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Commentary

Separate mechanisms for placebo and opiate analgesia?

One of the basic assumptions underlying all standard, double-blind clinical trials is the assumption that the "non-specific" component – the placebo response – is additive with the effect of the drug or device studied. Unfortunately, this fundamental assumption has rarely been tested in the scientific literature. If placebos are inert, there is little reason to test their effectiveness against a no-treatment (natural history) control group, or test whether drugs enhance or interfere with placebo effects (and vice versa). In fact, however, placebo treatments do have effects on the *endogenous* pharmacology of patients [1,2,4,5,12,17,20]. Thus, interactions between drugs and placebo-induced brain processes are quite probable [9] – and must be assessed in clinical trials.

In this issue, Petrovic et al. [14] report a double dissociation in brain responses during a period of painful stimulation under the opiate agonist remifentanil and placebo conditions. Remifentanil caused greater increases than placebo in the rostral anterior cingulate (rACC, an area thought to be principally involved in both opiate and cognitive effects on pain), whereas the placebo condition produced greater increases in the lateral orbitofrontal cortex (lOFC) and ventrolateral prefrontal cortex (VLPFC). These findings are important and provocative because they provide evidence against the additivity assumption – in this case, the assumption that open-label remifentanil treatment produces an additive increment in effectiveness over placebo.

The standard assumption is that open-label remifentanil involves the same "non-specific" benefits as placebo, plus specific pharmacological effects. If the remifentanil and placebo conditions differed only in the specific drug effects, the placebo would have to activate a subset of the brain regions affected in the open drug condition. However, each of the drug and placebo conditions activated an area of the brain more than the other condition. The most straightforward conclusion is that each involves unique processes. If both brain processes are related to pain relief, then the net predicted effect would be an under-additive interaction, an analgesic drug effect that is masked by weaker placebo effects during drug administration. Petrovic et al. [14] supplemented these findings with additional brain connectivity analyses showing that lOFC–rACC connectivity was stronger in the placebo condition, in both the remifentanil study mentioned above and a second study of placebo effects on brain responses related to anxiety. Thus, Petrovic et al.'s results suggest that lOFC is involved in the top-down generation of conceptual knowledge that leads ultimately to pain relief, and that this mechanism is not required (or at least, not as much) with the opiate.

The authors provide a provocative explanation for the unique lOFC placebo-related activity [14]. Drawing on research on prediction errors in learning, they suggest that it is the *discrepancy* between actual and expected pain that is unique to the placebo condition, and that discrepancy activates lOFC and produces pain relief. Indeed, previous studies have shown that the lOFC activity tracks aversive prediction errors [6,18], i.e. how much worse an outcome is than expected.[1]

The reason why this should produce analgesia remains more speculative, but it is possible that the discrepancy between expected and experienced pain triggers the engagement of endogenous pain-control mechanisms. This suggestion parallels similar proposals about the role of the VLPFC in the resolution of sensorimotor response conflict [3]. Prediction errors could generate placebo analgesia through two plausible mechanisms. First, it is evolutionarily adaptive for sensory experiences of all kinds to reflect combinations of sensory input and prior expectations, which may function to stabilize perception under changing environmental conditions (e.g., [10]). Second, worse-than-expected pain may increase desire for pain relief, which appears to promote placebo analgesia [16], possibly by motivating spontaneous self-distraction or reappraisal of pain.

Interestingly, both accounts require one to posit at least two kinds of pain-related signals in the brain. An initial nociceptive signal must reflect the sensory input, so that it is compared with expectations (of reduced pain) and produces prediction errors (worse than expected). A second pain-related signal must track the outcome of weighting sensory experience by the prediction error (deviation from expectations) – a process presumably designed to minimize anomalous perceptions. The presence of a secondary discounting process is compatible with the findings that some of the strongest placebo effects on noxious stimulus-evoked responses are often seen in the late phase of the response [7,19].

Thus, a testable prediction based on Petrovic et al.'s results is that there are at least two kinds of placebo effects. One kind, mediated by lOFC, must influence pain after the initial sensory experience is compared with expectations. Evidence for a second kind, which operates on early sensory experience, is provided by studies that show placebo effects on early nociceptive processes [8,11], which cannot be caused directly by prediction errors. In support of this idea, we have found that lOFC responses predict placebo analgesia in pain reports, but not placebo-induced reductions in pain-processing regions [19]. It is thus an open question whether lOFC provides a top-down signal that shapes sensory experience or, alternatively, is the source of a cognitive bias in pain-related decision-making.

Finally, the implication of under-additivity has important consequences for how placebo suggestions and drug treatments

[1] We note, however, that prediction errors are generally highly correlated with the aversiveness of events, and primary representation of value and affective (and possibly cognitive) salience signals are also likely to be represented in this area of OFC. See Ref. [13].

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should be combined to maximize pain relief. If placebo treatments do not work as well in the presence of verum opiates, then the placebo effects are of little clinical importance, as most patients are treated pharmacologically. Ironically, in this case placebo effects are all the *more* important to consider in clinical trials, as *smaller* placebo effects in the drug arms of studies compared to the placebo arms may prevent even effective drugs from reaching statistical significance in the drug vs. placebo comparison. However, the empirical prediction of under-additive placebo *x* remifentanil interactions has not, to our knowledge, been directly tested.

In conclusion, it is interesting that Petrovic et al.'s initial, striking finding was the substantial commonality in brain responses to placebo and remifentanil [15]. This new report focuses on processes that are unique to drug and placebo treatment, with implications that are perhaps just as scientifically rich and even more directly important for clinical trials. Ultimately, a better understanding of both commonalities and differences between placebo and drug treatment will not only advance our understanding of placebo analgesia, but will also contribute to more accurate assessment of drug efficacy.

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