ORIGINAL ARTICLE

Effects of Expectation on Placebo-Induced Dopamine Release in Parkinson Disease

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Context: Expectations play a central role in the mechanism of the placebo effect. In Parkinson disease (PD), the placebo effect is associated with release of endogenous dopamine in both nigrostriatal and mesoaccumbens projections, yet the factors that control this dopamine release are undetermined.

Objective: To determine how the strength of expectation of clinical improvement influences the degree of striatal dopamine release in response to placebo in patients with moderate PD.

Design: Randomized, repeated-measures study with perceived expectation as the independent between-subjects variable.

Setting: University of British Columbia Hospital, Vancouver, British Columbia, Canada.

Patients: Thirty-five patients with mild to moderate PD undergoing levodopa treatment.

Intervention: Verbal manipulation was used to modulate the expectations of patients, who were told that they had a particular probability (25%, 50%, 75%, or 100%) of receiving active medication when they in fact received placebo.

Main Outcome Measures: The dopaminergic response to placebo was measured using [^{11}C]raclopride positron emission tomography. The clinical response was also measured (Unified Parkinson Disease Rating Scale) and subjective responses were ascertained using patient self-report.

Results: Significant dopamine release occurred when the declared probability of receiving active medication was 75%, but not at other probabilities. Placebo-induced dopamine release in all regions of the striatum was also highly correlated with the dopaminergic response to open administration of active medication. Whereas response to prior medication was the major determinant of placebo-induced dopamine release in the motor striatum, expectation of clinical improvement was additionally required to drive dopamine release in the ventral striatum.

Conclusions: The strength of belief of improvement can directly modulate dopamine release in patients with PD. Our findings demonstrate the importance of uncertainty and/or salience over and above a patient's prior treatment response in regulating the placebo effect and have important implications for the interpretation and design of clinical trials.

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THE PROMISE OF SYMPTOM improvement that is elicited by a placebo is a powerful modulator of brain neurochemistry. Understanding the factors that modify the strength of the placebo effect is of major clinical as well as fundamental scientific significance. Several studies have demonstrated the critical role of expectation in the mechanism of the placebo effect. The expectation of symptom improvement is associated with endogenous dopamine release[1,2] and changes in subthalamic nucleus neuronal firing[3] in Parkinson disease (PD), the release of endogenous opioids and dopamine in placebo analgesia,[4,5] and changes in brain glucose metabolism in depression.[6] Manipulation of expectation has been shown to affect the clinical motor performance of PD patients.[7-10]

The anticipation of therapeutic benefit in response to placebo administration has been likened to the expectation of reward,[11,12] particularly in patients with a chronic debilitating illness who have already experienced symptom relief from frequent doses of medication or other interventions. In keeping with this view, placebos have been shown to activate reward circuitry, including stimulation of dopamine release in the ventral striatum.[2,5,13] On presentation of a reward-predicting cue, midbrain dopamine neu-

Table 1. Time Elapsed Between Days 1 and 2 for Each Patient per Group

Group	Group[a] A (n=8)	B (n=7)	C (n=7)	D (n=8)
Time elapsed, d	1 (n=7) 4 (n=1)	1 (n=6) 3 (n=1)	1 (n=5) 2 (n=1) 50 (n=1)	1 (n=5) 4 (n=1) 14 (n=1) 19 (n=1)

[a]Subjects were told that they might receive levodopa or placebo and that their chances of receiving active levodopa were 25% (group A), 50% (group B), 75% (group C), or 100% (group D); all subjects actually received placebo.

rons display short phasic responses that encode the probability of reward delivery, the expected magnitude of the reward, and the product of these parameters, the expected reward value.[14] This burst firing increases in a monotonic fashion, with increasing expected reward value.[14] Dopamine neurons also demonstrate slower, more sustained activations during the interval between a reward-predicting stimulus and reward delivery. These encode the variance of the probability distribution, interpreted as the uncertainty associated with reward expectation.[15] These tonic responses follow an inverted U-shaped dose-response curve that is maximal at a probability of 0.5, corresponding to the point of maximal uncertainty.

We wondered whether the magnitude of placebo-induced dopamine release in PD patients would reflect the reward-related activity of midbrain dopamine neurons and to what extent it could be modulated by the degree of expectation of clinical benefit. If the placebo effect is indeed analogous to the expectation of reward, we would predict that dopamine release could be modified by probability alone, by the expected magnitude of the clinical benefit associated with active medication or by the product of these 2 variables, the expected reward value. In a chronic condition such as PD, in which patients demonstrate relatively consistent motoric responses to medication, which may vary from one individual to another, the expected value of clinical improvement would likely reflect the degree of clinical benefit derived from active treatment. We therefore sought to examine whether this clinical benefit, or expected reward magnitude, in addition to probability alone, modulated the degree of placebo-induced dopamine release. We hypothesized that the degree of placebo-induced striatal dopamine release in PD patients could be modulated in either a monotonic or an inverted U–shaped fashion in response to probability and might additionally depend on the degree of clinical improvement that the subject expects. We predicted a bilateral release of dopamine in both the dorsal and ventral striatum, compatible with activation of both the nigrostriatal and mesoaccumbens dopamine pathways.

