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The Placebo Response as a Reward Mechanism

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Placebo responses occur in a wide range of medical conditions, yet the underlying mechanisms remain poorly understood. On the basis of our observations of patients in Parkinson's disease, we have argued that the placebo effect is partly mediated by the activation of reward circuitry and that mesocorticolimbic dopamine release, particularly in the ventral striatum, plays a central role. Expectation has been shown to be critically involved in placebo responses. We argue that in patients with Parkinson's disease, placebo-induced expectation of clinical improvement is a form of expectation of reward, which results in striatal dopamine release. Reward circuitry also may be involved in other placebo responses, such as placebo analgesia, given the interactions between dopamine and endogenous opioid systems. Despite the heterogeneity of placebo responses, we propose that activation of reward circuitry may represent a common mechanism underlying the placebo effect, and that dopamine and prefrontal cortical circuits interact to produce a condition-specific physiological response.

Semin Pain Med 3:37-42 © 2005 Elsevier Inc. All rights reserved.

KEYWORDS dopamine, reward, expectation, Parkinson's disease, placebo effect, probability

The placebo effect is a fascinating phenomenon that has long puzzled medical practitioners and researchers. Prominent placebo effects occur in patients with pain, depression, Parkinson's disease (PD), and some surgical procedures, but whether or not the various placebo responses observed in these conditions share a common mechanism—although an intriguing possibility—is not yet known.

Our observations in patients with PD have advanced the hypothesis that the placebo effect is mediated by the activation of reward circuitry in the brain. Specifically, we have argued that the placebo-induced motor improvement seen in patients with PD represents a form of expectation of reward, that is, the patient's own expectation of symptom improvement (which is elicited by the placebo) activates the same

circuitry that is involved in the expectation of rewards in general. This hypothesis extends the expectation model of the placebo effect, originally described by Kirsch to explain placebo effects that arose in the absence of classical conditioning.¹ It essentially states that a person's expectations about their subsequent response to a placebo are central to the placebo effect, that is, the cognitive expectation triggers the biochemical placebo response. Expectation has been shown to play a critical role in placebo effects in PD^{2,3} and pain.^{2,4-6} On the basis of our findings in PD, there is reason to believe that the "expectation" of clinical benefit and the "expectation" of reward activate common circuitry in the brain and that these contribute to the mechanism of the placebo response.

Reward Circuitry and Midbrain Dopamine (DA) Neurons

Stimuli which, when administered to an organism after a correct or desired response, produce repeated approach behaviors or the repetition of responses are called rewards.^{7,8} Thus, a reward is an operational concept used to describe the positive value that an animal attributes to an object, behavior, or internal physical state (for discussion, see Breiter and Rosen⁹). In the early 1950s, Olds and Milner⁸ conducted a series of experiments using intracranial self-stimulation in

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Supported in part by the Canadian Institutes of Health Research Training Award in Neurobiology and Behaviour (S.C.L.), Canadian Institutes of Health Research, National Parkinson Foundation (Miami, FL), British Columbia Health Research Foundation (Canada) (R.F.F.), Pacific Parkinson's Research Institute (Vancouver, BC, Canada) (R.F.F.) and Canada Research Chairs Program (A.J.S.).

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rats that set the basis for the characterization of the reward circuitry. They demonstrated that rats would consistently press a lever to receive electrical stimulation through an electrode implanted in several different areas of the brain. Through these experiments, they concluded that the stimulation of certain brain areas was sufficient to be rewarding to the animal. These findings were soon extended to humans.⁷ During the past 3 decades, drug addiction research has provided further insight into reward circuitry by identifying brain areas that sustain active intracranial self-administration by animals, as well as areas activated in neuroimaging studies on human drug addicts. Not surprisingly, these areas contain many of the same sites originally identified by Olds and Milner.

