

# Dose-dependent Effects of Propofol on the Central Processing of Thermal Pain

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**Background:** Anatomic and physiologic data show that multiple regions of the forebrain are activated by pain. However, the effect of anesthetic level on nociceptive input to these regions is not well understood.

**Methods:** The authors used positron emission tomography to measure the effect of various concentrations of propofol on pain-evoked changes in regional cerebral blood flow. Fifteen volunteers were scanned while warm and painful heat stimuli were presented to the volar forearm using a contact thermode during administration of target propofol concentrations of 0.0  $\mu\text{g/ml}$  (alert control), 0.5  $\mu\text{g/ml}$  (mild sedation), 1.5  $\mu\text{g/ml}$  (moderate sedation), and 3.5  $\mu\text{g/ml}$  (unconsciousness).

**Results:** During the 0.5- $\mu\text{g/ml}$  target propofol concentration (mild sedation), the subjects' pain ratings increased relative to the alert control condition; correspondingly, pain-evoked regional cerebral blood flow increased in the thalamus and the anterior cingulate cortex. In contrast, when subjects lost consciousness (3.5  $\mu\text{g/ml}$ ), pain-evoked responses in the thalamus and the anterior cingulate cortex were no longer observed, whereas significant pain-evoked activation remained in the insular cortex.

**Conclusion:** These data show that propofol has a dose-dependent effect on thalamocortical transfer of nociceptive information but that some pain-evoked cortical activity remains after loss of consciousness.

ADVANCES in human brain-imaging techniques have led to the identification of multiple brain regions that are activated by painful stimuli.<sup>1-3</sup> However, images acquired using both positron emission tomography (PET) and functional magnetic resonance imaging may not reflect only neuronal activity related to the perception of pain, but also coupled epiphenomena of the pain experience, such as autonomic, homeostatic, or behavioral reactions.

Anatomic and physiologic evidence repeatedly points toward a network of cortical regions that subserve the pain experience. Nociceptive input is communicated *via* the somatosensory thalamus to the primary and secondary somatosensory cortices (S1 and S2),<sup>4,5</sup> where information related to stimulus intensity, location, and

temporal aspects are thought to be encoded.<sup>6-10</sup> However, the anterior cingulate cortex (ACC) and the insular cortex (IC) also respond to pain stimuli in a graded manner,<sup>9</sup> suggesting their possible importance in pain perception. Both ACC and IC receive direct input from thalamic nuclei,<sup>11,12</sup> and single-unit recordings within the ACC of rabbits,<sup>13</sup> monkeys,<sup>14</sup> and humans<sup>15</sup> have revealed nociceptive neurons. Pain-related activity in ACC may be particularly important for the affective dimension of pain because ACC activity correlates with pain unpleasantness more strongly than other cortical regions.<sup>16</sup> The IC has been implicated in nociceptive and innocuous thermal processing, but other data suggest its importance in autonomic regulation, cardiovascular functioning, and homeostatic regulation.<sup>12,17,18</sup>

To evaluate the possible participation of sensory and limbic regions in pain processing, we examined nociceptive transmission during different levels of propofol anesthesia, which alters pain perception at subanesthetic doses. We have previously shown that propofol sedation and anesthesia interfere with thalamocortical information transfer of a vibrotactile stimulus.<sup>19</sup> However, because noxious stimuli induce a wide range of physiologic responses, we hypothesized that the activation of only some anatomically discrete forebrain regions would correspond with propofol-induced changes in pain perception. Further, these activations would be distinguishable from other pain-evoked forebrain activations that could correspond to the broader epiphenomena of pain processing and would be less directly influenced by the level of sedation (*e.g.*, autonomic function, homeostasis, behavioral reactions). Therefore, in the current study, we used the anesthetic propofol to induce sedation and loss of consciousness and examined its influence on pain-evoked neural activation.

## Materials and Methods

### Subjects

Fifteen healthy subjects (six men, nine women; all right-handed) aged between 18 and 33 yr (mean, 24.0 yr) participated. Before the study, all subjects underwent a thorough medical evaluation. They were pain-free and had no history of neurologic disorders. All procedures were approved by the Ethics and Research Committee of the Montreal Neurologic Institute and Hospital (Montreal, Quebec, Canada). Before initiating study-specific procedures, subjects signed a written consent form.

