Great Expectations: The Placebo Effect in Parkinson's Disease

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Abstract

Our understanding of the neural mechanisms underlying the placebo effect has increased exponentially in parallel with the advances in brain imaging. This is of particular importance in the field of Parkinson's disease, where clinicians have described placebo effects in their patients for decades. Significant placebo effects have been observed in clinical trials for medications as well as more invasive surgical trials including deep-brain stimulation and stem-cell implantation. In addition to placebo effects occurring as a byproduct of randomized controlled trials, investigation of the placebo effect itself in the laboratory setting has further shown the capacity for strong placebo effects within this patient population. Neuroimaging studies have demonstrated that placebos stimulate the release of dopamine in the striatum of patients with Parkinson's disease and can alter the activity of dopamine neurons using single-cell recording. When taken together with the findings from other medical conditions discussed elsewhere in this publication, a unified mechanism for the placebo effect in Parkinson's disease is emerging that blends expectation-induced neurochemical changes and disease-specific nigrostriatal dopamine release.

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1 Parkinson's Disease as a Model for Studying the Placebo Effect

The primary neuropathology of Parkinson's disease is the selective loss of dopaminergic neurons in the midbrain that project to the motor areas of the striatum (nigrostriatal pathway). It is diagnosed based on the presence of the classic motor symptoms of tremor, cogwheel rigidity, slowness of movement (bradykinesia), and postural instability. The goal of pharmacological therapy—either dopamine replacement with levodopa or dopamine receptor agonists—is to alleviate the disabling motor symptoms. Less well-recognized but equally disabling are the autonomic, mood, sleep, and cognitive symptoms of Parkinson's disease which generally do not respond to dopamine replacement and are treated with adjunctive therapies (Calne et al. 2008).

Parkinson's disease is an excellent model to study the placebo effect. Firstly, and most generally, it is a true patient population and thus clinical improvements (whether they be attributable to active medication or placebo effects) have direct relevance to the clinical realm and need not be extrapolated. This is in contrast to studies using healthy control subjects, who cannot fully represent the myriad of complex psychosocial factors underlying the experience of living with a chronic disease, which strongly influences expectation. Unique to Parkinson's disease is that the deficits occur primarily in the motor system, thus the placebo effect is represented by improvement in motor function (although any symptom patients experience is subject to a placebo response, including mood, autonomic, or any other aspect of their illness causing reduced quality of life). In an experimental design, the patients' neurological status can therefore be assessed objectively following active treatment or placebo administration by a blinded examiner trained to perform a neurological exam. This is in contrast to experimental placebo analgesia or depression in which patients are often required to use visual analog scales to quantify reductions in pain or changes in mood. This being said, it is equally important to emphasize that the clinical scales used for measuring motor function are subjective themselves. Also, patients may be less prone to report clinical changes than the clinicians are to observe them (Freed et al. 2001). Finally, in addition to the clinical placebo effect (i.e., improvement in motor symptoms), the neurochemical/neurophysiological response to placebo can be measured directly. Endogenous dopamine release can be quantified using [^{11}C] raclopride positron emission tomography, and the activity of dopaminergic neurons in the subthalamic nucleus can be recorded intraoperatively during STN deep brain stimulation surgery (Benedetti et al. 2004). Together, these techniques have provided valuable

insights into the mechanisms of the placebo effect in Parkinson's disease and have extended to other conditions as well.

2 Evidence for the Placebo Effect in Parkinson's Disease

Clinical trials for oral anti-Parkinson's medications demonstrate significant clinical improvement in 14–21 % of patients receiving placebo, which can be sustained to 6 months (Goetz et al. 2002a, b). In a double-blind trial of the dopamine agonist pergolide, significant improvement was seen in both the pergolide-treated group (30 % after 24 weeks) and the placebo group (23 % after 24 weeks) (Diamond et al. 1985). Finally, a meta-review demonstrated that 12 of 36 articles reported a 9–59 % improvement in patient motor symptoms following placebo (Shetty et al. 1999). Surgical trials also demonstrate substantial placebo effects, consistent with the observation that stronger interventions result in stronger placebo effects (Benedetti, et al. 2004; Benedetti 2012). Patients who underwent intrastriatal implantation of fetal porcine ventral mesencephalic tissue had the same the degree of improvement at 18 months as those in the sham group (Watts et al. 2001). In a human fetal transplantation trial for Parkinson's, there was no significant clinical benefit of the transplant compared to sham surgery (Olanow et al. 2003). In another study, at 18-month post-transplant, quality of life outcomes were better predicted by which treatment the patient thought she/he was assigned to rather than the actual treatment assignment (Freed et al. 2001; McRae et al. 2004).

