2021-06

# Exposure to an Immersive Virtual Reality Environment can Modulate Perceptual Correlates of Endogenous Analgesia and Central Sensitization in Healthy Volunteers

Mehesz, E

http://hdl.handle.net/10026.1/18551

**Exposure to an immersive virtual reality environment modulate perceptual correlates of endogenous analgesia and central sensitisation in healthy volunteers**

Mehesz Erzsebet[1]*, Hajer Karoui[1]*, Paul H Strutton[1], Sam W Hughes[2]

* These authors contributed equally to this manuscript

[1] The Nick Davey Laboratory, Department of Surgery and Cancer, Imperial College London

[2] The Pain Neuroplasticity and Modulation Laboratory, School of Psychology, University of Plymouth

Number of text pages including figures: 23

Number of figures: 3

Number of tables: 0

**Corresponding author and address:** Dr Sam Hughes; The Pain Neuroplasticity and Modulation Laboratory, Brain Research and Imaging Centre (BRIC), School of Psychology, Faculty of Health, University of Plymouth, United Kingdom, PL4 8AA.

**Disclosures**

**Abstract**

Virtual reality (VR) has been shown to produce analgesic effects during different experimental and clinical pain states. Despite this, the top-down mechanisms are still poorly understood. In this study, we examined the influence of both a real and sham (i.e. the same images in 2D) immersive arctic VR environment on conditioned pain modulation (CPM) and in a human surrogate model of central sensitisation in 38 healthy volunteers. CPM and acute heat pain thresholds (HPT) were assessed before and during VR/sham exposure in the absence of any sensitisation. In a follow-on study, we used the cutaneous high frequency stimulation (HFS) model of central sensitisation and measured changes in mechanical pain sensitivity (MPS) in an area of heterotopic sensitisation before and during VR/sham exposure. There was an increase in CPM efficiency during the VR condition compared to baseline ($P<0.01$). In the sham condition, there was a decrease in CPM efficiency compared to baseline ($P<0.01$) and the real VR condition ($P<0.001$). Neither real nor sham VR had any effect on pain ratings reported during the conditioning period or on HPT. There was also an attenuation of MPS during the VR condition indicating a lower sensitivity compared to sham ($P<0.05$). We conclude that exposure to an immersive VR environment has no effect over acute pain thresholds but can modulate dynamic CPM responses and mechanical hypersensitivity in healthy volunteers.

**Key words:** Endogenous analgesia; virtual reality; secondary hyperalgesia; central sensitisation

**Perspective**

This study has demonstrated that exposure to an immersive virtual reality environment can modulate perceptual correlates of endogenous pain modulation and secondary hyperalgesia in a human

surrogate pain model. These results suggest that virtual reality could provide a novel mechanism-driven analgesic strategy in patients with altered central pain processing.

**Introduction**

Exposure to immersive 360° virtual reality (VR) environments has been shown to produce analgesic effects during acute medical procedures as well as in human surrogate pain models and chronic pain states [12, 21, 30, 31]. Growing evidence suggests that cognitive and attentional factors are known to have an influence on spinal cord representations of central sensitisation as well as endogenous analgesic circuitry implicated in the descending control of pain [10, 45]. However, there is a lack of research into whether the pain-relieving effects of an immersive VR experience are due to top-down influences on perceptual correlates of descending pain modulation.

Descending pain modulation pathways form part of an endogenous analgesic system which is the target of many pharmacological and non-pharmacological pain therapies [5, 16, 20, 27]. Top-down influences from cortical and sub-cortical regions on descending pain modulation are also thought to underpin placebo-based analgesia [13-15, 17] as well as mediate the analgesic effects linked to alcohol [25]. It is therefore feasible that similar top-down processes could be associated with the analgesic effects seen during exposure to immersive 360° VR environments.

It is possible to measure the activity of the descending pain modulation system in humans using psychophysical approaches [3, 28, 29]. Conditioned pain modulation (CPM) is the human equivalent to diffuse noxious inhibitory control (DNIC) measured in rodents and is used to measure perceptual correlates of descending inhibitory control in both healthy volunteers and chronic pain patients [11, 42]. Previous research has suggested that the effects of VR could be related to baseline CPM levels [30], however it is still unclear whether there are any direct effects on the CPM response. In this study, we first aimed to measure psychophysical changes

in the response of the descending pain modulation system during exposure to a immersive 360° arctic VR environment by examining the direct effects of VR on CPM responses in the absence of experimentally induced sensitisation in healthy volunteers.

Human surrogate pain models can also provide a means by which to evaluate the effects of novel centrally acting analgesics on perceptual correlates of central sensitisation at the spinal level [1, 26, 29, 48]. Given the top-down influence of descending pain modulation systems on spinal cord nociceptive processing, we then hypothesised that exposure to the same immersive VR environment will also modulate spinal cord representations of central sensitisation (i.e. mechanical secondary hyperalgesia), by using cutaneous high frequency stimulation (HFS) as a model of heterotopic sensitisation in the dorsal horn.

