Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Manipulation of Expectancy and Anxiety in Placebo Research and Their Effects on Opioid-Induced Analgesia

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Review of Atlas et al.

Placebo analgesia is the reduction in pain due to the administration of a pharmacologically inert substance or sham treatment. Research has shown that placebo analgesia is triggered by psychosocial factors associated with the treatment context, such as the interaction between therapist and patient, environmental cues, or previous experience (Finniss et al., 2010). Most importantly, though, expectation of treatment outcome plays a crucial role in placebo analgesia (Benedetti et al., 2003). Expectation has also been found to influence the efficacy of active pharmacological treatments, which is illustrated by the decreased effectiveness of covert (hidden) treatments compared with open treatments (Benedetti et al., 2011). Hidden treatments entail the covert administration of a drug, using, for example, a computer-controlled infusion machine. They are thought to be free of any psychosocial or cognitive influences, thus allowing for the dissociation of the "pure" pharmacological effect of a treatment from drug-unspecific effects (i.e., expectancy or placebo effects) that are associated with its open administration (Levine and Gordon, 1984). Open treatments, in contrast, make explicit use of the psychosocial context in which a treatment or drug is administered, thus inducing treatment expectancy/placebo effects. Open administration has been found to substantially enhance the pain-relieving effect of analgesic medication, including opioids (Amanzio et al., 2001). One of the crucial questions yet to be answered, however, is whether drug-induced analgesia and expectation-based (placebo) analgesia combine in an additive manner or whether they interact synergistically (Bingel et al., 2012). This question has large implications for drug research, as traditional randomized clinical trials (RCTs) assume that pure drug effects and placebo effects are additive and that the pure pharmacological drug effect of a new medication can be measured by simply subtracting the response in the placebo arm from the response in the drug arm.

The question whether placebo analgesia and opioid analgesia are of an additive nature was recently investigated by Atlas et al. (2012). In two studies, they administered the opioid agonist remifentanil during experimental thermal pain in healthy subjects. The behavioral study entailed a full-factorial, balanced placebo design where remifentanil was administered during hidden and open conditions, and no drug was given during control and placebo conditions. Subjects' knowledge of drug delivery (i.e., manipulation of treatment expectation) was manipulated by verbal instruction. Subjects were told that they would receive remifentanil in the placebo and open conditions, and were told they would receive no drug in the control and hidden conditions. In the second study, using functional magnetic resonance imaging (fMRI), remifentanil was administered in an open-hidden design only, with visual cues indicating the drug or no-drug condition.

In the behavioral experiment, using the balanced placebo design, open and hidden administration of remifentanil reduced pain ratings relative to the control condition. Manipulation of expectancy alone (placebo condition) also resulted in reduced pain ratings relative to the control condition. With a factorial analysis of their results, the authors could show that drug effects and expectancy effects were of an additive nature, as no interactions were observed. In the fMRI experiment, using the open-hidden design only, again both remifentanil and expectation reduced pain ratings; however, the magnitude of the drug effect on pain reports did not differ between the open and hidden conditions. For brain activation, activity in the pain-processing network (PPN) was modulated in both the remifentanil and the expectancy conditions. While reduced activity due to remifentanil was observed in a major part of the PPN, expectancy showed activation reduction in a more restricted part of the PPN. The time course of these expectancy effects paralleled be-

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havioral pain reports. Expectancy effects began with drug infusion, and reached a peak before remifentanil reached its pharmacological peak. Additionally, expectancy influenced activity outside of the PPN: it reduced activation in areas of the limbic system and increased activation in prefrontal regions. Atlas et al. (2012) interpret their findings as support for dissociable effects of opioidergic drugs and expectancy. They suggest that the effects of expectancy operate alongside those of remifentanil, and view their findings as support for the assumption of additivity of expectation-based (placebo) analgesia and drug-induced analgesia.

One of the great merits of the Atlas et al. study is that theirs is the first to explicitly examine the interaction of expectancy and opioidergic drug effects on pain. Research on this issue is very sparse, and, as Bingel et al. (2012) note, the nature of the relationship of expectancy and drug effects may be dependent on the drug itself: for one substance, effects may be additive; for another, effects may interact synergistically, as was found for the cholecystokinin antagonist proglumide on pain (Benedetti et al., 1995).

Atlas et al. (2012) state that in their experiments, hidden and open administrations of remifentanil only differed in one aspect, namely expectation (no expectation of pain relief in the hidden administration vs positive expectation of pain relief in the open administration). This was manipulated via verbal instructions ("[. . .] you will not receive any drug" vs "[. . .] you will receive remifentanil"). In both hidden and open conditions, participants knew that painful stimulation was about to occur. Previous research has, however, shown that information about impending pain can increase negative emotions such as nervousness and anxiety, which in turn can influence pain (for review, see Flaten et al., 2011). In this respect, we would like to point out that the open-hidden paradigm used by Atlas et al. (2012) may not only have manipulated treatment expectancy, as intended, but may also have induced differential levels of anxiety in the hidden versus open administration of remifentanil: relative to the open administration, where a positive expectation of pain relief was induced, anxiety may have been substantially increased in the hidden condition. Support for our hypothesis is provided both by previous research and by Atlas et al.'s (2012) own fMRI data. Bingel et al. (2011) found that anxiety was substantially higher in the no-expectancy condition (corresponding to hidden administration of remifentanil) relative to the positive expectancy condition (i.e., open administration of remifentanil). Atlas et al. (2012) themselves report high responses off drug in the hidden condition (higher initial amygdala activity before drug infusion started, i.e., during the instruction of "you will not receive any drug") in several brain regions, among them left amygdala. They interpret their findings as neurobiological responses related to anxiety in the hidden condition. Unfortunately, no subjective measures of anxiety were included in the studies of Atlas et al. (2012), and results on skin conductance, which can serve as a measure of arousal, are not reported.

As illustrated above, the hidden administration of remifentanil may thus have also been influenced by anxiety. As a consequence, the authors might not have succeeded in identifying the pure pharmacological effect of remifentanil and may thus not be able to dissociate the influences of expectation and anxiety on the observed results. This could, at least in part, account for the fact that no interaction between expectancy and opioidergic drug effects was observed in their data.

In conclusion, Atlas et al. (2012) have taken an important and overdue step in the investigation of the relationship between expectancy and opioid analgesia. They explicitly addressed the question whether expectancy interacts synergistically with opioidergic drug effects, or whether the effects are independent, i.e., of additive nature. The answer to this question will have a large impact on how drug effects are measured in RCTs. Thus their findings mark an important step toward a better understanding of how effects of expectancy and opioidergic drugs combine both at the behavioral and at the neurobiological level.

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