Placebo and Opioid Analgesia-- Imaging a Shared Neuronal Network

Predrag Petrovic, *et al.*

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cating that many V1 neurons project to both pale and thick stripes (Fig. 3, F to I). By contrast, paired tracer injections ($n = 2$) in adjacent thin and pale stripes revealed virtually no double-labeled cells. Thus, the V1 projections from interpatches to pale and thick stripes arise from a common source, although most neurons do project exclusively to either a pale stripe or a thick stripe.

The V2 tracer injections revealed novel projections from other cortical layers. Layer 4A is the thinnest layer in V1 (<50 μm thick), receives a direct projection from the parvocellular system, and has a characteristic cytochrome oxidase honeycomb pattern (*26*). It sent a dual pattern of projections to V2. Thick and pale stripe injections produced 4A label in interpatch columns [Web fig. 1A (*27*)]. Thin stripe injections resulted in 4A label that coincided with patch columns [Web fig. 1B (*27*)]. This projection from layer 4A adds a second potential disynaptic route from the geniculate to V2: parvocellular → layer 4A → V2, in addition to the known koniocellular → patches → V2 pathway (*28*). Injections in all stripes labeled numerous large neurons, often Meynert cells, near the layer 5/6 border. These cells were distributed indiscriminately with respect to patches and interpatches.

These findings recast the V1-to-V2 pathway. Previous studies found projections arising from only single layers, organized in a tripartite fashion: layer 2/3 patches → thin stripes, layer 2/3 interpatches → pale stripes, and layer 4B → thick stripes (*6*, *7*). It has subsequently been recognized that considerable mixing of magno, parvo, and konio geniculate channels occurs within V1 (*29*). However, the apparent existence of three distinct, partitioned V1 projections to thick, pale, and thin stripes implied that three channels—dominated by magno, parvo, and konio inputs—survived after processing within V1. We now show that thick, thin and pale stripes all receive projections from the same V1 layers: heaviest from layer 2/3 and less from layers 4A, 4B, and 5/6. The dominant theme is not tripartite, but bipartite segregation defined by cytochrome oxidase columns: patches → thin stripes, and interpatches → pale and thick stripes (Fig. 4). These anatomical data explain the relatively poor segregation of receptive field properties in pale and thick stripes found by some investigators (*30*–*32*). Our results provide a new connectional foundation for the cortical hierarchy of visual areas (*16*, *33*). They suggest a rich intermingling of form, color, and motion signals between the streams bound for the dorsal "where" and ventral "what" pathways (*17*, *34*).

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23. Experiments were conducted in adult macaques (7 *Macaca mulatta* and 10 *M. fascicularis*) by using surgical procedures approved by the UCSF Committee on Animal Research and in accordance with NIH guidelines. Pressure injections of ~140 nl 1% CTB (List Biological Laboratories, Campbell, CA) spaced 5.5 mm apart were made along the posterior lip of the lunate sulcus in both hemispheres. Injections were made blindly with respect to cytochrome oxidase stripe type and location. Monocular enucleation was performed in 11 animals to delineate ocular dominance columns in V1. No difference in the projection pattern was observed between enucleated and control animals. After 3 to 7 days for transport, the animals were killed with pentobarbital (150 mg/kg) and perfused transcardially with 1% paraformaldehyde. The cortex was flattened (*35*), sectioned tangentially at 50 μm, slide mounted, and processed for cytochrome oxidase histochemistry (*36*). Assignment of V2 stripe type for each injection was made before CTB was visualized by silver enhancement with the IntenSE-M kit. Intensification was performed by two 30-min rinses in 0.1 M sodium acetate solution, 25 min in IntenSE-M, 30 min in sodium acetate, and 40 min in fresh IntenSE-M before a brief rinse and coverslipping.
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25. A pressure injection of 40 nl of 4% WGA-HRP was placed 1.25 mm lateral to each CTB injection. Processing for CTB and WGA-HRP was performed in free-floating sections. CTB was reacted as above, with the addition of a 5-min exposure to a 2% sodium thiosulfate solution after silver enhancement. WGA-HRP was then reacted according to a tetramethylbenzidine-ammonium molybdate protocol (*37*) followed by diaminobenzidine stabilization (*38*). Selected V1 fields 380 × 260 μm located in regions of maximum tracer overlap were examined at 400× to count each WGA-HRP, CTB, and double-labeled cell.
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39. Cells labeled with CTB in sections stained for cytochrome oxidase were photographed through crossed Polaroid filters with dark-field illumination, by using a cooled charge-coupled device (CCD) camera. Images were digitally inverted. Contour plots of label density were made with custom software written in Matlab 5.0. Contours were selected after the following image processing steps: subtracting a low-pass Fourier-filtered version of the image (cutoff frequency = 8 cyc/mm), thresholding at 3 SD above the mean image gray-level, blurring with a gaussian kernel ($\sigma_{1/2}$ = 45 μm).