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### Stimulation Procedures

During each 1-min PET scan, thermal stimuli were administered to the subject's left volar forearm using a contact thermode (1 cm<sup>2</sup> for 11 subjects and 9 cm<sup>2</sup> for 4 subjects). Both thermode sizes have previously been shown to reliably induce pain and pain-evoked cerebral activation.<sup>1,2,20</sup> Twelve 5-s stimuli were presented manually, using a single thermode, to six loci on a 3 × 2 matrix with two nonconsecutive stimulus presentations at each locus. The thermode temperature was either slightly warm (35°C) or painfully hot (43.5°–49.5°C, adjusted for each subject to produce moderate pain). In a preexperimental training session, subjects were familiarized with the rating scales and evaluated the intensity of a range of noxious stimuli (42°–50°C) to determine temperatures that were rated as moderately painful. For each subject, a temperature was chosen that corresponded to a pain intensity rating of approximately 60 on a 100-point magnitude-estimation scale. During the scanning sessions, subjects rated both pain intensity and unpleasantness after each scan using separate magnitude-estimation scales of 0–100. Verbal descriptor endpoints were given for each scale. For the intensity scale, 0 was defined as “no burning, pricking, stinging sensation,” the most frequently chosen words describing the sensory aspect of heat pain in an independent study,<sup>21</sup> and 100 indicated an “extremely intense pain sensation.” For the unpleasantness scale, 0 was designated as “not at all unpleasant,” and 100 denoted “extremely unpleasant.” To avoid ceiling effects, subjects were instructed that responses could surpass 100 if larger values were needed to describe sensations relative to previous ratings.<sup>22,23</sup> However, no subject used numbers greater than 100. If the stimulus was not rated as painful, the subject was instructed to rate warmth intensity on a 0–100 magnitude-estimation scale. For the warmth scale, 0 was defined as “no warm sensation,” and 100 indicated “just hot, barely painful.”

### Experimental Design

Subjects received one trial each of pain and warm stimulation during each of the following target propofol concentrations: 0.0 µg/ml (alert control), 0.5 µg/ml (mild sedation), 1.5 µg/ml (moderate sedation), and 3.5 µg/ml (unconsciousness; unable to respond to verbal stimuli). An additional pain scan was added during the alert control condition with subjects being told to withdraw the arm every two to three stimulations to mimic withdrawal responses that sometimes occurred during moderate propofol concentrations. This condition was used to identify areas in which activity observed during pain conditions might be secondary to stimulus-evoked movement under propofol anesthesia. During all conditions, subjects were instructed to rest quietly with their eyes closed and to focus on the stimulation. The alert control condition was always presented first, followed

by the three target propofol concentrations in ascending order. The inclusion of a placebo control group would have optimized our ability to assess temporal changes in pain. However, in previous studies, using similar stimulation and scanning techniques, we have shown that subjects exhibited no habituation or sensitization in either pain ratings or regional cerebral blood flow (rCBF) activations.<sup>1,2</sup> The stimulus order of the warm (35°C) and pain (43.5°–49.5°C) scans was counterbalanced across subjects within each condition.

### Propofol Infusion

In addition to the alert control condition (baseline, 0.0 µg/ml propofol in plasma), three levels of propofol were targeted: 0.5 µg/ml (mild sedation), 1.5 µg/ml (moderate sedation), and 3.5 µg/ml (unconsciousness; and increased in 0.5-µg/ml increments until unconsciousness was achieved). Propofol was infused *via* a forearm venous catheter (on the side not used for pain stimulation) using a computer-controlled infusion pump (for details see Bonhomme *et al.*<sup>19</sup>). As in our previous studies,<sup>19</sup> to limit the time spent in the scanner, as well as the duration of anesthesia, propofol concentrations were always presented in ascending order. This served to avoid delays related to the elimination of the drug from the brain if nonascending orders had been used. At the lowest concentration of propofol, the subjects were awake and mildly sedated and promptly followed commands to rate their pain. At the intermediate concentration, the subjects were deeply sedated, their speech was sluggish, and responses to verbal commands were slow. At the highest concentration, the subjects were unconscious and did not produce pain ratings on command.

To ensure the subjects' safety, they were under the care of a certified anesthesiologist. Electrocardiographic activity, pulse rate, oxygen saturation, end-tidal carbon dioxide, and blood pressure (invasive for 10 subjects, noninvasive for 5) were monitored. Throughout the course of the experiment, subjects wore a nonrebreathing oxygen mask, which had a flow rate of 3 l/min. Airway support (chin lift) was given to all subjects. Resuscitation equipment was immediately accessible.