The reward circuitry comprises striatal, limbic, and prefrontal cortical structures in which midbrain dopamine (DA) neurons play a critical modulatory role. DA-producing neurons with cell bodies in the ventral tegmentum and dorsal area of the substantia nigra, pars compacta send widespread projections throughout the forebrain, making up the mesocortical and mesolimbic DA systems. Mesocortical DA neurons innervate several frontal cortical structures such as the orbital, dorsolateral, and medial prefrontal cortices, and to a lesser extent the motor cortex and hippocampus. Conversely, mesolimbic DA neurons project heavily to the ventral striatum, especially the nucleus accumbens, and to limbic structures including the septal nuclei and amygdala, among others. These systems are distinguished from the nigrostriatal DA system which consists of neurons in the more ventral areas of the substantia nigra that project to the dorsal striatum (caudate and putamen). The ventral tegmental area, nucleus accumbens, prefrontal cortex, and amygdala (including the so-called "extended amygdala") are considered to be major structures in reward processing,⁹⁻¹¹ and DA is the key neurochemical involved. Indeed, Schultz and colleagues have shown that in primates, 55% to 80% of DA neurons are activated in response to primary liquid and food rewards as well as visual and auditory stimuli that predict such rewards.¹²

Although these neurons project to both the ventral and dorsal striatum, it is the DA release in the nucleus accumbens, the major structure of the ventral striatum, that is particularly associated with rewards.^{13,14} Natural rewards, as well as drugs of abuse, including psychostimulants, opiates, nicotine, and alcohol, preferentially increase DA release in the nucleus accumbens, and this release is thought to underlie their addictive and reinforcing properties.¹⁵ In addition, DA neuron activation occurs at different phases of the reward signaling process. For example, as mentioned, electrophysiology studies indicate that DA neurons show short, phasic activation after the presentation of liquid or food reward, or a cue that predicts the delivery of reward.¹⁶ These neurons also show similar activations in response to intense, novel stimuli or stimuli with rewarding or attentional properties.^{17,18} Interestingly, when a reward becomes fully predictable, DA neuron activity no longer increases, and when a predicted reward is omitted, DA neurons exhibit depressed firing.^{18,19} These observations have provided the basis for the hypothesis that

the phasic DA signals occur not in response to the reward itself but instead to what has been termed the reward prediction error, which in its most basic definition is the discrepancy between the predicted reward and the actual occurrence of the reward (however, see Montague and coworkers, 2004 for a more comprehensive review of temporal-difference error²⁰). In this way, the phasic bursting of DA neurons has been proposed to act as a teaching signal, being maximal when an unexpected reward is presented, and gradually decreasing as the animal learns the contingency associated with the reward, or the behavior it must perform to obtain that reward.

DA Signals and the Expectation of Reward

As the association between a reward-predicting stimulus (or a particular behavior, in the case of operant conditioning) and reward delivery becomes learned, that stimulus or behavior will evoke a state of expectation in the subject. Implicit in the notion of reward expectation is the likelihood, or probability, of the occurrence of the reward, which must also be coded for by DA neurons. As mentioned previously, the phasic DA signal that occurs in response to the delivery of a reward decreases as the reward becomes predictable. In fact, the magnitude of this phasic DA signal decreases monotonically as the probability of reward increases, being absent when $P = 1$, and highest when the reward is surprising and unexpected (ie, at $P = 0$).²¹ In addition, there is a second type of response these neurons display to reward: a tonic, sustained activation that precedes the reward and seems to reflect reward uncertainty.²¹ These activations are maximal at $P = 0.5$, or when the uncertainty is the greatest, and decline both at $P = 0.25$ and $P = 0.75$, and are virtually zero at both extremes (ie, $P = 0$ and 1, or when the reward is certain not to occur, or to occur, respectively). The time course of these activations is also intriguing because they demonstrate a gradual increase from the time of the reward-predicting stimulus up to the potential time of reward, ie, during the reward-expectation phase of the paradigm. These sustained activations are of great relevance to the expectation model of the placebo effect and may have profound implications in the design of investigations of the placebo effect itself, as well as clinical trials in which a placebo effect may be prominent.²²

