

2019-11

Attenuation of capsaicin-induced ongoing pain and secondary hyperalgesia during exposure to an immersive virtual reality environment

Hughes, SW

<http://hdl.handle.net/10026.1/16118>

10.1097/pr9.0000000000000790

PAIN Reports

Ovid Technologies (Wolters Kluwer Health)

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

1 **Attenuation of capsaicin-induced ongoing pain and secondary hyperalgesia during exposure to an immersive**
2 **virtual reality environment**

3 Sam W Hughes, Hongyan Zhao, Edouard J Auvinet, Paul H Strutton

4 The Nick Davey Laboratory, Faculty of Medicine, Imperial College London, UK.

5 Number of text pages (including figures): 21

6 Number of figures: 5

7 Number of tables: 0

8 Corresponding author Address: Dr Sam Hughes; The Nick Davey Laboratory, Human Performance Group,

9 Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, W6 8RF.

10 Tel: +44 (0)20 331 38837; fax: +44 (0)20 331 38835. Email sam.hughes@imperial.ac.uk

11

12

1 **Abstract**

2 **Introduction:** There is growing evidence that virtual reality (VR) can be used in the treatment of chronic pain
3 conditions. However, further research is required in order to better understand the analgesic mechanisms
4 during sensitised pain states.

5 **Objectives:** We examined the effects of an immersive polar VR environment on capsaicin-induced ongoing pain
6 and secondary hyperalgesia. We also investigated whether the degree of analgesia was related to baseline
7 conditioned pain modulation (CPM) responses.

8 **Methods:** Nineteen subjects had baseline CPM and electrical pain perception (EPP) thresholds measured prior
9 to the topical application of capsaicin cream. Visual analogue scale (VAS) ratings were measured to track the
10 development of an ongoing pain state and EPP thresholds were used to measure secondary hyperalgesia. The
11 effects of a passive polar VR environment on ongoing pain and secondary hyperalgesia were compared to sham
12 VR (i.e. 2D monitor screen) in responders to capsaicin (n=15).

13 **Results:** VR was associated with a transient reduction in ongoing pain and an increase in EPP thresholds in an
14 area of secondary hyperalgesia. Baseline CPM measurements showed a significant correlation with VR-induced
15 changes in secondary hyperalgesia, but not with VR-induced changes in ongoing pain perception. There was no
16 correlation between VR-induced changes in pain perception and VR-induced changes in secondary
17 hyperalgesia.

18 **Conclusions:** Virtual reality can reduce the perception of capsaicin-induced ongoing pain perception and
19 secondary hyperalgesia. We also show that CPM may provide a means by which to identify individuals likely to
20 respond to VR therapy.

21

1 Introduction

2 Virtual reality (VR) interventions have shown promise as a novel distraction-based analgesic therapy for use in
3 painful medical procedures [5; 10; 12; 13] and during acute pain states [15; 16; 33]. There is now a growing
4 body of evidence that suggests VR can be used in the management of chronic pain conditions [21-23; 35; 38;
5 45] and visual distraction is a key component of cognitive behavioural therapy [24]. However, there has been
6 limited investigation into the analgesic mechanisms of VR stimulation during sensitised pain states.

7 Distraction-based analgesia is a form of non-pharmacological therapy that has been shown to alter the
8 perception of acute pain by reducing the activity within pain-related brain regions [1; 15]. The use of an
9 immersive virtual environment has been shown to be effective at reducing the perception of pain during dental
10 procedures which normally require local anaesthesia [5]. The use of VR in distraction analgesia has also shown
11 clinical utility during wound debridement associated with severe to excruciating pain in burn patients [10; 13].
12 Interestingly, recent advances have shown that it is possible to predict the efficacy of VR in acute experimental
13 pain conditions by measuring the efficiency of endogenous pain inhibitory pathways using the conditioned pain
14 modulation (CPM) paradigm [3].

15 Attempts to apply immersive VR environments to chronic or ongoing pain conditions are still very much their
16 infancy [23]. The majority of studies to date have typically involved measuring changes in pain perception (i.e.
17 pain scores) in groups of patients with mixed aetiologies [21; 22; 45]. However, there is a distinct lack of research
18 into whether VR can reduce altered nociceptive processing associated with the development of sensitised pain
19 states (i.e. central sensitisation [46]). The capsaicin model can be used to measure distinct chronic pain features
20 in healthy volunteers, including spinal representations of secondary hyperalgesia and ongoing pain sensitivity
21 [8; 30]. It provides a means by which to determine the analgesic mechanisms associated with immersion within
22 a VR environment and may shed light on the future clinical utility of VR as a novel analgesic therapy in the
23 treatment of chronic pain conditions.

24 These lines of evidence have led us to examine the analgesic mechanisms of an immersive VR environment
25 during an experimentally induced sensitised pain state by measuring the effects on capsaicin-induced ongoing

1 pain perception and secondary hyperalgesia in healthy volunteers. We also wanted to determine whether the
2 efficiency of CPM measured at baseline could be used to identify individuals who were more likely to have a
3 stronger analgesic response to VR following the onset of capsaicin-induced pain sensitivity.

4 **Materials and methods**

5 *Subject screening and recruitment*

6 All procedures were approved by the Imperial College Research Ethics Committee (18IC4435). All participants
7 were informed of the experimental protocols and subsequently provided written consent in accordance with
8 the principles of the declaration of Helsinki. All subjects were recruited from Imperial College London and were
9 initially screened to see if they met any of the exclusion criteria for pain testing (i.e. pregnancy, diabetes, blood
10 disorders, neurological conditions, immune-suppression, inflammatory disease, psychiatric conditions, taking
11 steroid, antibiotic or pain medicines). Following initial screening, 19 healthy subjects (mean age: 24.74 ± 0.33 ;
12 10 females) participated in the study. According to their pain response to application of topical capsaicin cream,
13 15 subjects (mean age: 25.2 ± 0.47 ; 8 females) were defined as responders (i.e. A maintained pain intensity
14 rating >50 rating on a modified visual analogue scale (VAS) and a drop in pain threshold in an area of secondary
15 hyperalgesia [8; 28; 42]) and 4 subjects (mean age: 23 ± 0.35 ; 2 females) were defined as non-responders.

16 *Experimental design and protocol*

17 Using a within-subject design, the effects of VR and sham VR stimulation on capsaicin-induced ongoing pain
18 perception and secondary hyperalgesia were investigated in a randomised manner (Figure 1). Baseline CPM
19 responses were also examined (i.e. in the absence of capsaicin).

