non-responders, however, the mean MEP amplitude in the responders significantly decreased after placebo levodopa ($p<0.05$, Figure 1B). Although decrement in MEP was greater in the 100% responder group than in the 50% responder group, the difference did not reach significance ($p=0.2$).

C. Objective physical fatigue

Objective physical fatigue index (FI) did not change for any expectancy group after placebo levodopa. FI did not differ before and after placebo levodopa in the responders or the non-responders.

D. Questionnaires

In NEO-FFI, the responders tended to score higher than the non-responders on openness to experience ($p<0.1$, Table 2). There was no difference in the other four personality traits.

The scores for PSS (23.8 ± 2.1 vs. 22.0 ± 1.6) and GPSES (29.2 ± 0.6 vs 30.6 ± 1.2) were not different between responders and non-responders.

DISCUSSION

In summary, our results showed that the expectancy had significant effect on the MEP response ($p<0.05$). The subjects in the 0% expectancy group responded with an increase in MEP, while the subjects in the 50% and 100% expectancy groups responded with a decrease in MEP. However, we found no significant changes in objective physical fatigue between the expectancy groups or between responders and non-responders.

Expectancy plays an important role in the placebo effect. Patients with PD exhibit a prominent placebo effect. In one study, patients who thought they received transplantation of embryonic dopamine neurons reported more improvement in quality of life than those who believed they did not receive the transplant, regardless of the actual intervention they received.¹⁹ In two other studies, PD patients who received subthalamic DBS and believed that the stimulator was on had better UPDRS score⁷ or showed faster hand movements.²⁰ Our finding that the MEP amplitude decreased in subjects who were expecting to receive levodopa (50% and 100% groups) is consistent with the literature supporting the influence of expectancy on clinical outcomes in PD.

The degree of expectancy (i.e. uncertainty) may play a role in the magnitude of the placebo response. The placebo response is mediated, at least in part, by the dopaminergic system.⁴ A study in monkeys showed that dopamine neurons in the midbrain showed little response to fully predicted reward, yet they displayed the typical phasic activations when reward was uncertain. These findings suggest that the dopaminergic neuronal response codes uncertainty.²¹ Further studies showed the response of the dopaminergic neurons shifted relative to the expected reward value and therefore maintained their sensitivity to reward over a large range of reward values.²² Recently, a [¹¹C] raclopride PET study examined the effect of different degrees of expectancy (25%, 50%, 75% or 100%) on the placebo-induced dopamine release in PD; only the group with 75% expectancy showed a significant placebo response.²³ This study illustrates the importance of uncertainty in the placebo response. In our study, the 50% expectancy group had the highest level of uncertainty among the three groups assessed and the largest proportion of subjects with a decrement in MEP. These results may be further explained by the findings of a previous study that showed dopaminergic activation was present when reward was likely, but not certain.²⁴ Unfortunately, The MEP changes did not differ in the 50% and 100 % group in our study; likely due to lack of statistical power. Further studies with larger sample size are needed to address how the degree of uncertainty influences the placebo effect.

In earlier research, we found that PD patients had increased cortical excitability, as measured by MEP amplitude, at off state and that levodopa reduced the MEP amplitude.¹¹ In a double-blind placebo-controlled study, we demonstrated that both real levodopa and placebo reduced the MEP amplitude to the same degree.¹⁸ The results in the present study are consistent with our previous findings.

In a previous open-label study, we demonstrated that levodopa reduced both MEP amplitude and objective physical fatigue.¹¹ While in the present study expectation was associated with a reduction in cortical excitability as measured by MEP, it was not associated with any changes in objective physical fatigue. Because we did not perform UPDRS, we do not know if changes in MEP associated with expectancy have any clinical implications. However, another study showed that expectancy-induced dopamine release is associated with significant improvement in the motor UPDRS scores.²³ Further studies using both MEP and UPDRS as outcome measures are needed to examine if MEP changes associated with expectancy have any clinical implication.