As previously mentioned, mesolimbic DA release in the ventral striatum (nucleus accumbens) occurs in response to natural rewards and drugs of abuse but it is also associated with the expectation of rewards.^{12,23} A recent fast-scan cyclic voltametry experiment in rats, which enables the measurement of phasic DA release, demonstrated that DA release in the nucleus accumbens occurs both before and after reward occurrence.²⁴ Rats trained to self-administer cocaine by pressing a lever began to release DA in the nucleus accumbens approximately 4 seconds before the lever press, the extracellular DA concentration peaked 1.8 s after the lever press, and then fell to baseline levels 3 s later. Furthermore, there was an additional, transient increase in DA levels be-

tween 5 to 8 s before the lever press. Extending animal studies in reward prediction,^{11,12,25} human imaging studies have implicated the nucleus accumbens/ventral striatum in the anticipation or prediction of rewards. A functional magnetic resonance imaging study in human cocaine addicts showed increased activation in the nucleus accumbens during the preinfusion period for both saline and cocaine, in which there was a 50% expectancy condition for receiving cocaine.^{9,26} The fact that the same degree of activation occurred during the preinfusion period in both the saline and cocaine conditions indicates that the nucleus accumbens activity may reflect a computation of expectancy. This possibility is supported by other imaging studies indicating increased activity of the ventral striatum during the expectation of monetary rewards,²⁷⁻³⁰ primary rewards,³¹ drug rewards,³² and as will be discussed in the following section, the expectation of therapeutic benefit.³³

DA and the Placebo Effect in Patients With PD

PD is characterized by the progressive loss of DA in the brain, particularly in the dorsal striatum (caudate and putamen). This loss occurs as a result of the selective degeneration of the midbrain DA neurons in the ventral regions of the substantia nigra pars compacta that project to the dorsal striatum. Clinically, patients experience a poverty of movement, and standard levodopa therapy aims at increasing the DA levels in the striatum, thereby leading to motor improvement. As mentioned previously, a substantial placebo effect is found in patients with PD, where patients given placebos show improvements in their motor performance. Importantly, this placebo-induced motor improvement can be objectively assessed by examiners blinded to the specifics of a study, and indeed this has been the case in a number of studies.²²

Using positron emission tomography (PET) with the competitive D_{2/3}-DA receptor antagonist raclopride, we found that placebo administration stimulated the release of endogenous DA in the ventral³³ and dorsal³⁴ striatum of patients with PD. Although all patients in the study showed biochemical placebo responses (ie, increased DA release), only half of the patients reported placebo-induced motor improvement. This group of patients also released larger amounts of DA in the dorsal striatum, suggesting a relationship between the amount of dorsal striatal DA release and perceived clinical benefit. However, this relationship was not observed in the ventral striatum. Interestingly, all patients demonstrated an increase in DA release in this area, regardless of whether or not they felt any improvement as a result of placebo administration. Compared with the dorsal striatum, which is intrinsically linked to motor performance, the ventral striatum is classically associated with motivation and goal-directed behavior³⁵ and, as previously discussed, the anticipation of reward. We thus concluded that the DA release in the ventral striatum was associated with the patients' expectation of improvement in their symptoms, which could in turn be considered as a form of reward. Conversely, it follows that be-

cause the dorsal striatum is more involved in motor performance, the larger the amount of DA released after placebo, the greater the clinical improvement felt by the patient.

Several other studies also have demonstrated the importance of expectation to the placebo effect in PD.^{2,3,6,33,34} In patients who have undergone surgery for the implantation of chronic deep-brain-stimulating electrodes in the subthalamic nucleus, it is possible to increase or decrease the level of stimulation and objectively assess the subsequent changes in motor function. In one such study, patients were given verbal instructions that their motor performance (movement velocity of the hand) would either worsen or not change while the level of their stimulators was altered.³ When the subjects' stimulators were reduced to 20% of their original levels, the patients told that their motor performance was going to worsen displayed a significantly slower movement velocity than the patients who were told that they would experience no change in motor performance. Furthermore, when the stimulation was then increased to 40% of the original level, the group given the instruction that they were going to experience a "big improvement" in their motor performance did significantly better than the group told that they would notice only a "small improvement." In a unique electrophysiology study performed in human patients with PD undergoing deep-brain stimulation surgery, Benedetti and colleagues³⁶ showed for the first time that placebos evoked changes in firing in neurons in the subthalamic nucleus. The neurons displayed a decrease in frequency discharge and a shift from bursting to nonbursting activity in response to placebo, which was highly correlated with the clinical manifestation of the placebo effect, measured as a reduction in rigidity. Finally, strong support for the importance of expectation is derived from the recent report that quality of life after fetal transplantation for PD is determined not by the actual surgical procedure (transplant or sham) that was performed, but rather by the patient's belief as to which group s/he was assigned to.³⁷

