The Analgesic Effects of Opioids and Immersive Virtual Reality Distraction: Evidence from Subjective and Functional Brain Imaging Assessments

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BACKGROUND: Immersive virtual reality (VR) is a novel form of distraction analgesia, yet its effects on pain-related brain activity when used adjunctively with opioid analgesics are unknown. We used subjective pain ratings and functional magnetic resonance imaging to measure pain and pain-related brain activity in subjects receiving opioid and/or VR distraction.

METHODS: Healthy subjects ($n = 9$) received thermal pain stimulation and were exposed to four intervention conditions in a within-subjects design: (a) control (no analgesia), (b) opioid administration [hydromorphone (4 ng/mL target plasma level)], (c) immersive VR distraction, and (d) combined opioid + VR. Outcomes included subjective pain reports (0–10 labeled graphic rating scales) and blood oxygen level-dependent assessments of brain activity in five specific, pain-related regions of interest.

RESULTS: Opioid alone significantly reduced subjective pain unpleasantness ratings ($P < 0.05$) and significantly reduced pain-related brain activity in the insula ($P < 0.05$) and thalmus ($P < 0.05$). VR alone significantly reduced both worst pain ($P < 0.01$) and pain unpleasantness ($P < 0.01$) and significantly reduced pain-related brain activity in the insula ($P < 0.05$), thalmus ($P < 0.05$), and SS2 ($P < 0.05$). Combined opioid + VR reduced pain reports more effectively than did opioid alone on all subjective pain measures ($P < 0.01$). Patterns of pain-related blood oxygen level-dependent activity were consistent with subjective analgesic reports.

CONCLUSIONS: These subjective pain reports and objective functional magnetic resonance imaging results demonstrate converging evidence for the analgesic efficacy of opioid administration alone and VR distraction alone. Furthermore, patterns of pain-related brain activity support the significant subjective analgesic effects of VR distraction when used as an adjunct to opioid analgesia. These results provide preliminary data to support the clinical use of multimodal (e.g., combined pharmacologic and nonpharmacologic) analgesic techniques.

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A variety of nonpharmacologic, psychological techniques have been used alone or as adjuncts to opioid analgesics, reviewed in Ref. 1, to reduce pain reports during painful medical procedures. Cognitive distraction (e.g., listening to music, watching a movie) is one such class of psychological techniques that has been shown to favorably alter pain perception, reviewed in Ref. 2.

Immersive virtual reality (VR) is a particularly attention-grabbing distraction technique, and is designed to give users the illusion of going inside a computer-generated virtual environment. VR appears to provide significant cognitive distraction to users because it is interactive, it uses a head-mounted display that blocks visual and aural input to the user from the immediate real-world, and it provides multisensory input (visual, aural, and sometimes tactile). The use of adjunctive, immersive VR distraction has been reported to provide clinically meaningful pain relief (30%–50% reductions in subjective pain scores) when compared with standard care in a variety of clinical procedural pain settings, including burn wound debridement (3–5), after burn physical therapy (6,7), postoperative physical therapy (8), and prostate thermosurgery (9), without VR-associated side effects (e.g., motion sickness).

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Neuroimaging studies using positron emission tomography and functional magnetic resonance imaging (fMRI) techniques have identified several neuroanatomic regions that are consistently metabolically active during thermal nociceptive stimulation when subjects report subjective pain, with the most consistent regions of activation noted in the anterior cingulate cortex (ACC), the insula, the thalamus, and the primary (SS1) and secondary (SS2) somatosensory cortices (10–14), often referred to collectively as the "pain matrix." A key observation from such techniques is that interindividual differences in subjective reporting of the pain experience are associated with similar differences in pain-induced activation, with highly sensitive individuals exhibiting more frequent and robust activation than those less sensitive (15).

