ORIGINAL ARTICLE

Comparison of the effect of two virtual reality stimuli on pressure pain sensitivity and autonomic response

Comparação do efeito de dois estímulos de realidade virtual na sensibilidade de dor a pressão e na resposta autonômica

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ABSTRACT

BACKGROUND AND OBJECTIVES: Virtual reality can have a modulatory action on pain and the autonomic nervous system. This study sought to verify the effect of two different VR stimuli on the pressure pain threshold and heart rate variability.
METHODS: Healthy volunteers were randomized into two groups of virtual reality, nature and control. The pressure pain threshold was measured pre and post stimulus and heart rate variability measurements were collected pre, during and after virtual reality stimuli. The exploratory data analysis was performed. The t test was used to compare pressure pain threshold. For the differences in heart rate variability measurements, the linear mixed model was used. The level of significance adopted was 95%.
RESULTS: The virtual reality nature group was composed of 19 participants with mean age of 22.7±4.72 years and the control virtual reality group was composed of 22 participants with mean age of 21.13±2.42 years. The virtual reality nature group showed an increase in the pressure pain threshold after virtual reality and the mean difference was -0.41 [CI (95%)= -0.74 to -0.07; p=0.01]. There was no difference in heart rate variability parameters measured during and after virtual reality stimulation.
CONCLUSION: The group that was exposed to a virtual reality stimulus with scenes from nature showed an increase in the pressure pain threshold. There was no difference in heart rate variability between groups.
Keywords: Autonomic nervous system, Expression emotion, Heart rate, Virtual reality.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A realidade virtual pode ter ação modulatória sobre a dor e o sistema nervoso autônomo. O objetivo deste estudo foi verificar o efeito de dois estímulos diferentes de realidade virtual sobre o limiar de dor a pressão e a variabilidade da frequência cardíaca.
MÉTODOS: Os voluntários sadios foram randomizados para dois grupos de realidade virtual, natureza e controle. Foram coletadas as medidas do limiar de dor a pressão pré e pós-estímulo e as medidas da variabilidade da frequência cardíaca pré, durante e após o estímulo de realidade virtual. Foi realizada a análise exploratória dos dados. O teste t foi utilizado para comparar o limiar de dor a pressão. Para as diferenças nas medidas da variabilidade da frequência cardíaca utilizou-se o modelo linear misto. O nível de significância adotado foi de 95%.
RESULTADOS: O grupo realidade virtual natureza foi composto por 19 participantes com média de idade de 22,7±4,72 anos e o grupo realidade virtual controle foi composto por 22 participantes com média de idade de 21,13±2,42 anos. O grupo realidade virtual natureza apresentou um aumento do limiar de dor a pressão após realidade virtual e a diferença entre as médias foi de -0,41 [IC (95%)=-0,74 a -0,07; p=0,01]. Não houve diferença para os parâmetros da variabilidade da frequência cardíaca mensurados durante e após o estímulo de realidade virtual.
CONCLUSÃO: O grupo que foi exposto a um estímulo de realidade virtual com cenas da natureza apresentou um aumento do limiar de dor. Não foram observadas diferenças na variabilidade da frequência cardíaca entre os grupos.
Descritores: Emoções manifestas, Frequência cardíaca, Realidade virtual, Sistema nervoso autônomo.

INTRODUCTION

Virtual reality (VR) is an interface that provides a computerized immersive simulation of a real and three-dimensional environment. During the use of VR the individual interacts with multi-

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sensory experiences through the tracking of the head movement. VR is composed of three basic elements: immersion, interaction and engaging[1]. Immersion is the sensation of being totally within an environment, interaction is the way the individual reacts according to the presented VR stimulus and engaging is the degree of involvement of the user with the stimulus. These characteristics make VR a technology different from passively watching television, which is bidimensional[2]. Nowadays, the evolution of technology, the greater availability of videos and the reduction of the costs of VR devices have allowed the popularization and expansion of their use for entertainment, work situations and health applications[3-6].

