Expectation as Closure

A matched-design protocol for separating genuine physiology from reporting bias in open-label placebo response

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Abstract

The placebo effect sits under a standing suspicion. Much of what looks like a response to an inert treatment can be explained without invoking any change in the body: regression to the mean, natural fluctuation, the desire to please a clinician, and the soft plasticity of self-report under demand. The skeptical case, argued most forcefully by Hrobjartsson and Gotzsche, is that once you compare placebo against genuine no-treatment controls, the "power" of placebo largely evaporates except for subjective pain. This paper takes that challenge seriously and then presses back on a specific point. Open-label placebo studies, in which patients are told plainly that they are receiving an inert pill, remove deception and much of the reason to overreport, yet symptom improvement persists in several conditions. That persistence does not by itself prove a physiological effect; it could still be reporting bias under a different guise. The contribution here is methodological. I propose a matched-expectation, open-label design that measures an objective biomarker and a self-report outcome in the same participants under the same induced expectation, so that reporting bias and physiology can be dissociated rather than confounded. I frame expectation as a prior strong enough to reorganize physiology, a reading I label expectation-as-closure, while keeping that framing separate from the empirical claim. The design carries a sharp kill condition: if, under matched expectation, only self-report moves and the objective marker does not, the physiological claim dies for that outcome.

1. The problem, stated fairly

Anyone who has run a clinical trial knows that the placebo arm is rarely quiet. Symptoms improve, sometimes substantially, in patients who received nothing pharmacologically active. The interesting question is what that improvement is made of. There are at least four candidate ingredients, and only one of them is what people usually mean by "the placebo effect."

The first is regression to the mean. Patients enroll when symptoms are bad, and bad states tend to be followed by less bad states regardless of treatment. The second is the natural history of the disease, which for many conditions includes spontaneous remission and cyclical flares. The third is reporting bias in its several forms: demand characteristics, the wish to reward an attentive clinician, and the general

malleability of a number a patient assigns to a private sensation. The fourth, the one at issue, is a genuine change in the body or brain that is caused by the treatment context rather than by any active ingredient.

Hrobjartsson and Gotzsche put the field on notice about the first three [1]. In a meta-analysis of trials that included both a placebo arm and a no-treatment arm, they found that placebo had no significant effect on binary outcomes, whether subjective or objective, and that its apparent effect on continuous outcomes shrank as sample size grew, a signature of small-study bias. The clear exception was pain, where placebo produced a modest reduction on visual-analogue scales. Their conclusion was deliberately deflationary: there is little evidence that placebos have powerful clinical effects, and much of what is attributed to them belongs to the other three ingredients.

FACT: On the specific comparison of placebo versus no-treatment across pooled trials, the 2001 analysis found no reliable general effect and a bias-consistent pattern on continuous outcomes.

The honest position is that this analysis is largely correct as a critique of loose attribution. It is not, however, a proof that the fourth ingredient is empty. It is a proof that the fourth ingredient has usually been measured badly.

2. What open-label placebo changes, and what it does not

The deflationary account leans heavily on mechanisms that require either deception or ambiguity. Demand characteristics work because the patient thinks the pill might be active. The wish to please works partly through the same channel. Remove the deception, and you remove the most obvious motive for a patient to report improvement they do not feel.

This is what makes open-label placebo (OLP) studies methodologically valuable. In the landmark trial by Kaptchuk and colleagues, patients with irritable bowel syndrome were randomized to a no-treatment control or to a placebo pill they were explicitly told was inert, presented honestly and prescribed twice daily [2]. The OLP group reported greater improvement on standard IBS severity measures over three weeks. Subsequent work extended the paradigm. Schaefer, Harke, and Denke reported symptom improvement in allergic rhinitis under open-label placebo [3]. A broader synthesis by Kaptchuk and Miller argued that placebo effects are genuine biopsychosocial phenomena, not merely spontaneous remission or measurement noise, and are precipitated by the rituals and interactions of the therapeutic encounter [4].

HYPOTHESIS: Because OLP removes deception, its persisting effect is less easily explained by the demand-to-please channel than the classic blinded-placebo effect is.

Here I want to be careful, because it is easy to overclaim at exactly this point. OLP removes deception. It does not remove every reason a self-reported number might move. A patient who has been handed a pill and told, warmly and at length, that inert pills can help, has been given a reason to expect improvement and a social frame in which reporting improvement is the cooperative thing to do. Expectation itself is a reporting-bias channel, not only a physiological one. Symptom questionnaires in the IBS and allergic rhinitis trials are subjective instruments. So the persistence of OLP effects narrows the space of explanations without closing it. It rules out crude deception. It does not rule out expectation-driven reporting.

DISPUTED: Whether OLP effects reflect physiological change or expectation-shaped reporting is exactly the open question. The trials cited establish that the effect is robust and non-deceptive; they do not, on subjective endpoints alone, establish that it is physiological.