Additional neuroimaging studies have begun to explore the brain's response to pharmacologic analgesia, as well as nonpharmacologic interventions. Volunteers receiving subanesthetic levels of the nonopioid analgesic and *N*-methyl-D-aspartate antagonist, ketamine, report reductions in subjective thermal pain ratings that are associated with reductions in pain-related brain activity in the insula and thalamus (16). Similarly, the mu opioid agonist and clinically effective analgesic, remifentanil, is associated with decreased pain-related activity in the insula and ACC (17). Other neuroimaging studies have shown that nonpharmacologic, cognitive modulation of pain is also associated with specific regional reductions in metabolic brain activity. In the present study we used fMRI and subjective pain reports from subjects receiving painful thermal stimulation to measure the reported pain experience and associated changes in pain-related brain activation, and compared these results under conditions of no analgesia, target-controlled opioid (hydromorphone) administration alone, VR distraction alone, and combined opioid + VR distraction. Our specific goals were (a) to measure the presence and magnitude of changes in subjective pain reports and pain-related brain activity during opioid administration or VR distraction, and (b) to determine whether the combination of opioid + VR distraction reduces subjective pain reports and associated pain-related brain activity more than opioid administration alone.

METHODS

Subjects

Nine subjects (eight men and one woman) aged 20–38 yr completed the study after demonstrating tolerance in pretest screenings for VR use, opioid administration, and fMRI imaging (to exclude those susceptible to motion sickness, opioid-induced nausea, or claustrophobia). Informed written consent was obtained using a protocol reviewed and approved by the University of Washington Institutional Review Board (IRB).

Thermal Stimuli and Experimental Protocol

Thermal (heat) stimuli were presented by a Peltier thermode (www.medoc.com, Ramat-Yishai, Israel) and alternated every 30 s between nonpainful warm (36°C) and painful hot temperatures (mean pain temperature 47.6°C, range 47.0°C–48.5°C). In addition to delivering heat, the thermode measured skin surface temperature, which was 36°C for each participant when not receiving a thermal stimulus. Starting at 44°C, heat stimuli were delivered for 30 s through a thermode attached to the dorsal surface of the right foot, and the subject was asked to rate the pain of the stimulus using a verbal 0–10 scale. The temperature was gradually increased (1.0°C or less) after each rating until the subject identified a stimulus temperature that was painful but tolerable. That temperature was then used as the noxious stimulus temperature for all pain stimulations during the subsequent study protocol for that study day. Verbal worst pain ratings at the maximal tolerated temperature ranged from 7 to 9 (mean = 8.27).

The study protocol used a 2 × 2 repeated measures, within-subjects design, whereby the opioid treatment factor was different (present or absent) on each of two study days, and the VR treatment factor (present or absent) was varied on both study days. For example, on the first of 2 days a subject received no opioid, but both VR and no VR interventions; on the second day, the same subject again received both VR and no VR interventions, but this time received opioid. In addition, the treatment order was randomized among subjects for each factor (opioid and VR).

All subjects underwent a 7-min fMRI acquisition protocol on each of two study days (separated by at least 9 days). During each acquisition protocol, pain-related brain activity was measured for each participant during conditions of no VR for 3.5 min and of VR for 3.5 min, with immersive VR delivered to the subject while in the fMRI scanner. SnowWorld was specifically designed to minimize any side effects from VR (e.g., motion sickness). When in immersive VR (Fig. 1), subjects experienced the illusion of floating through an icy 3D virtual canyon along a predetermined path, and canyon walls minimized large changes in gaze direction (reducing computational demands on the "real time" computer). Low polygon count (i.e., simple virtual objects such as snowmen) rendered with our fast VR computer and accelerated graphics card helped avoid motion sickness side effects. Participants interacted with the virtual world using a trackball and button to "shoot" virtual snowballs at virtual objects (snowmen, igloos, robots and penguins, and a river). In addition, they heard integrated sounds effects in the SnowWorld virtual environment (www.

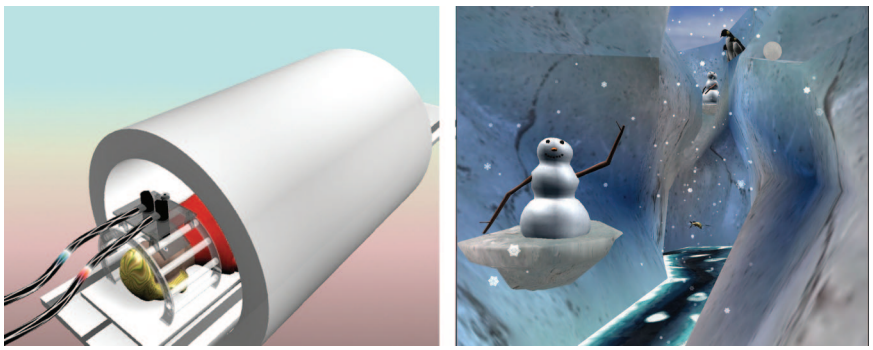

Figure 1. Graphic depiction of a subject wearing the nonferromagnetic virtual reality helmet while in the bore of the magnetic resonance imaging device (left). A snapshot of SnowWorld, the 3D virtual environment experienced by the subjects (right). (Left image by Duff Hendrickson, copyright Hunter Hoffman, University of Washington, right image by Ari Hollander, Imprintit.com, copyright Hunter Hoffman, University of Washington, 2006).