Arterial blood samples were drawn from a catheter inserted into the right radial artery (opposite side to thermal stimulation). Samples were obtained at least 5 min after the target plasma concentration was reached and 2 min before the initiation of each scan. Determination of the plasma concentration of propofol by high-performance liquid chromatography was assessed by France Varin, Ph.D. (Faculté de Pharmacie, Université de Montréal, Montreal, Quebec).<sup>24</sup>

### Scanning Procedures

Regional cerebral blood flow was measured using three-dimensional high-resolution PET (63 slices, 8.11 mm full-width, half-maximum in x, y, and z planes; Siemens

Table 1. Vital Signs

Hemodynamic Variable	0.0 $\mu\text{g/ml}$		0.5 $\mu\text{g/ml}$		1.5 $\mu\text{g/ml}$		3.5 $\mu\text{g/ml}$	
	Warm	Pain	Warm	Pain	Warm	Pain	Warm	Pain
Heart rate, beats/min	59.4 (10.6)	60.8 (12.2)	57.3 (10.6)	57.5 (9.8)	58.8 (8.7)	60.7 (9.4)	66.8 (9.8)	66.3 (8.6)
Systolic blood pressure, mmHg	134.6 (7.0)	135.5 (7.7)	125.7 (7.6)	128.4 (5.4)	110.7 (8.7)	116.8 (9.3)	97.2 (10.8)	97.7 (11.0)
Diastolic blood pressure, mmHg	66.2 (5.3)	66.9 (4.7)	62.6 (4.9)	64.5 (5.1)	57.1 (6.2)	60.3 (7.1)	52.9 (8.8)	53.2 (7.6)
SpO <sub>2</sub> , %	99.2 (0.8)	99.3 (0.5)	98.8 (0.8)	98.8 (0.7)	98.2 (0.8)	98.1 (1.0)	97.7 (1.1)	97.7 (1.2)
End-tidal CO <sub>2</sub> , mmHg	38.0 (4.7)	38.1 (4.8)	36.9 (6.2)	35.9 (6.8)	37.1 (9.3)	35.6 (9.3)	41.0 (7.2)	40.6 (7.2)
Respiration, breaths/min	16.0 (3.2)	15.5 (4.4)	16.2 (2.4)	15.5 (4.4)	17.0 (2.1)	17.3 (2.7)	16.5 (2.9)	17.0 (3.2)

Values are presented as mean (SD).

CO<sub>2</sub> = carbon dioxide; SpO<sub>2</sub> = oxygen saturation measured by pulse oximetry.

ECAT HR<sup>+</sup><sup>®</sup>; Siemens Medical Solutions, Malvern, PA) after bolus injection of H<sub>2</sub><sup>15</sup>O (10 mCi) without arterial blood sampling.<sup>25</sup> Stimulus onset was simultaneous with bolus injection and 1-min scans started approximately 15 s after injection. Data were collected in two sequential frames of 40 and 20 s. Results reported here are for the entire 60 s of data acquisition, which were found to produce the highest signal-to-noise ratio in preliminary analyses. An interscan interval of 12–15 min allowed the tracer to decay to background levels and minimized sensitization to repeated thermal stimulation. Subjects wore insert earphones connected to a microphone through which they received instructions before each scan. During each scan, the microphone was turned off, and subjects remained immobile and kept their eyes closed. After completion of the PET sessions, each subject underwent a high-resolution anatomic magnetic resonance imaging session (one hundred sixty 1-mm slices acquired on a 1.5-T Gyroscan system; Philips Medical Systems, Andover, MA).

#### Image Processing and Statistical Analysis

Each PET and magnetic resonance imaging volume was aligned and transformed<sup>26</sup> into a standardized space<sup>27</sup> to allow for intersubject averaging and localization of rCBF changes. PET volumes were smoothed with a 14-mm (full-width, half-maximum) Hanning filter and normalized to the average brain count. Data were analyzed using converging methods. Peak activation maps of pain-related changes in rCBF for each subject were obtained by subtracting normalized PET data recorded during the warm (35°C) scans from those of the pain (43.5°–49.5°C) scans during the alert control and each propofol condition. A peak activation map was also derived by subtracting the pain (43.5°–49.5°C) alert control scans from pain (43.5°–49.5°C) alert control movement scans to identify structures activated by stimulus-evoked movement.

Resulting volumes of pain-related changes in rCBF were averaged across sessions, and statistical *t* maps

were derived using the methods of Worsley *et al.*<sup>28</sup> Using a strict statistical criterion, we performed a global search of the brain that requires no *a priori* hypotheses about where activations would be expected.<sup>28</sup> The significance threshold was adjusted for multiple comparisons over the entire gray matter brain volume scanned ( $t = 4.5$ ;  $P < 0.05$ ). This correction gives an expected false-positive rate of 0.016 over the gray matter volume and corresponds to an uncorrected *P* value of 0.0001.<sup>28</sup> In addition, directed searches of rCBF changes were performed for sites at which activations have been observed related to painful heat stimuli. These sites included the contralateral (*i.e.*, right side) S1, S2, ACC, IC, thalamus, and cerebellum.<sup>1,2,9</sup> The significance threshold for these *a priori* directed searches was  $t = 2.63$  ( $P < 0.05$ ), after correction for multiple comparisons involving a six-structure search volume.<sup>28</sup>

## Results

#### Propofol Concentrations

The plasma propofol concentrations were available for 10 subjects and were calculated (mean  $\pm$  SD) as  $0.50 \pm 0.12$ ;  $1.77 \pm 0.27$ ; and  $3.73 \pm 0.84$  for the target propofol concentrations of 0.5, 1.5, and 3.5  $\mu\text{g/ml}$ , respectively. Propofol plasma concentrations were not available for five subjects, either because no arterial line could be placed or because problems occurred during the blood sample analysis. Therefore, the mean of the measured plasma concentrations of the 10 available subjects was used to approximate the average plasma concentrations.