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Placebo and Opioid Analgesia—Imaging a Shared Neuronal Network

Predrag Petrovic,[1] Eija Kalso,[2] Karl Magnus Petersson,[1] Martin Ingvar[1]*

It has been suggested that placebo analgesia involves both higher order cognitive networks and endogenous opioid systems. The rostral anterior cingulate cortex (rACC) and the brainstem are implicated in opioid analgesia, suggesting a similar role for these structures in placebo analgesia. Using positron emission tomography, we confirmed that both opioid and placebo analgesia are associated with increased activity in the rACC. We also observed a covariation between the activity in the rACC and the brainstem during both opioid and placebo analgesia, but not during the pain-only condition. These findings indicate a related neural mechanism in placebo and opioid analgesia.

Placebo analgesia is an important component in pain management (*1*), although the basic mechanisms are still poorly understood. At least some aspects of placebo analgesia are dependent upon endogenous opioid systems (*1*–*3*) because the effect may be partly abol-

ished by the opioid antagonist naloxone (*2*). Therefore, the underlying neurophysiology of opioid-dependent placebo analgesia can be elucidated by studying similarities and differences in the function of the opioid and placebo systems in the brain. The opioid system consists of a well-studied subsystem in the brainstem and a less well elaborated cortical opioid-dependent network (*4*, *5*). This system appears to be a likely candidate for the mediation of opioid-dependent placebo analgesia. The importance of the ACC in opioid effects has been suggested in several receptor-imaging studies of the brain (*6–10*), activation studies of opioid compounds (*11–14*), and theoretical frameworks of opioid analgesia (*15*). The rostral ACC (rACC)/ventromedial prefrontal cortex has been suggested as an important region in opioid analgesia and in other forms of pain modulation (*16–26*), which may suggest a similar involvement of higher order control of opioid-dependent placebo analgesia.

We compared the analgesic effects of a placebo treatment and a rapidly acting opioid (remifentanil) [supplement A (*27*)] in a standard pain-stimulus paradigm (*28*). We used six different conditions in the study: heat pain and opioid treatment (POP), nonpainful warm stimulation and opioid treatment (WOP), heat pain and placebo treatment (PPL), nonpainful warm stimulation and placebo treatment (WPL), heat pain only (P), and nonpainful warm stimulation only (W). We studied concomitant behavioral responses and regional cerebral blood flow (rCBF) using positron emission tomography (PET) (*29*, *30*) and compared the functional anatomy of the placebo analgesic response with that of the opioid response. We were especially interested in whether placebo analgesia and opioid effects induce a similar rCBF response in the rACC and the brainstem.

Comparison of scans in the pain conditions and in the warm conditions showed increased activity in the contralateral thalamus, in the insula bilaterally, and in the caudal ACC [Web table 1 (*27*) and Fig. 1A], all regions that have shown increased activity in previous imaging studies of pain (*31*). The opioid agonist remifentanil activated the cerebral network [Web table 2 (*27*) and Figs. 1B and 2A], which has been described previously in opioid receptor binding (*6–9*) and in rCBF studies (*11–14*). One of the major increases in rCBF was observed in the ACC and especially in the rACC. We also observed an increased activity in the lower brainstem. The subjects rated the pain intensity lower during POP compared with P in every experimental block [Web fig. 1 (*27*)]. The rCBF analysis showed that the insula, one of the major regions involved in pain processing, had an attenuated rCBF response bilaterally during POP-WOP as compared with P-W [Web table 2 (*27*)].

Although there was high interindividual variability in placebo ratings, most subjects decreased their pain intensity rating during PPL as compared with the P condition [Web fig. 1 (*27*)]. Recent experiments have revealed different types of placebo analgesia and indicate that some are dependent upon opioid systems (*32*, *33*). Placebo responses were induced in subjects

[1]Cognitive Neurophysiology Research Group, Department of Clinical Neuroscience, Karolinska Institute, Stockholm 171 76, Sweden. [2]Pain Clinic, Department of Anaesthesia and Intensive Care Medicine, Helsinki University Hospital, Finland.