The elements that compose VR provide multisensory experiences in a virtual environment that can influence the emotional processing of the brain and consequently of pain and the autonomous nervous system (ANS)[2,7-9]. Recently, some studies suggested that the emotional stimuli can influence the perception of pain, involving descendant modulatory paths, indicating that the positive emotions diminish the perception of pain, whereas negative emotions that trigger stimuli can increase the intensity of pain[10,11]. These findings were demonstrated in studies using pleasant (for example, erotic) and unpleasant (for example, mutilation) imagery[11-13]. On the other hand, the interaction between the processing of emotions and the ANS acts with the objective of adjusting physiologic functions in front of the modifications identified in the environment[14,15]. The bidirectional connection between superior cerebral regions related to the emotional processing like the pre-frontal cortex and the amigdala[16] and the heart makes it that the heart rate variability (HRV) be an index related to the flexible and adaptive regulation of the organism's capacity to adjust effectively to a complex environment[17,18]. The HRV, which reflects the periodic changes in heart rate (RR intervals)[19,20], can then serve as an easy-to-acquire measure of the emotion and heart interaction. This measure can indirectly reflect the activity of a set of neural structures and the ability to integrate internal and external signals and adaptively regulate cognition, perception, action and physiology[21]. The literature on health highlights the application of VR for anxiety[22], neurological rehabilitation[5], psychosis[23], Parkinson's disease[24,25], neurological syndromes[26], phobia[27], among other diseases. VR has also been applied to reduce pain in adults[28] and children[29]. Some applications of VR for people with pain involve, for example, cases of individuals with burns[30], post-surgical[31] patients and studies with experimental pain in healthy people[32]. Although it's recognized that VR provides a multi-sensory experience through a simulated environment and that it can have a modulatory effect on pain and the ANS, there is still a need to understand the effects of different stimuli on these variables.

Thus, this study aimed to compare the effects between a stimulus considered as relaxing (landscape) and a neutral stimulus, both presented by immersion in VR, on the PPT and the ANS.

METHODS

Healthy volunteers were recruited, from both sexes, from the population of students of the *Instituto Federal do Rio de Janeiro* (IFRJ) – *Campus Realengo*. The selection was based on the following inclusion criteria: (1) age between 18 and 40 years, (2) good health, (3) no complains of pain at the time of assessment or pain for more than three months. Were not considered eligible for the study volunteers that presented previous clinic diagnosis of arterial hypertension, diabetes *mellitus,* coronary artery disease, myocardiopathies, sensitive limb alterations, psychiatric illnesses, and those that were being treated with the use of substances acting on the central nervous system (e.g. antidepressants, anticonvulsants). The volunteers that presented some discomfort (nausea, dizziness) during the exposure to VR and the presence of sleepiness during collection were excluded. The heart registries that presented excessive noises were also excluded after the analysis. Volunteers who used glasses for visual correction were included only if they could visualize the VR stimulus without the glasses.

Before starting the protocol, the participants were randomized in their respective groups (VR nature group and VR control group). Randomization was done in Excel (Microsoft Corporation Office 2010 package) software for MAC OS X by one of the study researchers that was not involved in the recruiting neither the evaluation of the participants. This method of randomization was set in sequentially numbered envelopes, opaque and sealed, guaranteeing the secrecy of allocation. The envelopes were opened by the researcher that remained covered for the conditions of evaluation. Initially, the volunteers answered a sociodemographic data collection instrument containing information regarding name, gender, age, date of birth, telephone, e-mail, use of drugs, presence of any disease and/or psychiatric treatment. Next, the Trace-state Anxiety Inventory (IDATE) was applied, which was translated into Portuguese and adapted for Brazil[33]. The questionnaire consists of two parts: the first corresponds to state anxiety (IDATE-E), which evaluates the participant's current behavior, and the second to trace anxiety (IDATE-T), which evaluates the participant's personality. The instrument is made up of 20 questions varying in intensity from 1 to 4, of which 1 means "absolutely not" and 4 means "totally agree". The total score is characterized by low degree of anxiety (20-30), medium degree of anxiety (31-49) and high degree of anxiety (50 or more)[34].

The volunteers were allocated in a specific room for the data collection with controlled temperature, noise and humidity. For the assessment of the PPT, the examiner 1 used the digital pressure algometer (Wagner Instruments, Greenwich, CT, EUA), which is composed of a 1cm rubber tip which was pressed (1kg/minute) in the thenar region of the right hand. Two measurements were taken at each point, with an interval of at least 30 seconds between each measurement. The volunteer was previously instructed to inform the moment when the sensation of pressure turned into pain, with the verbal command "pain". This procedure was performed before and after the VR stimulus in both groups.