20 CPM: Pressure pain thresholds (PPT; test stimulus) were first determined by applying 3 continuous ramps of
21 increasing intensity (0.5 kg/s) on the dominant volar forearm using a pressure algometer (WAGNER® FDN 100;
22 contact area 1 cm²). After a 15-minute rest, participants were instructed to immerse the non-dominant hand in
23 ice cold water (maintained at 8 degrees Celsius) up to the wrist and palm-side down for 2 minutes (i.e. the cold
24 pressor test; conditioning stimulus). Participants were asked to rate pain perception every 10 seconds on a

1 conventional VAS from 0 - 100 (0 = no pain; 10-30 = mild pain; 40-60 = moderate pain; 70-90 = severe pain;
2 100 = worst pain imaginable). PPTs (i.e. test stimulus) were then immediately determined by re-applying 3
3 continuous ramps of increasing intensity (0.5 kg/s) to the dominant forearm [37; 48].

4 Baseline electrical pain perception (EPP) threshold testing: Following a 15 minute CPM wash-out period [25],
5 Participants were then familiarized with the EPP threshold testing. Each transcutaneous electrical stimulus
6 consisted of a standard, constant-current 1-ms duration square pulse using a constant current stimulator (DS7A,
7 Digitimer, UK) [20]. An area on the left L5 dermatome, one third the way along a line from the left lateral femoral
8 epicondyle to the left lateral malleolus was marked with a non-permanent marker and a measurement map
9 was drawn using four 4.5cm spokes from the central point in proximal, distal, medial and lateral directions. 4
10 modified Ag/AgCl electrodes (self-adhesive, 1 cm diameter, CareFusion, UK) were then positioned around each
11 of the 4 points (Figure 1A). Pain thresholds (mA) were then determined at each of the 4 points by increasing
12 the current intensity in 0.5 mA steps at 1 Hz and was defined as the mean of 3 intensities logged as the point at
13 which sensation transitioned from being a "heavy tapping" sensation (i.e. no pain) to a sharp "pinprick" pain
14 [20].

15 Capsaicin pain model: All Participants then received topical application of capsaicin cream (1% w/w,
16 Pharmaciege, London, UK). Using a 1 ml syringe, 50 μ l was ejected onto a 9 mm diameter clear plastic disc
17 which was then placed face-down in the centre of the measurement map, remaining in place for the remainder
18 of the protocol (area of capsaicin skin contact: 64 mm²) [8]. The participants used a modified VAS used
19 previously [8] where 0 = no sensation; 50 = pain threshold; 100 = worst pain imaginable. Following application
20 of capsaicin cream, the participants were instructed to rate the sensation every 3 minutes for 120 minutes. The
21 participants described the sensation initially as "tingling" which increased in intensity over approximately 45
22 minutes until a distinct "stinging" or "burning" pain was perceived (i.e. 50 VAS rating). Capsaicin responders
23 were defined as participants who had established a stable pain VAS rating >50 for at least 45 minutes [28].

24 Post-capsaicin EPP testing: Previous reports show that the mean area of punctate secondary mechanical
25 hyperalgesia following topical application of 50 μ l 1% capsaicin cream is 98.9 cm² [8]. Secondary hyperalgesia

1 was then measured by testing EPP thresholds around the 4 points which covered an area of 64cm² and avoided
2 the neurogenic flare response area (Figure 1B).

3 Virtual reality headset: An Oculus Rift VR headset connected to an MSI GT83 8RF laptop (Intel Core i7-8850H
4 2.6GHz processor with NVIDIA GTX 1070 SLI 8GB graphics card) was used to display the passive virtual
5 environment (Polar Obsession; National Geographic; Figure 1C). Participants were seated on a couch with knee
6 extended to 180° and the Oculus Rift motion sensor provided position and orientation data regarding the
7 subject's head. The tracker's sensor component was mounted on the Head-mounted Display (HMD), and its
8 source component was mounted on an adjustable tripod placed in front of the couch. Sham VR stimulation
9 consisted of playing the same video on a computer monitor screen.

10 VR assessment: VR or sham VR stimulation was then given in 10-minute blocks, separated by 10-minute rest
11 periods in a randomised manner (Figure 1D). Stimulation blocks were comprised of 5 minutes of VR or sham
12 stimulation alone followed by 5 minutes of VR or sham + EPP testing. VAS scores were recorded at the end of
13 each stimulation block. Each 10-minute rest period was comprised of a 5-minute wash out followed by 5
14 minutes of post- VR or sham stimulation EPP testing. VAS scores were recorded at the end of each rest period.

15 At the end of the study protocol, each participant was given an ice pack to cool any residual burning sensation
16 and advised to repeat if any re-kindling occurred over 24 hours.

17 *Statistical analysis*

18 All data were initially entered into Microsoft Excel before being analysed for normality and statistical
19 significance in GraphPad Prism (v8.0.1. GraphPad Software, Inc.). Percentage change in CPM effect was
20 calculated as the conditioned PPT test stimulus minus the baseline PPT test stimulus divided by the baseline
21 PPT test stimulus [47]. Therefore, more positive values indicated more efficient CPM. EPP thresholds were
22 averaged across all 4 points of the measurement map (i.e. proximal, distal, medial and lateral). Paired t-tests
23 were used to analyse the changes in EPP threshold following application of capsaicin. One-way RM ANOVA with
24 Holm-Sidak multiple comparison post hoc analysis was used to analyse the changes in raw EPP threshold or VAS

1 rating before, during and after either the real or sham VR stimulation. The difference between the percentage
2 change in VAS rating from post-capsaicin to during VR/sham was analysed by paired test. One-way RM ANOVA
3 with Holm-Sidak multiple comparison post hoc analysis was also used for comparing differences in the
4 percentage change in EPP between pre- and post-capsaicin and between post-capsaicin and VR or sham VR
5 conditions. Pearson correlation coefficient analysis was used to look for relationships between the VR-induced
6 change in secondary hyperalgesia and CPM and the VR-induced change in pain perception and CPM. Pearson
7 correlation analysis was also used to look for relationships between VR-induced changes in pain perception and
8 VR-induced changes in secondary hyperalgesia. Statistical significance was set at $p < 0.05$ and all data are
9 presented as mean \pm SEM in the figures and text, where appropriate.

