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Monitoring

Effects of remifentanil on brain responses to noxious stimuli during deep propofol sedation

Jesus Pujol[1,2,*], Gerard Martínez-Vilavella[1], Lluís Gallart[3,4], Laura Blanco-Hinojo[1,2], Susana Pacreu[3], Vincent Bonhomme[5,6], Joan Deus[1,7], Víctor Pérez-Sola[2,8], Pedro L. Gambús[9] and Juan Fernández-Candil[3]

[1]MRI Research Unit, Department of Radiology, Hospital Del Mar, Barcelona, Spain, [2]Centro Investigación Biomédica en Red de Salud Mental, CIBERSAM G21, Barcelona, Spain, [3]Department of Anesthesiology, Hospital Del Mar-IMIM, Barcelona, Spain, [4]Department of Surgery, Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Department of Anesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium, [6]Anesthesia and Intensive Care Laboratory, GIGA-Consciousness Thematic Unit, GIGA-Research, Liege University, Liege, Belgium, [7]Department of Psychobiology and Methodology in Health Sciences, Autonomous University of Barcelona, Barcelona, Spain, [8]Institute of Neuropsychiatry and Addictions, Hospital Del Mar- IMIM, Pompeu I Fabra University, Barcelona, Spain and [9]Systems Pharmacology Effect Control & Modeling Research Group, Anesthesiology Department, Hospital Clinic de Barcelona, Barcelona, Spain

*Corresponding author. E-mail: 21404jpn@comb.cat

Abstract

Background: The safety of anaesthesia has improved as a result of better control of anaesthetic depth. However, conventional monitoring does not inform on the nature of nociceptive processes during unconsciousness. A means of inferring the quality of potentially painful experiences could derive from analysis of brain activity using neuroimaging. We have evaluated the dose effects of remifentanil on brain response to noxious stimuli during deep sedation and spontaneous breathing.

Methods: Optimal data were obtained in 26 healthy subjects. Pressure stimulation that proved to be moderately painful before the experiment was applied to the thumbnail. Functional MRI was acquired in 4-min periods at low (0.5 ng ml^{-1}), medium (1 ng ml^{-1}), and high (1.5 ng ml^{-1}) target plasma concentrations of remifentanil at a stable background infusion of propofol adjusted to induce a state of light unconsciousness.

Results: At low remifentanil doses, we observed partial activation in brain areas processing sensory-discriminative and emotional-affective aspects of pain. At medium doses, relevant changes were identified in structures highly sensitive to general brain arousal, including the brainstem, cerebellum, thalamus, auditory and visual cortices, and the frontal lobe. At high doses, no significant activation was observed.

Conclusions: The response to moderately intense focal pressure in pain-related brain networks is effectively eliminated with safe remifentanil doses. However, the safety margin in deep sedation-analgesia would be narrowed in minimising not only nociceptive responses, but also arousal-related biological stress.

Keywords: deep sedation; functional MRI; neuroimaging; nociception; pain; propofol; remifentanil

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Editor's key points

- The combination of propofol and remifentanil is widely used for sedation and analgesia during unpleasant procedures.
- Functional MRI was used to analyse evoked brain responses to a nociceptive stimulus in spontaneously breathing volunteers sedated with propofol plus a range of remifentanil doses.
- The brain responses to a nociceptive stimulus in pain-related brain networks were eliminated at safe remifentanil doses, whereas arousal-related biological stress-activated networks were not completely suppressed.
- Moderate doses of remifentanil suppress activation of brain nociception responses during deep sedation with propofol without clinically significant respiratory depression.

A primary goal in anaesthesia is to increase efficacy while minimising medical risks. The need for balanced dosing is maximal during deep sedation in spontaneously breathing patients, which has a narrow safety margin.[1,2] The combination of propofol and remifentanil is widely used in anaesthesia for sedation and analgesia during unpleasant medical procedures. A controlled i.v. drug infusion is administered with the aim of providing sufficient sedation and analgesia without the need for mechanical ventilation.[2–4] However, the lower the doses, the greater the uncertainty as to the antinociceptive effect. A key question, therefore, is to determine whether the effect of remifentanil is optimal in the dose range used in deep sedation-analgesia. Nociceptive stimulus transmission persists to a relevant degree in sedated patients and generates a range of brain responses that can be measured to monitor adequacy of analgesic therapy.[5–7] However, the nociceptive response itself might not inform on the nature of the nociceptive processes during unconsciousness.

A means to infer the content of the painful experience in awake individuals could be analysis of brain activity using neuroimaging. Functional MRI (fMRI) has provided comprehensive information on distinct aspects of the conscious brain response to painful stimulation. The sensory-discriminative component of pain is processed in the primary and second somatosensory cortices, posterior insula, and supramarginal gyrus. Integrated activity in these areas identifies intensity, duration, location, and nature of the painful stimulus.[8–11] The emotional-affective component of pain is integrated in the anterior insula and anterior cingulate cortex, and in the motor, premotor, and supplementary motor areas. Activation at these levels is related to the emotional unpleasantness of pain and the evoked autonomic (e.g. heart rate) and motor (e.g. groaning and grimacing) responses.[8–11] The cognitive-evaluative component is mainly processed in prefrontal cortex networks, which have an essential role in both the appraisal and top-down modulation of pain.[11–13]

Despite its potential usefulness, fMRI has rarely been used to assess the effects of remifentanil on brain response to noxious stimuli in unconscious states.[14,15] For example, Lichtner and colleagues[15] used fMRI to identify brain responses to noxious electrical stimuli in mechanically ventilated subjects during general anaesthesia. They identified several brain activations to show how a level of stimulus processing persists during deep anaesthesia. However, the observed responses only marginally implicated pain-processing brain structures.