vrpain.com, Seattle, WA). In contrast, when in the no VR condition, subjects visually focused upon a black fixation cross on a white background and heard no sound effects. Both the SnowWorld and fixation cross stimuli were presented using custom-designed, MRI-compatible (nonferromagnetic) VR goggles (18).

Immediately after each 3.5-min intervention and fMRI acquisition session, subjects were asked to provide subjective ratings of three separate pain outcomes, as well as a rating of the "fun" experienced during the session, using 0–10 labeled graphic rating scales. Specifically, subjects rated the amount of time spent thinking about pain (cognitive pain dimension), pain unpleasantness (affective pain dimension), and worst pain intensity (sensory pain dimension) they experienced during thermal stimulation. See Ref. 4 for details. Such pain-rating scales have been shown to be valid through their strong associations with other measures of pain intensity, as well as their ability to detect treatment effects (19,20).

Opioid Intervention Condition

On one of the two study days, subjects received a computer-assisted, plasma target-controlled IV infusion (TCI) of hydromorphone (plasma target concentration 4 ng/mL) for 30 min before (to allow equilibration between plasma and central nervous system compartments), and throughout the approximately 45 min pain stimulation/scanning session. Hydromorphone was selected because it is a mu1 opioid receptor agonist commonly used for treatment of acute clinical pain, including its use as an analgesic premedication before painful medical procedures in conscious patients. In addition, our previous laboratory experience with the drug in human experimental pain models established pharmacokinetic parameters for the current microcomputer-controlled TCI protocol (21,22). Confirmation of plasma hydromorphone levels was performed on all subjects by blood sampling performed at the initiation and conclusion of the stimulation/scanning session (30 min and approximately 75 min, respectively, after start of TCI hydromorphone infusion). Blood was drawn into ethylenediamine tetraacetic acid-filled containers and immediately centrifuged, with resultant plasma samples stored at −20°C until batch processing. Plasma samples were subjected to solid phase extractions, and hydromorphone levels were measured by liquid chromatography/mass spectrometry as described previously (23).

To reduce the risk of opioid-induced nausea, all subjects completed a nausea-free screening opioid infusion (not involving fMRI) before study participation. No antinausea medications were administered during the screening. Before each study day, subjects were instructed to eat nothing after midnight and, in addition, a single 4-mg dose of ondansetron was administered IV before opioid infusion. We also confirmed that each participant was free of nausea before placing the subject into the MRI scanner bore. Subjects were instructed to abstain from caffeine or alcohol for 24 h before each opioid session, and to take no medications for 48 h before each opioid session.

fMRI Data Acquisition

Structural and fMRI were performed on a 1.5 T MRI system (version 5.8, General Electric, Waukesha, WI). Scanning included a 21-slice matching axial repetition time/echo time (TR/TE 200/2.2 ms; fast spoiled gradient echo pulse sequence 6-mm thick with 1-mm gap; 256 × 256 matrix). These anatomical series were followed by an fMRI series using 2D gradient echoplanar pulse sequence (TR/TE 3000)/50 ms, 21 slices; 6-mm thick and 1-mm gap, 64 × 64 matrix, 145 volumes total; time 435 s). An additional 3D, 124-slice anatomical MRI scan was performed with 1.4-mm sagittal slices using a 3D fast spoiled gradient echo pulse sequence (TR/TE 11/2.2 ms, flip angle 25 degrees, field of view 24 cm, acquisition time 4 min 36 s). A total of 145 brain volumes were acquired sequentially (only 140 were usable after the first 5 warm-up volumes were discarded), with a data acquisition time of 3 s/volume (7-min usable portion). Contrasts were calculated for both of the experimental conditions. The 3D anatomical location of the five brain regions of interest (ROIs) (ACC, insula, thalmus, SS1, and SS2) were drawn on a standardized brain (in Talairach space) using the program MEASURE under the guidance of a neuroanatomist.