Experiments aimed at studying the placebo effect itself have further demonstrated clinical improvement following placebo administration. Patients with subthalamic nucleus deep-brain stimulators as treatment for Parkinson's demonstrate improved motor performance when they believe their stimulators are turned on and perform worse than baseline when they believe their stimulators are turned off, compared to the conditions in which they were blind to stimulator function (Mercado et al. 2006). In an elegant series of studies using an overt-covert experimental design, Benedetti and colleagues demonstrated that sham STN-DBS improves bradykinesia as measured by hand velocity (Benedetti et al. 2003; Pollo et al. 2002).

Placebos have also been shown to stimulate the release of dopamine in the dorsal and ventral striatum (de la Fuente-Fernandez et al. 2001, 2002; Lidstone et al. 2010; Strafella et al. 2006). This is thought to represent the "disease-specific" component of the placebo effect in Parkinson's disease and is remarkable considering that patients must lose upwards of 80 % of their dopamine-producing cells before their symptoms become clinically apparent. Using [^{11}C] raclopride positron emission tomography, de la Fuente-Fernandez and colleagues demonstrated that a placebo injection stimulates the robust release of endogenous dopamine, in quantities comparable to the response to amphetamine in subjects with an intact dopamine system (de la Fuente-Fernandez et al. 2001). Furthermore, the dopamine release was greater in those patients who reported clinical improvement (i.e., placebo responders). Dopamine release has also been shown in response to sham repetitive

transcranial magnetic stimulation in Parkinson's patients (Strafella et al. 2006). These results suggest that the biochemical basis for the placebo effect in Parkinson's is to replace the depleted striatal dopamine. These results are corroborated by an electrophysiology study performed in PD patients undergoing STN-DBS surgery, in which it was shown that a placebo (saline injection) evoked changes in neuronal firing in the subthalamic nucleus in placebo responders (Benedetti et al. 2004; Lanotte et al. 2005). The neurons displayed a decrease in mean discharge frequency and a shift from bursting to non-bursting activity in response to placebo, which was correlated with a reduction in upper limb rigidity.

3 Placebos as Rewards

Dopamine is hypothesized to play a prominent role in all placebo effects through its key involvement in reward processing (Lidstone and Stoessl 2007). Dopamine is a neuromodulator of all thalamocortical-basal ganglia loops underlying cognitive, motor, and emotional processing (Haber and Fudge 1997). It is synthesized by a population of neurons localized in the ventral midbrain that project to the basal ganglia and forebrain in a topographic distribution, thereby modulating excitatory and inhibitory neural transmission. In the motor system, dopamine depletion such as occurs in Parkinson's disease results in overall hypoactivity of the circuit, resulting in the clinical syndrome of bradykinesia and rigidity. The mesolimbic projections to the ventral striatum (nucleus accumbens), ventral prefrontal cortex, anterior cingulate cortex, and other limbic areas represent a major component of motivation and reward processing.

"Rewards" are defined as stimuli which, when administered to an organism following a correct or desired response, produce repeated approach behaviors or the repetition of responses (Bishop et al. 1963; Olds and Milner 1954). Thus, a reward is an operational concept used to describe the positive value that an organism attributes to an object, behavior, or internal physical state (Breiter and Rosen 1999). The ability of an organism to detect, approach, and interact with (i.e., consume, in the case of food rewards) the rewarding stimuli in its environment is a fundamental component of goal-directed behavior and requires the integration of cognitive, motivational, and motor circuits, in which dopamine plays a crucial modulatory role. The majority of dopamine neurons show phasic activation in response to primary liquid and food rewards, visual, auditory, and somatosensory reward-predicting stimuli, and intense, novel stimuli (Horvitz 2000; Schultz 2000; Ljungberg et al. 1992). Rather than signaling the absolute presence of a reward, dopamine neuron activity codes the discrepancy between the predicted reward and the actual reward, which is termed the "prediction error." (Mirenowicz and Schultz 1994; Schultz 1998) Thus, dopamine neurons are activated when rewards occur without being predicted or are better than expected and are depressed when predicted rewards are omitted or are worse than predicted. These responses of dopamine neurons are stronger to either rewards or reward-predicting stimuli that are associated with higher reward magnitude, probability, and expected reward