**Methods**

*Participant recruitment and screening*

All procedures were approved by the local research ethics committee. The participants were informed of the experimental protocols and subsequently provided written consent in accordance with the principles of the declaration of Helsinki. In this study, a total of 38 healthy participants (mean age: 26.3 ± 6.9 SD; 17 F) were recruited from Imperial College London. Initially, 19 participants (mean age: 26.0 ± 7.2 SD; 10 F) underwent VR testing alongside heat pain threshold (HPT) and CPM testing. A separate cohort of 19 participants (mean age: 26.7 years ± 6.8 SD; 7 F) were then recruited to a follow-on study which included using the same VR design alongside mechanical pain sensitivity (MPS) testing in the HFS human surrogate model of central sensitisation. All participants were initially screened to see if they met any of the exclusion criteria for pain testing (i.e. history of chronic pain conditions, current acute or chronic pain conditions, pregnancy, diabetes, blood disorders, neurological conditions,

immune-suppression, inflammatory disease, psychiatric conditions, taking steroid, antibiotic or pain medicines).

*Virtual reality environment and headset*

An immersive360° video of a passive arctic scene was uploaded to a wireless Oculus Quest VR headset and was experienced by the participant via two diamond Pentile OLED displays (1440 x 1600 resolution; 72 Hz refresh rate). The passive nature of the VR design ensured participants could view but not control their environment. An inbuilt tracking system provided information about the participants head movements, which adjusted the environment accordingly. The sham VR condition consisted of displaying the same video but on a 2D PC monitor screen [30].

*Heat pain threshold*

HPT was determined using a thermode (TSA-II, Medoc, Israel) placed over the volar surface of the lower arm covering an area of 9 cm$^2$. The baseline temperature was set to 32 °C and the temperature ramp increased at 1 °C/s and the participant pressed a stop button when the impression of warmth or heat changed towards an additional impression of burning, stinging, drilling or aching sensation. HPT was measured 3 times with a fixed inter-stimulus interval of 10 seconds. HPT was defined as the mean of the 3 measurement repetitions [44].

*Conditioned pain modulation*

Pressure pain thresholds (PPT; test stimulus) were first determined by applying 3 continuous ramps, separated by 30 seconds, of increasing intensity (0.5 kg/s) on the dominant volar forearm using a pressure algometer (WAGNER® FDN 100; contact area 1 cm$^2$). The PPT was defined as the point at which the usual sensation of pressure changed towards an additional sensation of burning, stinging, drilling or aching. After a 5-minute rest, participants were

instructed to immerse the non-dominant hand in cold water (maintained at 8 °C) up to the wrist and palm-side down for 2 minutes (i.e. the cold pressor test; conditioning stimulus). Participants were asked to rate pain perception every 10 seconds throughout the 2 minute conditioning period on a conventional VAS from 0 – 100 (0 = no pain; 10 – 30 = mild pain; 40 – 60 = moderate pain; 70 – 90 = severe pain; 100 = worst pain imaginable). PPTs were then re-measured alongside the cold pressor conditioning by re-applying 3 continuous ramps of increasing intensity (0.5 kg/s) to the dominant forearm after 1 minute. The absolute change in CPM effect was calculated as the conditioned PPT minus the baseline PPT . Therefore, more positive values indicated more efficient CPM [51].

*High frequency stimulation*

Cutaneous electrical stimuli were applied to the right volar forearm (7cm distal to the cubital fossa) using a constant current stimulator (DS7; Digitimer Ltd; Welwyn Garden City, UK) controlled via a pulse generator (D4030; Digitimer Ltd; Welwyn Garden City, UK). An epicutaneous pin electrode comprised of a circular array of 15 cathodal electrodes (individual pin diameter: 0.2 mm; individual pin length: 1 mm; overall diameter: 10 mm; area: 79 mm$^2$) surrounded by a circular stainless-steel anode (inner diameter: 20 mm; outer diameter: 40 mm) was used to deliver each stimulus [8, 49, 50]. First, the electrical detection threshold (EDT) was determined using the method of limits approach. In 0.05 mA steps, the intensity of electrical stimuli was increased until the participant first noticed a sensation. The intensity was then decreased until the participant no longer experienced a sensation. This was repeated 3 times and the EDT was defined as the geometric mean of the 6 measurements. Each participant then received HFS by delivering 1 train of 100 Hz stimulation at 10 x EDT every 10 seconds until 5 trains had been delivered to induce LTP-like heterotopic sensitisation in the spinal cord [33, 49].

*Mechanical pain sensitivity*

MPS was assessed in the area surrounding the circular anode before and after HFS conditioning using a set of 7 weighted pinprick stimuli (MRC Systems GmbH, Heidelberg, Germany) with a set force of 8, 16, 32, 64, 128, 256 and 512mN which were pressed perpendicularly against the skin over the volar surface of the forearm within a heterotopic testing area (i.e. a secondary hyperalgesia zone) for ~1 second (contact area = 0.5mm tip diameter). Pain was rated using a conventional visual analogue scale (VAS) where 0 = no pain and 100 = worst pain imaginable. The 7 stimuli were applied a total of 5 times each in a pseudorandom sequence and a pain rating given after each stimulus. There was pause of ~10 seconds between each stimulus to prevent the occurrence of wind up. MPS was defined as the geometric mean of the 35 pain ratings of the pinprick stimuli, which were then log transformed and converted to z-scores for analysis of the effects of VR or sham [34, 44]. We performed intra-individual z-score comparisons relative to the same area before HFS conditioning (i.e. baseline) [36, 48]. Individual MPS parameter values were z transformed as:

$$Z_{MPS,individual} = \frac{MPS_{indivudual} - MPS_{baseline}}{standard\ deviation_{baseline}}$$