METHODS

Thirty-five patients with clinically definite PD[16] were recruited from the Movement Disorders Clinic at the University of British Columbia Hospital. All patients gave written informed consent. The study was approved by the University of British Columbia Clinical Research Ethics Board. The experiment took place on 2 consecutive days for most patients; however, this was not always possible (**Table 1**). Antiparkinson medication was withdrawn 12 to 18 hours prior to scanning. All subjects underwent 3 [^{11}C]raclopride positron emission tomographic (PET) scans. On the first day, a baseline scan was performed, followed by a scan beginning 1 hour following the open-label oral administration of immediate-release levodopa/carbidopa (250/25 mg, respectively). On the second day, subjects were randomly assigned to 1 of 4 groups, which determined the verbal instructions they were given regarding the probability, *P*, of receiving levodopa for the third scan. Subjects were told that they might receive levodopa or placebo and that their chances of receiving active levodopa were 25% (group A), 50% (group B), 75% (group C), or 100% (group D). In fact, all subjects were given placebo, regardless of the instructions. Scanning began 1 hour later so that the procedure would be directly comparable with that following open-label levodopa. The group allocation was not revealed to the patient until the time of placebo administration. All subjects received 20 mg of domperidone 30 minutes prior to both levodopa and placebo to prevent peripherally mediated adverse effects of levodopa, such as hypotension or nausea.

PET AND IMAGE ANALYSIS

All PET scans were performed in 3-dimensional mode using a high-resolution research tomograph (HRRT, CTI/Siemens).[17] A 10-minute transmission scan using a rotating caesium-137 source was conducted at the beginning of each scan for attenuation correction. Head motion was minimized using individually molded thermoplastic masks as well as tracked in a subset of patients.[18] Emission data were acquired over 60 minutes in 16 frames of progressively increasing duration following the bolus injection of 370 MBq (10 mCi) of raclopride (mean specific activity, 159.5 GBq/μmol [SD, 69.2 GBq/μmol]) into the left antecubital vein. Emission data were reconstructed using a statistical algorithm (ordinary Poisson 3-dimensional ordered subset expectation maximization) with corrections for scatter, attenuation, random events, and normalization.[19] Emission data were then corrected for motion by interframe realignment.[20] Intervention PET scans (following levodopa and placebo administration) were registered to the baseline image to facilitate region of interest (ROI) placement within subjects (ie, between scans). A time-integrated image with 206 planes, each 1.22 mm thick, was obtained from the emission data (30-60 minutes) for each subject. Nine consecutive transaxial slices (total thickness, 10.89 mm) in which the striatum was clearly visualized were selected. A combination of elliptical and circular ROIs was visually placed along the anterior-posterior axis of the striatum on each subject's baseline integrated image (**Figure 1**A). For the ventral striatum, integrated images were resampled in the coronal orientation, and a single elliptical ROI was placed bilaterally on 6 consecutive coronal slices (total thickness, 7.26 mm) (Figure 1B) according to published anatomical criteria.[21] The ROIs placed on the baseline integrated images for each patient were then placed in the same position on each patient's corresponding levodopa and placebo scans, with minor adjustments made when necessary to maximize the average activity within the ROI. The background activity was averaged from a single elliptical ROI (2055 mm^2) drawn over the cerebellum on the integrated image from 6 consecutive transaxial planes. Tissue input–defined raclopride binding potentials (RAC BP_{ND}), defined as B_{max}/K_d, were determined using a simplified reference tissue approach with the cerebellum as the reference region.[22]

OUTCOME MEASURES

The RAC BP_{ND} values were obtained for each striatal subregion (caudate, putamen, and ventral striatum) and each PET scan (baseline, RAC BP_{ND_BL}; following levodopa administration, RAC BP_{ND_LD}; and following placebo administration, RAC BP_{ND_PBO}).

In addition to these PET data, objective changes in motor function that the patients exhibited were assessed by a blinded examiner using the Unified Parkinson Disease Rating Scale (UPDRS, part III)[23] at the beginning of each day and throughout the scans. To ensure that the examiners were adequately blinded, the design of the study was kept confidential. Three qualified examiners were selected to perform the UPDRS assessments on the patients. They arrived a few moments prior to the beginning of the assessment and left immediately following each assessment. The same examiner was used for each patient to minimize interrater variability. During each PET scan, an abridged (modified) version of the UPDRS (mUPDRS) was conducted 30 minutes following raclopride injection, ie, baseline ($mUPDRS_{BL}$), following levodopa administration ($mUPDRS_{LD}$), and following placebo administration ($mUPDRS_{PBO}$). The mUPDRS was conducted during the PET scan and included only measures of tremor, bradykinesia and rigidity in the upper limbs, and tremor and rigidity in the lower limbs to minimize the impact of head motion on the PET data. The objective magnitude of improvement in motor function in response to levodopa thus also represented the maximal expected objective improvement prior to placebo administration. Additionally, the subjects were asked following all scans if they perceived any subjective improvement in their symptoms and to rate that improvement using an arbitrary scale from −1 to 3 (−1 = worse, 0 = no improvement, 1 = mild, 2 = moderate, and 3 = strong).