10 **Results**

11 *Capsaicin-induced ongoing pain and electrically evoked secondary hyperalgesia*

12 Topical application of capsaicin results in the development of an intense burning sensation and a neurogenic
13 flare response (i.e. the primary zone; Figure 1C). A slight tingling sensation (VAS: 1.53 ± 0.2) began to appear 3
14 minutes after the application of capsaicin cream (Figure 2A). The intensity of the sensation gradually increased,
15 and an obvious burning sensation was achieved 36 minutes after the application of capsaicin (VAS: $52.47 \pm$
16 1.07). Following the development of a stable ongoing pain response (i.e. $p > 0.05$ between 45 minutes post
17 capsaicin and 120 minutes post-capsaicin) there was a drop in EPP threshold in an area of capsaicin-induced
18 secondary hyperalgesia (pre-EPP: 6.64 ± 0.14 mA vs. post-EPP: 5.33 ± 0.12 mA; $P < 0.001$; Figure 2B).

19 *VR was associated with an attenuation of ongoing pain perception*

20 Exposure to an immersive 3D VR environment caused a drop in VAS ratings below the defined pain threshold
21 (post capsaicin VAS: 62.17 ± 2.07 versus during VR VAS: 47.67 ± 2.94 ; $p < 0.001$; Figure 3A) which had returned
22 to above pain threshold (i.e. > 50 VAS) when the VR headset was removed (post VR VAS: 54.40 ± 2.29 ; $p < 0.05$).
23 Sham VR was not associated with a drop in VAS rating during the stimulation (post capsaicin VAS: 62.17 ± 2.07
24 versus during sham VR VAS: 57.39 ± 2.38 ; $p > 0.05$; Figure 3B) and there was no difference between during and

1 post sham VR stimulation (post sham VR: 56.32 ± 1.87 ; $p > 0.05$). A paired t-test showed a significant difference
2 between the change in VAS rating during VR stimulation and the change in VAS rating during the sham VR
3 stimulation (VR VAS: $-23.08 \pm 1.2\%$ vs. sham VAS: $-6.41 \pm 1.18\%$; $p < 0.01$; Figure 3C).

4 *VR was associated with an attenuation of secondary hyperalgesia*

5 There was a significant increase in EPP threshold during VR stimulation (post capsaicin EPP threshold: $5.33 \pm$
6 0.47 mA versus during VR EPP threshold: 6.78 ± 0.54 mA; $p < 0.001$; Figure 4A) which was reversed following
7 removal of the VR headset (post VR EPP threshold: 5.78 ± 0.51 mA; $p < 0.05$). Sham VR stimulation was not
8 associated with a change in EPP threshold during (5.87 ± 0.65 mA; $p > 0.05$; Figure 4B) or after (5.62 ± 0.55 mA;
9 $p > 0.05$) the stimulation. Further analysis revealed there to be a significant difference in change in EPP threshold
10 compared to post-capsaicin between VR and sham stimulation (VR: $3.05 \pm 1.25\%$ vs. sham EPP: $-13.37 \pm 1.42\%$;
11 $P < 0.05$; Figure 4C).

12 *Relationships between baseline CPM responses and VR-induced analgesia*

13 Pressure pain thresholds were increased following the conditioning stimulus and therefore more efficient CPM
14 is represented as a more positive value (Figure 5). There was no correlation between VR-induced decrease in
15 VAS and CPM ($r^2 = 0.063$, $p > 0.05$; Figure 5A). However, a significant correlation was found between VR-induced
16 reduction in secondary hyperalgesia and CPM ($r^2 = 0.68$, $p < 0.001$; Figure 5B) in that higher levels of CPM
17 measured at baseline (i.e. in the absence of capsaicin-induced sensitivity) were associated with a greater
18 reduction in secondary hyperalgesia. There was no relationship between VR-induced changes in pain perception
19 and VR-induced changes in secondary hyperalgesia ($r^2 = 0.02$; $p = 0.6$).

20 **Discussion**

21 We have investigated the effects of distraction using an immersive VR environment on experimentally induced
22 ongoing pain sensitivity and secondary hyperalgesia. Using the capsaicin model of ongoing afferent drive in
23 healthy volunteers, we show an attenuation of ongoing pain ratings and electrically evoked secondary
24 hyperalgesia during exposure to an immersive, polar VR environment. Interestingly, we found that the

1 magnitude of CPM measured at baseline was related to the VR-induced analgesic effect over secondary
2 hyperalgesia but not the changes in pain ratings. These findings suggest that exposure to an immersive polar
3 VR environment can be used to alter sensitised pain states and that CPM may be able to predict the efficacy of
4 VR therapy in the treatment of chronic pain associated with hyperalgesia.

5 It has previously been speculated that VR stimulation may provide a new approach for pain management during
6 chronic pain conditions by distracting attention away from the ongoing pain [23; 39]. Our study provides new
7 evidence that VR-stimulation can reduce capsaicin-induced ongoing pain perception. We also show novel
8 mechanistic insight which supports the use of VR in patients with altered nociceptive processing and central
9 sensitisation by showing that exposure to an immersive VR environment can increase pain thresholds in an area
10 of spinally mediated enhanced pain sensitivity (i.e. secondary hyperalgesia).

11 In the current study we used a passive VR design that created the impression of an immersive arctic scene
12 during capsaicin-induced pain which is often described as 'burning'. This is in line with a previous study which
13 demonstrated, using an immersive cold environment, that is possible to reduce the perception of acute heat
14 pain in healthy volunteers [15]. It is therefore possible that the counter-acting nature of cold VR environments
15 has the ability to reduce the perception of an ongoing heat or burning pain. In the present study, we found that
16 immersion within a virtual polar world could produce robust analgesic effects in the absence of any interactive
17 elements which could make this approach favourable for use in patients with upper limb mobility issues.
18 However, it has been previously suggested that the magnitude of VR induced analgesia is influenced by the
19 addition of an interactive element [18; 41] as well as the quality of the visual display through the VR headset
20 [17]. The majority of studies using acute pain or pain tolerance paradigms have adopted interactive designs
21 with a view to optimise the shift in attention away from the pain and into the virtual world [5; 10; 12; 13; 15;
22 16; 33]. It is therefore possible that the analgesic effects seen in this study could be further enhanced if an
23 interactive element is used within the VR design.