*Experimental protocols*

Using a within-subject design, the effects of VR or sham VR on HPT and CPM responses were investigated in a semi-randomised manner to achieve an even split between the order of real and sham VR within a single test session (Figure 1A). First, baseline HPT and CPM measurements were made with a 10-minute interval between tests. The effects of VR or sham VR were then investigated by turning on the stimulation just before HPT testing and was

5

turned off at the end of the test. During exposure to both the real and sham VR environments, participants were asked to stop the thermal stimulation by clicking a mouse at the point at which impression of warmth or heat changed towards an additional impression of burning, stinging, drilling or aching sensation. For CPM, VR or sham VR was turned on just before the start of the conditioning stimulus and turned off at the end of the test. During this period of real or sham VR exposure, participants were asked to rate the intensity of the conditioning stimulus and say 'now' as soon as the usual sensation of pressure changes towards an additional sensation of burning, stinging, drilling or aching. There was a 15-minute period between VR and sham VR testing. Sham VR consisted of the same images used in the real VR condition, but displayed on a 2D computer monitor screen.

In a separate cohort, the effects of VR or sham VR on MPS after HFS conditioning were investigated using a within-subject design over a single test session, given in a randomised manner (Figure 1B – C). Following baseline MPS testing, participants underwent HFS conditioning and heterotopic sensitisation was established over a ~30-minute period. MPS was then re-examined in the area surrounding the electrode. The effects of VR or sham VR were then investigated by turning on the stimulation just before MPS testing and was turned off at the end of the test. There was a 15-minute period between VR and sham VR testing.

*Statistical analysis*

All data were initially entered into Microsoft Excel before being analysed for statistical significance in GraphPad Prism (v8.0.1. GraphPad Software, Inc.). Normality of data was assessed using a Shapiro-Wilk test and parametric or non-parametric statistical analysis was conducted accordingly. The effect of VR or sham treatment on HPT and CPM responses were analysed using separate one-way repeated measures (RM) ANOVA with Holm Sidak's multiple

comparison post-hoc tests. A Wilcoxon signed rank test was used to compare the effects of real and sham VR on the maximum pain ratings given during the conditioning stimulus. The effect of HFS conditioning on the geometric mean MPS ratings was analysed using a Wilcoxon signed rank test. The effects of VR and sham VR on MPS z scores were analysed using a one-way RM ANOVA with Holm Sidak's multiple comparison post-hoc tests. Statistical significance was set at $p<0.05$ and all data are presented as mean ± SD or median (interquartile range) in the text.

**Results**

*No change in HPT during VR exposure*

The effects of real and sham VR exposure on static quantitative sensory testing (QST) responses in the absence of central sensitisation was examined by measuring changes in HPT during real and sham VR conditions. There was no overall main effect of treatment condition on HPT ($F_{2, 56}$ = 1.79; P = 0.18; Figure 2A). There was no difference in HPT between baseline and VR conditions (baseline: 45.70 ± 2.81°C; VR: 46.49 ± 2.95°C; P = 0.33) or between real and sham VR conditions (sham: 45.78 ± 2.85°C; P = 0.33).

*Enhanced CPM responses during exposure to VR environment*

Changes in dynamic QST responses were examined by investigating the effects of real and sham VR on CPM. There was an overall main effect of treatment condition on CPM ($F_{2, 56}$ = 17.26; P<0.001; Figure 2B). Post-hoc analysis revealed a significant increase in the efficiency of CPM during exposure to the real VR environment compared to baseline (baseline: 11.76 ± 5.31 N; VR: 15.46 ± 6.94 N; P = 0.007). There was an opposite effect of the sham VR condition on CPM efficiency, showing a reduced CPM efficiency compared to both baseline (baseline:

11.76 ± 5.31 N; sham VR: 7.16 ± 5.10 N; P = 0.007) and the VR condition (VR: 15.46 ± 6.94 N; sham VR: 7.16 ± 5.10 N; P = 0.0002). There was no difference in the change in maximum pain rating from baseline given during the conditioning stimulus between real and sham VR (VR: (median (IQR); 0.00 (-17.24, 20.00); sham (median (IQR); -17.65 (-27.50, 8.33); W = 47, P = 0.32; Figure 2C).

*Attenuation of mechanical secondary hyperalgesia during VR exposure*

In a separate cohort of healthy participants, the effects of the same VR immersive arctic environment on HFS conditioned MPS responses (i.e. secondary hyperalgesia) were investigated. Following HFS conditioning there was an increase in MPS sensitivity in the heterotopic testing zone (baseline (median (IQR); 4.49 (3.43, 8.78); HFS (median (IQR); 18.21 (9.69, 25.03); W = 190, P<0.001; Figure 3A). There was an overall main effect of treatment condition on MPS z scores ($F_{2,56}$ = 7.93; P = 0.002; Figure 3B). Post-hoc analysis revealed a significant reduction in MPS z score during exposure to the VR environment compared to the HFS conditioned secondary hyperalgesia response (secondary hyperalgesia: 0.72 ± 0.44; VR: 0.47 ± 0.59; P = 0.01) and sham VR (sham VR: 0.63 ± 0.59; VR: 0.47 ± 0.59; P = 0.03), indicative of a reduction in sensitivity in the heterotopic testing zone in response to the real VR condition.