For the HRV measurement, the recommendations for data acquisition were used according to the study[20]. For the day before the collection, participants were instructed to seek a good night's sleep, not to engage in vigorous physical activity and not to consume stimulant drinks for at least 12 hours. The data collection was carried out in the morning and the volunteers should not have drank coffee or made any physical activity.

The HRV collection (R-R intervals) was done in three moments (pre-stimulus, during VR stimulus and post-stimulus), each 5 minutes long. Prior to the HRV collection, the examiner 2, who was responsible for collecting the HRV and performing the VR protocol, instructed the participant to remain seated and resting in a chair with no armrests for 5 minutes.

After this resting moment, the examiner 2 positioned the Polar H7 frequency meter (Polar, Electro, Oy, Kempele, Finland) in the chest region taking as reference the xiphoid appendix of the sternum. The literature demonstrates the use of Polar H7 as valid for the R-R interval measurements for HRV analysis[35].

The frequency meter registry was transmitted by bluetooth to the Elite HRV application. The use of the frequency meter for the HRV acquisition showed a small absolute mistake when compared to the electrocardiogram (ECG). Nevertheless, this small mistake is acceptable[36,37]. During the collection the participant was instructed to breath normally, not talk and remain awake. All R-R files were exported from the Elite HRV application to a cloud storage service to be analyzed on a separate computer with the help of the Kubios HRV 2.2 software. Each file was corrected for ectopic beats and artifact before analysis using an artifact correction method provided in Kubios HRV 2.2. A mean level of artifact correction identifying R-R intervals varying above or below 0.25 seconds compared to the mean was chosen to help preserve variability while addressing the presence of any artifacts. It has been recommended that this artifact correction technique should use for occasional artifacts and ectopic beats when examining R-R intervals[38]. Data extracted from HRV analysis included the frequency domains (BF, AF, AF/BF).

The VR stimuli were presented through an Iphone application attached to the VR glasses (VR Box 2.0, 360). The glasses were adjusted to the volunteers, which remained in the sitting position and using the frequency meter. In the VR nature protocol, the Dreambeach 2 (Atmosphaeres VR Experiences) application was used, which consists of a small photo-realistic beach with several bushes, trees, a variety of large and small rocks, besides the water movement and birds flying around. For the VR control group, the Virtual Apartment Tour (V2i Group) application was used, in which a walk inside an apartment was simulated. The volunteers could explore the apartment rooms (living room with balcony, dining room, kitchen, bathroom and bedroom) using only head movement. Each virtual reality stimuli was presented for five minutes.

This study was previously approved by the Ethics and Research Committee of the *Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro* (CAAE 95102918.3.0000.5268), in accordance with the *Resolução do Conselho Nacional de Saúde 466/12*, respecting the defined ethical precepts. The research participants signed the Free and Informed Consent Term (FICT).

Statistical analysis

The data obtained was tabulated in an electronic spreadsheet in the SPSS software (*StatisticalPackage for Social Sciences*, SPSS Inc, Chicago, USA) version 20 for Microsoft Windows 8. The data distribution was performed by the means of visual inspection of the histograms. The descriptive analysis presented the absolute and relative frequency data of the categorical variables, as well as the central tendency (mean) and dispersion (standard, minimum and maximum deviation) of the continuous variables.

The mean effects of interventions and group differences for all HRV outcomes were calculated using mixed linear models[39] that incorporated terms for the VR groups, pre, during, and post stimuli moment for HRV, and "group" and "moment" interaction terms. For the PPT, the means between groups were calculated using the Student t-test for independent samples.

The size of the sample was calculated using the G Power software (Heinrich-Heine-Universität Düsseldorf) based on the difference of the PPT at 20% (d=1.0), with power of 80% and significance level of $\alpha = 0.05$. Therefore, a sample size of 17 individuals per group for a total of n = 34 was necessary for the study. The statistical significance adopted for the study was 95%.

RESULTS

Sixty volunteers were randomized, being 30 for the VR nature group and 30 for the VR control group. Seventeen individuals were excluded from the analysis due to vertigo during the VR stimulus and 10 for excessive noises during the HRV reading (Figure 1). Thus, 41 volunteers participated in the study, being 19 in the VR nature group and 22 in the VR control group (Figure 1).