24 Previous research in chronic pain patients has focused on using VR involving the active navigation through
25 fantasy landscapes and has been shown to reduce pain ratings in groups of patients with different aetiologies

1 [21; 22]. Despite showing clinically-relevant reductions in pain ratings, applying a single VR design to a mixed
2 group of patients did not show any pain-relief at all in 10% of those recruited [22]. This could be attributed to a
3 misalignment with the type of pain experienced by individual patients and the choice of VR environment. It is
4 possible that specific VR environments could be more effective if aligned with the types of pain experienced,
5 such as the use of a 'snow world' in burns patients [11]. In line with this, a case study demonstrated clinically-
6 relevant pain relief using an interactive cold environment in a treatment-resistant radiculopathy patient [35].
7 Future randomised controlled trials comparing the efficacy of different types of VR design in well-defined
8 populations of chronic pain patients may therefore lead to more targeted use of VR therapy based on the types
9 of pain experienced.

10 We also show that during exposure to an immersive VR environment it is also possible to reduce capsaicin-
11 induced secondary hyperalgesia by measuring changes in electrically evoked pain thresholds. Previous research
12 has shown that VR can be used to modulate acute pain thresholds in the absence of capsaicin-induced central
13 sensitisation [9]. To our knowledge, our study is the first to show an analgesic effect over spinally mediated
14 sensitised pain thresholds during exposure to a passive VR environment. Interestingly, we found no correlation
15 between the VR-induced changes in ongoing pain perception and the VR-induced changes secondary
16 hyperalgesia. This could either be explained through the different outcome measures obtained (i.e. pain scores
17 versus pain thresholds) or that VR can exert analgesic effects on pain perception and secondary hyperalgesia
18 via two separate mechanisms.

19 Previous neuroimaging studies have shown that exposure to an immersive VR environment can activate a
20 network of pain-related brain regions involved in top-down inhibitory control [14; 15] and that there is an
21 increase in functional connectivity between the medial prefrontal cortex (mPFC) and spinally-projecting centres
22 in the midbrain and brainstem during distraction-based analgesia [4; 29; 36; 40]. It is therefore possible that
23 VR can engage similar top-down analgesic pathways involved in the descending modulation of spinal cord
24 nociceptive processing in a manner akin to that seen during non-invasive brain stimulation [19; 20; 31]. The
25 analgesic effects on capsaicin-induced ongoing pain ratings could be due to activation of a cortico-cortical

1 analgesic pathway associated with emotion and memories as well as auditory or visual stimuli, which is distinct
2 from the top-down activation of the descending pain modulatory network [7; 43].

3 It has been previously shown that measuring CPM at baseline can be used to identify individuals likely to benefit
4 from VR during an acute pain tolerance test [3]. The present study extends these findings to show that CPM can
5 be also be used to identify those likely to show a greater reduction in experimentally induced secondary
6 hyperalgesia. It is becoming increasingly clear that CPM is not just dependent on activation of a spino-bulbo-
7 spinal loop mechanism first proposed in rodents [26; 27], but is also open to interaction with psychological and
8 cognitive factors [6; 34]. It is therefore possible that the association observed in the present study is due to
9 distraction playing a role in both the CPM effects as well as the VR-induced changes in secondary hyperalgesia.
10 This is supported through recent neuroimaging studies which have shown that both CPM and VR are associated
11 with activation of the anterior cingulate cortex (ACC) [15; 32]; an area of the brain closely linked with distraction
12 analgesia which has been shown to be involved in top-down pain control [2; 14-16]. CPM has been previously
13 shown to predict the response to duloxetine in diabetic neuropathy patients, by mimicking the action of
14 descending monoaminergic inhibitory pathways [48]. The association seen between CPM and VR-induced
15 changes in secondary hyperalgesia suggest that VR may exert a top-down influence on similar spinally-
16 projecting descending control pathways [43; 44]. Another possible explanation for the observed relationship
17 between CPM and VR-induced changes in secondary hyperalgesia is that they are both measuring changes in
18 pain threshold. However, as we were testing two separate modalities in these paradigms (i.e. PPT and EPP) it is
19 more likely that the CPM response and the VR-induced changes in secondary hyperalgesia share similar top-
20 down mechanisms. To confirm this, further psychophysical and neuroimaging research is required to show
21 whether exposure to VR can modulate the CPM response and activate common pain-related brain and
22 brainstem regions.

23 This proof-of-concept study is the first to show evidence that VR stimulation can modulate altered nociceptive
24 processing associated with the development of chronic pain states. However, there are a few limitations with
25 our study that should be addressed in larger randomised controlled trials. We used a within-subject design to

1 test the effects of short periods of VR or sham VR stimulation on established pain sensitivity. We found the
2 effects to be transient and dependent on the presence of the VR environment. Future studies adopting a cross-
3 over design with participants randomly assigned to either real or sham VR conditions will allow longer
4 stimulation times and measurement of the time course of the analgesic effects following cessation of the VR
5 environment. It would also be of interest to investigate the effects of VR on other measures of central
6 sensitisation such as dynamic mechanical allodynia or whether it is possible to reduce areas of punctate
7 mechanical secondary hyperalgesia.

8 In summary, the study presented here demonstrates the first evidence that a passive VR design can reduce
9 both ongoing pain perception and secondary hyperalgesia during an experimentally induced sensitised pain
10 state. We show that exposure to a cold immersive VR environment may be a promising new analgesic therapy
11 for use in chronic pain patients by providing a novel non-pharmacological approach to alleviate the severity of
12 ongoing pain and associated spinal cord excitability. It may also be possible to use CPM to guide future
13 phenotype-stratified trials with VR in the treatment of chronic pain.

14 **Acknowledgements**

15 We would like to thank Imperial College London for funding this study and all participants for taking part. We
16 would also like to thank Dr Helen Laycock for advice on mapping secondary hyperalgesia.

17 **Conflict of interest statement**

18 The authors report no conflicts of interest.

19 **Figure legends**

20 **Figure 1. Measuring capsaicin-induced secondary hyperalgesia and experimental protocol.** A) secondary
21 hyperalgesia measurement map. Central black zone indicates position of topical application of 50 μ l 1%
22 capsaicin cream. Dark grey zone indicates the region of the neurogenic flare response (i.e. primary hyperalgesia
23 zone). EPP thresholds are determined across proximal (P), distal (D), medial (M) and lateral (L) points in the
24 secondary hyperalgesia zone. B) Experimental protocol. C) Image showing the development of a neurogenic

1 flare response and placement of the 4 modified Ag/AgCl electrodes for measurement of secondary
2 hyperalgesia. D) Screen capture from the Polar Obsession VR environment.

