

Is Treatment Resistance Sometimes a State Mismatch?

Absurd Health Institute · Medical Concept Papers, Volume Three · Third editorial pass, 17 October 2026

Article type: Mechanistic research perspective · **Status:** Conceptual argument, not clinical guideline

Therapeutic failure may sometimes be a mismatch between intervention and state. A patient can receive a pharmacologically active treatment and show little clinical benefit. The conventional explanations include inadequate exposure, wrong diagnosis, progression, adherence, and true treatment resistance. The Institute adds a sharper possibility: the treatment's molecular action may be real, but the patient's present biological configuration may prevent that action from changing the dominant outcome. The difference is important because escalating dose does not necessarily remove the constraint.

In chronic inflammatory disease, for example, symptoms can persist after one inflammatory mediator is reduced if structural injury, pain sensitization, or another pathway now governs functional limitation. Conversely, apparent nonresponse may simply reflect insufficient treatment duration or inconsistent use. A state-mismatch model must first separate target engagement from clinical benefit. Without confirming the target changed, invoking an obscure system state is premature.

A falsifiable definition of state mismatch The model predicts that patients with comparable target engagement will show systematically different outcomes according to a prespecified functional or regulatory feature. One might measure baseline tissue damage, inflammatory phenotype, concurrent medication, sleep disruption, or rehabilitation capacity. It should then be possible to estimate which patients benefit from the original therapy, which require an additional intervention, and which are unlikely to respond because the presumed target is no longer dominant.

This theory differs from indiscriminate “personalization.” It requires a measurable moderator and a prospective treatment interaction. A retrospective chart showing that responders were healthier offers no proof, because healthier patients often improve under many treatments. The most convincing evidence would be that changing a proposed constraint shifts the response to the same target-directed treatment while control conditions do not. The uncomfortable implication is that calling a drug a failure may sometimes conceal a failure to identify the mechanism actually limiting recovery. Still, dangerous illness and established effective treatment must not be set aside while exploring a speculative state label.

Demonstrating mismatch requires confirming that the drug did what it was supposed to do Before proposing a hidden systems explanation for nonresponse, researchers need evidence of sufficient drug exposure and target engagement. Without that, resistance may reflect wrong dose, interactions, rapid clearance or incorrect diagnosis. Only then is it reasonable to ask whether a downstream state prevents functional improvement. This hierarchy is essential because an unmeasured “terrain” cannot explain every disappointing treatment result.

One valuable design compares participants with similar target engagement but divergent clinical responses. If baseline fibrosis, perfusion, inflammatory phenotype or another candidate feature predicts divergence, a causal experiment can test whether changing that feature restores responsiveness. Interaction analyses need enough participants and prespecified hypotheses; otherwise false-positive subgroups are easily produced. The ultimate objective is not to make nonresponse mysterious. It is to find an additional cause when an otherwise adequate molecular intervention fails to change the outcome that matters.

The critical clinical distinction This proposal is most informative when a specific biological measure separates patients with comparable drug exposure, not when the author declares every unsuccessful prescription a “state mismatch.” A treatment can be inappropriate because the diagnosis is incorrect; it can also be appropriate yet insufficient because irreversible tissue damage has accumulated. Only after these familiar possibilities are investigated should the model posit a newly measured constraint. The paper's affirmative prediction is that changing the constraint shifts the clinical response to the original treatment. The relevant analysis must compare patients before and after that change, using functional endpoints rather than a post hoc description of who happened to improve.

Distinguish absent target engagement from downstream failure When a drug appears ineffective, therapeutic monitoring may reveal inadequate exposure, while molecular assays may show that the target was never meaningfully altered. These failures cannot support a state-mismatch interpretation, because the proposed mechanism has not been tested. The critical subgroup comprises patients with verified target engagement and persistently impaired function. It is among them that the Institute should seek downstream bottlenecks such as tissue scarring, altered perfusion or parallel compensatory pathways.

A competing explanation is that the original endpoint is insensitive or the observation period too short. A well-designed study needs enough time for the expected target effect and outcome, with a protocol that does not invent new explanatory states only when results disappoint. Prospective prediction is essential. If a baseline feature forecasts response and its deliberate modification restores treatment efficacy, the state-mismatch thesis becomes a concrete scientific finding. Without this, it remains a plausible but dispensable description of clinical heterogeneity.

A prospective threshold for declaring true nonresponse The model must specify a minimum exposure period, objective target engagement and a clinically meaningful outcome before declaring mismatch. Otherwise ordinary delayed response can be misclassified as a new phenotype. A negative trial meeting these conditions would count against the proposed moderator.

Detailed considerations from the original investigation

Treatment resistance is a clinical descriptor that can hide multiple phenomena: wrong diagnosis, inadequate dose or duration, nonadherence, comorbidity, drug interactions, severe disease and genuine nonresponse. The coherence framework proposes one additional contributor: an intervention may demand more cognitive, energetic or regulatory capacity than is currently available. This is a conditional hypothesis, not an explanation for every failed treatment.

Consider a patient in severe insomnia and panic who is prescribed cognitively demanding psychotherapy homework. The intervention may be sound in principle but difficult to execute before attention and sleep improve. In rehabilitation, an excessive exercise load can similarly exceed current tolerance. By contrast, a patient with severe depression may benefit from immediate evidence-based therapy or medication despite poor energy; capacity rhetoric should never serve as a reason to postpone urgent care. The conceptual advance is matching treatment burden, sequence and supports to measurable limitations.

A patient failing psychotherapy might need a different modality, improved access, higher-quality delivery, medication, treatment of sleep apnea or simply more time. State mismatch is one hypothesis among several. Its value emerges when it predicts a specific adjustment that succeeds without postponing necessary care. A framework that explains every failure after the fact has no meaningful predictive advantage.

Existing stepped-care and personalized medicine frameworks already adjust treatment to ability, disease severity and patient preference. The Institute's proposal must be more precise than suggesting that all negative experiences prove state mismatch. Sometimes an intervention is ineffective, harmful, misdiagnosed or applied badly. Escalation can be lifesaving in psychosis, suicidality or acute organ dysfunction. A model that always blames the patient's state is unfalsifiable and ethically unsound.

A useful comparison is whether baseline sleep, autonomic instability and cognitive load predict adherence and differential outcomes after adjusting for diagnosis. State matching should improve outcomes only if it changes the intervention appropriately, not simply because patients receiving more support do better for nonspecific reasons.

For the website, this paper should invite a better clinical question: is the intervention wrong, premature, overly burdensome, insufficient or correctly targeted but genuinely ineffective? The answer is not determined by the framework alone.

State mismatch proposes that a useful intervention fails when prerequisites for its intended effect are absent, rather than because the molecular target is intrinsically irrelevant.

Exercise can improve rehabilitation outcomes but be poorly tolerated during unresolved acute organ dysfunction; this cannot justify universal inactivity.

Define the prerequisite before treatment and test effect modification with prospective interaction analyses rather than explaining nonresponse retrospectively.

Selected scientific reading

1. McEwen (1998), Protective and damaging effects of stress mediators, New England Journal of Medicine.
<https://doi.org/10.1056/NEJM199801153380307>
2. Barabási, Gulbahce & Loscalzo (2011), Network medicine: a network-based approach to human disease, Nature Reviews Genetics.
<https://doi.org/10.1038/nrg2918>

Editorial source note: The inherited selected readings are retained from the source manuscript and have not all been independently verified. Newly checked evidence is identified separately. The mechanistic extensions are hypotheses

except where explicitly described as established physiology.