#### Vital Signs

The means and SDs of the vital signs for the 15 subjects across levels of anesthesia are shown in table 1. The painful stimuli did not significantly affect any of these variables. There was a significant decrease in systolic blood pressure across levels of anesthesia (repeated-



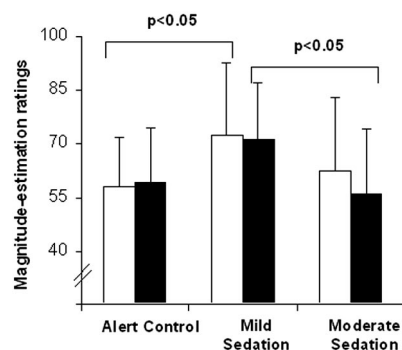


Fig. 1. Ratings for pain intensity (open bars) and pain unpleasantness (filled bars) evoked by a 47°C stimulus on subjects' volar forearms across conditions ( $\pm$  SD). Ratings were not available for four subjects who were arousable but could not produce an intelligible verbal response during the target propofol concentration of 1.5  $\mu$ g/ml (moderate sedation). Therefore, data are presented for the 11 subjects who rated the pain during all three conditions.

measures analysis of variance,  $P < 0.05$ ), but there was no significant alteration of any other reported vital sign.

#### Magnitude-estimation Ratings

Figure 1 shows that ratings of pain intensity ( $F = 6.07$ ,  $P < 0.05$ ) and unpleasantness ( $F = 4.44$ ,  $P < 0.05$ ) were significantly different across conditions, with the highest ratings occurring during the 0.5- $\mu$ g/ml target propofol concentration (mild sedation). *Post hoc* analysis revealed that pain intensity ratings were significantly higher during the 0.5- $\mu$ g/ml target propofol concentration (mild sedation) than the alert control condition ( $P < 0.05$ ), with a similar trend when the 0.5- $\mu$ g/ml target concentration (mild sedation) was compared with the 1.5- $\mu$ g/ml target concentration (moderate sedation;  $P = 0.08$ ), suggesting that the low concentration of propofol produces hyperalgesia. Pain unpleasantness ratings were also highest during the 0.5- $\mu$ g/ml target propofol concentration, but in this case, the ratings during the 0.5- $\mu$ g/ml target concentration were significantly higher than those during the 1.5- $\mu$ g/ml target concentration ( $P < 0.05$ ), with a similar trend when the 0.5- $\mu$ g/ml target was compared with the alert control condition ( $P = 0.09$ ).

#### Brain Imaging

**Pain-related Changes in rCBF.** To evaluate regions of pain-related activation, rCBF maps acquired during innocuous warm stimulation were subtracted from those acquired during painful heat stimulation. Results of directed and global searches are summarized in table 2 and figure 2. As can be seen in table 2, there were only a limited number of pain-evoked rCBF changes that reached the global significance criterion ( $t = 4.5$ ). Similarly, because of the limited number of scans and limited number of subjective ratings of pain, a covariate analysis did not reveal any significant correlations between rCBF

and pain intensity or unpleasantness, so these data are not presented.

For the alert control condition (table 2 and fig. 2), there were significant pain-related increases in the ACC, the thalamus, the cerebellum, and the brainstem. A directed search did not reveal significant peaks in the S1, the S2, or the IC, but trends were observed in these regions (table 2). During the target propofol concentration of 0.5  $\mu$ g/ml (mild sedation) (table 2 and fig. 2), a directed search revealed significant increases in the ACC, the IC, the thalamus, and the cerebellum. A directed search failed to find a significant peak in the S1; however, subthreshold activation was observed in the S2 and the brainstem. Pain-related increases in rCBF during the 1.5- $\mu$ g/ml target concentration (moderate sedation) did not reach significance in the S1, the S2, the ACC, or the IC, but a significant pain-related increase in rCBF was still present in the thalamus and the cerebellum (table 2 and fig. 2). At the 3.5- $\mu$ g/ml propofol target (unconsciousness), the only remaining significant activation was in the IC (table 2 and fig. 3). However, subthreshold trends were observed in the cerebellar vermis and S2 regions (table 2 and figs. 2 and 3).