Subjective Pain/Fun Rating Analysis

The 2 × 2 factorial study design used factors for opioid (with two levels, opioid and no opioid) and for VR (with two levels, VR and no VR). A linear statistical model was used to assess factor (e.g., opioid and

VR) main effects, as well as their potential interaction for the primary outcome variable (worst pain intensity) and secondary outcome variables (pain unpleasantness, time spent thinking about pain, and amount of "fun" experienced during the session). Univariate, repeated measures analyses of variance (ANOVAs) were computed ($\alpha = 0.05$, two-tailed) to ascertain the relative effects of opioid, VR, and their combination on the same outcome variables. All analyses of subjective pain ratings were performed using SPSS version 11.

fMRI Image Analysis

Initially the fMRI data were analyzed using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Oxford, UK) software for both the first level (individual fMRI activation) and second level analysis (group maps). The time series of the fMRI data (after correction for hemodynamic delay) was segmented into four parts: 1) pain "on" + No VR; 2) pain "off" + No VR; 3) pain "on" + VR; and 4) pain "off" + VR. Then, the fMRI contrast *z*-score maps were calculated for each phase within each of the following comparisons: 1) pain on > pain off; no VR; no opioid; 2) pain on > pain off; VR; no opioid; 3) pain on > pain off; no VR; with opioid; and 4) pain on > pain off; VR; with opioids. Once fMRI average *z*-scores were calculated for individual brains, group difference maps were calculated.

Preprocessing

The following prestatistics processing was applied using FSL: motion correction using MCFLIRT (24); nonbrain removal using BET (25); smoothing using a Gaussian kernel of FWHM 5 mm; high-pass temporal filtering (Gaussian-weighted LSF straight line fitting, with $\acute{o} = 30.0$ s).

First Level

Analysis was performed using FEAT (FMRI Expert Analysis Tool) Version 5.1, part of FSL. Time-series statistical analysis was performed using FILM [FMRIB's Improved Linear Model, (26)] in a block-design with local autocorrelation correction. *Z* (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $P = 0.01$ (27). Registration to high resolution and/or standard images was performed using FLIRT (24,28). Effects at each voxel were estimated, and regionally specific effects compared using linear contrasts.

Group Level

The contrasts for the individual subjects were aggregated for the group in a random effects analysis. Higher-level analyses were performed using FLAME [FMRIB's Local Analysis of Mixed Effects, (29,30)]. *Z* (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster.

ROI Analysis Based on Group Maps

For the five pain-related brain ROIs defined above, quantitative ROI data were obtained using software developed in our laboratory to apply the same anatomical mask to all subjects' brains and automatically calculate the mean *z*-score and significant number of pixels within a cluster within each ROI.

The design allowed for analyses of pain-related brain activity in each of the four treatment conditions. Because visual fixation on the black cross was common to both "pain on" and "pain off" segments of the no VR condition, the brain activation observed was specifically indicative of the pain manipulation. Neural correlates of pain were similarly analyzed during the VR condition. Because VR stimulation was common to both "pain on" and "pain off" segments of the VR condition, changes observed in brain activation reflected only pain-related brain activity and not artifactual brain activity that may have been elicited by VR (31).

As with the subjective pain rating analyses, brain activations for each ROI were compared using both a linear statistical model (to assess for factor main and interaction effects) and univariate, repeated measures ANOVAs (to assess the relative effects of opioid, VR, and their combination on the same outcome variables). Raw voxel outcomes were transformed by adding one and taking the logarithm. In addition to the factor effects, a term for the sequence order of VR or no VR was also included in the model to adjust for period effects. To account for repeated measures made on the same subject, generalized estimating equations were used with identity link function and the assumption that the outcomes were normally distributed (32). Normal plots of the residuals gave no evidence to contradict this assumption. All statistical analyses were performed using SAS version 11, and comparisons differing at the level of $P < 0.05$ were considered significant.