EXPECTED REWARD VALUE

Expected reward value is the product of the probability of reward delivery (P) and the reward magnitude (MAG): $ERV = P \times MAG$. In this experiment, the probability was dictated by the group allocation ($P = 0.25–1$). In a chronic condition such as PD, in which patients demonstrate variable motoric responses to medication, the expected value of clinical improvement would likely reflect the degree of clinical benefit derived from active treatment (in this case, open-label levodopa). Thus, the expected reward magnitude could be defined objectively as the magnitude of change in mUPDRS score following levodopa (ie, MAG_{obj_LD}) or subjectively by patient self-report (ie, MAG_{subj_LD}) following the PET scan. Therefore, as the maximum expected improvement on placebo is defined by the magnitude of the response (either objective or subjective) to levodopa, the ERV following placebo administration was calculated as follows: $ERV_{obj} = P \times MAG_{obj\_LD}$ and $ERV_{subj} = P \times MAG_{subj\_LD}$.

STATISTICAL ANALYSIS

The change in raclopride binding potentials in response to placebo (RAC BP_{ND_BL} − RAC BP_{ND_PBO}) was explored using analyses of covariance (ANCOVA), including age and RAC BP_{ND_BL} as covariates. A multiple regression adjusted for age and baseline RAC BP_{ND} was also conducted to investigate the relationship between dopamine release in response to levodopa and to placebo (ie, RAC BP_{ND_BL} − RAC BP_{ND_LD} vs RAC BP_{ND_BL} − RAC BP_{ND_PBO}).

ETHICAL CONSIDERATIONS OF THE MANIPULATION OF EXPECTATION

In this experiment, expectations were manipulated verbally, and it was essential that the patients clearly understood their probability of receiving levodopa. Patients were given the following instructions to specifically illustrate the probability of receiving active drug to most convincingly manipulate expectation:

> You have been randomly assigned, like pulling numbers out of a hat, to Group A. As you read in the consent form, this means that you have a 25% chance, or 1 in 4 chance, of receiving active Sinemet, exactly the same dose that you were given yesterday for the second scan. We took one real Sinemet pill and three placebos and shook them up and withdrew one. This is what we are giving you. You will be told what you have been given after the scan is complete.

Following this, the patients were then asked to confirm that they understood their chances of receiving medication.

Since this study required the use of deception, the consent form given to the patients upon recruitment represented the true beginning of expectation manipulation. The consent form stated:

> The purpose of this study is to examine the different factors that contribute to a person's response to the treatment of their Parkinson's disease. The study requires the use of some deception, and as a result the full purpose of the study cannot be revealed to you at this time. However, nothing that has been described above about the purpose is false. We have simply omitted some details. These will be described to you once the study has been completed. At that time, we will fully debrief you about the background, purpose and methods that were used during the experiment and answer any questions that you may have.

Thus, the patients were told that deception would be used, but that we could not inform them as to the nature of the deception. This approach is considered ethically acceptable for a study such as this.[24,25] Immediately following the completion of the experiment, the subjects were debriefed as to the true purpose of the study and the nature of the deception used. The subjects were informed that they were given placebo for the final scan and in fact could never have received levodopa for that final scan, and any questions were answered.

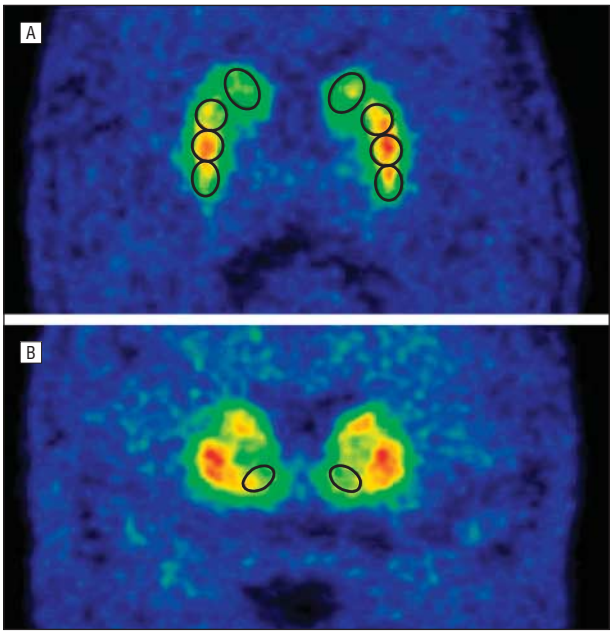

Figure 1. Regions of interest (ROIs) used for determining [^{11}C]raclopride binding potentials. A, Dorsal striatum (caudate, large elliptical ROIs; and putamen, smaller circular/elliptical ROIs). B, Ventral striatum. Regions of interest are depicted on a positron emission tomographic image with each pixel averaged over 6 planes (7.32 mm). Cerebellar ROIs used to generate the reference time activity curves are not shown.

Table 2. Clinical Characteristics of Patients

Characteristic	Mean (SD) by Group[a] A (n=8)	B (n=7)	C (n=7)	D (n=8)
M/F, No.	7/1	5/2	6/1	7/1
Age, y	65.75 (4.86)	64.17 (5.8)	59.85 (8.27)	59.57 (9.49)
Disease duration, y	11.5 (5.4)	9.6 (2.8)	9.0 (3.2)	9.5 (3.1)
Levodopa dose, mg	667.7 (305.6)	402.2 (315.5)	556.6 (128.9)	561.5 (234.2)
Agonist dose, mg	12.1 (14.1)	10.00 (14.1)	22.6 (17.4)	12.5 (13.2)

[a]Subjects were told that they might receive levodopa or a placebo and that their chances of receiving active levodopa were 25% (group A), 50% (group B), 75% (group C), or 100% (group D); all subjects actually received placebo.