We tested brain response to a pressure stimulus that proved to be painful before sedation in healthy subjects during deep sedation-analgesia and spontaneous breathing. Depression of consciousness was maintained with stable doses of propofol i.v., and antinociceptive effect was gradually increased using low (0.5 ng ml^{-1}), medium (1 ng ml^{-1}), and high (1.5 ng ml^{-1}) target plasma concentrations of remifentanil i.v. Remifentanil doses were selected to cover the range from slight clinical effect[16] to apnoea risk when combined with propofol.[17] The aim of the study was to analyse evoked brain responses qualitatively using the functional anatomy of pain described in previous fMRI studies as a reference.

Methods

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The protocol was approved by the Spanish Agency of Medicines and Medical Devices (AEMPS) (reference 5NFNF6V55C) and by the Ethical Committee of Clinical Research of the Parc de Salut Mar of Barcelona (reference number 2017–7165); EudraCT: 2016-004833-25. Written informed consent was obtained from all participants. The current study is part of a larger project aimed at assessing the effects of anaesthesia on brain activity with two separate experiments. The first experiment focused on characterising the neurophysiology of propofol-induced loss of consciousness.[18] Here we present the results of the second experiment testing the effects of remifentanil on brain response to noxious stimuli.

A total of 26 right-handed healthy volunteers participated in this study with a mean age of 26.5 (range 22–47) yr and included 14 males and 12 females. Participants were selected from an original sample of 30 individuals based on having at least one remifentanil dose test with optimal fMRI data quality. The characteristics of the sample and participant selection were described previously.[18] Participants were required to be American Society of Anesthesiologists (ASA) physical status 1 (healthy, non-smoking, no or minimal alcohol use)[19] and to have normal physical and laboratory exams for eligibility.

Experimental design

Functional MRI was continuously acquired for a total of 15 min, during which the effect of remifentanil on brain response to the noxious stimulus was tested in sedated, unconscious participants under a stable infusion of propofol. The experiment included three periods of 4 min for testing low, medium, and high doses of remifentanil, and a final period of 3 min once the infusion of both propofol and remifentanil was stopped to estimate duration of action. The pressure stimulus was applied in periods of 10 s and repeated every 30 s throughout fMRI acquisition (Fig 1).

Noxious stimulation

Pressure stimuli were delivered using an MRI-compatible algometer developed in-house and designed to fit the ergonomics of the thumb. Controlled pressure was applied on the subject's thumbnail with a probe surface of 1 cm^2 in the form of 0.5 Hz pulses. Each stimulation block of 10 s included five pressure pulses of 1 s. A total of 30 pressure blocks of 10 s were administered during fMRI acquisition, interspersed with baseline periods of 20 s.

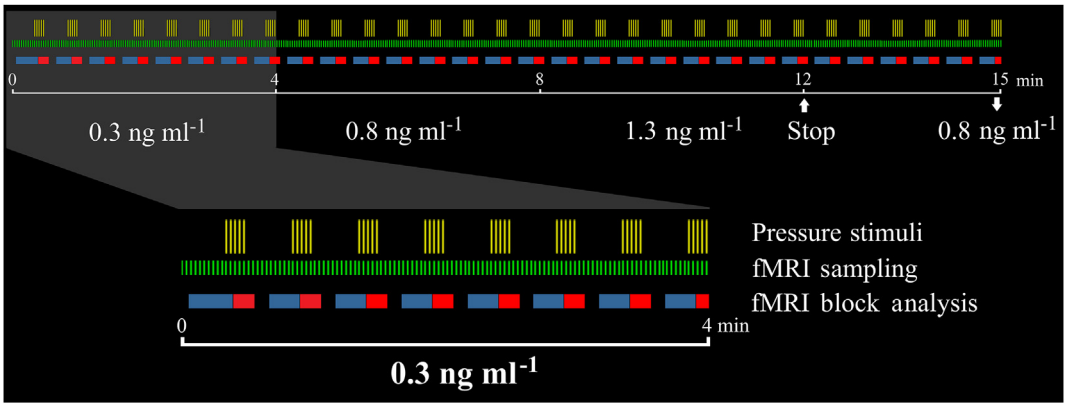

Fig 1. Functional MRI paradigm. Pressure stimuli were alternated with baseline periods each 30 s throughout the experiment. The fMRI sampling rate (TR) was 2 s. The fMRI block analysis included baseline (blue) and activation (red) periods and a delay of 4 s to adjust for the haemodynamic response latency. Remifentanil effect-site concentrations (ng ml^{-1}) for each level are indicated. fMRI, functional magnetic resonance imaging.

The pressure to be applied was established before fMRI acquisition in the waking state according to individual pain thresholds. Pressure was applied (30 kPa s^{-1}) until the participant defined the pressure as pain of intensity 6/7 in an 11-point numerical rating scale (NRS) (from 0, no pain, to 10, the most severe pain). The pressure evoking pain intensity of 6/7 in each participant was used in the experiment. As a group, applied pressure had a mean of 6.2 (standard deviation [SD]: 1.1) kg cm^{-2}. In a previous study, a similar pressure (6 kg cm^{-2}) repeatedly applied on the thumbnail every 30 s for 7 min to awake healthy volunteers produced pain of similar intensity (6.5 points in an 11-point NRS) during the fMRI test.[12] No evidence of pain sensitisation (i.e. higher pain scores at the last pressure blocks) or tissue damage was observed in this study.