value (Fiorillo et al. 2003; Schultz 1998, 2001; Tobler et al. 2005). In humans, increases in striatal dopamine release have been demonstrated in response to primary food reward (Small et al. 2003) and monetary rewards (Koepp et al. 1998; Zald et al. 2004). Dopamine neurons also demonstrate sustained activations during the interval between a reward-predicting cue and the delivery of the reward, which is thought to encode the uncertainty associated with reward expectation (Fiorillo et al. 2003). This represents the organism's natural environment, in which rewards occur with some degree of uncertainty. If the reward value is held constant, and if an animal is trained to associate certain conditioned stimuli with discrete probabilities of reward delivery, more than one third of dopamine neurons show a relatively slow, sustained, and moderate activation between the onset of the reward-predicting stimulus and the delivery of the reward. These tonic dopamine responses are maximally active at a probability of 0.5 ($p = 0.5$), decline both at $p = 0.25$ and $p = 0.75$, and are virtually zero at both extremes of the probability distribution ($p = 0$ and $p = 1$) (Fiorillo et al. 2003). This response reflects the uncertainty associated with reward expectation, as uncertainty can be expressed as the variance of the probability distribution, which is an inverted-U-shaped function with a peak at $p = 0.5$ (intuitively, it can be understood that an outcome is most uncertain when the likelihood of its occurrence is 50 %, and most certain to occur or not occur, at 100 and 0 %, respectively). These findings have been extended to humans using fMRI (Dreher et al. 2006).

The dopaminergic reward circuits are the same, fundamental neural pathways that have been shown to be involved in the mechanism of the placebo effect. The anticipation of therapeutic benefit in response to placebo can easily be conceptualized as a form of reward expectation, particularly in patients suffering from a chronic illness (de la Fuente-Fernandez et al. 2002, 2004; Lidstone et al. 2010). The relief of discomfort from unpleasant symptoms (i.e., removal of pain or suffering) is also a form of reward expectation, for potentially increasing or prolonging survival. Unsurprisingly, placebos have been shown to activate reward circuitry in both pain and Parkinson's disease, including stimulation of dopamine release in the ventral striatum (de la Fuente-Fernandez et al. 2002; Scott et al. 2008; Strafella et al. 2006).

4 The Importance of Expectation

As previously mentioned, patients' expectations play a central role in the mechanism of the placebo effect. Expectation is now recognized as a major driving force for the downstream physiological changes underlying placebo responses across most medical conditions and experimental paradigms (Benedetti 2013). An expectation can be loosely defined as a person's subjective sense of the probability of some future event. As it applies to the placebo effect, this can be conceptualized as two distinct entities depending on the situation. In a clinical encounter, an expected efficacy is produced when the patient believes that the treatment they are receiving will alleviate their symptoms. In a clinical trial, an expectation of perceived

treatment is generated depending on whether the patient believes they have been assigned to active treatment or placebo. In both cases, the expectation of therapeutic benefit and symptom alleviation is produced. Interestingly, a placebo effect is absent in patient populations with frontal lobe pathology such as Alzheimer's disease (Benedetti et al. 2006), which is attributed to the inability to generate and/or maintain cognitive expectations (Benedetti 2010).

Manipulation of expectation has been shown to affect the clinical motor performance of patients with Parkinson's disease (Benedetti et al. 2003, 2004; Colloca et al. 2004; Mercado et al. 2006; Pollo et al. 2002). The relationship between the strength of expectation of improvement generated by a placebo and the resulting placebo effect was studied in Parkinson's disease (Lidstone et al. 2010). The outcome measures were dopamine release ("biochemical" placebo effect), the objective clinical symptoms, and the patients' subjective feeling of improvement/worsening. Patients were given a specific numeric probability that they were receiving active medication, in order to capture the distribution of the probability curve: 25, 50, 75, or 100 %, but in all cases they received placebo. Dopamine release was measured using [^{11}C] raclopride positron emission tomography and results compared to the response to active medication. Striatal dopamine release was significantly increased when the stated probability of receiving active medication was 75 %, i.e., some degree of uncertainty but reasonable sure they would receive medication and hence symptom relief. Those patients also demonstrated the greatest clinical benefit as measured by a modified version of the Unified Parkinson's Disease Rating Scale, motor component (tremor, rigidity, and bradykinesia in the supine position). Importantly, patients who had a more robust dopaminergic response to active treatment also had stronger placebo-induced dopamine release, indicating that prior treatment experience was the major determinant of dopamine release in the dorsal striatum. However, expectation of clinical improvement (i.e., the probability) was additionally required to drive dopamine release in the ventral striatum, indicating the involvement of reward expectation pathways in the placebo response (Lidstone et al. 2010). We concluded that these results illustrated a dissociation between the different dopamine circuits involved in the placebo effect in Parkinson's disease: a permissive, or reward-expectation component, driven by expectation and mesolimbic dopamine release, and a disease-specific component, represented by nigrostriatal dopamine release in the motor striatum, aimed at replenishing the depleted dopamine that occurs in the disease state.