**Discussion**

In this study, we investigated the effects of an immersive 360° arctic VR environment on CPM, acute pain responses and perceptual correlates of central sensitisation in healthy participants. We have shown that CPM responses were enhanced, whilst acute HPTs were unaffected by VR in the absence of experimentally induced sensitisation. Interestingly, we show no difference in pain ratings reported during the cold pressor conditioning stimulus

between real and sham VR. In a separate cohort, we also demonstrated that exposure to the same VR environment could attenuate pinprick hypersensitivity in the HFS model of central sensitisation. These psychophysical results suggest that VR-induced analgesia is likely to be dependent on activity induced in endogenous analgesic pathways, which may work to preferentially modulate sensitised pain responses over acute pain in healthy volunteers.

There is now a growing body of research showing direct effects of novel therapies, environmental influences as well as traditional pharmacological approaches on CPM efficiency which has been attributed to the increased activation of endogenous pain modulation processes [4, 16, 18, 25, 38, 39]. Our study extends these findings, by showing that exposure to an immersive VR environment can also increase the efficiency of endogenous pain modulation. Exposure to VR can be attributed to a shift in attentional focus and it is feasible that VR-induced analgesia is in part a distraction process which can engage top-down analgesic processes[10]. However, we saw no change in pain measures during the sham condition which is also associated with distraction whilst watching the same images on a 2D monitor. It is therefore possible that as well as attention, pain relief associated with exposure to immersive VR environments could also be attributed to the immersive nature of the experience, which provides a different context to the pain. We have also shown that despite having a beneficial effect on CPM efficiency, there was no difference in the maximum pain ratings reported during the cold pressor conditioning period for real or sham VR. This suggests that the immersive aspect of a real VR experience may bring into play top-down analgesic mechanisms which are not present during simple distraction-based methods.

VR-induced analgesic effects were only seen in dynamic (i.e. CPM) or sensitised (i.e. HFS conditioned MPS) psychophysical measures. There was no effect on static HPT or cold pressor

responses in the absence of sensitisation, which suggests that provoking plasticity within descending pain modulation pathways may be required in order for VR to have its beneficial analgesic properties. It has been previously suggested that other therapeutic strategies including non-invasive brain stimulation and pharmacological approaches have no effect over acute physiological nociceptive activity [2, 9, 28, 29] and VR has been proposed to be more effective in patients with the highest pain intensity ratings [21]. It is also interesting to note that during the sham condition, we saw a reduction in CPM efficiency which could be attributed to a shift towards a pro-nociceptive phenotype in the absence of VR. Taken together, these lines of evidence suggest that VR may be more effective during prolonged or sensitised pain states and provides little benefit over acute pain thresholds in an experimental setting.

In this study, we have shown insight into the top-down mechanisms associated with VR-induced analgesia using psychophysical approaches. It should be noted that a possible limitation of using CPM as a measure of endogenous analgesia is the relatively poor reliability of some paradigms[32]. In this study, we used PPTs and the cold pressor test as test and conditioning stimuli, respectively, which has been shown to be among the most reliable CPM paradigms[32]. Despite this, our findings synergise well with neuroimaging studies using VR environments which have shown activation of regions of the brain, including the anterior cingulate cortex, which are known to have top-down influence on the descending pain modulation system [22, 23]. We have extended these findings by showing an additional effect on spinal cord representations of central sensitisation using the HFS model [33].

We have demonstrated the presence of LTP-like heterotopic facilitation of mechanically sensitive nociceptive pathways indicative of a secondary hyperalgesia response, in line with recent use of the HFS model [7, 19, 46, 47, 49]. It should be noted that the electrical stimulation used

within the HFS model is not a typical source of clinical pain induction. Nevertheless, the use of cutaneous pin electrodes allows for the selective activation of small and medium diameter nociceptive afferents which are implicated in the induction of central sensitisation in chronic pain patients[43]. The HFS model has also been shown to induce a pain phenotype which mimics the mechanical hyperalgesia profile often seen in neuropathic pain patients[6].

It has been suggested that human surrogate models of central sensitisation can be used to evaluate the spinal mechanisms of novel centrally acting therapeutics [1, 48]. With this in mind, in the current study, we have shown that during VR exposure there is an attenuation of spinally mediated MPS measured within a heterotopic zone on the volar surface of the forearm. From this, it is possible to infer a top-down influence of VR on spinal cord representations of central sensitisation which is in line with similar observations seen following the modulation of secondary hyperalgesia during a cognitive working memory task [45]. Future research using spinal cord functional MRI would provide further insights into the neural correlates of VR-induced analgesia in the spinal cord, in line with previous research showing a spinal cord involvement of placebo-induced analgesia [14].