**Movement-related Changes in rCBF during Alert Control Condition.** Because some uncoordinated movements occurred after stimulation during the target propofol concentrations of 1.5  $\mu$ g/ml (moderate sedation) and 3.5  $\mu$ g/ml (unconsciousness), we examined the effects of movement on rCBF by comparing the painful stimulation/movement scan data with those of the painful stimulation without movement (table 3). A global search revealed a movement-related increase in rCBF in the primary motor cortex, the S2, the supplementary motor area, the superior parietal lobule, the S1, the frontal lobe, and the cerebellum. No movement-related changes were observed in the regions of the ACC, the IC, or the thalamus that were activated by the painful stimuli.

#### Discussion

The results of the current experiment show that increasing concentrations of propofol alter both pain perception and forebrain pain-evoked activity, as measured by changes in rCBF. At a target propofol concentration of 0.5  $\mu$ g/ml (mild sedation), both pain perception and activity in the ACC and the thalamus were enhanced, and as the subjects progressed toward loss of consciousness, the pain-evoked rCBF increase in ACC was first lost during the 1.5- $\mu$ g/ml concentration (moderate sedation), followed by that in the thalamus during the 3.5- $\mu$ g/ml concentration (unconsciousness). Pain-evoked activity in other cortical areas, including the IC, the S2, the cerebellum, and the brainstem, showed an inconsistent relation with the propofol dose.

Table 2. Pain-related Activations

Region	Coordinates			t Score
	x	y	z	
Alert control* (pain-warm)				
M1/S1	33	-18	59	2.08
S2	41	-23	19	2.51
ACC	4	6.4	38	2.86
IC (middle/posterior)	29	13	13	2.01
Thalamus	13	-16	0	3.39
Cerebellum (hemisphere)	17	-59	-23	4.38
Cerebellum (vermis)	4	-49	-8	2.64
Brainstem#	-5	-37	-18	4.61
Mild sedation† (pain-warm)				
S1		No activation above 2.0		
S2/posterior insula	33	-14	12	2.43
ACC	15	17	36	4.11
IC (middle/posterior)	25	5	10	3.40
Thalamus#	9	-11	6	6.01
Cerebellum (vermis)	4	-54	-14	2.69
Moderate sedation‡ (pain-warm)				
S1		No activation above 2.0		
S2		No activation above 2.0		
ACC		No activation above 2.0		
IC		No activation above 2.0		
Thalamus#	9	-19	2	5.08
Cerebellum (hemisphere)#	24	-61	-23	4.82
	17	-64	21	4.77
	-13	-56	-18	7.17
	-28	-66	-21	5.54
Unconsciousness§ (pain-warm)				
S1		No activation above 2.0		
S2	41	-16	17	2.24
ACC		No activation above 2.0		
IC	31	-6	11	2.92
Thalamus		No activation above 2.0		
Cerebellum (vermis)	0	-49	-11	2.32

Stereotaxic coordinates (x = medial-lateral, x > 0 denotes right hemisphere; y = anterior-posterior; z = superior-inferior) of peak voxel based on the Talairach and Tournoux atlas.<sup>27</sup>

\* Target propofol concentration of 0.0 µg/ml. † Target propofol concentration of 0.5 µg/ml. ‡ Target propofol concentration of 1.5 µg/ml. § Target propofol concentration of 3.5 µg/ml. || Significant for directed search,  $t_{\alpha} = 2.63$ ;  $P < 0.05$ . # Significant for global search,  $t_{\alpha} = 4.5$ ;  $P < 0.05$ .

ACC = anterior cingulate cortex; IC = insular cortex; M1 = primary motor cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex.

An important variable that would be expected to change with different levels of propofol sedation is attention. We have observed in previous studies that attentional state can alter both pain perception and pain-evoked cortical activation.<sup>29</sup> In the current study, we cannot exclude the contribution of attentional changes to our results. However, our finding of increased activation at moderate sedation is inconsistent with such an interpretation because moderate sedation should reduce focused attention, not increase it.

