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# Bug Off Pain: an educational virtual reality game on spider venoms and chronic pain for public engagement

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## ABSTRACT

Virtual reality (VR) technology has been capturing the public imagination for decades. VR software applications that allow for interactive immersion are emerging as a renowned medium in many areas, including educating the public in biochemistry-related subjects via public engagement events. This report provides information about an immersive, interactive and educational virtual reality (VR) game named Bug Off Pain that increases scientific literacy about chronic pain and spider venoms among the public and high school students. Here, VR was shown to be an innovative and fun approach to learning and public engagement in biochemistry. Bug Off Pain places the viewer inside the brain and shows the molecular system that allows people to sense pain. After securing three (learning) points via the multimedia-based clips, this experience translates to the interactive game. Here, a player has to choose a venom that shuts down the pain until that results in “pain over.” Bug Off Pain can be played (free of charge) on two different VR platforms; Oculus Rift and Android devices.

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## GRAPHICAL ABSTRACT



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## KEYWORDS

Biochemistry, biological cells, drugs/pharmaceuticals, computer-based learning, games, general public, medicinal chemistry, multimedia-based learning, public understanding/outreach, natural products

## INTRODUCTION

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Scientists, educators, and policymakers continue to face challenges when it comes to finding effective approaches to engage the public on scientific research and communicate their findings in a meaningful fashion.<sup>1</sup> This quest has harnessed digital technology to benefit engagement in Science, Technology, Engineering, and Mathematics (STEM) by melding education, active learning, science communication and popular culture in an informal educational setting. Four of the most recent examples include “ReAction! Chemistry in the Movies”<sup>2</sup>, “Wow”<sup>3</sup>, “PubScience”<sup>4</sup> and “SciPop Talks”.<sup>5</sup> In the same respect, gamification (the application of game design elements and mechanics to engage users and solve problems) can encourage learning and enhance public interest in STEM-related subjects.<sup>6</sup> Various research groups have employed game aspects in teaching organic chemistry, and their educational software known as Chairs!<sup>7</sup> Chirality-2;<sup>8</sup> and Say My Name,<sup>9</sup> have shown positive effects on student academic performance, and engagement. Whereas these are excellent examples of using games as an educational tool for teaching chemistry, none of them tried to apply the same to virtual reality (VR).

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Several authors have recently suggested that incorporating aspects of gaming into interactive learning environments, such as VR, could be more effective in terms of improving learning outcomes, “makes learning fun” and offers powerful tools for “learning through doing,” as discussed in two comprehensive reviews.<sup>10-11</sup> Moreover, VR games have enormous appeal, reaching an audience of hundreds of thousands to millions.<sup>12-13</sup> Taken together with the difficulties enticing a general audience to STEM outreach activities and regaining the public’s trust in chemistry-related subjects,<sup>14</sup> VR games might be an alternative medium for STEM outreach and education with an aim to increase mass interest, engagement and appreciation of chemistry.<sup>11, 15-16</sup>

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Given this importance, several works have reported remarkably successful VR/AR methods to chemistry outreach and education such as EduChem VR;<sup>17</sup> VR-Engage;<sup>18</sup> AR calorimetric titration

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app;<sup>19</sup> and others such as Water VR, Molecular Zoo and Fishtank.<sup>20</sup> Barret et al.<sup>21</sup> applied mixed  
50 reality (MR) in chemical outreach and education that resulted in enhanced learning outcomes. Yet,  
none of them attempted to gamify any of the relevant biochemistry research topics in VR, and evaluate  
them accordingly. Since the primary research focus in our labs is the study of the spider venoms and  
their therapeutic applications for chronic pain diseases, we have chosen VR as the educational tool to  
present, communicate, increase awareness, and educate the public on harnessing the chemistry of  
55 venoms from spiders for its medical applications.<sup>22</sup> Furthermore, this topic has not been utilized in  
VR-environment until now.