5 Implications and Future Directions

This two-component model of the mechanism of the placebo effect could conceptually extend to other disease states and be used as a framework for further investigation and hypothesis generation. In this view, we have proposed that all placebo effects are created by (at least) two separate but related components: a generalized, fundamental reward-expectation component, driven by mesolimbic

dopaminergic systems, and a disease-specific component responsible for the specific physiologic improvement (Lidstone and Stoessl 2007). This disease-specific component is unique to the medical condition experienced by the patient and is responsible for the clinical improvement, and can be conceptualized as an "effector" physiological response, such as the release of endogenous opioids in placebo analgesia, or serotonin in depression and so forth. In support of this view, dopamine release in the ventral striatum has been demonstrated in experimental placebo analgesia, in addition to endogenous opioid release (Scott et al. 2007, 2008). That both components are mediated by dopamine in Parkinson's disease (i.e. the reward expectation and physiological dopamine depletion in the motor striatum) and can be measured by PET further illustrates how powerful this patient population is as a model for studying the mechanism of the placebo effect. Future studies should be directed towards applying these results to the clinical context, particularly in a disease population such as Parkinson's disease where patients take multiple doses of medication per day that are associated with long-term side effects, such as disabling dyskinesias. Elucidating the factors responsible for maximizing endogenous dopamine release, such as the expectation of benefit, could serve as another avenue of potential adjunctive treatment in the management of this chronic disease.

Conclusion

A growing body of literature supports the existence and beneficial effects of placebo effects in Parkinson's disease. What was previously noted anecdotally in clinics, or obscuring the results of clinical trials, has evolved as a legitimate area of study and possibly future treatment in its own right. Studying the placebo effect enables researchers and clinicians to work together to understand the neural mechanisms at the core of the physician–patient relationship, bridging the laboratory and the clinic in order to explore new avenues for patient-centered care. Equally as important are the contributions that research in this area provide to the knowledge of basic neuroscience. The concept of adding scientific rigor to understanding the intricacies of human relationships and their impact on health outcomes is an exciting and compelling area of future study.

References

Benedetti F (2010) No prefrontal control, no placebo response. Pain 148(3):357–358

Benedetti F (2012) Placebo-induced improvements: how therapeutic rituals affect the patient's brain. J Acupunct Meridian Stud 5(3):97–103

Benedetti F (2013) Placebo and the new physiology of the doctor-patient relationship. Physiol Rev 93(3):1207–1246

Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I (2003) Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci 23(10):4315–4323

Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L (2004) Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. Nat Neurosci 7(6):587–588

Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, Asteggiano G (2006) Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. Pain 121(1–2):133–144

Bishop MP, Elder ST, Heath RG (1963) Intracranial self-stimulation in man. Science 140:394–396

Breiter HC, Rosen BR (1999) Functional magnetic resonance imaging of brain reward circuitry in the human. Ann N Y Acad Sci 877:523–547

Calne SM, Lidstone SC, Kumar A (2008) Psychosocial issues in young-onset Parkinson's disease: current research and challenges. Parkinsonism Relat Disord 14(2):143–150

Colloca L, Lopiano L, Lanotte M, Benedetti F (2004) Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol 3(11):679–684

de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ (2001) Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293 (5532):1164–1166

de la Fuente-Fernandez R, Phillips AG, Zamburlini M, Sossi V, Calne DB, Ruth TJ, Stoessl AJ (2002) Dopamine release in human ventral striatum and expectation of reward. Behav Brain Res 136(2):359–363

de la Fuente-Fernandez R, Schulzer M, Stoessl AJ (2004) Placebo mechanisms and reward circuitry: clues from Parkinson's disease. Biol Psychiatry 56(2):67–71

