

Journal Club

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Believe in Your Placebo

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Review of Kong et al (<http://www.jneurosci.org/cgi/content/full/26/2/381>)

Introduction

Placebos are widely effective, as evidenced by randomized placebo-controlled drug studies, most of which show at least some effectiveness of placebo. One of the best examples of placebo effectiveness is relief of pain. In general, there is an assumption that placebo changes expectancy, needs, and/or belief about the perception related to the stimulus. These changes can be mediated by several mechanisms, including altered descending modulation via brainstem inhibitory systems and activation of endogenous opioid systems. Both of these mechanisms can lead to changes to the affective/motivational dimension of pain processing. Brain areas implicated in this pain dimension include the anterior cingulate cortex (ACC) and the right anterior insula (AI). Interestingly, a role for the rostral ACC (rACC) is frequently described in placebo analgesia. Strategically positioned to form a loop from limbic to brainstem to medial prefrontal regions, the rACC is densely populated with μ -opioid receptors and is activated by opioid as well as placebo analgesia (Petrovic et al., 2002).

The recent *Journal of Neuroscience* paper by Kong et al. (2006; <http://www.jneurosci.org/cgi/content/full/26/2/381>) reported placebo-related activation of rACC, right AI, lateral prefrontal cortex,

and inferior parietal cortex [Kong et al. (2006), their Fig. 2B,C (<http://www.jneurosci.org/cgi/content/full/26/2/381/FIG2>)]. The placebo was a validated sham acupuncture treatment, whereby a needle was applied to an acupuncture point, but the skin was not punctured. To establish a strong placebo effect, the authors manipulated subjects' beliefs about the treatment, first by telling subjects that some people respond very well to acupuncture, and second by changing the level of stimulus from painful to much less or barely painful after the treatment, such that subjects would associate treatment with reduced pain intensity [Kong et al. (2006) Fig. 1 (<http://www.jneurosci.org/cgi/content/full/26/2/381/FIG1>)]. During data collection in the functional magnetic resonance imaging session, however, stimulus intensities were kept the same. Overall, the subjective ratings of pain were reduced by placebo treatment, although there was also an increased rating on the control side [Kong et al. (2006), their Table 2 (<http://www.jneurosci.org/cgi/content/full/26/2/381/TBL2>)], somewhat confounding the assessment of differences. However, the effect of a placebo was supported by a correlation between placebo response in a subject and the degree of activation of several brain areas [Kong et al. (2006), their Table 4 (<http://www.jneurosci.org/cgi/content/full/26/2/381/TBL4>)]. In particular, rACC and pons activity correlated with placebo response, as did several prefrontal cortical regions. Although connectivity of these regions was not tested, one might predict a role of these regions in opioid mediated analgesia.

What should one call the experimental

treatment in this case? In a recent study, an endogenous opioid network supporting placebo analgesia was influenced by a subject's need or motivation for relief (Zubieta et al., 2006), whereas another study found that the effectiveness of real or sham acupuncture, reflected as increased activity in prefrontal cortex, ACC, and midbrain, depended on the subjects' belief in the treatment (Pariante et al., 2005). In a placebo-controlled drug study, the placebo is presumably the same in all respects to drug, and the effect of the drug is assumed to have efficacy beyond that of placebo. In the work by Kong et al. (2006), there was not a comparison with a "real" treatment, and thus the treatment might be better referred to as manipulation of expectancy or belief.

Rostral ACC, brainstem, dorsolateral, and orbitofrontal/ventrolateral frontal cortices are the most common sites reported in placebo imaging studies. Six recent papers point to a major role for rostral ACC in analgesia (Petrovic et al., 2002; Pariante et al., 2005; Bingel et al., 2006; deCharms et al., 2006; Kong et al., 2006; Zubieta et al., 2006). Of those studies, three showed a direct relationship between rACC and brainstem using functional connectivity approaches (Petrovic et al., 2002; Pariante et al., 2005; Bingel et al., 2006). One difficulty in interpreting these findings is the difference in locations of these activations. For instance, Bingel et al. (2006) described the rACC as a subgenual region, which has dense connections to several limbic structures including the amygdala. Kong et al. (2006) and Zubieta et al. (2006) report an area of

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rACC that is perigenual (directly anterior to the genu of the corpus callosum), whereas deCharms et al. (2005) and Pariante et al. (2005) refer to a much more posterior part of ACC that they call rACC. Furthermore, although there is a general consensus on the regions involved in placebo, there is little consistency in the activity of rACC, with some studies showing an increase with placebo, and others showing a decrease.

Somehow, these systems affect the way pain is experienced. Most authors take the view that rACC, when activated during placebo, activates descending control systems. Craig (2002) proposed that the ACC is active in response to a homeostatic imbalance requiring motivation for protective behavior. This idea fits with a recent study showing that active control of the ACC can reduce pain intensity and unpleasantness (deCharms et al., 2005). It is clear that ACC has a role in the control of pain, but additional experiments are

needed to delineate the functional divisions of the ACC.

Kong et al. (2006) replicate earlier findings on placebo analgesia, particularly concerning how belief alters placebo-related changes in neural activity. The authors conclude that multiple pathways and mechanisms may underlie the apparent inconsistencies in placebo imaging studies. However, the correlation between placebo-related activity and placebo effectiveness suggest that stronger belief in placebo can lead to an enhancement of pain control mechanisms. Thus, it could be that what determines placebo effectiveness is the subject's belief in the treatment. In this context, placebo emphasizes an ability to relieve pain with active control, which could have important implications for mechanisms for the treatment of chronic pain.

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