The VR nature group was composed of 12 (63.1%) women and 7 (36.8%) men with a mean age of 22.78 (SD=4.72; xmin=19 to xmax=39) years old. The VR control group was composed of 18 (81.8%) women and 4 (18.1%) men with a mean age of 21.00 (SD=2.42; xmin=17 to xmax=26).

Both the VR nature group and the VR control group presented IDATE-E and IDATE-T means that characterized the study participants with an intermediate degree of anxiety. The mean for the VR nature group for IDATE-E was 45.42 (SD=12.39) and for IDATE-T was 47.89 (SD=12.51). The VR control group had a mean of 40.90 (SD=9.52) and 47.00 (SD=10.45) for IDATE-E and IDATE-T, respectively.

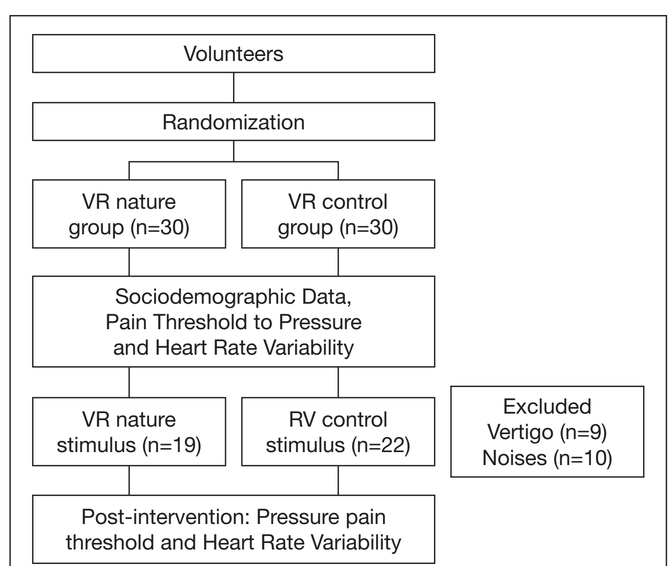

Figure 1. Participants allocation flowchart

The mean PPT before the VR stimulus was 3.46±2.02 Kgf for the VR nature group and 2.66±1.14 Kgf for the VR control group. After the VR stimulus, the mean PPT for the VR nature group was 3.88 (2.25) Kgf and 3.07 (1.44) Kgf for the VR control group. The difference between the means was -0.41 [CI(95%) = -0.74 to -0.07; p=0.01].

Table 1 presents the results of the means of the frequency domains at the pre (baseline) moments, during and after the stimulus according to the VR nature and VR control groups. The comparison between the groups did not show statistically significant differences for HRV parameters.

Table 1. Differences between the groups in the before and after VR stimulus moments

Outcome	Mean (SD)			
	VR nature (n=19)	VR control (n=22)	Mean adjusted difference (CI to 95%)	p-value
Frequency domain: BF(n.u)				
Baseline	70.86 (14.02)	63.17 (14.10)		
During	52.23 (11.72)	52.28 (15.68)	-5.17 (-17.60 to 7.26)	0.41
Post	60.17 (20.04)	57.72 (18.11)	-7.92 (-20.35 to 4.51)	0.20
Frequency domain: AF(n.u)				
Baseline	29.01 (13.97)	36.67 (14.02)		
During	47.73 (11.75)	47.46 (15.59)	5.20 (-7.16 to 17.58)	0.40
Post	39.72 (19.97)	42.17 (18.05)	7.93 (-4.44 to 20.30)	0.20
Frequency domain: BF/AF				
Baseline	3.19 (1.79)	2.34 (1.94)		
During	1.31 (1.05)	1.60 (1.37)	-0.44 (-1.72 to 0.83)	0.48
Post	2.47 (2.38)	2.07 (2.02)	-0.99 (-2.26 to 0.28)	0.12

DISCUSSION

The present study's objective was to verify whether a VR nature stimulus would have a greater effect for PPT outcomes and HRV frequency domains when compared to a VR control stimulus in a sample of healthy people. The differences between the groups for the PPT were statistically significant in the right thenar region. The mean differences for the HRV frequency parameters were not statistically significant, suggesting that the influence of a nature stimulus through VR does not present different results on HRV when compared to the other VR stimulus used as control.

