Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI

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This study investigated the neural correlates of virtual reality analgesia. Virtual reality significantly reduced subjective pain ratings (i.e. analgesia). Using fMRI, pain-related brain activity was measured for each participant during conditions of no virtual reality and during virtual reality (order randomized). As predicted, virtual reality significantly reduced pain-related brain activity in all five regions of interest; the anterior cingulate cortex, primary and secondary somatosensory cortex, insula, and thalamus ($p < 0.002$, corrected). Results showed direct modulation of human brain pain responses by virtual reality distraction. *NeuroReport* 15:1245–1248
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Key words: Analgesia; Anterior cingulate cortex; fMRI; Pain; Somatosensory cortex; Virtual reality

INTRODUCTION

Excessive pain during medical procedures is a widespread problem. Researchers have recently begun using immersive virtual reality as a powerful adjunctive pain control technique. Patients' subjective ratings of pain during a variety of painful medical procedures have been shown to drop ~40–50% when patients are distracted by immersive virtual reality [1].

Virtual reality analgesia may work via an attentional mechanism [1]. Pain requires conscious attention [2]. The more intense the patient's illusion of being drawn into the virtual environment (i.e. subjective presence), the more attention drawn into virtual reality, and the less pain patients experience. Although there is growing evidence that immersive virtual reality can lead to large reductions in the subjective experience of pain, there is currently no published evidence about the neural correlates of virtual reality analgesia in the brain. In the current study, we investigated the direct modulation of human brain pain responses by virtual reality distraction.

In a previous unpublished study of 16 volunteers, we used a laboratory thermal pain paradigm to elicit pain-evoked brain activity (noxious pain on/off every 30 s over a 6 min period). Consistent with previous neuroimaging studies [3–5], we found thermal pain-evoked brain activity in the anterior cingulate cortex (ACC), primary (SS1) and secondary (SS2) somatosensory cortices, the insula, and thalamus, and subjects showed no habituation to the thermal pain stimuli over the 6 min scans (no difference in pain-related brain activity for the first 3 min *vs* second 3 min). Based on this pilot work, we determined regions of interest for fMRI as well as the thermal pain stimulation paradigm adopted in the present study.

Functional imaging studies (PET and fMRI) provide evidence for attention/distraction-related reduction of pain activity in the ACC, SS1, and SS2 [6–9]. Hypnotic analgesia has also been associated with reductions in pain-related brain activity. In a study by Rainville *et al.* [4] subjects received hypnotic suggestions that thermal pain stimuli would feel less unpleasant. This specific manipulation produced significant drops in subjective ratings of pain unpleasantness, but no change in subjective ratings of pain intensity (ratings of worst pain). As predicted, subjects' ratings of pain unpleasantness were positively correlated with activity in the caudal ACC implicating the involvement of the ACC in the affective dimension of pain. In another study, researchers were able to manipulate subjective ratings of pain intensity, the sensory component of pain, reducing pain-related brain activity in the SS1 cortex [6], implicating SS1 in the perception of the sensory component of pain.

Because virtual reality analgesia typically reduces subjective ratings of both pain unpleasantness (emotional component of pain) and pain intensity (the sensory component of pain), as well as amount of time spent thinking about pain, we predicted that virtual reality would reduce pain in both the ACC and the SS1, as well as the other three brain regions of interest. Such findings might contribute to an initial understanding of the mechanisms underlying virtual reality analgesia in humans.

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MATERIALS AND METHODS

Subjects: Fourteen subjects (10 males and four females) initially participated after passing a thermal pain/virtual reality analgesia pre-test screening. Of these 14 participants, six were excluded from analysis due to excessive head movement during the fMRI, which precluded analyses (four subjects), or minimal/no pain-related brain activity in the no virtual reality baseline condition (two subjects). Eight male subjects aged 18–43 participated in the full study. Informed written consent was obtained using a protocol reviewed and approved by the University of Washington IRB.

Thermal stimuli and experimental protocol: All subjects underwent one 7 min scan during which thermal stimuli were presented by a Peltier thermode (www.medoc.com) [10] and alternated every 30 s between non-painful warm (36°C) and painful thermal stimuli (median painful temperature 47.6°C, range 46.5–49°C). Temperatures were individually tailored to and approved by each participant prior to use in the scanner. The temperature to be used for the noxious stimuli during fMRI was determined using the psychophysical method of ascending levels. 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 stimuli using a 0–10 scale. The temperature was gradually increased after each rating until the subject identified a stimulus that was painful but tolerable. That temperature was used as the noxious stimulus temperature during the fMRI.