3 **Figure 2. Development of capsaicin-induced ongoing pain and secondary hyperalgesia.** A) Time course for the
4 development of pain sensation following topical application of 50µl 1% capsaicin cream. The intensity of
5 sensation increased until pain threshold was reached at 36 minutes (i.e. dotted line; 50 VAS). B) There was a
6 significant drop in EPP threshold in an area of capsaicin-induced secondary hyperalgesia. Data are expressed as
7 mean ± SEM; *** - P<0.001. n = 15.

8 **Figure 3. Transient changes in ongoing pain perception following VR stimulation.** Changes in pain VAS ratings
9 before, during and after A) real and B) sham VR stimulation. C) Comparison between the changes in pain rating
10 during either real or sham VR stimulation. Data are expressed as mean ± SEM; * - P<0.05, ** - P<0.01, *** -
11 P<0.001. n = 15.

12 **Figure 4. Transient changes in secondary hyperalgesia following VR stimulation.** Changes in EPP threshold
13 before, during and after A) real and B) sham VR stimulation. C) Comparison between changes in EPP threshold
14 between real and sham VR with respect to sensitised post-capsaicin EPP thresholds. Data are expressed as mean
15 ± SEM; * - P<0.05, *** - P<0.001. n = 15.

16 **Figure 5. Baseline CPM correlated with VR-induced changes in secondary hyperalgesia but not VR-induced**
17 **changes in pain perception.** A) no relationship between the VR-induced reduction in ongoing pain perception
18 and levels of CPM. B) Reduction in secondary hyperalgesia is related to baseline CPM levels. n = 15.

19 References

- 20 [1] Brooks JC, Davies WE, Pickering AE. Resolving the Brainstem Contributions to Attentional Analgesia. *J*
21 *Neurosci* 2017;37(9):2279-2291.
- 22 [2] Chen T, Taniguchi W, Chen QY, Tozaki-Saitoh H, Song Q, Liu RH, Koga K, Matsuda T, Kaito-Sugimura Y,
23 Wang J, Li ZH, Lu YC, Inoue K, Tsuda M, Li YQ, Nakatsuka T, Zhuo M. Top-down descending
24 facilitation of spinal sensory excitatory transmission from the anterior cingulate cortex. *Nat Commun*
25 2018;9(1):1886.
- 26 [3] Demeter N, Josman N, Eisenberg E, Pud D. Who can benefit from virtual reality to reduce experimental
27 pain? A crossover study in healthy subjects. *Eur J Pain* 2015;19(10):1467-1475.
- 28 [4] Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Buchel C. Activation of the opioidergic
29 descending pain control system underlies placebo analgesia. *Neuron* 2009;63(4):533-543.

- 1 [5] Furman E, Jasinevicius TR, Bissada NF, Victoroff KZ, Skillicorn R, Buchner M. Virtual reality distraction for
2 pain control during periodontal scaling and root planing procedures. *J Am Dent Assoc*
3 2009;140(12):1508-1516.
- 4 [6] Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia--when the spine echoes what the
5 brain expects. *Pain* 2007;130(1-2):137-143.
- 6 [7] Gold JJ, Belmont KA, Thomas DA. The neurobiology of virtual reality pain attenuation. *Cyberpsychol*
7 *Behav* 2007;10(4):536-544.
- 8 [8] Harding LM, Murphy A, Kinnman E, Baranowski AP. Characterization of secondary hyperalgesia produced
9 by topical capsaicin jelly--a new experimental tool for pain research. *Eur J Pain* 2001;5(4):363-371.
- 10 [9] Hayashi K, Aono S, Shiro Y, Ushida T. Effects of Virtual Reality-Based Exercise Imagery on Pain in Healthy
11 Individuals. *Biomed Res Int* 2019;2019:5021914.
- 12 [10] Hoffman HG, Chambers GT, Meyer WJ, 3rd, Arceneaux LL, Russell WJ, Seibel EJ, Richards TL, Sharar SR,
13 Patterson DR. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain
14 during medical procedures. *Ann Behav Med* 2011;41(2):183-191.
- 15 [11] Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness TA, 3rd. Virtual reality as an adjunctive
16 pain control during burn wound care in adolescent patients. *Pain* 2000;85(1-2):305-309.
- 17 [12] Hoffman HG, Patterson DR, Magula J, Carrougher GJ, Zeltzer K, Dagadakis S, Sharar SR. Water-friendly
18 virtual reality pain control during wound care. *J Clin Psychol* 2004;60(2):189-195.
- 19 [13] Hoffman HG, Patterson DR, Seibel E, Soltani M, Jewett-Leahy L, Sharar SR. Virtual reality pain control
20 during burn wound debridement in the hydrotank. *Clin J Pain* 2008;24(4):299-304.
- 21 [14] Hoffman HG, Richards TL, Bills AR, Van Oostrom T, Magula J, Seibel EJ, Sharar SR. Using fMRI to study
22 the neural correlates of virtual reality analgesia. *CNS Spectr* 2006;11(1):45-51.
- 23 [15] Hoffman HG, Richards TL, Coda B, Bills AR, Blough D, Richards AL, Sharar SR. Modulation of thermal
24 pain-related brain activity with virtual reality: evidence from fMRI. *Neuroreport* 2004;15(8):1245-
25 1248.
- 26 [16] Hoffman HG, Richards TL, Van Oostrom T, Coda BA, Jensen MP, Blough DK, Sharar SR. The analgesic
27 effects of opioids and immersive virtual reality distraction: evidence from subjective and functional
28 brain imaging assessments. *Anesth Analg* 2007;105(6):1776-1783, table of contents.
- 29 [17] Hoffman HG, Seibel EJ, Richards TL, Furness TA, Patterson DR, Sharar SR. Virtual reality helmet display
30 quality influences the magnitude of virtual reality analgesia. *J Pain* 2006;7(11):843-850.
- 31 [18] Hoffman HG, Sharar SR, Coda B, Everett JJ, Ciol M, Richards T, Patterson DR. Manipulating presence
32 influences the magnitude of virtual reality analgesia. *Pain* 2004;111(1-2):162-168.
- 33 [19] Hughes S, Grimsey S, Strutton PH. Primary Motor Cortex Transcranial Direct Current Stimulation
34 Modulates Temporal Summation of the Nociceptive Withdrawal Reflex in Healthy Subjects. *Pain*
35 *Med* 2018.
- 36 [20] Hughes SW, Ali M, Sharma P, Insan N, Strutton PH. Frequency-dependent top-down modulation of
37 temporal summation by anodal transcranial direct-current stimulation of the primary motor cortex
38 in healthy adults. *Eur J Pain* 2018.
- 39 [21] Jin W, Choo A, Gromala D, Shaw C, Squire P. A Virtual Reality Game for Chronic Pain Management: A
40 Randomized, Controlled Clinical Study. *Stud Health Technol Inform* 2016;220:154-160.
- 41 [22] Jones T, Moore T, Choo J. The Impact of Virtual Reality on Chronic Pain. *PLoS One*
42 2016;11(12):e0167523.
- 43 [23] Keefe FJ, Huling DA, Coggins MJ, Keefe DF, Zachary Rosenthal M, Herr NR, Hoffman HG. Virtual reality
44 for persistent pain: a new direction for behavioral pain management. *Pain* 2012;153(11):2163-2166.
- 45 [24] Keefe FJ, Somers TJ. Psychological approaches to understanding and treating arthritis pain. *Nat Rev*
46 *Rheumatol* 2010;6(4):210-216.
- 47 [25] Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: a
48 systematic review. *Pain* 2016;157(11):2410-2419.
- 49 [26] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn
50 convergent neurones in the rat. *Pain* 1979;6(3):283-304.