*To whom correspondence should be addressed. E-mail: martin@ingvar.com

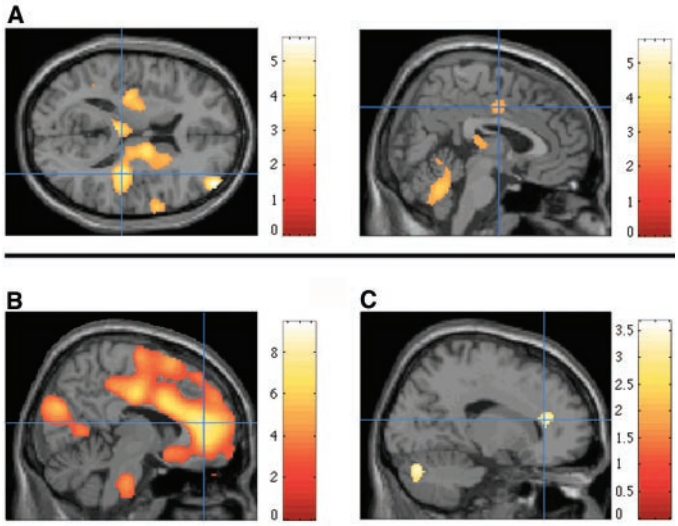

Fig. 1. (**A**) Increased activity was observed in the right (cross) and left insula (left panel, horizontal section), in the thalamus (left panel), and in the caudal ACC (right panel, sagittal section) during the main effect of pain [(POP + PPL + P)-(WOP + WPL + W)]. (**B**) The activation was most pronounced in the rACC during the main effect of opioids [(POP + WOP)-(P + W)]. Increased activity is apparent in the lower pons. (**C**) Increased activity in the same area of the rACC was also seen in the placebo effect during pain (PPL-P). The activations are presented on an SPM99-template. The activation threshold is at $P = 0.005$.

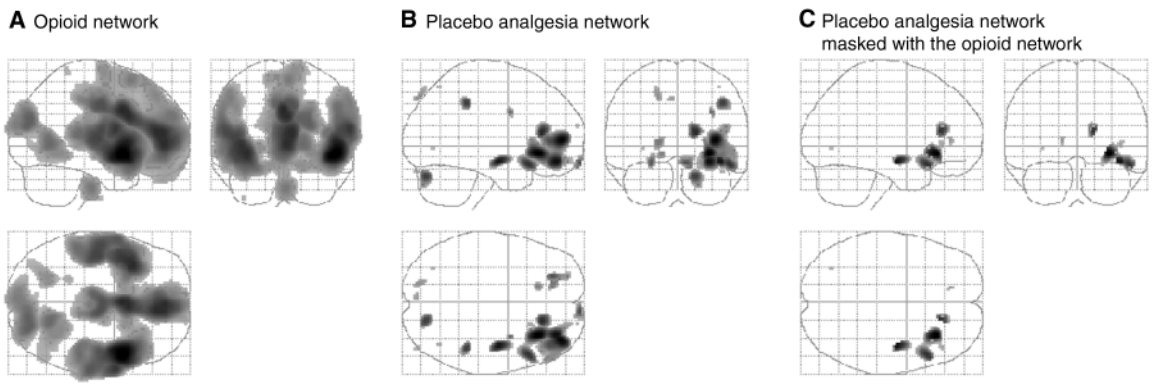

Fig. 2. (**A**) The main effect of remifentanil [(POP + WOP)-(P + W)] showed increased activity bilaterally in the rostral and caudal ACC (extending into the ventromedial prefrontal cortex), insula, orbitofrontal cortex (extending into the temporopolar areas), and lower pons. The effect was widespread in the rACC and bilaterally in the anterior insula. (**B**) The placebo effect during pain (PPL-P) showed increased activity in the orbitofrontal regions bilaterally (most extensively in the right hemisphere) and in the contralateral rACC. (**C**) To observe the overlapping activation in the two different conditions, we used the placebo analgesia effect (activation threshold at $P = 0.001$) and masked the main effect of remifentanil (same activation threshold). Several of the orbitofrontal regions in the right hemisphere and in the rACC remained after the high-threshold masking, indicating that these regions were activated both during opioid stimulation and during the pain and placebo conditions. Thus, these regions were activated both by opioids in general and by placebo during pain. The activations are presented on an SPM99-template. The activation threshold is at $P = 0.005$.