Drug dose

Participants were sedated with a slow infusion of propofol until losing consciousness before fMRI remifentanil tests. As described,[18] a target-controlled system (Base Primea Orchestra®, Fresenius Kabi, Brézins, France) was used for a progressive i.v. infusion of propofol individually programmed based on the Schnider model,[20] with a target plasma concentration of 3.5 μg ml^{-1} and steeply increased by 0.5 μg ml^{-1} every 2 min until loss of consciousness. Propofol was then targeted at the effect-site (brain) concentration estimated by the model[18] with the aim of maintaining a stable state of light unconsciousness at which subjects no longer responded to verbal prompting, but could be awakened with relatively intense stimulation, and breathing was spontaneous with no need for tracheal intubation. Mean time between loss of consciousness and start of remifentanil testing was 7 (SD 3) min.

Subsequently, remifentanil infusion and fMRI acquisition commenced synchronously while participants were under propofol-induced deep sedation. Remifentanil infusion was programmed based on the Minto model[21] with a target plasma concentration of 0.5 ng ml^{-1} for the low-dose test, followed by a target concentration of 1 ng ml^{-1} for the medium-dose test and finally 1.5 ng ml^{-1} for the high-dose test (each 4 min). Once dose testing was complete (12 min), infusion of both propofol and remifentanil was stopped. The remaining 3 min of the fMRI acquisition served to test the duration of action on brain response to the painful stimulus. This 'offset of action test' included six painful stimulation blocks (each 30 s).

Remifentanil doses were selected to cover a range of target plasma concentrations usable in clinical practice in spontaneously breathing patients.[22,23] A steady-state remifentanil target plasma concentration of 0.5 ng ml^{-1} is associated with a minor analgesic effect.[16] Plasma concentration of 1 ng ml^{-1} has been reported to give a relevant analgesic response to painful stimulation without blood oxygen desaturation.[24] In contrast, concentrations of 1.5 ng ml^{-1} can cause 50% depression of ventilation when combined with propofol.[17]

Peripheral oxygen saturation (SpO_2) and expired capnography (Oral-Trac®, Salter Labs, Arvin, CA, USA) were used to monitor respiratory function with oxygen 2 L min^{-1} administered by nasal cannula throughout the study for safety purposes.[18] Respiration was monitored using a pneumatic sensor (Philips 3T Respiratory Sensor, Philips Healthcare, Best, The Netherlands) located between the thorax and abdomen.[25] Drug infusion was discontinued in case of hypopnoea with ventilatory frequency <5 bpm or $SpO_2 \leq 90\%$.[22] The experiment had to be interrupted in one case during the medium remifentanil dose test and in eight cases during, or immediately after, the high remifentanil dose test (total nine interruptions). The completed dose tests of these nine participants were included in the data analysis.

Functional MRI acquisition, preprocessing, and analysis

A Philips Achieva 3.0 Tesla MRI (Philips Healthcare) was used. Acquisition parameters, preprocessing and control of potential head motion effects are detailed in Supplementary material. After exclusions because of both movement (see Supplementary material) and hypoventilation risk, the final analysis showed $n=23$ in the low-dose test, $n=23$ in the medium-dose test, $n=21$ in the high-dose test, and $n=16$ in the offset of action test.

A data analysis and statistical plan was approved by the authors before analyses began according to the protocol submitted to the Spanish AEMPS (reference 5NFNF6V55C).

First-level (single-subject) analysis

Brain activation was modelled using a boxcar regressor that considered blocks of 10 s for the activation condition and a delay of 4 s to adjust for haemodynamic response latency.[26,27] The three volumes (6 s) after each activation block were not modelled, as pain and brain response to the applied stimulus can last ~16 s in awake individuals according to temporal analysis of independent samples.[12,28] The rationale for not including this period was that the duration of pain cannot be anticipated during sedation-analgesia. Independent models of 4 min (eight activation blocks) were generated for the low-, medium-, and high-dose tests. These analyses were repeated after including end-tidal CO_2 measures as a nuisance variable with a delay of 12 s to adjust for latency of the artefactual CO_2 effects on fMRI signal.[29,30] For the offset of action test (the last 3 min), each stimulation block was modelled separately to estimate the duration of brain response attenuation with six data points in periods of 30 s.

Group-level analysis

The resulting first-level SPM contrast (activation >baseline and baseline >activation) images were carried forward to group-level analyses. One-sample *t*-test designs were used to generate group activation maps. Two-sample paired *t*-tests were used to compare brain activity evoked in different conditions. In the offset of action analysis, the first block was used as a reference to compare separately with the other five blocks. Results were considered significant when clusters formed at a threshold of $P<0.005$ survived whole-brain family-wise error (FWE) correction ($P<0.05$), calculated by means of SPM. Small volume correction was occasionally applied for regions of interest identified in the primary (one-sample) analysis.

Results

At the low dose level, the group mean (SD) effect-site concentration of remifentanil was 0.3 (0.01) ng ml^{-1}, effect-site concentration of propofol 3.9 (0.7) μg ml^{-1}, ventilatory frequency 17.6 (3.5) bpm, end-tidal CO_2 5.0 (0.6) kPa, and SpO_2 98.8 (0.8)% (see also Supplementary Table S1 and Supplementary Fig. S1). The one-sample *t*-test map showed significant activation in the primary somatosensory cortex at the level of the thumb cortical representation extending to the primary motor cortex, in the dorsal anterior cingulate cortex and adjacent supplementary motor area, and in visual areas in the occipital lobe (Fig 2 and Table 1).