- 1 [27] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-
2 convergent neurones, supraspinal involvement and theoretical implications. *Pain* 1979;6(3):305-327.
- 3 [28] Lin RL, Douaud G, Filippini N, Okell TW, Stagg CJ, Tracey I. Structural Connectivity Variance Underlies
4 Functional and Behavioral Changes During Pain Relief Induced by Neuromodulation. *Sci Rep*
5 2017;7:41603.
- 6 [29] Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex
7 in pain modulation. *Brain* 2003;126(Pt 5):1079-1091.
- 8 [30] Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal
9 injection of capsaicin in humans. *Pain* 1998;74(2-3):257-268.
- 10 [31] Meeker TJ, Keaser ML, Khan SA, Gullapalli RP, Seminowicz DA, Greenspan JD. Non-invasive Motor Cortex
11 Neuromodulation Reduces Secondary Hyperalgesia and Enhances Activation of the Descending Pain
12 Modulatory Network. *Front Neurosci* 2019;13:467.
- 13 [32] Moont R, Crispel Y, Lev R, Pud D, Yarnitsky D. Temporal changes in cortical activation during distraction
14 from pain: a comparative LORETA study with conditioned pain modulation. *Brain Res*
15 2012;1435:105-117.
- 16 [33] Morris LD, Louw QA, Grimmer-Somers K. The effectiveness of virtual reality on reducing pain and
17 anxiety in burn injury patients: a systematic review. *Clin J Pain* 2009;25(9):815-826.
- 18 [34] Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the
19 conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain*
20 2012;153(1):170-176.
- 21 [35] ONeal BJ, Patterson DR, Soltani M, Teeley A, Jensen MP. Virtual reality hypnosis in the treatment of
22 chronic neuropathic pain: a case report. *Int J Clin Exp Hypn* 2008;56(4):451-462.
- 23 [36] Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-- imaging a shared neuronal
24 network. *Science* 2002;295(5560):1737-1740.
- 25 [37] Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory
26 control (DNIC)-like effect in humans. *Pain* 2009;144(1-2):16-19.
- 27 [38] Sato K, Fukumori S, Matsusaki T, Maruo T, Ishikawa S, Nishie H, Takata K, Mizuhara H, Mizobuchi S,
28 Nakatsuka H, Matsumi M, Gofuku A, Yokoyama M, Morita K. Nonimmersive virtual reality mirror
29 visual feedback therapy and its application for the treatment of complex regional pain syndrome: an
30 open-label pilot study. *Pain Med* 2010;11(4):622-629.
- 31 [39] Sharar SR, Carrougher GJ, Nakamura D, Hoffman HG, Blough DK, Patterson DR. Factors influencing the
32 efficacy of virtual reality distraction analgesia during postburn physical therapy: preliminary results
33 from 3 ongoing studies. *Arch Phys Med Rehabil* 2007;88(12 Suppl 2):S43-49.
- 34 [40] Valet M, Sprenger T, Boecker H, Willloch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction
35 modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis.
36 *Pain* 2004;109(3):399-408.
- 37 [41] Wender R, Hoffman HG, Hunner HH, Seibel EJ, Patterson DR, Sharar SR. Interactivity Influences the
38 Magnitude of Virtual Reality Analgesia. *J Cyber Ther Rehabil* 2009;2(1):27-33.
- 39 [42] Werner MU, Petersen KL, Rowbotham MC, Dahl JB. Healthy volunteers can be phenotyped using
40 cutaneous sensitization pain models. *PLoS One* 2013;8(5):e62733.
- 41 [43] Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cogn Sci*
42 2008;12(8):306-313.
- 43 [44] Wiech K, Seymour B, Kalisch R, Stephan KE, Koltzenburg M, Driver J, Dolan RJ. Modulation of pain
44 processing in hyperalgesia by cognitive demand. *Neuroimage* 2005;27(1):59-69.
- 45 [45] Wiederhold BK, Gao K, Sulea C, Wiederhold MD. Virtual reality as a distraction technique in chronic pain
46 patients. *Cyberpsychol Behav Soc Netw* 2014;17(6):346-352.
- 47 [46] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152(3
48 Suppl):S2-15.
- 49 [47] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P,
50 Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of
51 psychophysical DNIC testing. *Eur J Pain* 2010;14(4):339.

1 [48] Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation
2 predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 2012;153(6):1193-1198.