The PPT is frequently used for measuring pain related to a pressure stimulus[40] and has the advantage of being an objective, valid and reliable measurement[41]. The initial hypothesis was that the individuals submitted to the VR nature would present an increase in the PPT after the stimulus. This hypoalgesic effect had already been reported in other studies. In a study with 45 healthy volunteers submitted to a VR intervention associated with a pain stimulus by immersion of the hand in cold water (cold pressure), it was demonstrated that VR promoted an increase in the threshold and in the tolerance to pain[42]. Nevertheless, it's worth noting that the results could have been different if the sample was composed of people with chronic pain, since they can present higher sensibility to the pain stimulus due to the central and peripheral sensitization mechanisms and the impairment of descendant modulatory pathways[43].

Regarding the HRV, no difference between the groups was observed. The initial hypothesis was that the individuals submitted to the VR nature would present a greater vagal predominance when compared to the control group. However, the absence of difference in HRV between the types of stimuli could be due to the attention shifting mechanisms (distraction) that occur in both stimuli during the VR immersion. This way, it's possible that VR has an effect on the ANS independently of the exposed scenario because of the emotional regulation promoted by attention[44].

Therefore, it's possible that the mechanisms acting on HRV are related to the emotional regulation

in the presence of a attentive task[45] which involves a network composed of the lateral prefrontal cortices, temporal and parietal regions, as well as the supplementary motor area and the cingulate cortex[46]. Some studies have also obtained similar results. The study[47] with 18 individuals compared three different scenarios in VR, an empty room, a field and the beach. The authors observed that, although the nature scenes presented through the VR provided relaxation, there were no differences for the LF, HF and LF/HF parameters. In another study which investigated the effects of stimulating VR with nature scenes on heart rate in a sample of 22 healthy volunteers, there was no difference in the R-R interval between the groups according to visual manipulations, nature scenes in 360 degrees presented in VR versus abstract art in slideshow presented in VR[48]. The present study stands out for having investigated the effects of two VR stimuli on PPT and HRV. Another strength of the study was the randomization of the subjects and the data collection made by two covered evaluators. Nevertheless, the study is not free from limitations. One of the limitations was the loss of some subjects after the data collection. The main motive for the participant's exclusion was the presence of noises during the HRV collection. Although the evaluators have been trained for the collection, it's possible that during the exploration of the VR environment the movement of some of the participants could have influenced the HRV data capture. The method of acquisition using the frequency meter could have facilitated the displacement of the equipment during the acquisition in the presence of movements made by some of the participants. Even after using filters for improvement of the signal, it was preferred to exclude these data. Another point that can be considered as limiting was the reduced time of acquisition for HRV. Although the time of acquisition used is recognized in the literature[20], it's possible that the results would turn out different for larger collection times.

This study's results can be important for generating hypothesis on the mechanisms involved in pain modulation and emotional regulation promoted using VR. It's still necessary to understand how VR can have immediate, medium- and long-term effects when used as therapeutic intervention. Once VR becomes accessible and reaches lower costs, it is recommended that clinical studies investigate the effect over the intensity of pain and other components present in chronic pain like fear of movement, anxiety and catastrophization.

CONCLUSION

The present study's results show that the group that was exposed to the VR stimulus with scenes of nature presented an increase of the PPT when compared to the group that was submitted to the control stimulus in VR. However, no difference between the groups' frequency parameters of HRV was found.