Reward Circuitry and the Placebo Effect in Other Medical Conditions

It has not yet been established whether DA plays a role in the mechanism of placebo responses in other conditions, but there is PET evidence to suggest that reward circuitry is activated in pain³⁸ and depression.³⁹ Importantly, placebo antidepressants activate the ventral striatum early in therapy, before the perception of therapeutic benefit (H. Mayberg, personal communication, 2002). Placebos activate cortical areas known to respond to reward expectation,¹² such as the orbitofrontal cortex, the dorsolateral prefrontal cortex, and the anterior cingulate gyrus,³⁸⁻⁴⁰ indicating that placebo responses involve higher cognitive processing. It should be noted that any lack of reported placebo-induced changes in the striatum does not necessarily imply that DA release did not occur; studies of patients with PD have shown that

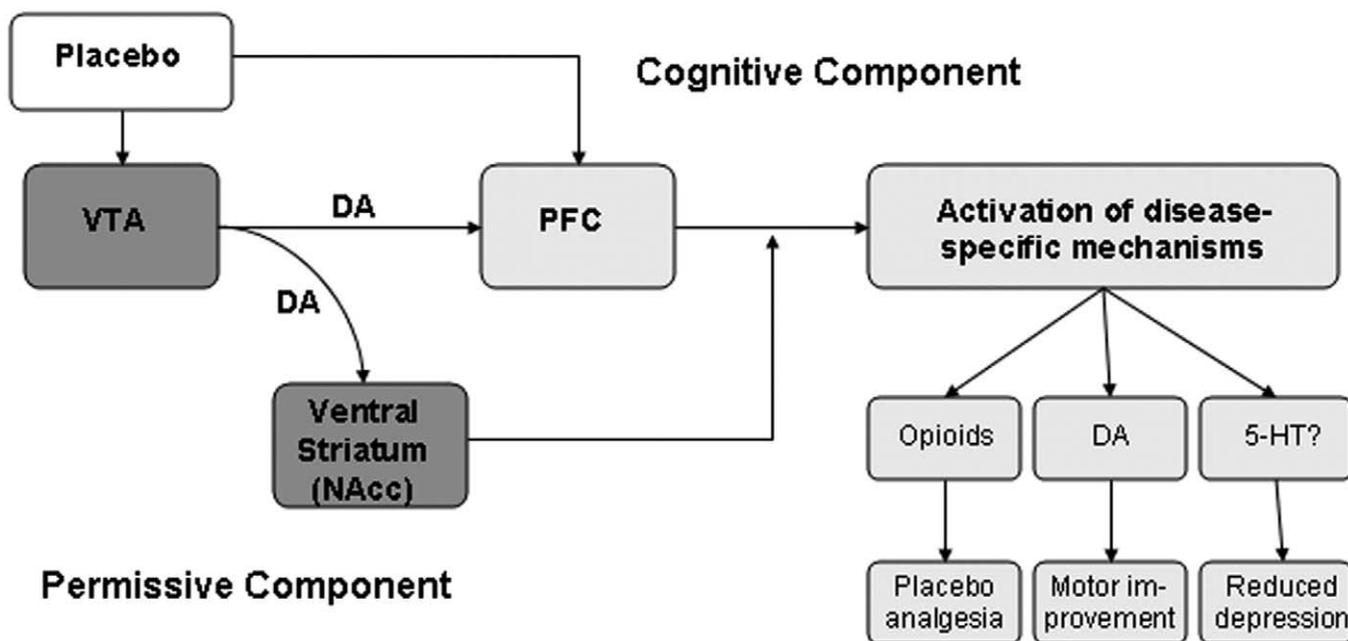


Figure 1 Theoretical schematic of the role of the reward circuitry in the placebo effect. DA-producing neurons arising in the ventral midbrain (ventral tegmental area, VTA) that send projections to the ventral striatum (including the nucleus accumbens, NAcc) are activated by placebo-induced expectation of clinical benefit, which is a form of expectation of reward. This represents the permissive component of the placebo response (dark gray). Reward-activated mesocortical DA projections to the prefrontal cortex (PFC) modulate higher cognitive processing, which in turn activate downstream disease-specific mechanisms that mediate the different placebo responses, including a reduction in pain (placebo analgesia), improvement in motor performance in PD, and reduced depression. This pathway represents the cognitive component of the placebo effect (light gray). The permissive component is common to all placebo effects, whereas the cognitive component is unique to the disease or condition of the patient. In this case, “placebo” refers to the actual placebo itself as well as the environmental context in which the placebo is administered, which also may produce anticipatory effects as the result of conditioning.