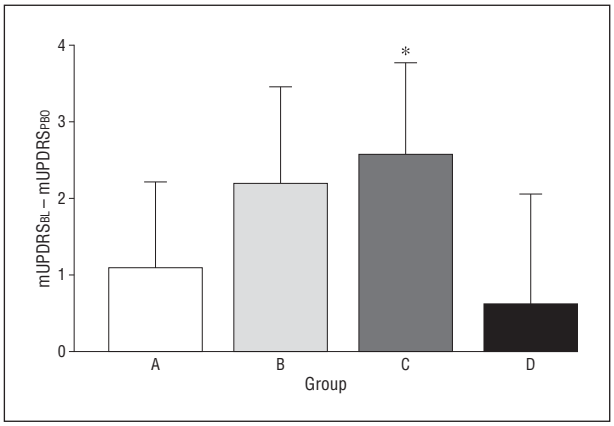

Figure 2. Clinical response to placebo (modified Unified Parkinson Disease Rating Scale score at baseline [$mUPDRS_{BL}$] – mUPDRS score following placebo [$mUPDRS_{PBO}$]), adjusted for mUPDRS baseline and age. Values are given as mean (SD). There was no significant main effect of group. Only the change in group C was significant. *$P<.05$. In group A, subjects were told that their chances of receiving active levodopa were 25%; group B, 50%; group C, 75%; and group D, 100%.

RESULTS

PATIENT CHARACTERISTICS

Five subjects withdrew owing to claustrophobia or the discomfort associated with PET. The characteristics of the 30 remaining subjects who completed the study are presented in **Table 2**. All patients had clinically definite PD[16] and, with a single exception, were taking levodopa. Patients with atypical forms of parkinsonism or with other significant neurological disease were excluded, as were patients with psychiatric disease, including a history of substance abuse. Patients were specifically selected based on having mild to moderate disease (mean Hoehn and Yahr stage, 2.2 [SD, 0.5]; mean motor UPDRS score without medication, 20.9 [SD, 1.8]) and a history of unequivocal response to dopaminergic medication, including noticeable subjective benefit from most doses. Four subjects were taking low doses of antidepressants (selective serotonin reuptake inhibitors), but were not depressed at the time of scanning. One subject was taking amantadine. Patients were free of depression (Beck Inventory of Depression mean score, 6.3 [SD, 2.3]) and cognitive impairment (Mini-Mental Status Examination mean score, 29.2 [SD, 1.1]). One subject had participated in a previous study on placebo-induced dopamine release.

CLINICAL RESULTS

Placebo administration resulted in varying degrees of clinical improvement from baseline as measured by the mUPRDS (see the "Methods" section), which was significant only in the patients allocated to group C (those told they had a 75% chance of receiving levodopa; $P=.03$, Wilcoxon rank sum test, 2-tailed, not adjusted for multiple comparisons), as can be seen in **Figure 2**. No significant difference was detected between groups. Subjective self-reports indicated that 13 patients felt no benefit from the placebo and 13 reported mild, 2 reported moderate, and 1 reported strong benefit. Interestingly, those reporting a benefit were found in all 4 groups. No correlation was seen between the objective changes in motor function and subjective reporting following placebo administration.

[^{11}C]RACLOPRIDE PET RESULTS

As expected, a significant reduction in raclopride binding potential was detected in the putamen in response to levodopa ($F_{2,27}=4.35$, $P=.02$, ANCOVA with age and baseline RAC BP_{ND} [RAC BP_{ND_BL}] as covariates) (**Figure 3** and **Table 3**). No differences were detected in the caudate nucleus or ventral striatum ($P=.85$ and $P=.49$, respectively). No significant correlation was found between the degree of dopamine release and either the objective or the subjective clinical response to levodopa.

All groups were statistically comparable in terms of RAC BP_{ND_BL}, change in RAC BP_{ND} in response to levodopa, and change in UPDRS and subjective response to levodopa, indicating that randomization was effective. We found significant differences in the changes of RAC BP_{ND} following placebo administration compared with baseline observations among the 4 groups, indicating that the probability of receiving active drug (ie, the strength of expectation) modulated the degree of endogenous dopamine release. A significant difference in the change from baseline among the 4 groups was detected in both the putamen (ANCOVA, $F_{3,24}=3.957$, $P=.02$) and the ventral striatum (ANCOVA, $F_{3,24}=5.569$, $P=.005$), while the changes in the caudate were nonsignificant ($F_{3,24}=2.091$, $P=.13$) (Table 3, Figure 3, and **Figure 4**).