REFERENCES

1. Keefe F, Nowlin L, France CR, Zakhidov D, Trost Z, Zielke M, et al. The promise and challenge of virtual gaming technologies for chronic pain: the case of graded exposure for low back pain. Pain Manag. 2015;5(3):197-206.
2. Marques FLSN, Costa RMEM, Machado LS, Moraes RM. Realidade virtual para saúde no brasil: conceitos, desafios e oportunidades. Rev Bras Eng Biomed. 2011;27(4):243-58.
3. Malińska M, Zużewicz K, Bugajska J, Grabowski A. Heart rate variability (HRV) during virtual reality immersion. Int J Occup Saf Ergon. 2015;21(1):47-54.
4. Pourmand A, Davis S, Marchak A, Whiteside T, Sikka N. Virtual reality as a clinical tool for pain management. Curr Pain Headache Rep. 2018;22(8):53.
5. Massetti T, da Silva TD, Crocetta TB, Guarnieri R, de Freitas BL, Bianchi Lopes P, et al. The clinical utility of virtual reality in neurorehabilitation: a systematic review. J Cent Nerv Syst Dis. 2018;10:1179573518813541.
6. Oing T, Prescott J. Implementations of virtual reality for anxiety-related disorders: systematic review. JMIR Serious Games. 2018;6(4):e10965.
7. Blum J, Rockstroh C, Göritz AS. Heart rate variability biofeedback based on slow-paced breathing with immersive virtual reality nature scenery. Front Psychol. 2019;10:2172.
8. Tsai CF, Yeh SC, Huang Y, Wu Z, Cui J, Zheng L. The effect of augmented reality and virtual reality on inducing anxiety for exposure therapy: a comparison using heart rate variability. J Healthc Eng. 2018;25:6357351.
9. Van Den Houte M, Van Oudenhove L, Bogaerts K, Van Diest I, Van Den Bergh O. Endogenous pain modulation: association with resting heart rate variability and negative affectivity. Pain Med. 2018;19(8):1587-96.
10. Keefe FJ, Lumley M, Anderson T, Lynch TR, Studts JL, Carson KL. Erratum. Pain and emotion: new research directions. 2001;57(4):587-607.
11. Rhudy JL, Meagher MW. The role of emotion in pain modulation. Curr Opin Psychiatry. 2001;14(3):241-5.
12. Kenntner-Mabiala R, Pauli P. Affective modulation of brain potentials to painful and nonpainful stimuli. Psychophysiology. 2005;42(5):559-67.
13. Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): do affective valence and arousal play a role? Pain. 2008;136(3):250-61.
14. Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. Pain. 2016;157(1):7-29.
15. Williams DW, Cash C, Rankin C, Bernardi A, Koenig J, Thayer JF. Resting heart rate variability predicts self-reported difficulties in emotion regulation: a focus on different facets of emotion regulation. Front Psychol. 2015;6:261.
16. Ravinder, J Crawford M. How does the body affect the mind? Role of cardiorespiratory coherence in the spectrum of emotions. Adv Mind Body Med. 2015;29(4):4-16.
17. Thayer JF, Brosschot JF. Psychosomatics and psychopathology: Looking up and down from the brain. Psychoneuroendocrinology. 2005;30(10):1050-8.
18. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. J Affect Disord. 2000;61(3):201-16.
19. Task Force of The European Society of Cardiology and The North American Electrophysiology Society of Pacing and Electrophysiology. Guidelines Heart rate variability. Eur Heart J. 1996;354-81.
20. Catai AM, Pastre CM, Godoy MF, Silva ED, Takahashi ACM, Vanderlei LCM. Heart rate variability: are you using it properly? Standardisation checklist of procedures. Braz J Phys Ther. 2020;24(2):91-102.
21. Thayer JF, Åhs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. Neurosci Biobehav Rev. 2012;36(2):747-56.
22. Tsai CF, Yeh SC, Huang Y, Wu Z, Cui J, Zheng L. The effect of augmented reality and virtual reality on inducing anxiety for exposure therapy: a comparison using heart rate variability. J Healthc Eng. 2018;2018:6357351.
23. Rus-Calafell M, Garety P, Sason E, Craig TJK, Valmaggia LR. Virtual reality in the assessment and treatment of psychosis: A systematic review of its utility, acceptability and effectiveness. Psychol Med. 2018;48(3):362-91.
24. Scapin S, Echevarría-Guanilo ME, Boeira Fuculo Junior PR, Gonçalves N, Rocha PK, Coimbra R. Virtual reality in the treatment of burn patients: a systematic review. Burns. 2018;44(6):1403-16.
25. Bluett B, Bayram E, Litvan I. The virtual reality of Parkinson's disease freezing of gait: a systematic review. Parkinsonism Relat Disord. 2019;61:26-33.