Diamond SG, Markham CH, Treciokas LJ (1985) Double-blind trial of pergolide for Parkinson's disease. Neurology 35(3):291–295

Dreher JC, Kohn P, Berman KF (2006) Neural coding of distinct statistical properties of reward information in humans. Cereb Cortex 16:561–573

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299(5614):1898–1902

Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 344(10):710–719

Goetz CG, Leurgans S, Raman R (2002a) Objective changes in motor function during placebo treatment in PD. Neurology 54(3):710–714

Goetz CG, Leurgans S, Raman R (2002b) Placebo-associated improvements in motor function: comparison of subjective and objective sections of the UPDRS in early Parkinson's disease. Mov Disord 12(2):283–288

Haber SN, Fudge JL (1997) The primate substantia nigra and VTA: integrative circuitry and function. Crit Rev Neurobiol 11(4):323–342

Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96:651–656

Koepp MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T, Brooks DJ, Bench CJ, Grasby PM (1998) Evidence for striatal dopamine release during a video game. Nature 393:266–268

Lanotte M, Lopiano L, Torre E, Bergamasco B, Colloca L, Benedetti F (2005) Expectation enhances autonomic responses to stimulation of the human subthalamic limbic region. Brain Behav Immun 19(6):500–509

Lidstone SC, Stoessl AJ (2007) Understanding the placebo effect: contributions from neuroimaging. Mol Imaging Biol 9(4):176–185

Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, Fuente-Fernandez R, Phillips AG, Stoessl AJ (2010) Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry 67(8):857–865

Ljungberg T, Apicella P, Schultz W (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. J Neurophysiol 67:145–163

McRae C, Cherin E, Yamazaki TG, Diem G, Vo AH, Russell D, Ellgring JH, Fahn S, Greene P, Dillon S, Winfield H, Bjugstad KB, Freed CR (2004) Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial. Arch Gen Psychiatry 61 (4):412–420

Mercado R, Constantoyannis C, Mandat T, Kumar A, Schulzer M, Stoessl AJ, Honey CR (2006) Expectation and the placebo effect in Parkinson's disease patients with subthalamic nucleus deep brain stimulation. Mov Disord 21(9):1457–1461

Mirenowicz J, Schultz W (1994) Importance of unpredictability for reward responses in primate dopamine neurons. J Neurophysiol 72:1024–1027

Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 54(3):403–414

Olds J, Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 47:419–427

Pollo A, Torre E, Lopiano L, Rizzone M, Lanotte M, Cavanna A, Bergamasco B, Benedetti F (2002) Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. NeuroReport 13(11):1383–1386

Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurophysiol 80(1):1–27

Schultz W (2000) Multiple reward signals in the brain. Nat Rev Neurosci 1:199–207

Schultz W (2001) Reward signaling by dopamine neurons. Neuroscientist 7(4):293–302

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2007) Individual differences in reward responding explain placebo-induced expectations and effects. Neuron 55(2):325–336

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK (2008) Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 65 (2):220–231

Shetty N, Friedman JH, Kieburtz K, Marshall FJ, Oakes D (1999) The placebo response in Parkinson's disease. Parkinson Study Group. Clin Neuropharmacol 22(4):207–212

Small DM, Jones-Gotman M, Dagher A (2003) Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. NeuroImage 19:1709–1715

Strafella AP, Ko JH, Monchi O (2006) Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. NeuroImage 31(4):1666–1672

Tobler PN, Fiorillo CD, Schultz W (2005) Adaptive coding of reward value by dopamine neurons. Science 307(5715):1642–1645

Watts RL, Freeman TB, Hauser RA, Bakay RAE, Ellias SA, Stoessl AJ, Eidelberg D, Fink JS (2001) A double-blind, randomised, controlled, multicenter clinical trial of the safety and efficacy of stereotaxic intrastriatal implantation of fetal porcine ventral mesencephalic tissue (NeurocellTM-PD) vs. imitation surgery in patients with Parkinson's disease (PD). Parkinsonism Relat Disord 7(S87)

Zald DH, Boileau I, El Dearedy W, Gunn R, McGlone F, Dichter GS, Dagher A (2004) Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 24:4105–4112