RESULTS

Hydromorphone Plasma Levels

Plasma hydromorphone levels measured at the beginning of the stimulation/scanning session (i.e., 30 min after initiation of TCI administration) were median 4.6 (mean 5.6 ± 1.6) ng/mL, whereas those measured immediately after completion of the approximately 45-min study session (approximately 75 min after initiation of infusion) were median 3.6 (mean 5.3 ± 2.3) ng/mL. Thus, the pharmacokinetic model and TCI protocol targeting 4 ng/mL plasma concentrations slightly underestimated actual concentrations, although with reasonable mean performance errors and expected interindividual variability for such infusion protocols (31% ± 41% and 31% ± 58%, respectively).

Table 1. Subjective Pain/Fun Assessments by Treatment Condition

Outcome variable	VR−/opioid−	VR+/opioid−	VR−/opioid+	VR+/opioid+
Worst pain intensity	8.28 (0.83)	5.94 (2.21)*	7.72 (1.86)	4.50 (1.87)*‡
Pain unpleasantness	8.56 (0.53)	5.33 (2.16)*	7.17 (1.60)†	4.05 (1.98)*‡
Time spent thinking about pain	8.72 (1.25)	4.56 (2.46)*	7.78 (1.79)	3.78 (1.72)*‡
Fun	0.56 (1.33)	6.56 (2.19)*	0.33 (0.50)	6.17 (3.04)*‡

Mean (SD) ratings for the primary (worst pain intensity) and secondary (pain unpleasantness, time spent thinking about pain, and amount of fun during the procedure) outcome measures for participants in each treatment condition ($n = 9$), including results of univariate ANOVA analyses.

VR = virtual reality distraction.

† $P < 0.05$ indicates difference between treatment group and control (VR−/opioid−) group.

* $P < 0.01$ indicates difference between treatment group and control (VR−/opioid−) group.

‡ $P < 0.01$ indicates difference between combined treatment (VR+/opioid+) group and opioid alone (VR−/opioid+) group.

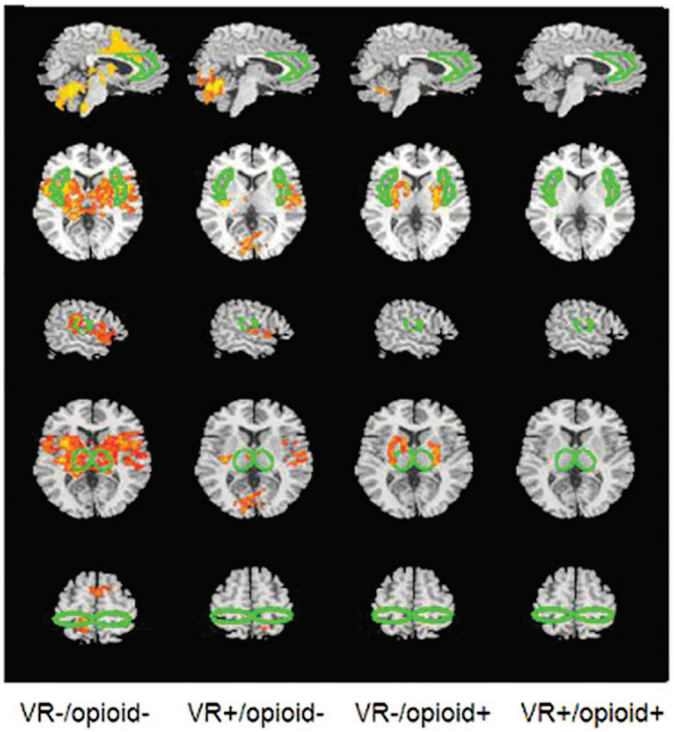

Figure 2. Summary of group functional magnetic resonance imaging (fMRI) results ($n = 9$ subjects) showing voxel maps of significant differences in voxels between "pain" and "no pain" conditions, for each of the four treatment conditions (control, VR only, opioid only, and combined VR + opioid). Regions of interest are outlined in green. Alone, VR and opioid each appear to attenuate pain-related neural activity in the five regions of interest, whereas the combination of VR+ opioid appears to further reduce pain-related activity compared with either treatment condition alone. VR = virtual reality distraction; ACC = anterior cingulate cortex; SS2 = secondary somatosensory cortex; SS1 = primary somatosensory cortex.