3

4

Figure 1

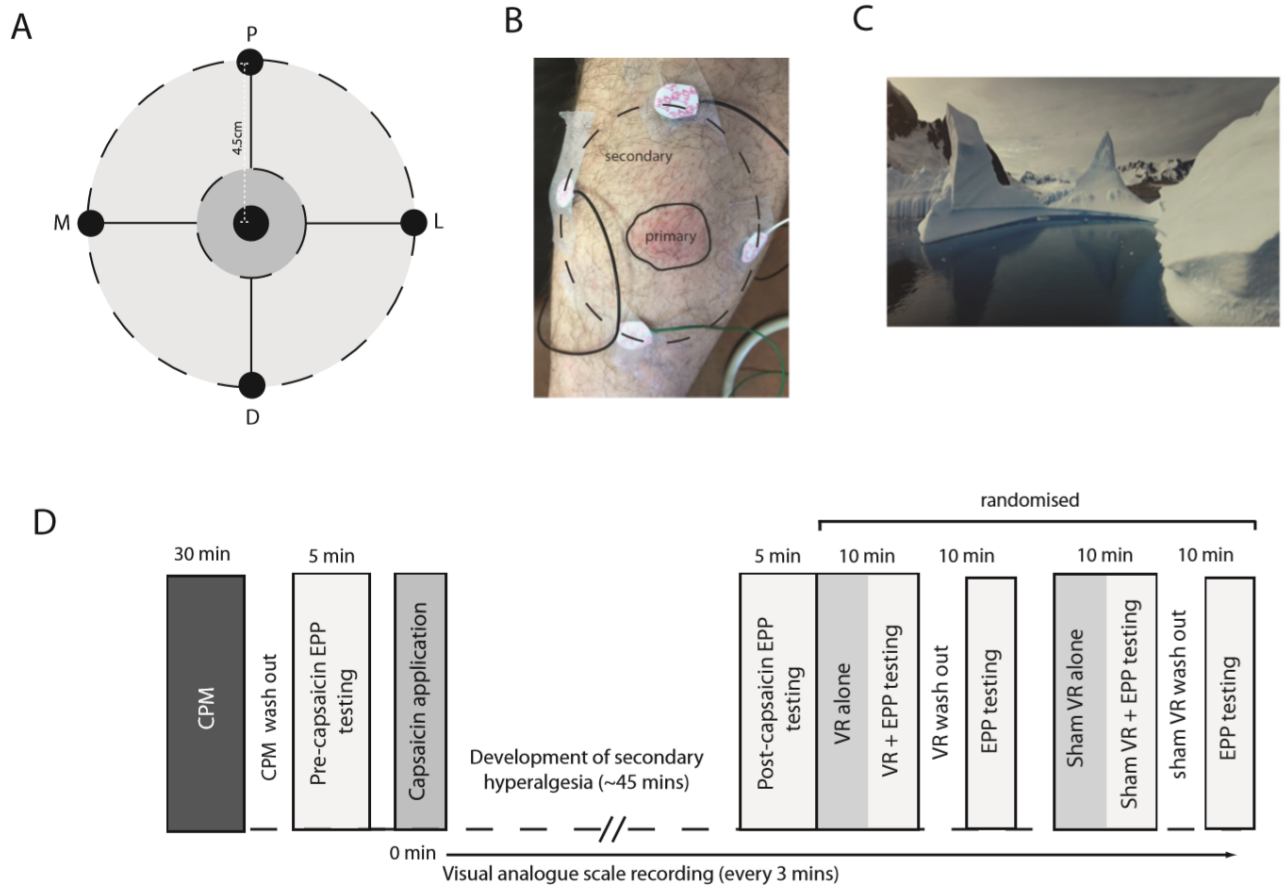


Figure 2

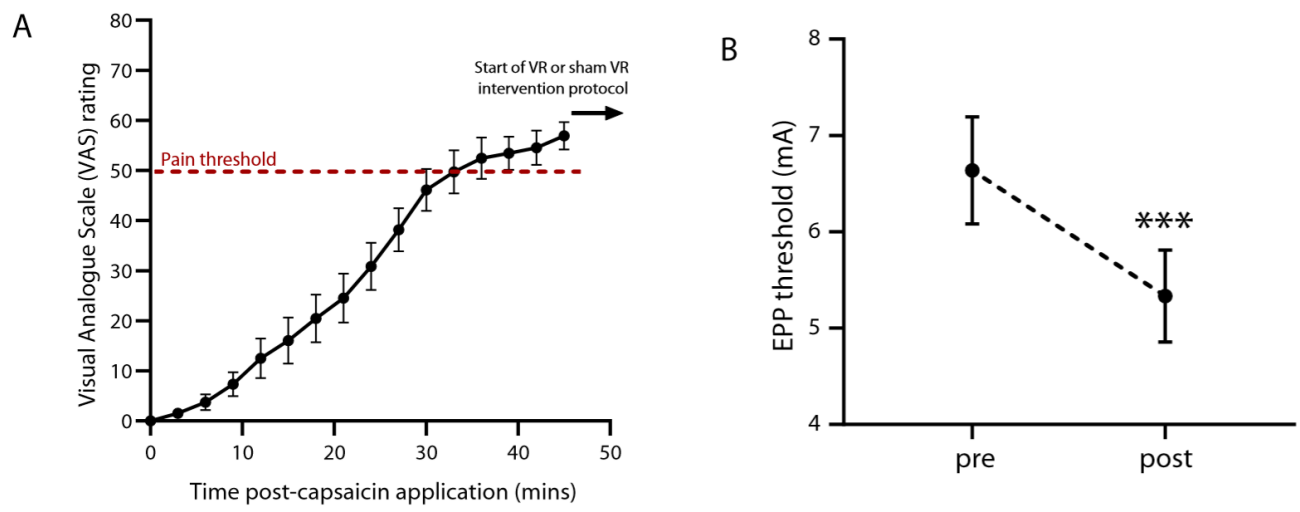


