



## Commentary

## No prefrontal control, no placebo response

Evidence suggests that placebo response is mediated by the opioidergic descending pain control system described by Basbaum and Fields [2]. The response is initiated in the dorsolateral prefrontal cortex, a likely cortical cognitive-evaluative area, and involves downstream circuits that include the anterior cingulate cortex, the hypothalamus, periaqueductal gray and rostroventromedial medulla [4,7]. The opioidergic nature of this pain modulating system is supported by both pharmacological studies that used the opioid antagonist, naloxone [1,4,6] and in vivo receptor binding approaches [8]. Indeed, activation of opioid neurotransmission circuits has been shown to occur in prefrontal regions [4,8]. Interestingly, the degeneration of the prefrontal lobes that occurs in Alzheimer's disease, and their consequent functional disconnection from the rest of the brain, abolishes completely the placebo analgesic response [3]. Taken together, these findings strongly suggest that normal functioning of the prefrontal areas is a necessary condition for initiating the placebo analgesic response.

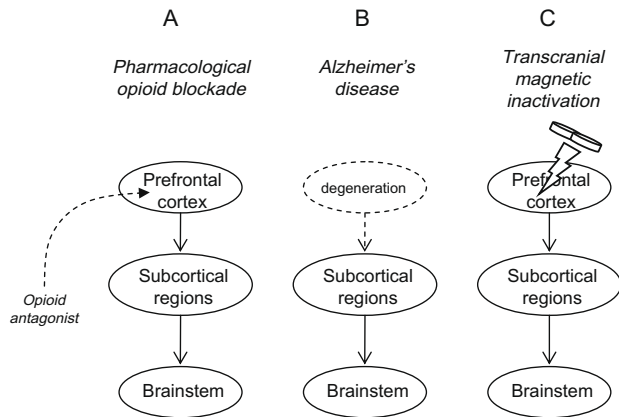
In this issue of Pain, Krummenacher et al. [5] used repetitive transcranial magnetic stimulation (rTMS) to disrupt transiently and bilaterally the function of the dorsolateral prefrontal cortex, while inducing a placebo analgesic response in healthy volunteers. Since rTMS is known to depress cortical excitability of the targeted cortical region, this represents an excellent experimental model to investigate how loss of prefrontal control may affect complex cognitive functions, such as expectation-induced placebo responses. Indeed, by using the rTMS device itself as a placebo (sham stimulation), Krummenacher et al. [5] revealed at least two important effects. First, sham rTMS, along with expectation of analgesia, induced an increase of both pain threshold and pain tolerance, thereby confirming the powerful effects of a placebo device on pain. Second, inactivation of the prefrontal cortex by means of rTMS blocked the placebo analgesic response completely.

The study by Krummenacher et al. [5] is important for several reasons. First and foremost, it shows that normal functioning of prefrontal areas is critical for placebo responsiveness. If there is a loss of prefrontal control, there also is a loss of placebo response.

This is in line with previous studies in different models and medical conditions. Fig. 1 illustrates that there are different conditions whereby placebo responses are disrupted. In A, the loss of placebo responsiveness is induced through pharmacological opioid blockade with an opioid antagonist [1,6]; this pharmacological manipulation is known to affect the dorsolateral prefrontal cortex [4]. In B, disruption of placebo responses is attributable to degeneration and functional disconnection of prefrontal regions, as occurs in Alzheimer's disease [3]. In C, experimental disruption of prefrontal function by means of rTMS blocks placebo analgesia completely [5]. Therefore, rTMS has the same effects as those induced by pharmacological blockade or prefrontal degeneration in Alzheimer's disease.

A second reason why the study by Krummenacher et al. [5] is important resides in its novel approach in the experimental setting. The use of rTMS may represent a new tool in placebo research, as it permits reversible inactivation of regions of the brain that have been involved or implicated in placebo analgesia. Somewhat unfortunately, in this study the localization of the dorsolateral prefrontal cortex relied only on the 10–20 EEG international system as a reference, whereby the F3–F4 locations roughly correspond to the target areas. This approach does not take into account inter-individual neuroanatomical differences, so that precise localization of the target region in particular subjects was not possible. This lack of anatomical precision does not detract from the significance of the study, but it will be of interest in future research to determine whether only the dorsolateral prefrontal cortex is involved, or whether adjacent areas are recruited during rTMS.

Based on the experimental studies using opioid antagonists and rTMS, as well as the clinical condition of Alzheimer degeneration, we can conclude that prefrontal executive control is critical for triggering the descending pain control system and the placebo analgesic response. In this regard, the study by Krummenacher et al. [5] opens up new and exciting directions of research that, hopefully, will shed even more light on the mechanisms of placebo analgesia.



**Fig. 1.** No prefrontal control, no placebo response. There are at least three conditions in which it is not possible to evoke placebo responses because of the disruption of the prefrontal cortex and the descending pain control system [2] with which it is connected. (A) Pharmacological blockade of opioid receptors [1,4,6]. (B) Prefrontal degeneration in Alzheimer's disease [3]. (C) Inactivation of the prefrontal cortex by repetitive transcranial magnetic stimulation [5].

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