It is not clear why MEP amplitudes increased in the 0% expectancy group. Since there was no significant difference between test and retest at baseline, it is unlikely that the test-retest is the cause of the variation. Other studies have suggested that uncontrolled factors in this study, such as menstruation cycle and eye opening or closing, may affect cortical excitability.^{25,26,27}

In addition to expectancy, other factors such as personality, self-efficacy, and stress may modulate the placebo effect. Several studies have examined the effect of personality on

placebo effect in non-PD subjects.^{8,15,28} Normal subjects with high optimism had higher placebo and less nocebo effect.²⁸ Our study showed a trend for responders to be more open to experience than the non-responders. It is possible that larger sample size and use of different measurements of personality would yield associations with expectancy.

While we found no difference in self-efficacy and stress scores between placebo responders and non-responders, other studies have found self-efficacy predicted the effect of exercise for low-back pain relief and correlated with patients' tolerance of stressful procedures.^{29,30, 31}

In conclusion, the results of this small study show that expectancy mediates the placebo effect in PD as monitored and measured by changes in cortical excitability. Further studies are needed to clarify the relationship between personality variability among subjects and the placebo effect.

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Figure 1.

Figure 2.

Table 1

Demographic data.

Subjects	Age	Gender	PD duration	Medications	UPDRS	Motor UPDRS	Hoehn & Yahr	Schwab & England
100% expectancy								
E1	56	M	4	LD	41	20	2.5	80
E2	69	M	12	LD	54	25	2	80
E3	52	F	9	LD	39	18	1.5	80
E4	61	M	4	LD	34	18	1.5	90
E5	70	M	6	LD	30	18	3	90
E6	62	M	7	LD,P	27	12	1.5	80
E7	55	M	2	none	34	18	1.5	90
E8	46	F	3	none	31	15	1.5	85
Mean ± SD	58.9 ± 8.3		5.9 ± 3.4		36.3 ± 8.5	18.0 ± 3.7	1.9 ± 0.6	84.4 ± 5.0
50% expectancy								
H1	80	M	10	LD	34	19	3	90
H2	65	M	7	LD,P	20	12	1.5	90
H3	82	F	11	LD	42	15	1.5	80
H4	63	M	3	LD	20	10	1	90
H5	56	M	12	LD,R	49	22	2.5	80
H6	73	F	9	LD	42	23	2	60
H7	67	M	10	LD,P	39	18	1.5	90
H8	70	M	7	LD,R	28	16	1.5	90
H9	68	M	3	P	29	15	2	90
Mean ± SD	69.3 ± 8.2		8.0 ± 3.3		33.7 ± 10.2	16.7 ± 4.3	1.8 ± 0.6	84.4 ± 10.1
0% expectancy								
N1	81	F	3	LD,R	37	19	3	90
N2	92	M	7	LD,R	38	13	1.5	85
N3	65	F	5	LD,P	35	23	2.5	90
N4	59	F	4	LD,P	24	14	1	90

Subjects	Age	Gender	PD duration	Medications	UPDRS	Motor UPDRS	Hoehn & Yahr	Schwab & England
N5	84	M	5	LD,P	34	17	1.5	90
N6	68	M	17	LD	17	7	1.5	90
N7	60	F	3	Am	29	14	1	90
N8	67	M	6	P	39	13	1.5	90
N9	70	M	3	P	35	19	1.5	90
Mean $\pm$ SD	71.8 $\pm$ 11.4		5.9 $\pm$ 4.4		32.0 $\pm$ 7.3	15.4 $\pm$ 4.6	1.7 $\pm$ 0.7	89.4 $\pm$ 1.7

LD – Levodopa; P – Pramipexole; R – Ropinirole; Am – Amantadine

Table 2

Comparison of the NEO-FFI domains in responders and non-responders of the 50% and 100% expectancy groups (mean $\pm$ SE raw scores). Responders did not show significant difference from non responders.

NEO-FFI	Responders (n=11)	Non-responders (n=6)	T-test (p-value)
Openness to experience	23.0 $\pm$ 2.4	17.2 $\pm$ 2.1	0.099
Neuroticism	29.7 $\pm$ 3.2	34.2 $\pm$ 2.2	0.251
Extraversion	22.8 $\pm$ 2.5	22.7 $\pm$ 2.8	0.980
Agreeableness	14.2 $\pm$ 1.2	12.7 $\pm$ 1.3	0.485
Conscientiousness	14.5 $\pm$ 2.0	14.9 $\pm$ 1.6	0.877