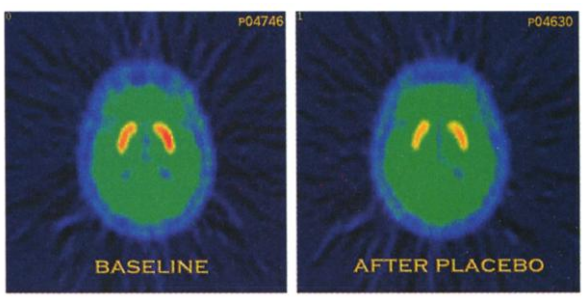
The Use and Usefulness of Placebo Controls

CONSIDERABLE DEBATE HAS FOCUSED ON the effects of placebos and whether control groups that receive placebo should be required in clinical trials (*1, 2*). Two issues are at the heart of these discussions: (i) whether assignment to a placebo condition deprives or delays access to beneficial treatment (*2, 3*), and (ii) placebos are not inert treatments and might elicit sufficient change in and of themselves to obscure or render ambiguous treatment effects (*2, 4, 5*). The report by R. de la Fuente-Fernández and colleagues provides strong evidence that a placebo, at least when administered to patients with Parkinson's disease, has clinically important druglike effects ("Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease," 10 Aug., p. 1164). Specifically, using positron emission tomography (PET), they found that Parkinson's patients administered a placebo release significant dopamine from their disease-compromised nigrostriatal system.

Although these observations are important for understanding residual capability in some patients, whether they represent a placebo effect that results from patient expectation is not so clear. The reason is that when an individual has received the active treatment in the past (in this instance, therapeutic drug administration), conditioned drug anticipatory responses can develop, responses that can subsequently be elicited by the administration of a placebo. Indeed, classical conditioning has been suggested as a mechanism underlying the placebo effect (*6*). Extensive reviews of conditioned drug effects document that the specific parameter measured can appear similar or opposite in nature to what occurs when the active drug is given (*7*). In the case of the de la Fuente-Fernández *et al.* report, all of their Parkinson's participants "were familiar with the effect of an active drug (levodopa)...." Such participants, with extensive therapeutic drug experience, would be expected to activate conditioned neural responses in anticipation of an impending drug administration, and that is what likely occurred. Although the authors emphasize the importance of expectation as mediating the observed placebo effect, classical conditioning is more likely the actual causal mechanism.

Placebo effects can certainly occur in individuals without prior drug-taking history, and these are presumably based on expectations and other cognitive factors (*2–4*). Further, these effects are presumed to be constant for individuals in the treatment and placebo arms of a clinical trial. Hence, drug effects can be directly compared with placebo effects in these instances. However, when a placebo elicits conditioned responses in individuals with extensive drug-taking history, the efficacy of a test treatment cannot be evaluated. We offer this caution because the interpretation of placebo effects is more complex than the simple expectancy model offered by de la Fuente-Fernández and colleagues.



CREDIT: UBC-TRIUMF PET PROGRAM

Picturing the placebo effect. Axial [^{11}C]raclopride PET scans showing dopamine D_2 receptor binding at the level of the striatum in a patient with Parkinson's disease studied in an open baseline (no injection) condition (left) and after the subcutaneous injection of saline (right). The marked reduction in D_2 binding after placebo injection indicates the release of endogenous dopamine.

DOUGLAS S. RAMSAY,[1]* STEPHEN C. WOODS[2]
[1]Departments of Pediatric Dentistry and Orthodontics, University of Washington, Seattle, WA 98195–7136, USA. [2]Department of Psychiatry, University of Cincinnati Medical School, Cincinnati, OH 45267–0559, USA
*To whom correspondence should be addressed. E-mail: ramsay@u.washington.edu

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Response

WE RECOGNIZE THE POSSIBILITY THAT THE placebo effect observed in our study could in part be a conditioned response; we stated that the treatment experience our patients had with levodopa could have enhanced their expectation. There are, however, several points in our study that do not fit with classical conditioning: (i) our patients had never been exposed to apomorphine, the drug we used in our study; (ii) they had never received treatment by subcutaneous injections; and (iii) the time course of the response to apomorphine is quite different from that of levodopa. Therefore, it is hard to reconcile our paradigm with the stimulus substitution model—a requirement for classical conditioning.

Other more general arguments against the view that the placebo response is explained by classical conditioning can be found elsewhere (*1*). Also, there are several instances of placebo effect in patients with no previous exposure to any treatment. The most parsimonious explanation is that the placebo effect is mediated by the expectation of clinical benefit, which fits with current theories of dopamine-related reward mechanisms (*2*).

RAÚL DE LA FUENTE-FERNÁNDEZ, A. JON STOESSL*
Neurodegenerative Disorders Centre, Purdy Pavilion, Vancouver Hospital and Health Sciences Centre, Vancouver, BC V6T 2B5, Canada
*To whom correspondence should be addressed. E-mail: jstoessl@interchange.ubc.ca

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