Subjective Pain Assessments

Results summarizing the three subjective pain assessments and the subjective assessment of "fun" are shown in Table 1. Pain ratings were generally reduced under the conditions of VR distraction alone or opioid alone, compared with baseline, and were further reduced under the combined VR + opioid condition. Subjective fun ratings were higher under both VR conditions than under either no VR condition.

fMRI Activity Results

Significant pain-related brain activation was observed in all five ROIs (bilateral insula, bilateral thalamus, bilateral ACC, contralateral SS1, and bilateral SS2) compared with the no pain condition (Fig. 2 and Table 2) in the no VR + no opioid (control) condition.

Neither VR nor opioid alone significantly affected pain-related brain activity in the ACC or in SS1; however, effects were noted in the remaining ROIs and are summarized in Table 2. VR without opioid significantly reduced pain-related brain activity in the insula, SS2, and thalamus. Opioid without VR significantly reduced pain-related brain activity in the insula and thalamus.

Comparison of Subjective Pain Score and Imaging Outcomes

With rare exception, the analgesic interventions of VR, opioid, or their combination resulted in lower subjective pain scores compared with the baseline pain condition, in all subjects. However, two participants reported a paradoxical increase in subjective pain unpleasantness and worst pain intensity ratings during the opioid condition (no VR). Of note, these two participants also showed a pattern of more pain-related brain activity in all five ROIs during the opioid condition when compared with the other three treatment conditions. In contrast, the two subjects who reported the largest reductions in subjective pain unpleasantness and worst pain intensity during the opioid condition were also those who showed the largest reductions in pain-related

Table 2. Regional Pain-Related Brain Activity by Treatment Condition

Region of interest	VR−/opioid−	VR+/opioid−	VR−/opioid+	VR+/opioid+
ACC	3.24 (2.23)	1.61 (1.97)	2.13 (2.84)	0.72 (1.63)*
Insula	5.85 (1.10)	3.70 (2.32)*	3.56 (1.87)*	2.96 (1.89)†
SS2	4.31 (2.16)	2.09 (2.19)*	2.63 (1.82)	1.04 (1.97)†‡
Thalamus	4.83 (1.98)	2.63 (2.52)*	1.96 (1.74)*	0.62 (1.11)†§
SS1	3.48 (2.63)	2.87 (2.52)	3.07 (2.26)	2.48 (2.11)

Average (SD) transformed voxel counts for participants in each treatment condition ($n = 9$), including results of univariate ANOVA analyses.

VR = virtual reality distraction; ACC = anterior cingulate cortex; SS2 = secondary somatosensory cortex; SS1 = primary somatosensory cortex.

* $P < 0.05$ indicates difference between treatment group and control (VR−/opioid−) group.

† $P < 0.01$ indicates difference between treatment group and control (VR−/opioid−) group.

‡ $P < 0.05$ indicates difference between combined treatment (VR+/opioid+) group and opioid alone (VR−/opioid+) group.

§ $P < 0.05$ indicates difference between combined treatment (VR+/opioid+) group and VR alone (VR+/opioid−) group.

brain activity in all five ROIs during the same opioid condition.

DISCUSSION

The current study was designed to integrate both psychophysical and neuroimaging assessments in healthy subjects receiving painful thermal stimulation, to compare the changes in reported pain experience with associated changes in pain-related brain activation under conditions of no treatment, as well as clinically relevant conditions of target-controlled opioid (hydromorphone) administration alone, immersive VR distraction alone, and the combination of opioid + VR. Opioid alone and VR alone each significantly reduced pain and pain-related brain activity compared with no treatment. At the chosen dose of opioid and the chosen "dose" (33) of VR distraction used in the present study, adjunctive use of VR (i.e., opioid + VR) reduced pain reports and pain-related brain activity more effectively than opioid alone.