Previous research has shown that the combined use of VR and pharmacological agents may provide added analgesic benefit [24, 35]. It is therefore possible that centrally acting monoaminergic analgesics, such as duloxetine, that work to mimic or enhance the activation of the descending pain modulation system [53] could be used in conjunction with VR to boost analgesic efficacy in chronic pain patients. This approach could be particularly beneficial for groups of patients with deficient endogenous pain modulation; such as those with fibromyalgia [40] and chronic low back pain [37] as well as those likely to develop chronic post-surgical pain [41, 52]. It is therefore feasible that VR could either be used alone or in combination

with centrally acting monoaminergic pharmacology as a novel mechanism-driven approach to analgesia in some patients.

In summary, we have demonstrated that exposure to a 360° immersive VR environment can modulate perceptual correlates of endogenous analgesia and central sensitisation in healthy volunteers. It is possible that VR exerts a top-down influence on descending pain modulation pathways which may preferentially inhibit sensitised pain responses, with little or no effect over acute pain thresholds. With this in mind, VR could be used as part of novel mechanism-driven analgesic strategies in chronic pain patients with deficient endogenous pain modulation or altered MPS profiles.

**References**

1. Arendt-Nielsen L, Curatolo M, Drewes A. Human experimental pain models in drug development: translational pain research. *Curr Opin Investig Drugs.* 8:41-53, 2007
2. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of N-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesth Analg.* 81:63-68, 1995
3. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain.* 10:556-572, 2009
4. Baba Y, Kohase H, Oono Y, Fujii-Abe K, Arendt-Nielsen L. Effects of dexmedetomidine on conditioned pain modulation in humans. *Eur J Pain.* 16:1137-1147, 2012
5. Bannister K, Dickenson AH. What do monoamines do in pain modulation? *Curr Opin Support Palliat Care.* 10:143-148, 2016
6. Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, Finnerup NB, Haanpaa M, Hansson P, Hullemann P, Jensen TS, Freynhagen R, Kennedy JD, Magerl W, Mainka T, Reimer M, Rice AS, Segerdahl M, Serra J, Sindrup S, Sommer C, Tolle T, Vollert J, Treede RD. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain.* 158:261-272, 2017
7. Biurrun Manresa J, Kaeseler Andersen O, Mouraux A, van den Broeke EN. High frequency electrical stimulation induces a long-lasting enhancement of event-related potentials but does not change the perception elicited by intra-epidermal electrical stimuli delivered to the area of increased mechanical pinprick sensitivity. *PLoS One.* 13:e0203365, 2018

8. Biurrun Manresa JA, Morch CD, Andersen OK. Long-term facilitation of nociceptive withdrawal reflexes following low-frequency conditioning electrical stimulation: a new model for central sensitization in humans. *Eur J Pain.* 14:822-831, 2010

9. Bradley C, Perchet C, Lelekov-Boissard T, Magnin M, Garcia-Larrea L. Not an Aspirin: No Evidence for Acute Anti-Nociception to Laser-Evoked Pain After Motor Cortex rTMS in Healthy Humans. *Brain Stimul.* 9:48-57, 2016

10. Brooks JC, Davies WE, Pickering AE. Resolving the Brainstem Contributions to Attentional Analgesia. *J Neurosci.* 37:2279-2291, 2017

11. Cummins TM, Kucharczyk M, Graven-Nielsen T, Bannister K. Activation of the descending pain modulatory system using cuff pressure algometry: Back translation from man to rat. *Eur J Pain.* 2020

12. Darnall BD, Krishnamurthy P, Tsuei J, Minor JD. Self-Administered Skills-Based Virtual Reality Intervention for Chronic Pain: Randomized Controlled Pilot Study. *JMIR Form Res.* 4:e17293, 2020

13. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Buchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron.* 63:533-543, 2009

14. Eippert F, Finsterbusch J, Bingel U, Buchel C. Direct evidence for spinal cord involvement in placebo analgesia. *Science.* 326:404, 2009

15. Fields HL. How expectations influence pain. *Pain.* 159 Suppl 1:S3-S10, 2018

16. Flood A, Waddington G, Cathcart S. High-Definition Transcranial Direct Current Stimulation Enhances Conditioned Pain Modulation in Healthy Volunteers: A Randomized Trial. *J Pain.* 17:600-605, 2016

17. France CR, Burns JW, Gupta RK, Buvanendran A, Chont M, Schuster E, Orlowska D, Bruehl S. Expectancy Effects on Conditioned Pain Modulation Are Not Influenced by Naloxone or Morphine. *Ann Behav Med.* 50:497-505, 2016

18. Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. *Pain.* 154:2317-2323, 2013

19. Henrich F, Magerl W, Klein T, Greffrath W, Treede RD. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. *Brain.* 138:2505-2520, 2015

20. Hodkinson DJ, Khawaja N, O'Daly O, Thacker MA, Zelaya FO, Wooldridge CL, Renton TF, Williams SC, Howard MA. Cerebral analgesic response to nonsteroidal anti-inflammatory drug ibuprofen. *Pain.* 156:1301-1310, 2015

21. Hoffman HG, Chambers GT, Meyer WJ, 3rd, Arceneaux LL, Russell WJ, Seibel EJ, Richards TL, Sharar SR, Patterson DR. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. *Ann Behav Med.* 41:183-191, 2011