At the medium remifentanil dose, the effect-site concentration of remifentanil was 0.8 (0.01) ng ml^{-1}, effect-site concentration of propofol 3.9 (0.8) μg ml^{-1}, ventilatory frequency 16.7 (4.1) bpm^{-1}, end-tidal CO_2 5.0 (0.7) kPa, and SpO_2 98.3 (1.6)%. At this level, activation in the somatosensory cortex was residual and brain response primarily involved the visual cortex, auditory cortex, thalamus, dorsal frontal lobe, brainstem, and cerebellum.

At the high dose level, the effect-site concentration of remifentanil was 1.3 (0.03) ng ml^{-1}, effect-site concentration of propofol 3.9 (0.8) μg ml^{-1}, ventilatory frequency 12.8 (5.1) bpm, end-tidal CO_2 5.2 (0.7) kPa, and SpO_2 95.9 (5.0)%. The one-sample *t*-test map showed no significant activation.

No significant results were obtained in the one-sample analyses indicating neural inhibition (i.e. stimulation <baseline). Similar results were obtained after adjusting the analyses for end-tidal CO_2 measurements (Supplementary Table S2).

Pairwise comparisons between conditions confirmed the dose effects. Greater activation at low than high remifentanil doses was observed in the primary somatosensory cortex, anterior cingulate cortex, and visual areas (Fig 3 and Table 1). Similarly, significantly greater activation at medium than high doses was observed in visual and auditory areas. No significant differences were found between low- and medium-dose

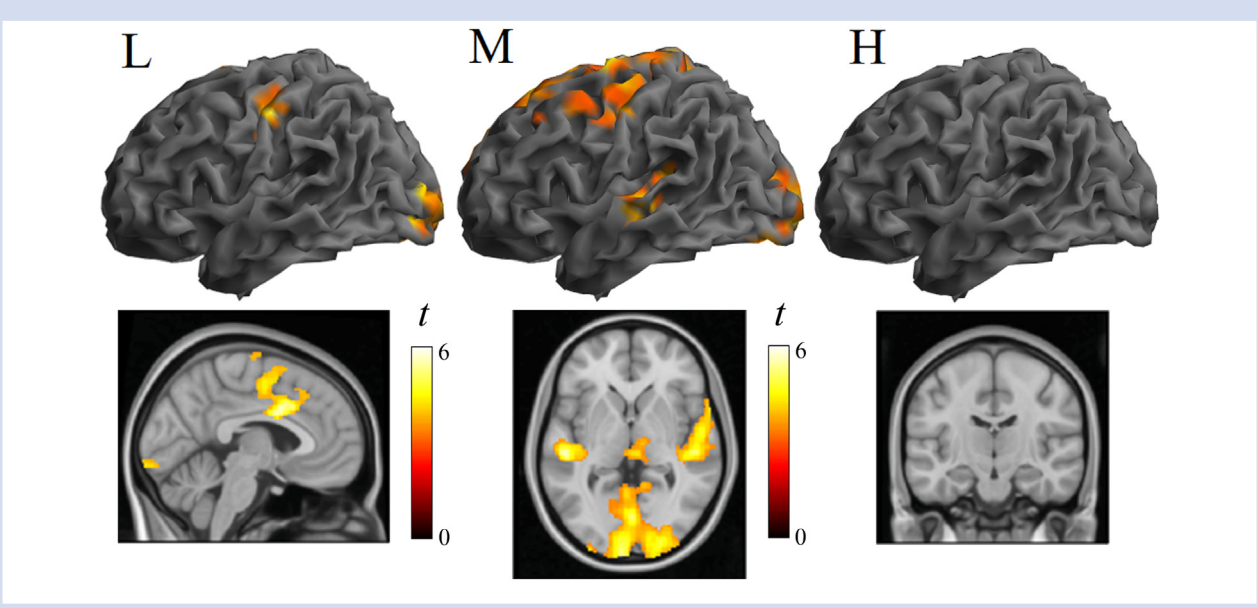

Fig 2. Brain activation during pressure stimulation in the low (L), medium (M), and high (H) remifentanil dose tests. The maps show the results obtained in one-sample *t*-tests (activation >baseline contrast) for the study group at each level.

Table 1 Functional MRI statistical results.

Brain region	Cluster-level		Peak-level		
	Voxels	$P_{FWE\text{-}corr}$	x y z	t	P
Low remifentanil doses					
Primary somatosensory cortex	3141	8e−7	−48 −18 44	4.7	0.00006
Anterior cingulate cortex	3141	8e−7	−6 14 36	5.5	0.000009
Supplementary motor area	3141	8e−7	−8 −6 48	3.9	0.0004
Visual cortex	3414	3e−7	20 −90 −6	4.9	0.00004
Medium remifentanil doses					
Visual cortex	12397	6e−16	−2 98 −10	6.3	0.000002
Thalamus	12397	6e−16	6 −24 2	4.0	0.0003
Brainstem/cerebellum	12397	6e−16	6 −30 −34	4.9	0.00004
Right auditory cortex	2229	0.00009	50 −24 0	5.1	0.00002
Left auditory cortex	828	0.033	−52 −24 0	5.9	0.000004
Dorsal frontal lobe	114 450	4e−15	12 −16 72	6.0	0.000003
Low doses >high doses					
Right primary somatosensory cortex	1124	0.008	28 −30 58	5.4	0.00004
Precuneus	1124	0.008	10 −42 48	3.9	0.001
Left primary somatosensory cortex	457	0.01*	−52 −18 46	5.0	0.00007
Anterior cingulate cortex	267	0.02*	−6 6 28	4.8	0.0001
Visual cortex	2961	7e−6	32 −80 −12	5.8	0.00002
Medium doses >high doses					
Visual cortex	4286	2e−6	−8−102 −8	5.3	0.00005
Right auditory cortex	1342	0.009	48 −24 −2	4.3	0.0003
Left auditory cortex	1485	0.005	−42 −42 10	5.7	0.00002
Paracentral lobule/precuneus	4690	6e−7	6 −34 50	5.2	0.00005
Offset of Action Analysis					
Last (sixth) block >first block					
Right SI/supramarginal gyrus	382	0.04	46 −40 50	4.4	0.0003
Left SI/supramarginal gyrus	364	0.05	−50 −42 42	5.2	0.00007

x y z, coordinates in Montreal Neurological Institute space.
$P_{FWE\text{-}corr}$, P (family-wise error-corrected), whole brain; SI, primary somatosensory cortex.
* *Small volume correction.*

effects. Adjusting for end-tidal CO_2 measurements did not show any relevant effect (Supplementary Table S2).