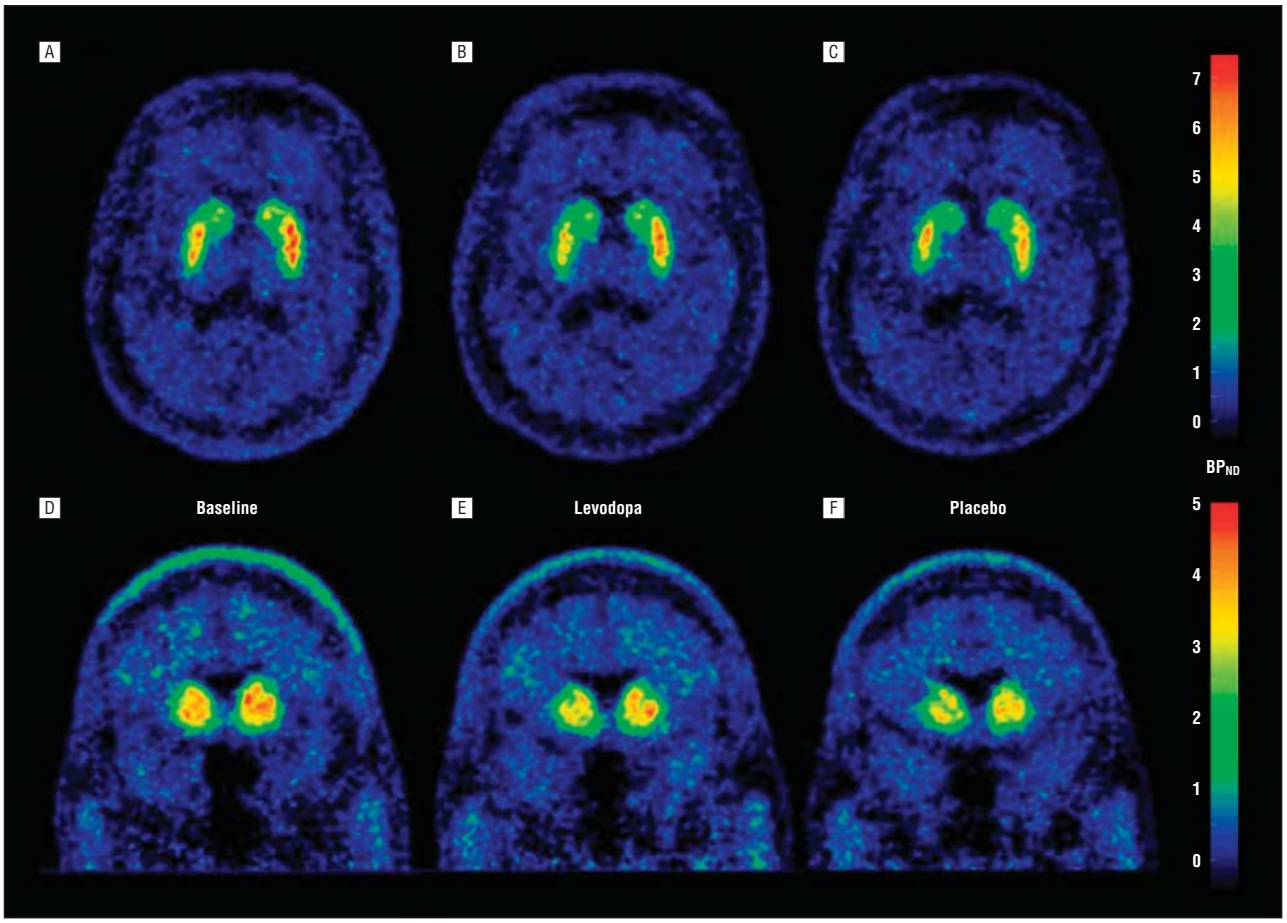

Figure 3. Parametric [^{11}C]raclopride positron emission tomographic (PET) images of a representative patient with Parkinson disease from group C (P=.75) scanned at baseline (A and D) and following open administration of levodopa (B and E) and placebo (C and F). Each image pixel represents the binding potential (BP_{ND}) calculated from the dynamic PET data, with the magnitude indicated by the color bars on the right. Images are presented in horizontal sections (A-C) for visualization of the dorsal striatum and in coronal sections (D-F) for visualization of the ventral striatum. The bars are scaled to different maxima in the horizontal and coronal sections to accommodate the higher BP_{ND} values in the dorsal striatum and optimize visualization of the change from baseline. A decrease in raclopride BP_{ND} is seen following levodopa administration in the putamen (B vs A), indicating an increase in dopamine release in this region. Placebo administration resulted in an increase in endogenous dopamine release (reduced BP_{ND}) in the putamen comparable with that seen following levodopa (C vs A) and in the ventral striatum (F vs D).

Table 3. Raclopride Binding Potentials Values at Baseline and Following Administration of Open Levodopa and Placebo

	Raclopride Binding Potentials Value by Group[a]											
	A			B			C			D		
Brain Region	Baseline	Levodopa	Placebo	Baseline	Levodopa	Placebo	Baseline	Levodopa	Placebo	Baseline	Levodopa	Placebo
Caudate	2.88 (0.58)	2.90 (0.68)	2.85 (0.42)	2.98 (0.65)	3.06 (0.71)	3.08 (0.80)	2.65 (0.70)	2.50 (0.71)	2.50 (0.60)	2.84 (0.65)	2.72 (0.61)	2.80 (0.56)
Putamen	3.45 (0.43)	3.17 (0.35)	3.35 (0.25)	3.84 (0.95)	3.62 (1.04)	4.00 (1.16)	3.70 (1.27)	3.27 (1.11)	3.38 (1.05)	3.75 (0.86)	3.57 (0.94)	3.78 (0.81)
Ventral striatum	3.29 (0.59)	3.26 (0.64)	3.31 (0.49)	3.49 (0.73)	3.53 (0.85)	3.56 (0.81)	3.04 (0.80)	2.81 (0.66)	2.75 (0.74)	3.17 (0.71)	3.15 (0.61)	3.22 (0.59)

[a] Subjects were told that they might receive levodopa or placebo (during the placebo phase) and that their chances of receiving active levodopa were 25% (group A), 50% (group B), 75% (group C), or 100% (group D); all subjects actually received placebo.