Graded infusions of the mu1 opioid agonist, remifentanil, in clinically relevant doses are reported to have a subjective analgesic effect associated with reductions in pain-related activity in the insula and ACC bilaterally (17). In addition, this subjective analgesic effect has a time course that is temporally associated with the time course of brain activation reductions specific to the contralateral insula (34). For the first time, the present protocol extends these observations to a more commonly used mu1 opioid agonist (hydromorphone). In contrast to remifentanil and its association with paradoxical opioid-induced secondary hyperalgesia (35), hydromorphone is administered in a wider variety of clinical acute pain settings and with more predictable analgesic effect. Although subjective opioid analgesia was observed in the current study with hydromorphone plasma concentrations targeted to 4 ng/mL (measured slightly higher), significant reductions were found for only one of the three subjective pain outcomes (emotional dimension of pain unpleasantness). However, significant reductions in pain-related brain activity during opioid treatment were found in two (bilateral insula and thalamus) of the five ROIs with notable thermal pain activations. In the present study, one of these regions (insula) showed reductions in pain-related brain activity with hydromorphone administration consistent with previous reports under remifentanil analgesia (17). The mechanism of analgesic action for immersive VR distraction is not clear, but likely involves diversion of attention away from the noxious stimulus that initiates pain perception. Distraction is achieved both by visual and aural exclusion (by an occlusive head-mounted display and headphones) of the immediate real-world environment and by multisensory (audio, visual, and sometimes tactile) input to the user that typically includes user interaction with the virtual environment. By commanding the user's limited capacity for conscious attention, immersive VR limits the conscious attention available for pain perception, resulting in an attenuated pain experience. One indirect measure of the pain reduction from immersive VR is the finding that VR increased subjective ratings of fun during thermal pain stimulation. The amount of fun reported during thermal pain stimulation was significantly higher during VR use, regardless of the opioid condition.

Attentional modulation of the pain experience in both positive and negative directions, as assessed by psychophysical and neuroimaging outcomes, has been described (10,36), and similar specific evidence for a potential attention-related mechanism of VR analgesia is threefold. First, using a well-established divided attention paradigm (37,38), Hoffman et al. (39) reported a significant reduction in subjects' accuracy in identifying auditory strings of odd numbers (among random numbers) when engaged in a virtual environment, compared with a control, nonengaging, real-world environment. Although the divided attention task provides a nonspecific measure of conscious attention (involving arithmetic, hearing, memory, and executive functions), the results are consistent with attentional distraction by VR. Second, and specific to the issue of multisensory input and VR analgesia effect, in another study, Hoffman et al. (33) described an increased analgesic effect on thermal pain, as measured by subjective pain ratings, when the audio, video, and

interactive components of the VR experience were maximized (e.g., highly immersive VR) compared with lesser degrees of sensory stimulation and user interaction (e.g., low resolution video display, no sound, and no user interaction). The increased analgesic effect was associated with higher user reports of "presence" (the feeling of being inside the virtual environment), and suggests that simple video stimulation in the absence of high-resolution, wide field-of-view head-mounted display, 3D sound effects, head-tracking and user interaction with the environment will result in a weaker illusion of going "inside" the virtual world and less effective distraction analgesia than with highly immersive VR. Lastly, in addition to its effects on the subjective pain experience in both clinical and experimental pain settings, VR distraction has also been shown to attenuate pain-related brain activity in the five ROIs of the pain matrix, including bilateral ACC, Insula, and Thalamus, and contralateral SS1 and SS2 (13). In the current study, significant reductions in pain-related brain activity during VR were consistent with this report, but limited to the insula, thalamus, and SS2.

One advantage of the current study design was its ability to assess for potential additive or positive/negative combined analgesic effects of both a controlled opioid infusion and adjunctive immersive VR. There is limited clinical experience comparing the subjective analgesic effects of opioid analgesia alone with the combination of opioid plus VR distraction analgesia. This is the first study to make this comparison in a controlled experimental pain setting and is also the first study to make this comparison using functional brain imaging as a dependent measure. Our results demonstrate that the combined intervention of opioid + VR reduced pain reports significantly when compared with opioid alone. In addition, the present results provide preliminary data to support the clinical use of multimodal (e.g., combined pharmacologic and nonpharmacologic techniques) analgesic therapies. Because the current study was not designed to address specific mechanisms and/or sites of analgesic action (e.g., modified neuronal plasticity or periaqueductal gray modification of ascending nociceptive signals) future research should explore whether the analgesic actions of opioid and VR distraction are independent and unrelated, the former dependent upon opiate agonist-receptor interactions and the latter possibly dependent upon modulation of conscious attention. Further studies with opioid receptor antagonists, combined with specific manipulation of attentional processes and assessment of attentional outcomes, are needed to define the individual mechanisms and explore the limits of additive analgesic effects with various pharmacologic and distraction interventions.

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