In addition to delivering heat, the Medoc thermode measures the temperature at the skin surface. The baseline skin surface temperature was 36°C for each participant i.e. the temperature of the subject's foot at the location of the thermode was controlled by the thermode, and was the same for all participants. Pain-related brain activity was measured for each participant during conditions of no virtual reality for 3.5 min and during virtual reality for 3.5 min while in the fMRI scanner. Condition order was randomized such that each person was equally likely to experience virtual reality first or no virtual reality first, but all subjects received both conditions.

When in virtual reality, subjects experienced the illusion of floating along a pre-determined path through an icy 3D virtual canyon, and shot virtual snowballs at virtual objects in SnowWorld. Subjects used a track ball (mouse-like device) to look around or aim and shoot. In the no virtual reality condition, subjects visually focused upon a black fixation cross on a white background with no sound effects. Both types of stimuli were presented via a unique virtual reality helmet [11]. With this design, the virtual reality *vs* no virtual reality condition was manipulated within subjects. Immediately after fMRI scanning all subjects were asked to rate the amount of time spent thinking about pain, pain unpleasantness, worst pain, amount of fun, amount of nausea, and the extent to which they felt like they had gone inside the virtual world (i.e. presence) [11] during the virtual reality condition using 0–10 subjective Graphic Rating Scales [12,13]. They also gave pain and fun ratings for the no virtual reality condition.

Imaging data acquisition: Structural and fMRI were performed on a 1.5 T MRI system (version 5.8, General Electric, Waukesha, Wisconsin, USA). Scanning included a 21-slice matching axial (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 with 1 mm gap, 64×64 matrix, 145 volumes total; time 435 s). Of this 7 min 15 s only 7 min of fMRI data were usable after the first 15 s of non-steady-state data were discarded. 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°, field of view 24 cm, acquisition time 4 min 36 s). The start of the stimulus sequence was synchronized to the start of the fMRI scan so that brain activity and stimulus condition were matched for analysis. 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). Blood oxygen level dependent (BOLD) functional MRI scans were performed using T2*-weighted rapid gradient echo planar images (EPI) to identify activation sites. Heavily susceptibility-weighted sequences were used to maximize the BOLD response. This was accomplished by choosing an echo time of 50 ms to enhance the contrast in brain fMRI signal between the thermal on and the off conditions. Contrasts were calculated for both of the experiment conditions. The 3D anatomical location of the five brain regions were drawn on a standardized brain (in Talairach space) using the program MEASURE [14] under the guidance of a neuroanatomist.

Data analysis: fMRI data were analyzed using Brain Voyager software (version 4.8, Brain Innovations, Netherlands, www.brainvoyager.com) with motion correction, temporal Gaussian smoothing of 4 s, spatial Gaussian smoothing of 4 mm, linear detrending, general linear model (multiple regression) for fitting the time domain fMRI data. Structural and fMRI data was transformed into Talaraich space; both individual and group analyses were performed on z-score transforms. Group analyses were performed separately on each of the two conditions (no virtual reality *vs* virtual reality) and then contrasts were calculated between the two different conditions using Brain Voyager's multi-subject statistical contrast parameters (general linear model using the fixed effects model, z transforms and

Table 1. The mean subjective pain (and fun) ratings during thermal pain stimulation with no virtual reality *vs* virtual reality (VR). Ranges of scores on a 0–10 scale are shown in parentheses.

	No VR	VR		*p*	MSE
Time spent thinking	8.06 (6–10)	4.50 (3–6)	$F(1,7)=51.81$	$p<0.001$	0.98
Pain unpleasantness	8.13 (7–9)	4.50 (3–6)	$F(1,7)=44.94$	$p<0.001$	1.17
Worst pain	7.50 (6–9)	5.23 (3–7)	$F(1,7)=20.25$	$p<0.005$	1.00
Fun	1.43 (0–4)	6.71 (4–8)	$F(1,6)=60.40$	$p<0.001$	1.62

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separate subject predictors). A cluster analysis was performed on the results of the contrast image using a t value threshold of 5.6. This cluster analysis produces a t value, cluster size, and p value for each cluster.