3. Where the physiology actually lives

If placebo response were purely a matter of what patients say, it would leave no fingerprint on measures that patients cannot consciously author. The neuroscience literature says it does leave such fingerprints, at least for some outcomes.

Wager and Atlas, reviewing the field, describe placebo effects as brain responses to treatment context, mediated by learning, expectation, and social cognition, with measurable correlates: reduced activity in regions associated with pain and negative affect, increased activity in lateral and medial prefrontal cortex, ventral striatum, and brainstem, and neurochemical mediation by endogenous opioids and dopamine [5]. Colloca and Barsky, in a clinical review, catalogue the mechanisms by which positive and negative expectations produce real effects, and treat the neurobiology as established for particular endpoints such as analgesia and Parkinsonian motor signs [6].

The cleanest single demonstration that a placebo can move physiology and not only opinion comes from pharmacological dissection. Amanzio and Benedetti showed that placebo analgesia induced by expectation is blocked by naloxone, an opioid antagonist, while placebo responses built by conditioning with a non-opioid drug are not [7]. This matters for the present argument in a specific way. Naloxone does not act on a patient's willingness to report. It acts on opioid receptors. If an antagonist at those receptors abolishes the effect, the effect ran through those receptors. That is a physiological pathway, demonstrated by intervention on the pathway rather than by the patient's testimony.

FACT: Placebo analgesia from expectation is naloxone-reversible, which locates at least part of the effect in endogenous opioid signaling rather than in reporting.

So the field already contains proof of concept that placebo can be physiological. What it lacks is a general method for deciding, outcome by outcome and condition by condition, whether a given open-label placebo effect is physiological or is reporting under the flag of expectation. That is the gap this protocol addresses.

4. Expectation as closure: the framework reading

Before the method, a word on interpretation, kept deliberately to the side of the empirical claim. The Academy's working lens describes cognition as openness settling into a determinate "this," a movement it calls Closure. In that vocabulary there is presence (C), the content it settles on (c), an openness or field of possibility (M), a horizon of what remains available (m), the act of settling (Cl), and a remainder (R) that the settling does not resolve.

On this reading, an expectation is not a passive prediction sitting alongside the body. It is a prior strong enough to close the field in advance, to fix a "this" that the body is then organized around. When a patient is told, credibly and within a trusting encounter, that relief is coming, the system does not merely wait to see; it settles, and the settling has downstream physiological consequences through the pathways the neuroscience has mapped. The remainder R is the part of the symptom that the prior cannot reorganize, the

stubborn residue that no expectation dissolves. Expectation-as-closure is thus a way of saying that a sufficiently strong prior reaches into physiology, not only into report.

WAGER: I am willing to bet that the physiological component of placebo response scales with the strength and credibility of the prior, not with the patient's motive to please, and that it will appear most clearly on outcomes governed by pathways an expectation can recruit (opioidergic, autonomic, inflammatory) and least on outcomes with no such pathway.

FIREWALL: This paragraph is interpretation. It is not a mechanism, and it is emphatically not a claim that mind conjures matter from nothing. "Reorganize physiology" means "modulate existing regulatory pathways via the brain," the same pathways naloxone can block. The closure vocabulary earns its place only if the clinical evidence carries the weight; if the biomarkers do not move, the framework reading is idle and should be dropped for that outcome.

5. The matched-design protocol

The core problem in the whole debate is a confound: expectation drives both real physiology and reporting, and standard designs measure only report, so the two cannot be separated. The remedy is to hold expectation fixed and measure two outcomes of different kinds in the same person.

Design in brief. Recruit patients with a condition that has both a validated self-report symptom scale and a validated objective biomarker plausibly on an expectation-recruitable pathway. Candidate pairings include allergic rhinitis (self-reported congestion and itch, plus objective wheal size on skin-prick testing and nasal eosinophil or tryptase measures), asthma (symptom score, plus spirometric FEV1 and exhaled nitric oxide), and experimental pain (rated intensity, plus pupillometry, skin conductance, and opioid-sensitive autonomic indices). The autonomic marker matters because placebo analgesia has been shown to reduce heart rate and beta-adrenergic response in a naloxone-reversible way, giving an objective channel that tracks the same physiology.

Arms. (a) Open-label placebo with high-credibility induction. (b) A no-treatment monitoring control. (c) Critically, a matched-expectation control in which participants receive the identical verbal induction and ritual but are told the measurement is of a natural process, decoupling the expectation from the pill. The purpose of arm (c) is to equalize the reporting incentive across conditions so that any divergence between biomarker and self-report is attributable to physiology rather than to differential demand.