Analysis of the brain response after ceasing administration of both propofol and remifentanil infusion showed that activation of the primary somatosensory cortex and supramarginal gyrus was stronger during the last (sixth) block compared with the reference first block (Fig 4 and Table 1). No significant activation was detected on one-sample maps in any of the six 30-s periods.

Discussion

We assessed the dose effects of remifentanil on brain response to moderately intense noxious stimulation during deep sedation-analgesia. A sustained propofol infusion was used to maintain hypnosis level throughout the experiment as three doses of remifentanil were administered. Results showed notably distinct activation patterns indicating that processing of the nociceptive stimulus varies at different remifentanil levels in sedated individuals.

We used previous fMRI data that have consistently characterised the functional anatomy of pain as a reference to analyse the qualitative aspects of the evoked brain response.[8–11] Fig 5 shows a representative data set obtained in awake healthy volunteers using similar imaging and painful stimulation procedures.[31] Brain activation in this group includes all relevant brain structures processing the sensory-discriminative, emotional-affective, and cognitive-evaluative components of pain. The pattern is consistent with previous evidence from our group,[12,32] meta-analyses and reviews,[8,10,11] and multivariate pattern analyses.[33,34]

Brain activation at low doses involved the sensorimotor cortex at the level of the thumb cortical representation, supplementary motor area, and anterior cingulate cortex. These brain areas are part of the brain network activated by painful pressure in the waking state in the reference subject group, and are core elements of both the sensory-discriminative and emotional-affective components of pain.[8–11] Therefore, we infer that the low remifentanil dose investigated did not completely attenuate the nociceptive response in our experiment.

In contrast, at a medium remifentanil dose, activation in core areas was residual and brain response largely implicated non-somatic sensory systems including bilateral auditory and visual areas, and the thalamus. Activation was also notable in the brainstem, cerebellum, and dorsal frontal lobe. All these structures are highly sensitive to general brain arousal,[18,35–37] which suggests that the evoked response is more closely related to arousal phenomena, as a form of neural stress, than to processing of specific nociceptive features. The increased remifentanil (opioid) effect at this dose may be more efficient in modulating neural transmission in specific pain pathways than in collateral arousal systems, which could even be excited. This phenomenon was paradoxically more evident at medium than low concentrations of remifentanil. A possible explanation could be based on the reciprocal, mutually inhibitory relationships between specific nociceptive and non-specific arousal pathways.[38,39] That is, the inhibitory effect of

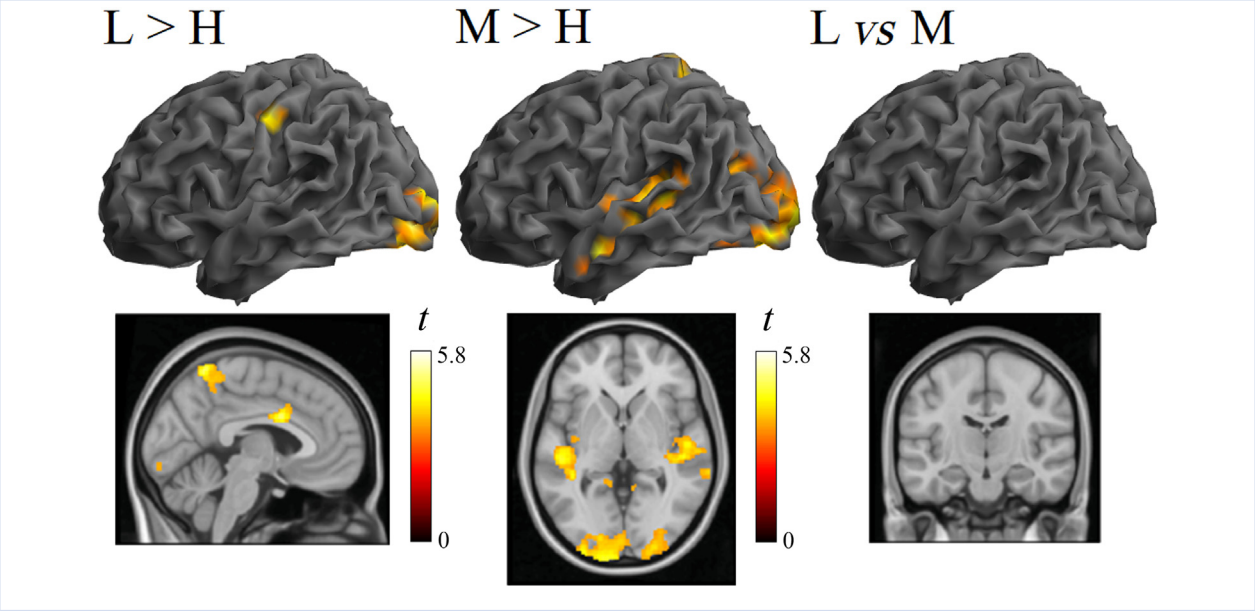

Fig 3. Pairwise comparisons between low (L), medium (M), and high (H) remifentanil dose tests. Two-sample paired *t*-tests were used to compare brain activity evoked in different conditions.