In both the putamen and the ventral striatum, significant dopamine release was present when the stated probability of levodopa treatment was P=.75 (putamen, P=.002; ventral striatum, P<.001), while no significant change was detected at the other levels of expectation. Adding the subjective or objective expected reward value as covariates to the analysis had no impact on the findings in any region. This suggests that the expected reward value had no significant additional effect on placebo-induced dopamine release, beyond that conferred by the group-assigned probability of receiving active medication.

To further verify that the degree of placebo-induced dopamine release was related to the expectation of benefit, and not the actual or perceived benefit experienced by the patients while they underwent the PET scan, we additionally examined the effects of adding the objective magnitude of change in motor function following placebo ($mUPDRS_{BL} - mUPDRS_{PBO}$) or the subjective magnitude of change following placebo (determined by patient

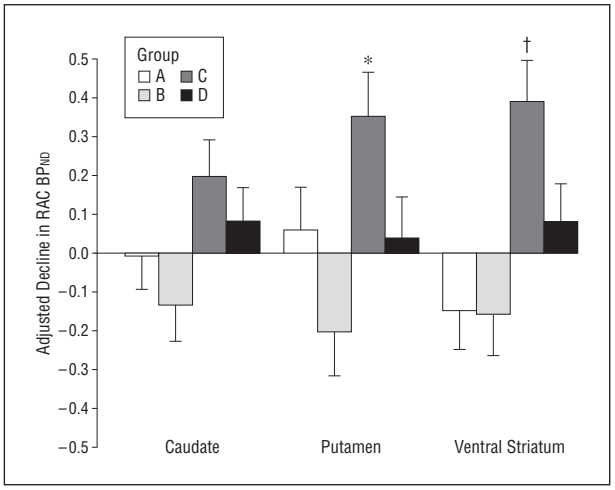

Figure 4. Mean decline in [^{11}C]raclopride binding potential (RAC BP_{ND}) from baseline in response to placebo, adjusted for age and raclopride binding potential at baseline in the caudate, putamen, and ventral striatum. A significant increase in dopamine release in response to placebo was seen in group C in the ventral striatum and putamen, with nonsignificant results in the caudate (P=.15). See Table 3 for RAC BP_{ND} values. *P<.05; †P<.01. In group A, subjects were told that their chances of receiving active levodopa were 25%; group B, 50%; group C, 75%; and group D, 100%.

self-report) as covariates to the ANCOVA assessing the effect of group on placebo-induced dopamine release. Neither variable had a significant impact on this analysis in either the putamen or the ventral striatum, indicating that it was the expectation rather than the perception or experience of benefit that modulated dopamine release. Furthermore, there was no correlation between the degree of dopamine release and either the subjective or objective motor responses to placebo.

However, dopamine release in response to placebo, irrespective of group, was highly correlated with the degree of dopamine release in response to openly administered levodopa in all striatal subregions (caudate, r=0.59, P<.001; putamen, r=0.58, P=.008; ventral striatum, r=0.59, P<.001) (**Figure 5**). Given the strength of these correlations, we added group as a covariate to the regression of age, RAC BP_{ND_BL}, and levodopa-induced dopamine release on placebo-induced dopamine release, and still found a significant additional effect of probability in the ventral striatum ($F_{3,23}$=3.05, P=.049), but the addition of group did not significantly improve the results in the caudate ($F_{3,23}$=0.97, P=.42) or putamen ($F_{3,23}$=2.34, P=.1).

COMMENT

To our knowledge, this is the first study to quantify dopamine release (as implied by change in raclopride binding) in patients with PD in response to varying the expectation of symptom improvement, and at the very least, to demonstrate that verbal instructions have the capacity to directly modulate dopamine release in humans. Nigrostriatal and mesoaccumbens dopamine release was significantly increased when the stated probability of receiving active medication was 75%. Importantly, whereas prior medication experience (ie, the dopaminergic response to levodopa) was the major determinant of dopamine release in the dorsal striatum, expectation