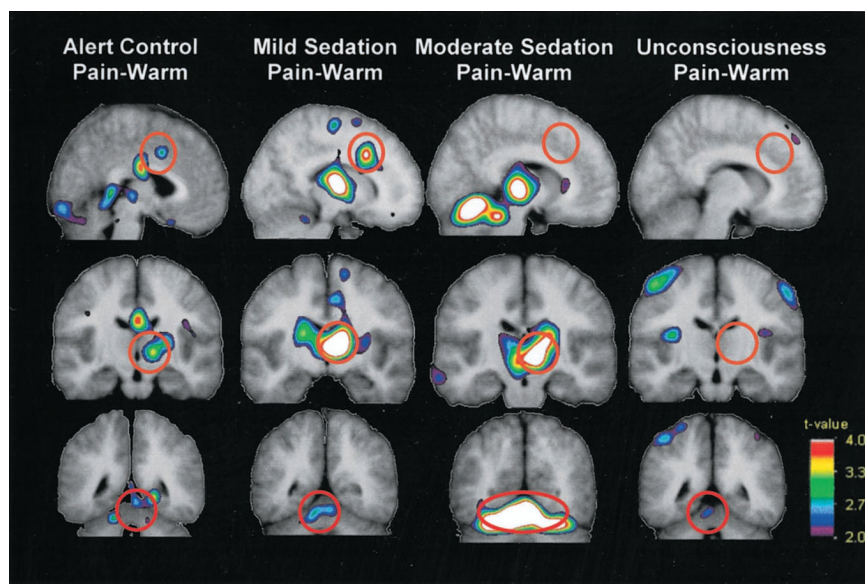
The finding of enhanced pain perception, *i.e.*, hyperalgesia, at the target propofol concentration of 0.5 µg/ml (mild sedation) is similar to previous observations during pilot testing of our experimental paradigm (unpublished data, presented in abstract form at the Society of Neuroscience, New Orleans, Louisiana, October 25–30, 1997) and to findings of Petersen-Felix *et al.*<sup>30</sup> of mechanical hyperalgesia after sedative concentrations of propofol. The mechanism of this hyperalgesia is not known, but

because propofol has been shown to depress spinal nociceptive transmission in an isolated spinal cord model,<sup>31</sup> the enhanced perception may involve supraspinal mechanisms.

#### Pain-evoked Cortical Increases in rCBF

Pain-evoked rCBF changes in the ACC increased during the hyperalgesia condition and decreased again as pain ratings, particularly unpleasantness ratings, decreased. Such changes in cerebral blood flow suggest that ACC activity could contribute to the appreciation of pain and are consistent with other types of evidence implicating the ACC in pain perception. Nociceptive neurons have been identified in the ACC using single-unit recordings in humans,<sup>15</sup> monkeys,<sup>14</sup> and rabbits.<sup>13</sup> Further, among human brain-imaging studies, ACC is probably the cortical region most reliably activated by pain.<sup>32,33</sup> Studies that used pharmacologic manipulations to reduce pain perception also showed reduced pain-evoked ACC activity.

Fig. 2. Cortical activation in anterior cingulate cortex (*top*), thalamus (*middle*), and cerebellum (*bottom*) evoked by noxious heat stimulation during alert control and target propofol concentrations of 0.5  $\mu\text{g/ml}$  (mild sedation), 1.5  $\mu\text{g/ml}$  (moderate sedation), and 3.5  $\mu\text{g/ml}$  (unconsciousness). All images show subtractions of noxious heat minus warm. The *left side* of the images corresponds to the left side of the brain. The *color scale* shows *t* values are between 2.0 and 4.0.

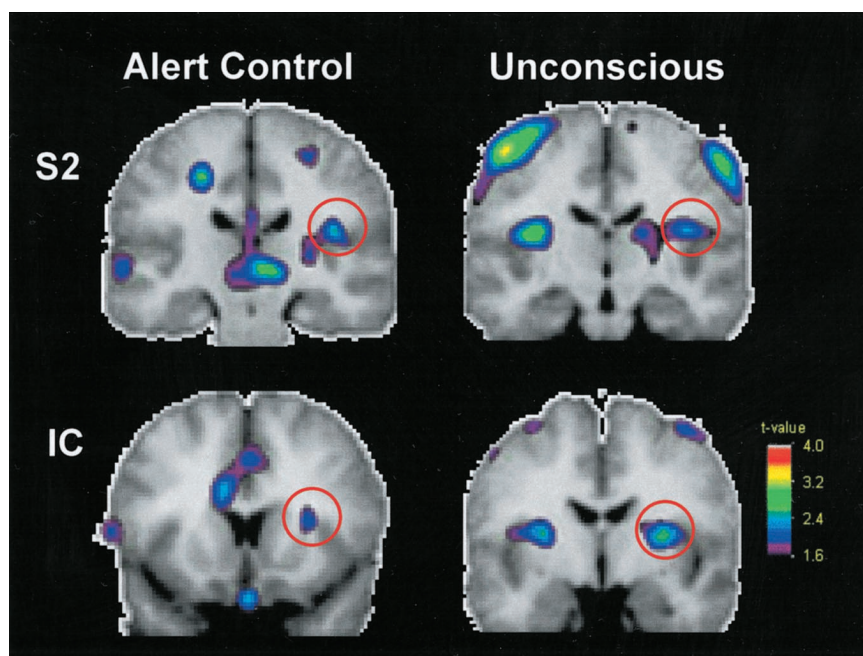


For example, Casey *et al.*<sup>34</sup> observed that fentanyl reduced both pain ratings and pain-evoked ACC activity. Similar to our findings, Gyulai *et al.*<sup>35</sup> showed that ACC pain-evoked activity was reduced commensurate with reduced pain perception after conscious sedation with nitrous oxide.