22. Hoffman HG, Richards TL, Bills AR, Van Oostrom T, Magula J, Seibel EJ, Sharar SR. Using FMRI to study the neural correlates of virtual reality analgesia. *CNS Spectr.* 11:45-51, 2006

23. Hoffman HG, Richards TL, Coda B, Bills AR, Blough D, Richards AL, Sharar SR. Modulation of thermal pain-related brain activity with virtual reality: evidence from fMRI. *Neuroreport.* 15:1245-1248, 2004

24. Hoffman HG, Richards TL, Van Oostrom T, Coda BA, Jensen MP, Blough DK, Sharar SR. The analgesic effects of opioids and immersive virtual reality distraction:

evidence from subjective and functional brain imaging assessments. *Anesth Analg.* 105:1776-1783, table of contents, 2007

25. Horn-Hofmann C, Capito ES, Wolstein J, Lautenbacher S. Acute alcohol effects on conditioned pain modulation, but not temporal summation of pain. *Pain.* 160:2063-2071, 2019

26. Hughes S, Grimsey S, Strutton PH. Primary Motor Cortex Transcranial Direct Current Stimulation Modulates Temporal Summation of the Nociceptive Withdrawal Reflex in Healthy Subjects. *Pain Med.* 20:1156-1165, 2019

27. Hughes S, Hickey L, Donaldson LF, Lumb BM, Pickering AE. Intrathecal reboxetine suppresses evoked and ongoing neuropathic pain behaviours by restoring spinal noradrenergic inhibitory tone. *Pain.* 156:328-334, 2015

28. Hughes SW, Ali M, Sharma P, Insan N, Strutton PH. Frequency-dependent top-down modulation of temporal summation by anodal transcranial direct-current stimulation of the primary motor cortex in healthy adults. *Eur J Pain.* 2018

29. Hughes SW, Ward G, Strutton PH. Anodal transcranial direct current stimulation over the primary motor cortex attenuates capsaicin-induced dynamic mechanical allodynia and mechanical pain sensitivity in humans. *Eur J Pain.* 2020

30. Hughes SW, Zhao H, Auvinet EJ, Strutton PH. Attenuation of capsaicin-induced ongoing pain and secondary hyperalgesia during exposure to an immersive virtual reality environment. *Pain Rep.* 4:e790, 2019

31. Keefe FJ, Huling DA, Coggins MJ, Keefe DF, Zachary Rosenthal M, Herr NR, Hoffman HG. Virtual reality for persistent pain: a new direction for behavioral pain management. *Pain.* 153:2163-2166, 2012

32. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a systematic review. *Pain.* 157:2410-2419, 2016

33. Klein T, Magerl W, Hopf HC, Sandkuhler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci.* 24:964-971, 2004

34. Lotsch J, Dimova V, Hermens H, Zimmermann M, Geisslinger G, Oertel BG, Ultsch A. Pattern of neuropathic pain induced by topical capsaicin application in healthy subjects. *Pain.* 156:405-414, 2015

35. Maani CV, Hoffman HG, Fowler M, Maiers AJ, Gaylord KM, Desocio PA. Combining ketamine and virtual reality pain control during severe burn wound care: one military and one civilian patient. *Pain Med.* 12:673-678, 2011

36. Magerl W, Krumova EK, Baron R, Tolle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain.* 151:598-605, 2010

37. McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pro-nociceptive and anti-nociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain.* 2019

38. Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo-controlled cross-over proof-of-concept study. *Br J Anaesth.* 110:1010-1016, 2013

39. Nilsen KB, Christiansen SE, Holmen LB, Sand T. The effect of a mental stressor on conditioned pain modulation in healthy subjects. *Scand J Pain.* 3:142-148, 2012

**40.** O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, Carrillo-de-la-Pena MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. *J Pain.* 19:819-836, 2018

**41.** Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *Pain.* 156:55-61, 2015

**42.** Petersen KK, McPhee ME, Hoegh MS, Graven-Nielsen T. Assessment of conditioned pain modulation in healthy participants and patients with chronic pain: manifestations and implications for pain progression. *Curr Opin Support Palliat Care.* 13:99-106, 2019

**43.** Poulsen AH, Tigerholm J, Meijs S, Andersen OK, Morch CD. Comparison of existing electrode designs for preferential activation of cutaneous nociceptors. *J Neural Eng.* 17:036026, 2020

**44.** Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain.* 123:231-243, 2006

**45.** Torta DM, De Laurentis M, Eichin KN, von Leupoldt A, van den Broeke EN, Vlaeyen JWS. A highly cognitive demanding working memory task may prevent the development of nociceptive hypersensitivity. *Pain.* 161:1459-1469, 2020

**46.** van den Broeke EN, de Vries B, Lambert J, Torta DM, Mouraux A. Phase-locked and non-phase-locked EEG responses to pinprick stimulation before and after experimentally-induced secondary hyperalgesia. *Clin Neurophysiol.* 128:1445-1456, 2017