The design allowed for analyses of pain in each of the two conditions. Since visual fixation on the black cross was common to both pain on and pain off segments of the no virtual reality condition, the brain activation observed was specifically indicative of the pain manipulation. In other words, there was a constant visual stimulus for both pain on and pain off time periods which helps in the interpretation of brain activation. However, fixation to a black cross is not required to detect pain-related brain activity. Neural correlates of pain were similarly analyzed during the virtual reality condition. Since virtual reality stimulation was common to both pain on and pain off segments of the virtual reality condition, changes observed in pain-related brain activity reflected only pain-related brain activity and not artifactual brain activity that may have been elicited by virtual reality. All statistical comparisons on subjective ratings showing $p<0.05$ were considered significant. All statistics involving fMRI are corrected for multiple comparisons using a conservative t value threshold of 5.6. This threshold was chosen based on a Bonferroni multiple-comparison correction using the number of brain voxels (the smallest spatial element of the brain image) and 57 690 voxels were used in this calculation.

RESULTS

Virtual reality significantly reduced all subjective pain reports (Table 1). On average, subjects reported a moderately strong illusion of presence in virtual reality (mean 6.38, range 4–8). Mean nausea from virtual reality was <1 (range 0–4).

Modulation effect of virtual reality distraction on the cerebral response to pain: In the no virtual reality condition, brain activation was found in all five brain regions of interest: the ACC, SS1, SS2, insula and thalamus. As predicted, for the group contrast comparing no virtual reality *vs* virtual reality, all five brain regions of interest showed statistically significant reductions in pain-related brain activity using a threshold of $p<0.002$ (conservatively corrected for multiple comparisons, $t>5.6$; Fig. 1, Table 2).

DISCUSSION

Published works to date have only measured virtual reality analgesia using subjective pain ratings. No research has explored whether virtual reality reduces pain-related brain activity. The present study measured the patterns of brain activity associated with virtual reality analgesia. In this study, virtual reality reduced subjective reports of time spent thinking about pain by 44%, reduced emotional pain by 45%, reduced sensory pain ratings by 30% and virtual reality increased subjects ratings of fun by 79%. Furthermore, the present study shows for the first time that immersive virtual reality can also significantly reduce pain-related brain activity in the caudal ACC (associated with emotional component of pain [4]), SS1 (associated with sensory component of pain [6]), SS2, insula and thalamus. Thus, our results show converging evidence from subjective and objective measures that virtual reality reduces pain via