as a result of suggestions that each of the drugs used in the experiment was a potent analgesic (*28*) (i.e., expectation of pain relief) and by preceding the placebo treatment by active opioid during noxious stimulation in the first (five subjects) or second experimental block (four subjects) (i.e., opioid conditioning). Both of these placebo mechanisms can be abolished by the opioid antagonist naloxone and thus appear to be opioid dependent (*32*). Therefore, we expected similarities between activity observed in the opioid network and in the placebo analgesia network. The placebo analgesia was accompanied by increased activity in the orbitofrontal and ACC areas during PPL when compared with P [Web table 3 (*27*); Figs. 1C and 2B]. When we controlled for unspecific placebo effects (WPL-W), we observed an activation in the ACC [Web table 3 (*27*)], somewhat caudal to the rACC effect in PPL-P but rostral to the ACC activation during pain.

Previous imaging studies have shown that the rACC is more reliably activated by opioids, whereas the caudal ACC is more reliably activated by pain (*11*, *12*). This distinction was also observed here, pointing to the importance of the rACC in opioid analgesia. This area of the human ACC contains a high concentration of opioid receptors (*9*). Moreover, studies examining stimulus-induced analgesia (*16*, *18*, *19*, *21*, *23*), nitrous oxide–induced analgesia (*22*), and hypnosis-induced change in pain perception (*24*, *25*) have shown an increased activation in the rACC associated with the modulation mechanism. Rainville *et al.* (*25*) noted a similar functional division of the ACC: Pain (and unpleasantness) activated a more caudal region in the ACC, whereas the conditions involving suggestion, resulting in modulation of the pain experience, activated a more rostral part in the ACC. Hence, the increased activity in the rACC during PPL-P may support its involvement in the analgesic response mechanism during placebo. In addition, a post hoc analysis indicated that during opioid analgesia, the high placebo responders activated this area, whereas the low responders did not (Fig. 3). This suggests a relation between how effectively opioids may activate the rACC and adjacent areas and how well subjects respond to placebo during pain. Earlier studies have shown a behavioral correlation between opioid analgesia and placebo analgesia (*32*). The suggestion that the opioid system may vary among subjects is supported by the finding that the opioid receptor binding potential during rest and pain is highly specific to an individual (*10*), leading to the hypothesis that high placebo responders have a more efficient opioid system.

The placebo analgesic effect is dependent on complex cognitive information processing, including analysis of threat in a given context, expectations of treatment outcome, and desire for relief (*1*, *3*, *4*). The brainstem opioid system may thus be under cognitive control from higher order cortical regions. The ACC might play a key role in the cortical control of the brainstem during opioid analgesia (*15*, *34*) by way of fiber tracts projecting directly to the periaqueductal gray (PAG) (*35*) or by way of the medial thalamic nucleus (*36*). A similar mechanism may be necessary in placebo analgesia, which implies that a functional connection should exist between these regions, both in opioid and placebo analgesia. Regression analysis supported this hypothesis (*30*) [Web table 4 (*27*) and Fig. 4]. The activity in the rACC covaried with activity in areas close to the PAG and the pons in the POP condition. We also observed a significant covariation in activity between the rACC and the pons, and a subsignificant covariation in activity between the rACC and the PAG, during PPL. No effect was observed in the pain-only condition (P), and the differences between these regressions (POP versus P and PPL versus P) were significant. The area in the pons is in the same region as the area activated in the main effect of opioids (Fig. 1). The brainstem opioid system consists of the PAG, which alters the neuronal activity in the rostral ventromedial medulla (*4*, *5*). Additional nuclei in the pons, such as the parabrachial nuclei, also contain opioid-dependent neurons (*4*, *5*). The positive covariation between rACC and these regions during POP and PPL, but not during P, may thus indicate that the higher cortical systems may, in specific circumstances, exert direct control over the analgesic systems of the brainstem not only during opioid analgesia but also during placebo analgesia.