nociception-related signals on arousal transmission could be more efficiently suppressed at medium than low remifentanil doses. The interactions with propofol could also have contributed to the paradoxical phenomenon, as increasing propofol concentrations increased processing of noxious stimuli in arousal-related cortical areas in an fMRI study in healthy volunteers during deep anaesthesia.[40]

At high doses, we found no significant brain activation, which would suggest greater attenuation of the response at doses with apnoea risk.[17] Paired comparisons between conditions confirmed that brain activation is significantly reduced at high doses compared with the other doses. However, the absence of significant findings in the fMRI analysis does not demonstrate the absence of nociceptive processing. Brain responses could exist at this sedation level and in deeper general anaesthesia according to evidence from anaesthesia monitoring during surgery.[5–7] The absence of significant brain activation in the higher dose analysis could therefore be related to inherent sensitivity limitations of fMRI and use of a noxious stimulus of relatively low intensity compared with surgical stimulation.

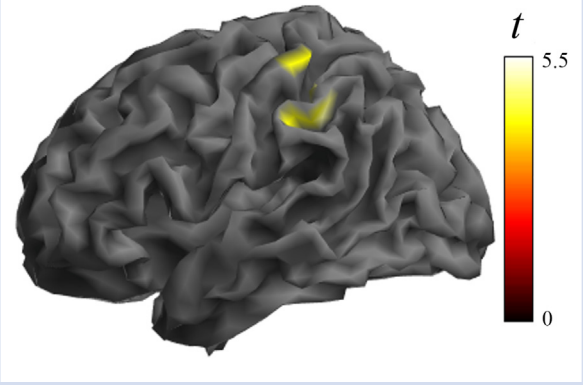

Fig 4. Offset of action analysis results. Regions showing higher brain response to noxious stimulation during the last (sixth) block compared with the reference first block after ceasing to administer both propofol and remifentanil.

Alternatively, or additionally, the nature of the noxious stimulus could also account for a substantial response suppression at high remifentanil doses in our study. We applied controlled pressure to the thumb as a stimulus. The largest effect of intense focal pressure is to stimulate mechanical nociceptors in peripheral nerves[41] and activate the relevant pain-related areas in the brain.[12,32,42] Therefore, a large response suppression might be expected when high doses of a potent opioid[43] are used. In contrast, brain responses to less selective stimuli might be only partially eliminated. For instance, whereas fentanyl, another powerful μ-opioid receptor agonist, dramatically suppresses the response to painful stimulation, the response to vibrotactile stimulus is unaffected.[44] Moreover, Lichtner and colleagues[15] observed fMRI brain responses at higher doses of remifentanil during general anaesthesia. They used tetanic electrical stimulation of the sural nerve in their study to generate nociceptive responses in the spinal cord and brain. However, electrical stimulation in a nerve trunk is not selective and activates both nociceptive and non-nociceptive fibres.[45,46]

In a previous study, the offset of remifentanil action was estimated in awake volunteers also using a neuroimaging approach,[24] which showed a half-life to recover the fMRI signal in the insula after stopping remifentanil infusion of 3 min. We found significant activation of the primary somatosensory cortex and supramarginal gyrus during the last block compared with the reference first block of stimuli. This

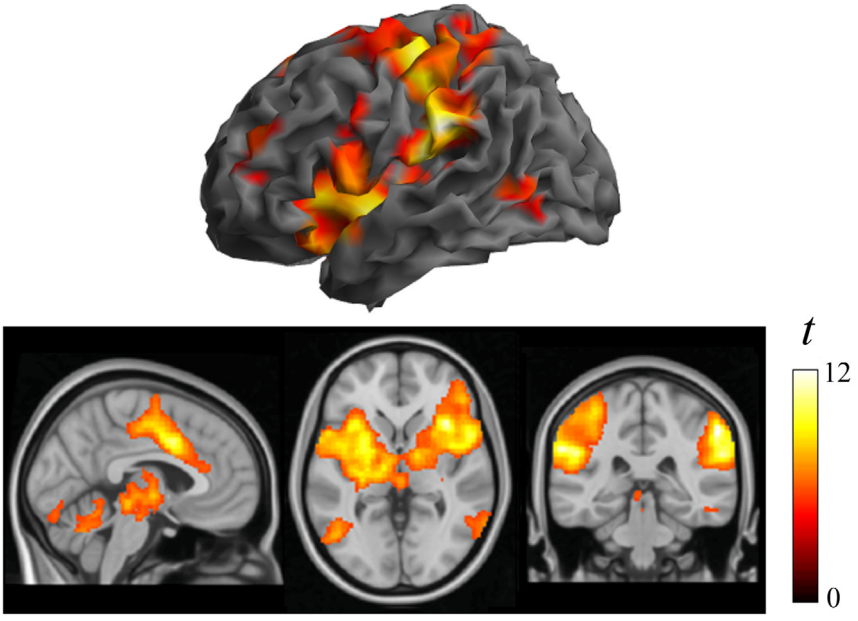

Fig 5. Representative fMRI map of brain activation during painful pressure in awake healthy individuals. The one-sample *t*-test analysis included 21 healthy women, aged 43.1 yr (standard deviation, 4.7 yr), selected from a control group examined in an earlier study.[31] Identical MRI tools and a pain stimulation device were used in this experiment. A pressure of 4.5 kg cm^{-2} was applied to the right thumbnail in blocks of 10 s every 30 s for 4 min, evoking moderate-intensity pain (mean 5, standard deviation 2 points in an 11-point rating scale). Results are cluster-level family-wise-error whole-brain corrected for multiple comparisons. fMRI, functional magnetic resonance imaging.