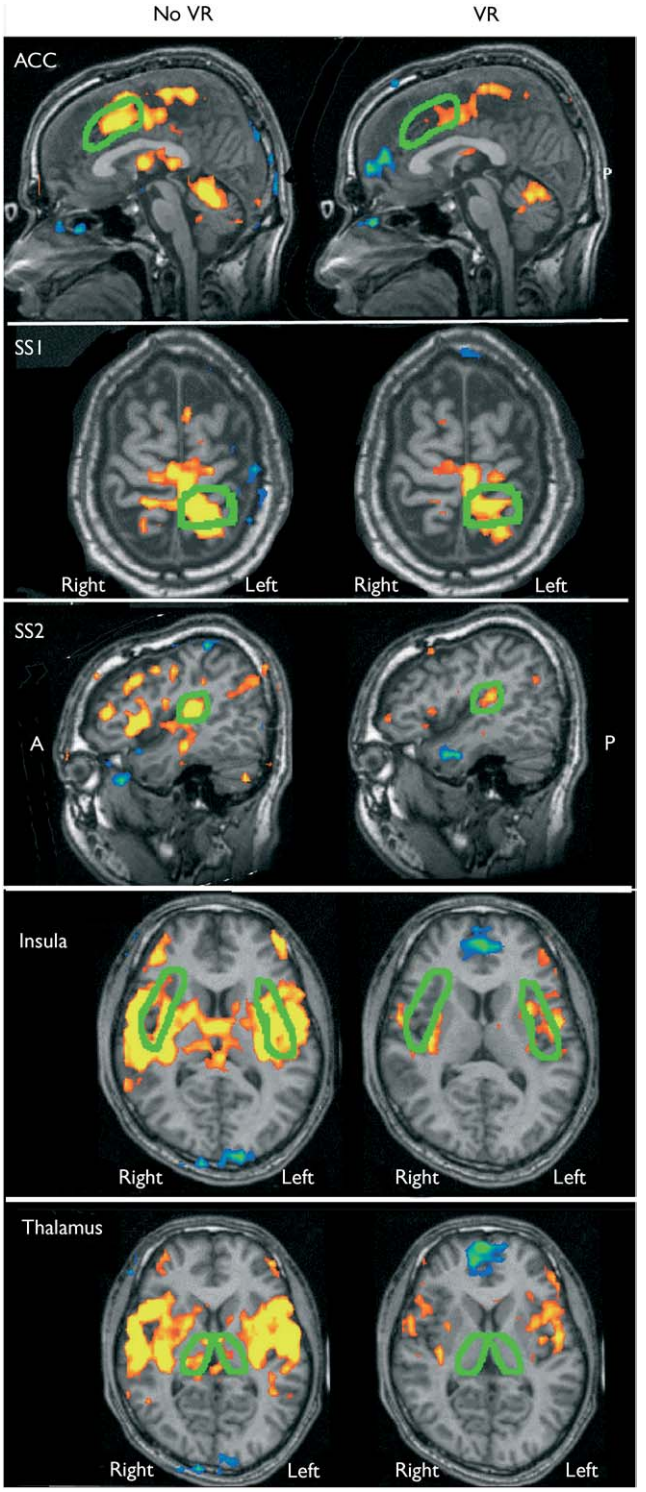

Fig. 1. fMRI group analysis showing no virtual reality for 3.5 min *vs* virtual reality for 3.5 min ($n=8$). The green line outlines the anterior cingulate cortex, primary somatosensory cortex, secondary somatosensory cortex, insula, and thalamus respectively (from top to bottom). The five images (one for each region of interest) on the left half of the figure represent brain activity during no virtual reality. The images on the right half of the figure show pain-related brain activity during virtual reality. Subjects showed a reduction in pain-related brain activity when in virtual reality.

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Table 2. Talairach coordinates, mean difference, t-values, activation volumes, and probability for clusters in 6 different regions of the brain-ACC-anterior cingulate cortex (cognitive division and affective/emotional division), SSI – primary somatosensory cortex, SS2 – secondary somatosensory cortex, thalamus and insula. The statistics and activation volume was based on a multi-subject contrast map using Brain Voyager software using a threshold t-value of 5.6. The mean difference value is based on the GLM model fit of the MR signal and is related to the amplitude of the change in MR signal between the no virtual reality *vs* the virtual reality condition. The volume given in column 7 is the volume of one cluster within the region of brain specified in column 1. For example, in the insula, there were several main clusters each with its own t value, volume, and probability. The probability listed in column 8 is the probability that a cluster with specific t-value and size shown in columns 6 and 7 would occur by chance. This probability is Bonferroni corrected using a value of 57690 which is the number of voxels in the brain mask.

Region	Stereotaxic coordinates (mm)			Mean difference based on MR sig.	t value	Volume (cc)	Probability (Corrected)
	Lateral x	*Anterior y*	*Superior z*				
ACC– cognitive division	0	10	39	No cluster		0	NS
ACC–affective division	6	53	10	227.595	5.128	0.117	1.99E-02
SSI	−63	−8	17	235.477	8.577	0.972	1.85E-12
	62	−13	21	194.472	6.473	0.232	8.25E-06
SS2	60	−5	8	304.927	8.686	1.806	7.56E-13
	−57	−20	14	259.87	8.348	1.355	1.17E-11
SS2/Post. Insula	36	−16	16	154.591	8.997	1.221	5.60E-14
Insula	39	−2	9	141.619	6.772	0.116	7.04E-02
	−40	−13	11	169.19	8.691	0.57	4.53E-08
	−41	−1	−2	146.82	6.499	0.018	4.15E-01
Thalamus	4	−6	9	331.562	6.912	0.042	2.76E-02

Note: Anterior cingulate cortex (ACC) was subdivided into the cognitive and affective divisions of the ACC as defined by Bantick *et al.* [8]. SSI, primary somatosensory cortex; SS2, secondary somatosensory cortex.

modulation of both the sensory and the emotional aspects of pain processing. As the pain decreases in intensity, it typically becomes less unpleasant, reducing motivation for escape or avoidance behaviors, and reducing autonomic activation [4].

Our results also help reduce the plausibility of a demand characteristics explanation of virtual reality analgesia, since patterns of pain-related brain activity are presumably not under the participant's volitional control. Virtual reality analgesia has been shown to reduce subjective pain ratings during wound care in severe burn patients [1] and virtual reality may have important widespread clinical applications, particularly in the management of procedural pain from numerous etiologies. The results of the present study provide converging evidence from subjective and objective measures that virtual reality reduces pain. Additional research on mechanisms and clinical efficacy of virtual reality analgesia is warranted.

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