26. Massetti T, da Silva TD, Crocetta TB, Guarnieri R, de Freitas BL, Bianchi Lopes P, et al. The clinical utility of virtual reality in neurorehabilitation: a systematic review. J Cent Nerv Syst Dis. 2018;10:117957351881354.
27. Botella C, Fernández-Álvarez J, Guillén V, García-Palacios A, Baños R. Recent progress in virtual reality exposure therapy for phobias: a systematic review. Curr Psychiatry Rep. 2017;19(7):42.
28. Mallari B, Spaeth EK, Goh H, Boyd BS. Virtual reality as an analgesic for acute and chronic pain in adults: a systematic review and meta-analysis. J Pain Res. 2019;12:2053-85.
29. Eijlers R, Utens EMWJ, Staals LM, de Nijs PFA, Berghmans JM, Wijnen RMH, et al. Systematic review and meta-analysis of virtual reality in pediatrics: effects on pain and anxiety. Anesth Analg. 2019;129(5):1344-53.
30. Maani C V, Hoffman HG, Morrow M, Maiers A, Gaylord K, McGhee LL, et al. Virtual reality pain control during burn wound debridement of combat-related burn injuries using robot-like arm mounted VR goggles. J Trauma. 2011;71(Suppl 1):S125-30.
31. Chan E, Foster S, Sambell R, Leong P. Clinical efficacy of virtual reality for acute procedural pain management: a systematic review and meta-analysis. PLoS One. 2018;13(7):e0200987.
32. Hoffman HG, Richards TL, Van Oostrom T, Coda BA, Jensen MP, Blough DK, et al. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. Anesth Analg. 2007;105(6):1776-83.
33. Biaggio AMB, Natalício L, Spielberger CD. Desenvolvimento da forma experimental em português do Inventário de Ansiedade Traço-Estado (IDATE), de Spielberger. Arq Bras Psicol. 1977;29(3):31-44.
34. Fioravanti ACM, Santos LF, Maissonette S, Cruz APM, Landeira-Fernandez J. Avaliação da estrutura fatorial da Escala de Ansiedade-Traço do IDATE. Aval Psicol. 2006;5(2):217-24.
35. Giles D, Draper N, Neil W. Validity of the Polar V800 heart rate monitor to measure RR intervals at rest. Eur J Appl Physiol. 2016;116(3):563-71.
36. Dobbs WC, Fedewa MV, MacDonald HV, Holmes CJ, Cicone ZS, Plews DJ, et al. The accuracy of acquiring heart rate variability from portable devices: a systematic review and meta-analysis. Sports Med. 2019;49(3):417-35.
37. Georgiou K, Larentzakis AV, Khamis NN, Alsuhaibani GI, Alaska YA, Giallafos EJ. Can wearable devices accurately measure heart rate variability? A systematic review. Folia Med. 2018;60(1):7-20.
38. Peltola MA. Role of editing of R–R intervals in the analysis of heart rate variability. Front Physiol. 2012;3:148.
39. Twisk JW. Longitudinal data analysis. A comparison between generalized estimating equations and random coefficient analysis. Eur J Epidemiol. 2004;19(8):769-76.
40. Laura Frank PM VB. The repeatability of pressure algometry in asymptomatic individuals over consecutive days. Int J Osteopath Med. 2013;16(3):143-52.
41. Waller R, Straker L, O'Sullivan P, Sterling M, Smith A. Reliability of pressure pain threshold testing in healthy pain free young adults. Scand J Pain. 2015;9(1):38-41. Erratum in: Scand J Pain. 2016;13:17.
42. Gutiérrez-Maldonado J, Gutiérrez-Martínez O, Loreto-Quijada D, Nieto-Luna R. The use of virtual reality for coping with pain with healthy participants TT - El uso de la realidad virtual para el afrontamiento del dolor con participantes sanos. Psicothema. 2012;24(4):516-22.
43. Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK. Altered central sensitization and pain modulation in the CNS in chronic joint pain. Curr Osteoporos Rep. 2015;13(4):225-34.
44. Pessoa L, Padmala S, Kenzer A, Bauer A. Interactions between cognition and emotion during response inhibition. Emotion. 2012;12(1):192-7.
45. Strauss GP, Ossenfort KL, Whearty KM. Reappraisal and distraction emotion regulation strategies are associated with distinct patterns of visual attention and differing levels of cognitive demand. PLoS One. 2016;11(11):e0162290.
46. Morawetz C, Bode S, Baudewig J, Kirilina E, Heekeren HR. Changes in effective connectivity between dorsal and ventral prefrontal regions moderate emotion regulation. Cereb Cortex. 2016;26(5):1923-37.
47. Anderson AP, Mayer MD, Fellows AM, Cowan DR, Hegel MT, Buckey JC. Relaxation with immersive natural scenes presented using virtual reality. Aerosp Med Hum Perform. 2017;88(6):520-6.
48. Valtchanov D, Barton KR, Ellard C. Restorative effects of virtual nature settings. Cyberpsychol Behav Soc Netw. 2010;13(5):503-12.

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