observation illustrates how response attenuation in areas processing the sensory-discriminative component of pain can start to decline within 3 min of stopping propofol and remifentanil. This analysis was limited, as optimal data were obtained at this stage from only 16 participants and only one stimulation block was included in each comparison. Despite potential limitations in statistical power, the duration of brain response attenuation estimated was consistent with the time reported for remifentanil alone,[24] and with the documented short action of remifentanil analgesia (3–10 min)[43,47] and its effect-site concentration half-life (≤3 min).[43]

Another potential limitation of our study is the absence of an additional fMRI exam assessing brain response to the painful stimulus in the awake state. Such a limitation would be relevant if our approach was based on quantitative measures of activation changes between conscious and unconscious states. Nevertheless, we considered that a qualitative analysis of the areas implicated was adequate for the study's purposes and that the functional anatomy of pain characterised by previous studies could be used as a reference. Likewise, it could have been relevant to include evaluation of brain activation with the participants sedated with propofol, but without remifentanil to distinguish the effects of remifentanil from those of propofol.

Functional MRI has potential confounders that might be particularly relevant in the context of sedation and anaesthesia. The drugs used, particularly remifentanil, reduce breathing and subsequently increase CO_2 levels, and changes in CO_2 can affect the fMRI signal.[48] However, analysis with and without adjustment for CO_2 measurements showed similar results. Drug-related changes in blood pressure might also affect the fMRI signal. However, our experiment was limited in that we did not continuously monitor blood pressure. Importantly, EEG can provide relevant support for proper interpretation of fMRI data during unconsciousness.[48] Unfortunately, we do not have reliable EEG measures to ensure the level and stability of the cerebral state of sedation in our study.

Another potential limitation is the short duration of 4 min per remifentanil level to relate the observed effects on brain activation to specific concentrations. The plasma effect-site equilibration lag is ~1 min in the Minto model[21] and the time to fMRI response might be even longer.[24] Also, we emphasise that the reported fMRI results are not the effect of different doses of remifentanil alone, but reflect the dynamic interaction over time between different remifentanil doses and a stable concentration of propofol.

In conclusion, we assessed brain response to moderately intense focal pressure in deep sedation-analgesia with spontaneous breathing preserved, a common practice in anaesthesia with a narrow safety margin. Positive findings include incomplete attenuation of the characteristic brain response to nociceptive stimulation at a low remifentanil dose, relevant brain activations at medium doses that might better express enhanced arousal effects, and significant reduction of the evoked responses at high compared with low and medium remifentanil doses. In terms of the practical implications, the data suggest that the antinociceptive effect is optimal with relatively safe doses of remifentanil. However, the dose

margin of deep sedation-analgesia is narrowed if the intervention is intended to minimise not only the nociceptive processes, but also potentially associated biological stress expressed in terms of brain arousal.

Authors' contributions

Study conception and design: JP, LG, JD, VPS, PLG, JFC
Acquisition of data: JP, GMV, LG, SP, JFC
Interpretation of data: JP, LG, VB, PLG, JFC
Writing up of the first draft of the paper: JP
Analysis of data: GMV, LBH
Revised the article critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.06.038.