**47.** van den Broeke EN, Lambert J, Huang G, Mouraux A. Central Sensitization of Mechanical Nociceptive Pathways Is Associated with a Long-Lasting Increase of Pinprick-Evoked Brain Potentials. *Front Hum Neurosci.* 10:531, 2016

**48.** Vollert J, Magerl W, Baron R, Binder A, Enax-Krumova EK, Geisslinger G, Gierthmuhlen J, Henrich F, Hullemann P, Klein T, Lotsch J, Maier C, Oertel B, Schuh-Hofer S, Tolle TR, Treede RD. Pathophysiological mechanisms of neuropathic pain: comparison of sensory phenotypes in patients and human surrogate pain models. *Pain.* 159:1090-1102, 2018

**49.** Xia W, Morch CD, Andersen OK. Exploration of the conditioning electrical stimulation frequencies for induction of long-term potentiation-like pain amplification in humans. *Exp Brain Res.* 234:2479-2489, 2016

**50.** Xia W, Morch CD, Andersen OK. Test-Retest Reliability of 10 Hz Conditioning Electrical Stimulation Inducing Long-Term Potentiation (LTP)-Like Pain Amplification in Humans. *PLoS One.* 11:e0161117, 2016

**51.** Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH. Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain.* 19:805-806, 2015

**52.** Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain.* 138:22-28, 2008

53. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain.* 153:1193-1198, 2012

**Figure legends**

**Figure 1. Experimental protocols.** A) Protocol for testing the effects of VR/sham on HPT and CPM. B) Electrode configuration consisting of 15 cathodal pin electrodes and a surrounding anode. The heterotopic MPS testing zone was in the area surrounding the circular anode (red line). C) Protocol for testing the effects of VR/sham on HFS conditioned MPS responses.

**Figure 2. Effects of VR on HPT and CPM.** A) VR and sham VR had no effect on acute HPT. B) The CPM effect was calculated as the absolute change in PPT following cold conditioning which was enhanced during VR exposure and reduced during sham VR. C) Change in maximum pain tolerance ratings given during the cold pressor conditioning stimulus compared to baseline. Data in A) and B) expressed as mean and individual data points. Data in C) expressed as median, box = $25^{th}$ and $75^{th}$ percentiles, bars = min and max value. ns – not significant, ** - $p<0.01$; *** - $p<0.001$; n = 19.