The increased activity in the lateral orbitofrontal cortex during placebo analgesia is of interest because previous PET studies have implicated this region in cognitively driven pain modulation (*25*, *37*). Stimulation of this region in rats (*38*) and primates (*39*) also induces analgesia. A right predominance of the orbitofrontal activation was observed during placebo analgesia, but interpretation of this finding is uncertain because it may reflect a threshold effect. Placebo analgesia

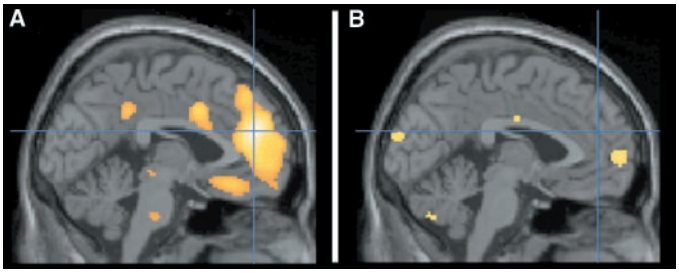

Fig. 3. Post hoc analysis comparing the activation of the rACC in high placebo responders with that in low responders revealed no significant differences in PPL-P between groups. However, activation of the rACC and adjacent areas by the high placebo responders was significant during POP-P [(x, y, z) = (−2, 46, 22); Z = 4.77] (**A**), whereas activation by the low responders was not significant (**B**). The difference between groups was significant in the rACC/ventromedial prefrontal cortex [(x, y, z) = (−2, 46, 26); Z = 3.24]. The activation threshold is at P = 0.005.

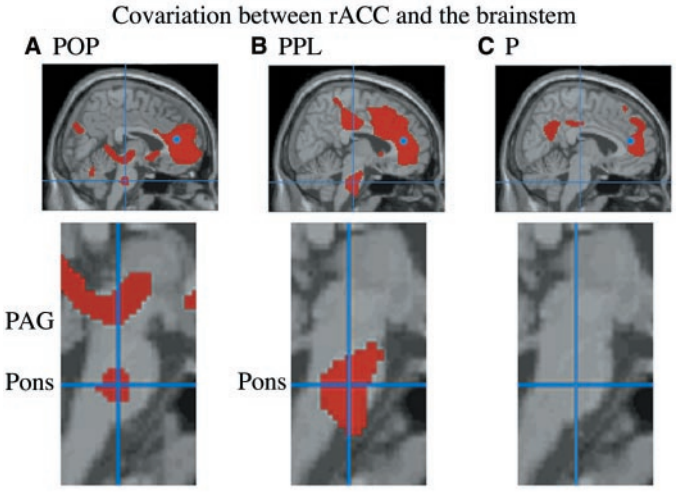

Fig. 4. (**A** to **C**) Covariation of activity in brainstem regions with activity in the rACC (denoted by the blue sphere) in different pain conditions. (A) Activity in the rACC covaried with activity in the PAG and in the lower pons/medulla during the POP condition. These covariations were significantly greater during POP as compared with P [Web table 4 (*27*)]. (B) A similar covariation between the rACC and the lower pons/medulla was observed during the PPL condition. This covariation was significantly greater during PPL as compared with P [Web table 4 (*27*)]. (C) No such regressions were observed during the P condition. The activations are presented on an SPM99-template and a more detailed image of the brainstem indicating the approximate position of the PAG and the pons. The threshold of activation is at P = 0.005.

seems to activate a more rostral part of the orbitofrontal cortex as compared with the general opioid effect. Because the orbitofrontal cortex has dense connections with both the ACC and the brainstem (*40*), which have also been implicated in placebo analgesia, we suggest that these regions belong to a network that uses cognitive cues to activate the endogenous opioid system.

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28. Nine subjects participated in the study, which was approved by the local ethics and radiation safety committees [supplement B (*27*)]. Tonic pain was induced by heat stimulation (48°C, 70-s duration) on the dorsum of the left hand. The control stimulation consisted of a tonic stimulation of 38°C. The stimulation onset time was 10 s before the scan. The subjects were informed that two potent analgesics would be used in the experiment and that one of these drugs was an opioid. The drugs—either remifentanil (0.5 μg/kg) [(*41*, *42*); supplement A (*27*)] or saline (placebo)—were injected intravenously (i.v.) 40 s before each stimulation. In one-third of the scans (both pain and warm stimulation) no drug was injected, and the subjects were told that these stimuli would be given without prior analgesics. Each subject underwent 12 scans in two blocks with the order of the conditions randomized within the block. Each subject tested the painful stimulation in a training session during the week preceding the PET study. The subjects rated the pain intensity after each scan using a visual analog scale (VAS) [supplement B (*27*)].
29. Standard rCBF PET procedures were used (www.fil.ion.ucl.ac.uk/spm) (*31*, *43*, *44*). Limiting the search area to a predefined network allowed us to consider any activation with $P < 0.001$ as significant [supplement C (*27*)].
30. A regression analysis was performed between rACC and the brainstem. Limiting the search area allowed for a threshold of $P < 0.005$ [(*45*, *46*); supplement D (*27*)].
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