References

1. Hinkelbein J, Schmitz J, Lamperti M, Fuchs-Buder T. Procedural sedation outside the operating room. *Curr Opin Anaesthesiol* 2020; **33**: 533–8
2. Barends CRM, Driesens MK, van Amsterdam K, Struys MMRF, Absalom AR. Moderate-to-deep sedation using target-controlled infusions of propofol and remifentanil: adverse events and risk factors: a retrospective cohort study of 2937 procedures. *Anesth Analg* 2020; **131**: 1173–83
3. Tesniere A, Servin F. Intravenous techniques in ambulatory anesthesia. *Anesthesiol Clin North Am* 2003; **21**: 273–88
4. Li Y, Picheca L. *Target-controlled infusion with propofol and remifentanil for moderate procedural sedation in medicine and dentistry: a review of clinical effectiveness, cost-effectiveness, and guidelines [internet]*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 Nov 10
5. Meijer FS, Martini CH, Broens S, et al. Nociception-guided versus standard care during remifentanil-propofol anesthesia: a randomized controlled trial. *Anesthesiology* 2019; **130**: 745–55
6. Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. *Br J Anaesth* 2019; **123**: e312–21
7. García PS, Kreuzer M, Hight D, Sleigh JW. Effects of noxious stimulation on the electroencephalogram during general anaesthesia: a narrative review and approach to analgesic titration. *Br J Anaesth* 2021; **126**: 445–57
8. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005; **9**: 463–84
9. Calvino B, Grilo RM. Central pain control. *Jt Bone Spine* 2006; **73**: 10–6
10. Fomberstein K, Qadri S, Ramani R. Functional MRI and pain. *Curr Opin Anaesthesiol* 2013; **26**: 588–93
11. De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. *Neurosci Biobehav Rev* 2021; **130**: 125–46
12. López-Solà M, Pujol J, Hernández-Ribas R, et al. Dynamic assessment of the right lateral frontal cortex response to painful stimulation. *Neuroimage* 2010; **50**: 1177–87
13. Woo CW, Schmidt L, Krishnan A, et al. Quantifying cerebral contributions to pain beyond nociception. *Nat Commun* 2017; **8**, 14211
14. Nagakubo D, Hamamoto Y, Hasegawa D, et al. Functional MRI-based identification of brain regions activated by mechanical noxious stimulation and modulatory effect of remifentanil in cats. *Res Vet Sci* 2017; **114**: 444–9
15. Lichtner G, Auksztulewicz R, Velten H, et al. Nociceptive activation in spinal cord and brain persists during deep general anaesthesia. *Br J Anaesth* 2018; **121**: 291–302
16. Tracey I, Hicks G, Rogers R, et al. Pharmacological modulation of the central pain response. *Proc Intl Soc Mag Reson Med* 2000; **8**: 913
17. Olofsen E, Boom M, Nieuwenhuijs D, et al. Modeling the non-steady state respiratory effects of remifentanil in awake and propofol-sedated healthy volunteers. *Anesthesiology* 2010; **112**: 1382–95
18. Pujol J, Blanco-Hinojo L, Gallart L, et al. Largest scale dissociation of brain activity at propofol-induced loss of consciousness. *Sleep* 2021; **44**. zsaa152
19. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status - historical perspectives and modern developments. *Anaesthesia* 2019; **74**: 373–9
20. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502–16
21. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology* 1997; **86**: 10–23
22. Borrat X, Valencia JF, Magrans R, et al. Sedation-analgesia with propofol and remifentanil: concentrations required to avoid gag reflex in upper gastrointestinal endoscopy. *Anesth Analg* 2015; **121**: 90–6
23. LaPierre CD, Johnson KB, Randall BR, White JL, Egan TD. An exploration of remifentanil-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. *Anesth Analg* 2011; **113**: 490–9
24. Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. *Neuropsychopharmacology* 2004; **29**: 626–35
25. Pujol J, Blanco-Hinojo L, Ortiz H, et al. Mapping the neural systems driving breathing at the transition to unconsciousness. *Neuroimage* 2021; **246**, 118779
26. Poldrack R, Mumford J, Nichols T. *Handbook of functional MRI data analysis*. Cambridge: Cambridge University Press; 2011
27. Khosla M, Ngo GH, Jamison K, Kuceyeski A, Sabuncu MR. Cortical response to naturalistic stimuli is largely predictable with deep neural networks. *Sci Adv* 2021; **7**: eabe7547
28. Pujol J, Martínez-Vilavella G, Llorente-Onaindia J, et al. Brain imaging of pain sensitization in patients with knee osteoarthritis. *Pain* 2017; **158**: 1831–8

29. Golestani AM, Chang C, Kwinta JB, Khatamian YB, Jean Chen J. Mapping the end-tidal CO2 response function in the resting-state BOLD fMRI signal: spatial specificity, test-retest reliability and effect of fMRI sampling rate. *Neuroimage* 2015; **104**: 266–77
30. Chang C, Glover GH. Relationship between respiration, end-tidal CO2, and BOLD signals in resting-state fMRI. *Neuroimage* 2009; **47**: 1381–93
31. López-Solà M, Woo CW, Pujol J, et al. Towards a neurophysiological signature for fibromyalgia. *Pain* 2017; **158**: 34–47
32. Pujol J, Martínez-Vilavella G, Doreste A, et al. Tapentadol effects on brain response to pain in sensitized patients with knee osteoarthritis. *Rheumatology (Oxford)* 2022; **61**: 2335–45
33. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med* 2013; **368**: 1388–97
34. Duff EP, Vennart W, Wise RG, et al. Learning to identify CNS drug action and efficacy using multistudy fMRI data. *Sci Transl Med* 2015; **7**: 274ra16
35. Paus T. Functional anatomy of arousal and attention systems in the human brain. *Prog Brain Res* 2000; **126**: 65–77
36. Munn BR, Müller EJ, Wainstein G, Shine JM. The ascending arousal system shapes neural dynamics to mediate awareness of cognitive states. *Nat Commun* 2021; **12**: 6016
37. Raut RV, Snyder AZ, Mitra A, et al. Global waves synchronize the brain's functional systems with fluctuating arousal. *Sci Adv* 2021; **7**, eabf2709
38. Comitato A, Bardoni R. Presynaptic inhibition of pain and touch in the spinal cord: from Receptors to circuits. *Int J Mol Sci* 2021; **22**: 414
39. Craig AD. Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* 2003; **26**: 1–30
40. Lichtner G, Auksztulewicz R, Kirilina E, et al. Effects of propofol anesthesia on the processing of noxious stimuli in the spinal cord and the brain. *Neuroimage* 2018; **172**: 642–53
41. Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. *J Clin Invest* 2010; **120**: 3760–72
42. Jackson JB, O'Daly O, Makovac E, et al. Noxious pressure stimulation demonstrates robust, reliable estimates of brain activity and self-reported pain. *Neuroimage* 2020; **221**, 117178
43. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. *Drugs* 2005; **65**: 1793–823
44. Casey KL, Svensson P, Morrow TJ, Raz J, Jone C, Minoshima S. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* 2000; **84**: 525–33
45. Burke D, Mackenzie RA, Skuse NF, Lethlean AK. Cutaneous afferent activity in median and radial nerve fascicles: a microelectrode study. *J Neurol Neurosurg Psychiatry* 1975; **38**: 855–64
46. Gaines JL, Finn KE, Slopsema JP, Heyboer LA, Polasek KH. A model of motor and sensory axon activation in the median nerve using surface electrical stimulation. *J Comput Neurosci* 2018; **45**: 29–43
47. Glass PS, Hardman D, Kamiyama Y, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesth Analg* 1993; **77**: 1031–40
48. Iannetti GD, Wise RG. BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magn Reson Imaging* 2007; **25**: 978–88

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