Pain-evoked rCBF changes in the IC showed a less systematic relation to both propofol concentration and pain perception. Activity in the mid insula showed similar levels during the alert control, target propofol concentration of 0.5  $\mu\text{g/ml}$  (mild sedation), and target propofol concentration of 3.5  $\mu\text{g/ml}$  (unconsciousness) conditions but was reduced during the target propofol concentration of 1.5  $\mu\text{g/ml}$  (moderate sedation). This finding suggests that pain-evoked IC activity may have a

less direct role in the perception of pain than does the ACC. Based on findings that pain activates the IC in human brain-imaging studies,<sup>2,3,9,10,35</sup> investigators have concluded that IC is important for pain perception. This interpretation is supported by reports of pain evoked by direct insular stimulation in patients.<sup>36</sup> Lesions of IC have been reported to lead to the condition of pain asymbolia, in which patients show inappropriate responses to pain.<sup>37</sup> However, when hypnotic suggestions were used to alter pain perception, activity in the ACC correlated with the perception, whereas that in the IC did not.<sup>16</sup> Other evidence shows that the IC has a particularly important role in autonomic control and homeostatic change, so that its activation during pain may be partially related to these factors.<sup>12,18</sup> Therefore,

Fig. 3. Cortical activation in secondary somatosensory (S2) and insular (IC) cortices evoked by thermal stimulation during alert control and unconsciousness. The contralateral S2 and IC showed trends toward significant activation during the alert control state, and these activations remained after loss of consciousness. The nonsignificant ipsilateral activations observed in these areas after loss of consciousness are similar to those often seen during conscious states. The *left side* of the images corresponds to the left side of the brain. The *color scale* shows *t* values are between 1.6 and 4.0.





**Table 3. Movement-related Changes during Alert Control Condition\***

Region	Coordinates			t Scores
	x	y	z	
Positive peaks				
Primary motor cortex	-1	-2	60	8.31
Secondary sensory cortex	58	-35	27	7.93
	-48	-37	30	6.20
Superior parietal lobe	9	-57	62	7.84
	-8	-57	63	6.72
Primary sensory cortex	28	-33	63	7.52
Frontal lobe	27	-13	63	7.49
Supplementary motor area	28	39	38	5.01
	40	-1	54	4.80
Cerebellum	-27	-52	-24	4.79
	-7	-54	-17	4.67
Negative peaks				
Medial front-orbital gyrus	1	24	-18	-7.37
Frontal lobe white matter	31	37	-8	-5.68
Middle temporal gyrus	64	-30	-11	-4.75
Middle frontal gyrus	40	53	5	-4.61
Cingulate region	9	41	-8	-4.50

Stereotaxic coordinates (x = medial-lateral, x > 0 denotes right hemisphere; y = anterior-posterior; z = superior-inferior) based on the Talairach and Tournoux atlas.<sup>27</sup>  $t_{\alpha} = 2.63$  (see Materials and Methods).

\* Alert control with pain and movement minus alert control with pain.

the IC activation we observed after loss of consciousness may be related to autonomic responses evoked by the noxious stimulation. Oppenheimer *et al.*<sup>39</sup> have demonstrated the importance of the IC in blood pressure change<sup>38</sup> and the consequence of its disruption after an IC lesion. Other evidence suggests a possible role of the IC in pain modulation. In rats, an opioid-responsive site has been identified in the rostral agranular insula,<sup>40</sup> and in humans, pain-evoked IC activity is reduced by fentanyl administration.<sup>34</sup> Therefore, although the IC seems to be an important structure in nociception and/or antinociception, pain-related activity in this region may represent more than just perceptual factors.

The S2 is activated by painful stimuli in a substantial majority of PET and functional magnetic resonance imaging studies.<sup>29,33</sup> Evoked-potential, single-unit, lesion, brain tumor, and neuroimaging-derived data all point toward a role for the S2 in the appreciation of pain and sensorial aspects pertaining to the stimulus parameters of the noxious stimulus.<sup>1,41-44</sup> In our study, we did not observe a significant rCBF increase in the S2 during the alert state, but there was a strong trend ( $t = 2.51$ ). A similar nearly significant peak was observed during target propofol concentrations of 0.5  $\mu\text{g/ml}$  (mild sedation;  $t = 2.43$ ) and 3.5  $\mu\text{g/ml}$  (unconsciousness;  $t = 2.24$ ) but not during the 1.5- $\mu\text{g/ml}$  target (moderate sedation). Because none of the S2 peaks reached statistical significance, it is difficult to draw conclusions about the relation of the S2 and the appreciation of pain, but our data suggest that the relation is less systematic than that observed in the ACC.