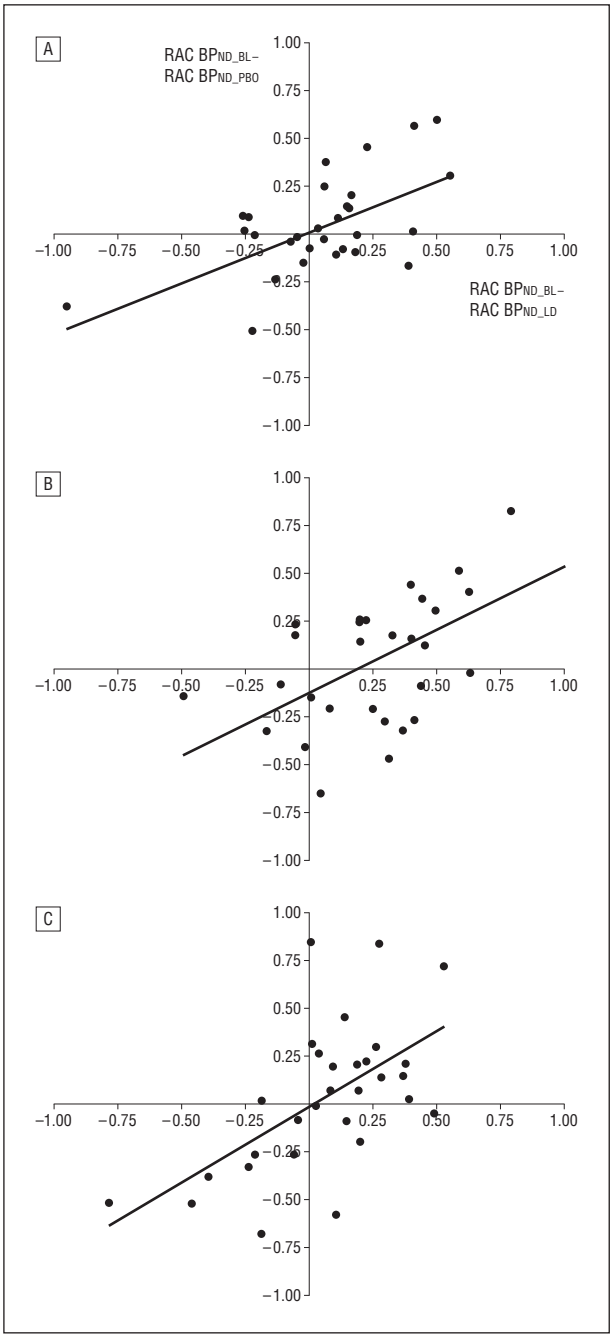

Figure 5. Correlations between the difference in [^{11}C]raclopride binding potential (RAC BP_{ND}) from baseline following the administration of levodopa (RAC BP_{ND_BL}−RAC BP_{ND_LD}, x-axes) and placebo (RAC BP_{ND_BL}−RAC BP_{ND_PBO}, y-axes), adjusted for baseline. A, Caudate nucleus. B, Putamen. C, Ventral striatum. Highly significant correlations were detected in all subregions of the striatum.

of clinical improvement (ie, the probability determined by group allocation) was additionally required to drive dopamine release in the ventral striatum. Indeed, preclinical studies designed to monitor changes in dopamine efflux in the ventral striatum during prolonged periods of reward expectation, as distinct from reward consumption, observed significant and extended elevation of extracellular dopamine in the ventral striatum.[26] These findings are consistent with the decrease in raclopride binding observed in the present study during the

expectation of antiparkinson medication. While changes in raclopride binding could conceivably be related to other factors, such as receptor internalization or changes in receptor affinity due to other factors,[27] it is likely that under the conditions of the current study, most of the change in raclopride binding within a given individual can be attributed to altered occupancy arising from release of endogenous dopamine.

Why should the response occur at $P = .75$ and not at other probabilities? This is in keeping with studies on conditioned learning in which dopaminergic activation is seen when reward is deemed likely but not certain[28] and with our previous work in which placebo-induced dopamine release was seen when subjects received an injection of placebo in 1 of 4 blinded treatments.[1] Although one might also anticipate a response at $P = .5$, when uncertainty is maximal,[15] unmedicated PD patients are impaired on tasks of probabilistic learning,[29] fail to activate the ventral striatum during reward prediction,[30] and show reduced capacity to learn based on prediction of positive feedback.[31,32] Thus PD patients may have difficulty distinguishing between $P = .5$ and lower probabilities of receiving active medication. If $P = 1$, the outcome is deemed to be certain, and associative learning (reward prediction) does not occur, as the reinforcer is fully predictable.[33] If patients were unblinded, this would also represent the probability associated with the highest reward prediction error, a situation hypothesized to be associated with maximal changes in dopamine signaling.[34] Indeed, given the lack of reward (active medication) delivery, one might anticipate a reduction in dopamine levels below baseline. However, assuming that patients cannot distinguish between placebo- and levodopa-induced benefit (and there was no evidence of unblinding in our study), this situation may not apply. If it did, our data would suggest that ventral striatal dopamine release is more closely linked to expectation than to encoding of reward prediction error. Furthermore, in the current study design it was impossible to assess the participants' subjective probabilities in response to the verbal instructions they were given. In other words, although the use of verbal manipulation of patients' expectations enabled us to segregate the patients into discrete probability groups, there was no way to confirm if each participant within a group perceived their assigned probability in the same way. One cannot rule out the impact of personality traits like optimism or skepticism on the individual handling and processing of probability.

It is conceivable that the medications the patients take on an ongoing basis could have acted to desensitize dopaminergic reward mechanisms and thereby modified the response to the stated probability of receiving active levodopa. Van Eimeren et al,[35] using functional magnetic resonance imaging, recently demonstrated that activation of both the ventral striatum and orbitofrontal cortex was blunted during performance of a probabilistic reward task in PD patients while taking medication (either levodopa or the dopamine agonist pramipexole), but found a robust response when patients were studied without taking medication for 12 hours or longer, as was the case in our studies. These authors also found a loss of deactivation in response to negative reward prediction errors in the orbitofrontal cortex in patients taking pramipexole. However, this effect was not seen in the ventral striatum.