changes in striatal DA levels have metabolic correlates that are not easily detected by PET.²²

DA also may contribute to the mechanism of the placebo effect through its interactions with other neurotransmitter and neuropeptide systems. The involvement of endogenous opioids in the placebo effect in pain has been well-established,^{4,5,41} and there is considerable anatomical⁴²⁻⁴⁷ and pharmacological⁴⁸⁻⁵⁰ evidence indicating that complex interactions occur between the DA system and endogenous opioids, especially in the nucleus accumbens and ventral tegmental area. This relationship is likely bidirectional,⁴⁶ for there is increasing evidence implicating opioids in reward processing,^{51,52} and the reward circuitry in analgesia.⁵³⁻⁵⁵ Animal studies have uncovered a critical role for the nucleus accumbens in the phenomenon of pain or environmental-induced analgesia,^{54,56} perhaps through connections with the amygdala and the periaqueductal gray, which also has been shown to be involved in reward.^{54,57} Altier and Stewart⁴⁸ have demonstrated that the activation of mesolimbic DA neurons by opioids inhibits tonic pain by increasing DA release in the nucleus accumbens. This pathway also can be naturally triggered by the release of endogenous opioids and substance P in the ventral tegmentum in response to stress, which is also known to activate mesolimbic DA neurons.⁴⁸ Human imaging studies also have demonstrated a role for the nucleus

accumbens in pain processing. A functional magnetic resonance imaging study reported that noxious thermal stimuli produced a significant signal change in reward circuitry, including the nucleus accumbens.⁵³ Using PET, Zubieta and colleagues showed significant binding of endogenous opioids in the nucleus accumbens during painful stimuli.⁵⁸ Thus, animal and human studies support the involvement of DA–opioid interactions in pain processing, whether it is in an analgesic or reward role. Although direct biochemical evidence supporting the involvement of DA in placebo analgesia is lacking, it is possible given the functional overlap between the opioid and DA systems and their interactions in reward and analgesia.

Conclusions

Direct biochemical evidence now exists supporting the involvement of reward circuitry and DA in the placebo effect in patients with PD. We propose that the expectation of benefit is equivalent to the expectation of reward, which triggers placebo responses by activating reward mechanisms in which DA plays a central role. However, whether or not reward processing is involved in placebo responses in other conditions, such as pain, remains to be determined. No doubt remains that the placebo effect is an extremely com-

plex phenomenon that manifests itself in several different ways depending on the medical condition and treatment experiences of the patient. Clearly, irrespective of the modality, the mechanism involves some type of top-down cognitive control that is able to influence other cortical and subcortical structures to elicit a unique physiological response. The role of higher cognitive processing in this (arguably) uniquely human phenomenon, cannot be overlooked nor underestimated; expectation itself involves the integration of several distinct cortical processes, such as the retrieval of episodic memory to bring on-line the subject's past experiences in similar contexts, the assessment of current sensory stimuli, and the ability to predict the subject's own physiological response to the stimuli (ie, response expectancies⁵⁹). We propose that these complex cognitive processes, largely localized to frontal cortical areas, have the ability to activate downstream disease or condition-specific mechanisms that are responsible for the subsequent placebo response (Fig. 1). Furthermore, these specific mechanisms are overlaid on a nonspecific activation of reward circuitry in response to placebo, involving the expectation-induced activation of mid-brain DA neurons carrying reward-related information. The subsequent release of DA in the ventral striatum may represent a common mechanism of reward expectation, whereas the DA released in the frontal cortex may modulate other, distinct processes leading to the activation of downstream specific placebo effects, such as the release of endogenous opioids in pain or dopamine in the dorsal striatum in patients with PD.

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