Matched expectation, operationalized. Expectation is not assumed equal; it is measured. Before outcome assessment, each participant rates expected improvement on a calibrated scale, and only strata with equivalent expectation ratings are compared. This converts "matched expectation" from a hope into an inclusion criterion. Analysis is stratified by expectation strength, which also tests the WAGER in section 4.

Blinded objective assessment. The biomarker is read by assessors and, where possible, automated instruments blind to arm and to the participant's self-report. Self-report is collected before the biomarker is revealed to anyone, so that a moving number cannot retro-shape a rating.

The two-outcome logic. Within a fixed expectation stratum, four patterns are possible. If both self-report and biomarker move together, that is evidence for a physiological effect. If self-report moves and the biomarker does not, that is reporting bias for that outcome. If the biomarker moves and self-report does not, that is a physiological effect below the threshold of felt symptom, which is itself informative. If neither moves, there is no effect to explain. The design's whole value is that it makes the second pattern, the artifact, directly visible instead of leaving it fused with the first.

6. Prediction and kill condition

The claim I am prepared to lose is narrow and specific: for at least one outcome on an expectation-recruitable pathway, open-label placebo under matched expectation produces a change in an objective biomarker that cannot be reduced to reporting.

> **Prediction.** In a matched-expectation, open-label placebo design, for at least one outcome on a plausibly recruitable pathway (opioidergic, autonomic, or inflammatory), the objective biomarker will show a reliable placebo-associated change in the same direction as self-report, of an effect size large enough to survive correction and independent of expectation-rating strata being unequal. Concretely, the biomarker change will remain significant after conditioning on matched expectation, and its magnitude will covary with induction credibility.
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> **Kill.** If, under matched expectation and blinded objective assessment, the self-report outcome moves while the objective biomarker does not (a null on the biomarker that is adequately powered, with a confidence interval excluding the pre-registered minimally meaningful physiological effect), then the "real physiology" claim dies for that outcome, and the open-label placebo effect there is classified as reporting or measurement artifact. Matched objective-versus-self-report under equalized expectation is the data-quality control that decides this.

The kill condition is not decorative. It is likely to fire for some outcomes. The allergic rhinitis and IBS trials cited above rest primarily on subjective scales, and it is entirely possible that when a hard biomarker is added under matched expectation, the biomarker stays flat. If so, that outcome should be reported as reporting-driven, and the paper's thesis narrows accordingly. The thesis survives if even one well-chosen outcome shows a dissociation in the other direction: biomarker moving, not merely opinion.

7. What could still go wrong

Several failure modes deserve naming, because a protocol that cannot fail is not doing science.

Biomarker choice can pre-decide the result. If the chosen marker sits on a pathway that expectation cannot recruit, a null is uninformative about closure and merely reflects a bad pairing. This is why the pathway must be specified in advance and justified, and why more than one condition should be run.

Objective does not mean incorruptible. Spirometry depends on effort; skin-prick reading has inter-rater variance; autonomic measures drift with arousal and room temperature. "Objective" here means "not authored by the participant's verbal report," not "immune to all bias." Blinding and automation reduce but do not eliminate these, and residual variance must be modeled.

Expectation may not equalize cleanly. Arm (c) assumes that the induction can be attached to a natural process as convincingly as to a pill. If it cannot, expectation will not truly be matched, and the manipulation check on expectation ratings must gate the analysis. Strata with unequal expectation are not comparisons; they are confounds.

Conditioning versus expectation. Benedetti's work shows these are separable mechanisms with different pharmacology [7]. A design that induces expectation verbally may still carry conditioning from participants' prior drug histories. Measuring and covarying prior treatment experience is necessary, not optional.

8. Limits, wager, and conclusion

The limits are real. This protocol decides the question one outcome at a time; it yields no verdict on "the placebo effect" as a whole, because there is no such single thing. It is expensive, since it requires biomarkers, blinded assessment, and expectation stratification in adequately powered arms. It says nothing about clinical durability beyond the measurement window. And it deliberately brackets the framework interpretation, so a positive result vindicates physiology, not the closure vocabulary; that vocabulary remains a reading, to be judged on whether it later earns predictive traction.

The wager is that the skeptics were right about method and wrong about metaphysics. Hrobjartsson and Gotzsche correctly showed that most placebo attribution has been sloppy, resting on missing controls and small-study bias [1]. But the naloxone reversibility of placebo analgesia [7] and the neural signatures catalogued by Wager and Atlas [5] and by Colloca and Barsky [6] indicate that a genuine physiological component exists for at least some outcomes. The open-label results [2,3,4] show that the effect does not require deception. What has been missing is a design that separates the physiology from the reporting instead of confounding them. Expectation-as-closure is the Academy's way of naming why a strong enough prior might reach the body; the matched-design protocol is the way to find out whether, for a given outcome, it actually does. If the biomarker stays flat while only the self-report moves, I will have lost that bet for that outcome, and the honest thing will be to say so.

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