This context motivated us to create Bug Off Pain – a VR game that aims to take the pain out of public  
engagement and helps to bridge the gap between scientific and non-scientific community (general  
public). Here, we report the development and implementation of an integrated three-dimensional  
60 educational VR-based game that may assist the general public in their understanding of the  
biochemistry behind the venoms in relation to chronic pain. Bug Off Pain is available for free  
worldwide on both Oculus Rift (computer) and Android (mobile) platforms by downloading the game or  
scanning its QR code, listed as Figure S3 (see Supplemental Information).<sup>23</sup>

## 65 THE GAME

The game was developed using the Unity3D platform and designed to be an immersive, interactive and  
easy-to-play VR game that allows the general public to learn about the biochemistry of venoms in  
relation to chronic pain. The story of the VR game Bug Off Pain incorporates a lot of elements from  
theatrical movies. The ultimate goal of the player is to navigate through the virtual world to find the  
70 right spider venom that shuts down pain signaling. To achieve this goal, the players have to gain three  
points by watching educational animated clips. The player initially begins by positioning themselves in  
the theatre (Figure 1A).

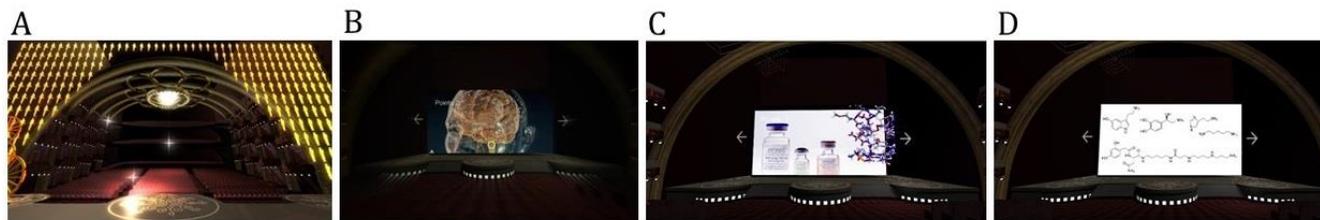
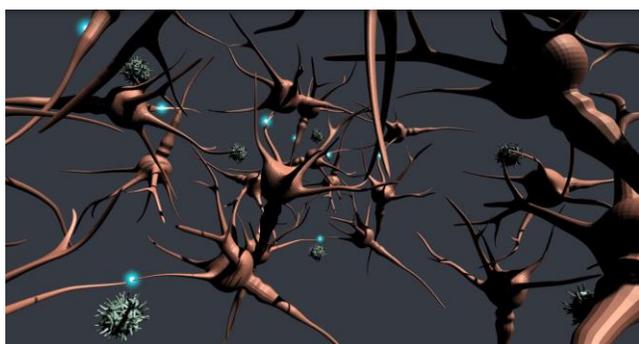


Figure 1. Various VR environments. A: Model of our academy theatre in the virtual reality environment. B: Close-up of the nervous system as part of the first movie. C, D: Exploiting the chemistry behind the cone snail peptide ziconotide (C) and low molecular weight compounds (D) that are found in the animal venoms

80 After finding a screen element “play,” the player starts by watching the first animated clip “Pain: Why does it hurt so much?” which is embedded into the game, and learning about the neuroscience behind chronic pain (Figure 1B). As soon as the player gets the first point, a new video appears. By clicking the right arrow on the user interface, followed by “play,” the player starts watching another clip (Figure 1C-D) and gets familiar with the chemical structures of some of the major components in the venoms.

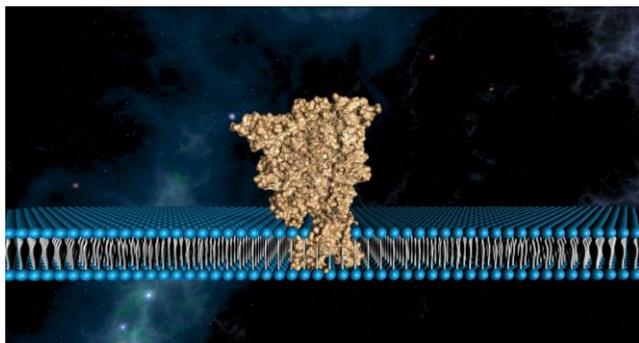
85 Here, one is educated on the biochemistry of toxins from venoms which can be either low-molecular-weight compounds, peptides, and proteins. Usually, small molecules consist of salts, carbohydrates, amines (neurotransmitters such as serotonin and noradrenaline), acids, and acylpolyamines. Peptides, meanwhile, are the main component in most spider venoms. These can be either linear or disulfide-containing peptides. Finally, the higher molecular weight components include enzymes and more