The S1 is activated by painful stimuli in approximately

one half of PET and functional magnetic resonance imaging studies.<sup>29</sup> Significant pain-evoked rCBF increases in the S1 were not present in this study despite its activation in previous studies conducted in our laboratory using similar stimuli.<sup>1,2,10</sup> One explanation for this difference is that the previous studies presented at least two repetitions of each stimulus to each subject, whereas the current study used only one repetition of each condition. Therefore, the previous studies may have produced data with higher signal-to-noise ratios. In addition, to reduce the likelihood of subject movement, which can be observed under propofol anesthesia during painful stimulation, the thermal stimuli used during the current study were less intense than those used previously, further reducing signal strength. Therefore, because of the lack of significant S1 activation in any condition, the results of the current study tell us little about the role of the S1 in the appreciation of pain. Other data indicate that the S1 may be more important in pain localization than in the perceived unpleasantness of the experience.<sup>44</sup>

### Cerebellar Activity

We observed significant pain-evoked cerebellar rCBF increases during alert control and target propofol concentrations of 0.5 and 1.5  $\mu\text{g/ml}$ . There was also a near-significant activation during the 3.5- $\mu\text{g/ml}$  concentration, when subjects were unconsciousness, thus suggesting that pain-evoked cerebellar activation may be independent of conscious pain perception. Pain-related cerebellar activity has been observed in a number of human brain-imaging studies,<sup>9,34</sup> as well as in electrophysiologic studies in rats.<sup>45</sup> Saab *et al.*<sup>45</sup> proposed that the primary role of nociceptive cerebellar activity may be in the modulation of peripheral nociceptive events.

The large cerebellar activation observed in our study during the target propofol concentration of 1.5  $\mu\text{g/ml}$  (moderate sedation) was most likely caused by factors other than pain transmission. During this condition, seven subjects showed uncoordinated, unintentional movements of the arms and legs during painful stimulation. Such movements were noted throughout the experiments, and an analysis was performed that correlated for each subject the amount of movement with rCBF. This analysis revealed a peak in the same region of the cerebellum as that observed during pain minus control. Similarly, Jenkins *et al.*<sup>46</sup> observed a systematic relation between movement frequency and cerebellar activation. Further, during the intentional movement condition of our study, we also observed activation in a similar region of cerebellum. Therefore, it is quite likely that the large cerebellar activation during the target propofol concentration of 1.5  $\mu\text{g/ml}$  (moderate sedation) is related to parameters of movement and not to nociceptive transmission.

### Pain-evoked Thalamic Activity

The alterations in thalamic blood flow during propofol-induced changes in consciousness seemed to correspond better with perceptual changes than did those in any cortical area. When the perceived pain intensity increased during the 0.5- $\mu$ g/ml propofol concentration (mild sedation), thalamic activity increased, and when subjects lost consciousness, thalamic activity abruptly decreased to insignificant levels. These results are similar to those previously observed using vibrotactile stimulation.<sup>19</sup> Using a similar paradigm, Bonhomme *et al.*<sup>19</sup> found that vibrotactile-evoked activity in the S1 and the S2 decreased below statistical significance during a propofol concentration of 1.5  $\mu$ g/ml (moderate sedation) when the subjects were still aware of the stimulus. In contrast, thalamic blood flow dramatically decreased only when the subjects lost consciousness.<sup>19</sup> Therefore, for both vibrotactile and pain transmission, propofol seems to suppress activity in the cortex before it interrupts transfer through the thalamus. However, unlike vibrotactile transmission, pain-evoked cortical activity was present, albeit reduced, after loss of consciousness and commensurate reductions in thalamic activation. The significant pain-evoked IC activation during unconsciousness could be *via* the thalamic ventromedial posterior nucleus, which transmits nociceptive information from the superficial layers of the spinal cord dorsal horn to the IC.<sup>47</sup> Because the ventromedial posterior nucleus is quite small in primates, activation through this nucleus may not have been detected using PET when the larger ventroposterior lateral and medial thalamic activation was reduced. Alternatively, the IC activation during unconsciousness could be *via* input that bypassed the thalamus, such as spinopontoamygdaloid pathways.<sup>48,49</sup>

### Conclusions

In conclusion, our study shows a differential effect of propofol on pain-evoked activity in different brain regions. Further, the data suggest that after loss of consciousness, some nociceptive information reaches both cortical and subcortical structures, including the IC and the cerebellum. However, the transfer of information to the thalamus and the ACC is dramatically reduced, suggesting a role of the medial thalamic pain system for the appreciation of pain.

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