Four of the patients in this study were undergoing treatment with antidepressant medications (3 with selective serotonin reuptake inhibitors and 1 with a low dose of amitriptyline). Although no one was depressed at the time of the study, it is conceivable that the medication itself may have affected dopamine release in response to either levodopa or placebo, especially in the case of selective serotonin reuptake inhibitor antidepressants. However, reanalysis of the data with these 4 subjects removed had no impact on (1) the finding of significant levodopa-induced dopamine release in the putamen (merged across all groups), or (2) the finding of significant placebo-induced dopamine release in group C (perceived 75% probability of receiving levodopa). The 2 antidepressant-treated subjects in group D (perceived 100% probability of receiving levodopa) actually had negative values for placebo-induced dopamine release, contrary to the expected theoretical effects of the medication, but overall the removal of these subjects from the analysis appeared to result in random variation in findings rather than a systematic effect.

Dopamine release in response to placebo, irrespective of expectation, was highly correlated with the degree of dopamine release in response to openly administered levodopa in all striatal subregions. This suggests that the stated probability of receiving active medication still has a significant impact in the ventral striatum, even after accounting for experience (levodopa-induced dopamine release). In contrast, while probability has a significant impact on placebo-induced dopamine release in the putamen, this effect could not be reliably separated from prior experience with levodopa. This predictive effect of levodopa-induced dopamine release on the response to placebo may reflect the capacity to release dopamine. Importantly, this "permissive effect," while necessary, is insufficient on its own to result in placebo-induced dopamine release. While prior experience clearly has an impact on placebo-induced dopamine release in the ventral striatum, there is an additional role for uncertainty or salience, highlighting the importance of expectation in driving the response.

Given the temporal resolution of PET, our findings might be seen to reflect tonic dopamine release rather than the more phasic bursts that are thought to be monotonically related to expected reward value. However, it has also been proposed that changes in RAC binding detected by PET are more likely to reflect occupancy of intrasynaptic dopamine receptors following burst firing.[36] It is unlikely that imaging would be able to distinguish between the slower more tonic anticipatory response described by Fiorillo et al[15] and shorter bursts linked to expected reward value.

These results indicate that the expectation of therapeutic benefit in PD patients can directly modulate dopamine release in both nigrostriatal and mesoaccumbens dopamine pathways. This is consistent with the suggestion that the placebo effect mimics the brain's response to the active drug-response pattern to which it was experimentally yoked,[37] but extends this notion to incorporate the role of conscious expectation and the perceived likelihood of symp-

tomatic improvement. This yoking of placebo-induced dopamine release to the response seen following open-label levodopa suggests that while the initial drug-induced increase in dopamine levels may be viewed as an unconditioned response, the increase in dopamine release in the placebo condition may represent a form of conditioned response. In this regard, it is of interest that while placebo-induced dopamine release in the dorsal striatum could be explained by prior experience, the effect seen in the ventral striatum represents a different form of learned response. O'Doherty et al[28] found a similar dissociation between the prediction of future reward (ventral striatum) and the maintenance of information about rewarding outcomes (dorsal striatum) during an instrumental conditioning task. Our findings can be seen as analogous, in that the prediction of reward (placebo-induced release of dopamine) is seen in the ventral striatum, where it is dependent on expectation.

Our finding of placebo-induced dopamine release in the ventral striatum does not exclude the possibility that other brain regions might be involved in the response. In particular, the prefrontal cortex—particularly the orbitofrontal cortex—may encode reward probability[38] and uncertainty,[39] and these responses might not only be mediated by cortical dopamine release (which we would have been unable to detect using raclopride PET), but may in fact drive the response seen in the ventral striatum.[40]

In this study, we did not observe a correlation between dopamine release and the changes in mUPDRS scores in response to either levodopa or placebo. This is not entirely surprising for the latter, as placebo-induced dopamine release is associated with expectation and would not necessarily lead to clinical improvement, though this would clearly be desirable. It should be noted that the overall pattern of clinical improvement paralleled the pattern of dopamine release in response to placebo; however, the correlation was not significant. Improvements in rigidity and bradykinesia, but not in tremor or axial symptoms, have been shown to be correlated with dopamine release in the putamen of PD patients in response to levodopa as measured by [^{11}C]raclopride PET,[41] though in that study the patients had a longer disease duration (12 years) and severity (the mean Hoehn and Yahr stage in the "off" state was 2.8) and the full UPDRS III was used after the scan was completed. The absence of correlations in the current study could reflect the fact that we only measured a subset of the UPDRS (rigidity, bradykinesia, and tremor, and only in the limbs) while the patient was lying in the scanner. We were unable to assess other aspects of the UPDRS, such as gait, that might be more functionally relevant to some patients. Anecdotally, we were surprised to note that following the post-placebo PET scan, several subjects demonstrated marked improvement in mobility compared with when they arrived in the morning following 12 hours of medication withdrawal; they were able to rise from the scanner, put on their shoes, and walk to the adjacent building (including a flight of stairs) for debriefing, clearly appearing as if they were taking medication.

Our findings may have important implications for the design of clinical trials, as we have shown that both the probability of receiving active treatment—which varies in clinical trials depending on the study design and the information provided to the patient—as well as the treatment history of the patient influence dopamine system activity and consequently clinical outcome. We have previously suggested that placebo responses in conditions other than PD may be seen as analogous to expectation of reward and may therefore also be mediated by dopamine release.[11] This appears to be supported by recent findings in placebo analgesia, which is also related to dopamine release in the ventral striatum and to activation in response to anticipated monetary reward.[42] While our finding of a biochemical placebo response restricted to a 75% likelihood of receiving active treatment may not generalize to diseases other than PD, it is extremely likely that both probability and prior experience have similarly profound effects in those conditions.

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