Figure 3

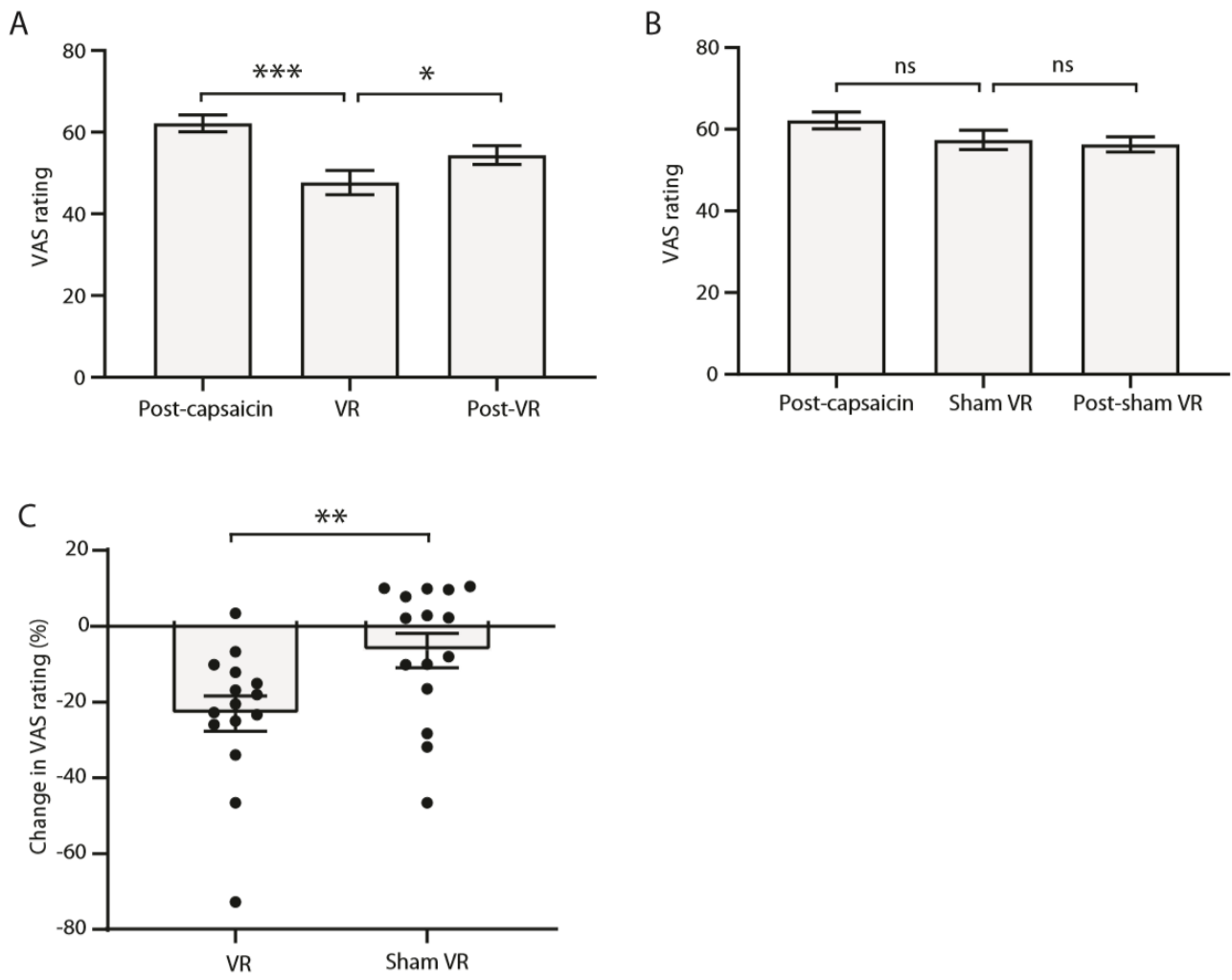


Figure 4

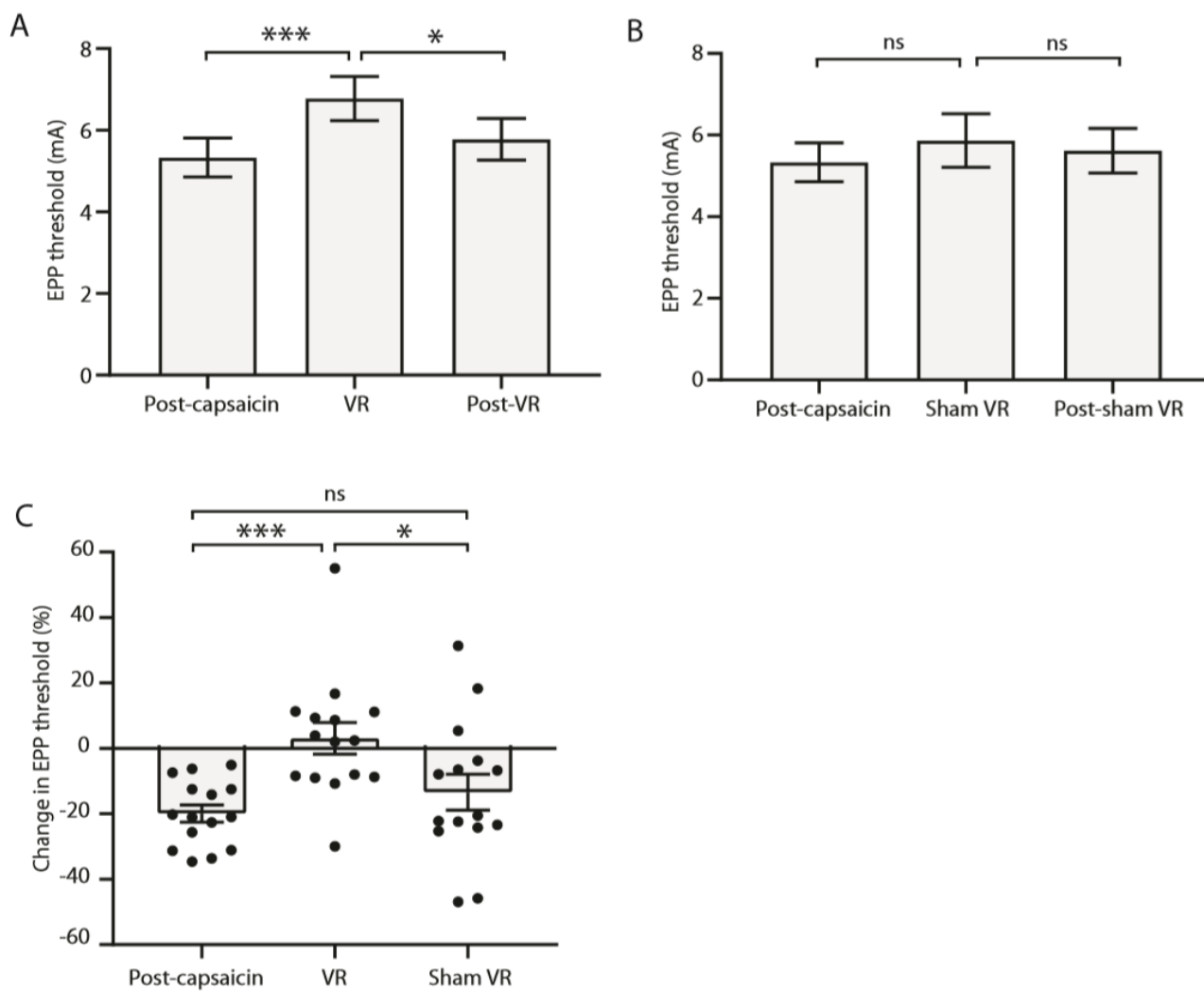


Figure 5