**Figure 3. Effect of VR on HFS-induced secondary mechanical hyperalgesia.** A) development of heterotopic MPS sensitivity (i.e. secondary hyperalgesia) following HFS conditioning. B) Changes in individual HFS conditioned MPS z-scores during real and sham VR exposure. Data in A) expressed as median, box = $25^{th}$ and $75^{th}$ percentiles, bars = min and max value. Data in B) expressed as mean and individual data points; * - $p<0.05$; *** - $p<0.001$; n = 19.
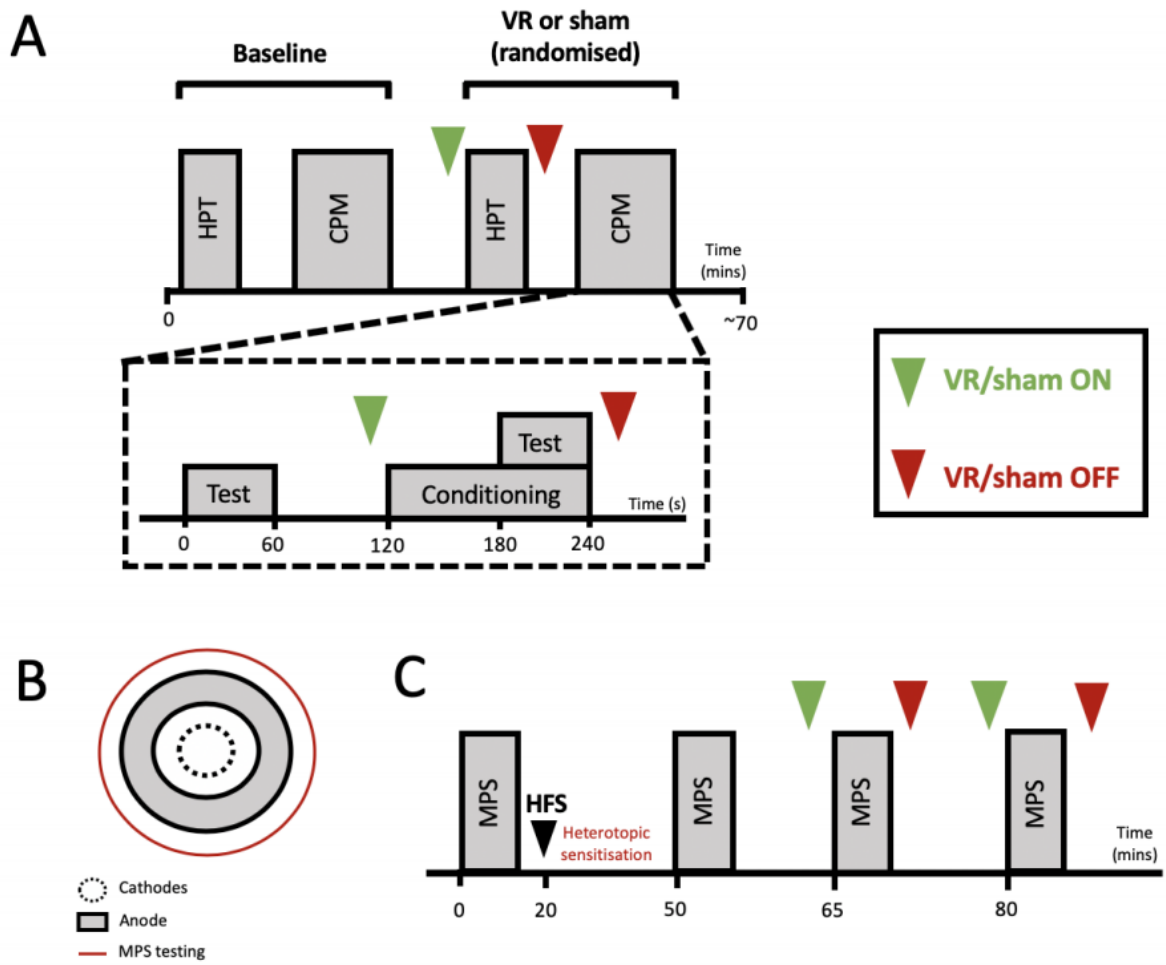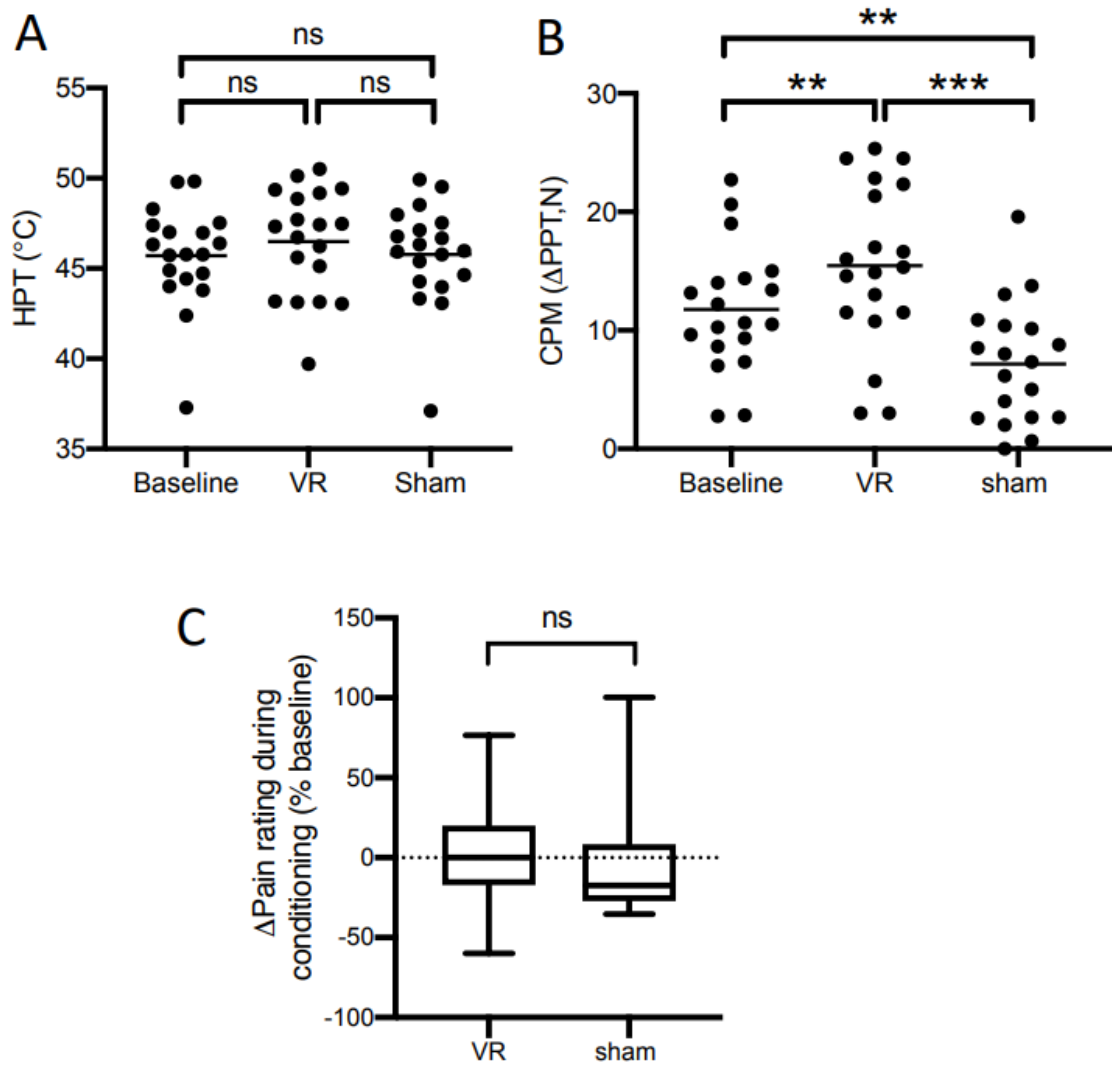
**Figure 1.**

**Figure 2.**

**Figure 3.**