90 abundant proteins.<sup>24</sup> In the game, the player is educated how this same venom’s chemical diversity makes them candidates for either acute or chronic pain. As soon as the player gets another point and clicks on the right arrow again (Figure 1D), they are transformed into the final scene: a 3D-movie (Figure 2).



100 Figure 2. 3D-movie that allows the player to travel inside the brain

By listening to the voice-over narration, the player learns how different cells, such as neurons and microglia are involved in chronic pain and what their contribution is (Figure 3).



110 Figure 3. Representation of one specific target (purinergic receptor) in the brain (PDB: 4DW1)

This experience ends when the player gets the final (third) point. Straight afterward that same -protein target appears on the main theatre's stage, and various spiders drop down from the theatre ceiling.

115 Additional instructions are provided in the game so the player can familiarize themselves with these surroundings. To start the game, the players must click on the individual spider. Each of them spits a venom (depicted as a building block that comes in various colors and shapes), and the player has to figure out the way on how to best “hit” the target on the stage with one particular “venom” (building block). Some venoms are active towards a target, and others are not.

120 If the player chooses the spider with the inactive venom, their venom is rejected by the target once probed, and the player cannot click on that spider anymore. Thus, after each inactive venom, the player must click another spider for a new venom to appear. However, the player is not penalized for their unsuccessful attempts (Figure 4).



Figure 4. VR environment after probing the wrong venoms

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Still, after four failed attempts, the largest of spiders (tarantula) drops down from the ceiling and spits  
135 another “venom.” The game finishes when a player drags that last venom to the target. That particular  
venom sticks to the target protein and fireworks appear (Figure 5).

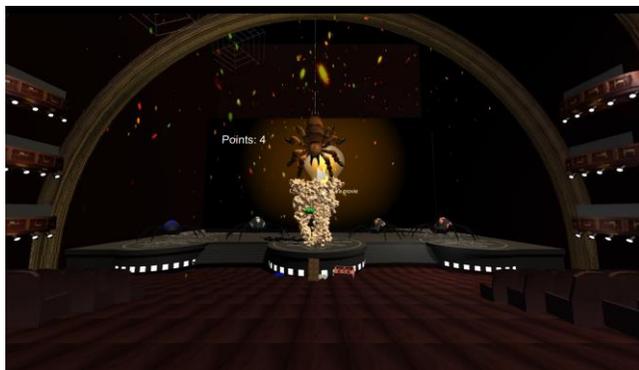


Figure 5. VR environment after probing the right venom

The player then gets to see a plot summary and how identifying the right spider venom towards these  
150 protein targets might bring novel discoveries to the research community one day. After finishing the  
game, the credits appear and the players can share their score and feedback to our website where we  
can gather their feedback for our research evaluation.

For the details on other software tools, 3D models, and voice-over contributions, please see the  
Supplemental Information.

## 155 **RESULTS AND DISCUSSION**

### Evaluation of general public opinions about Bug Off Pain

After Bug Off Pain’s successful launch at the Norwich Science Festival in 2017, the game has also  
been very favorably received at academic conferences, online and other events, such as “Cambridge  
160 Science Festival,” “Norwich Gaming Festival” and “UEA Innovation Showcase” in 2018. Feedback from  
the users online or attending these events has been universally positive, with some comments listed in  
Table S1. The form that was used to assess public opinion and evaluate feedback from the VR game  
Bug Off Pain is shown in Figure S1 (see the Supporting Information).

This was obtained manually and electronically through 14 statements with responses based on a 10  
165 point Likert-type scale (Figure 6).

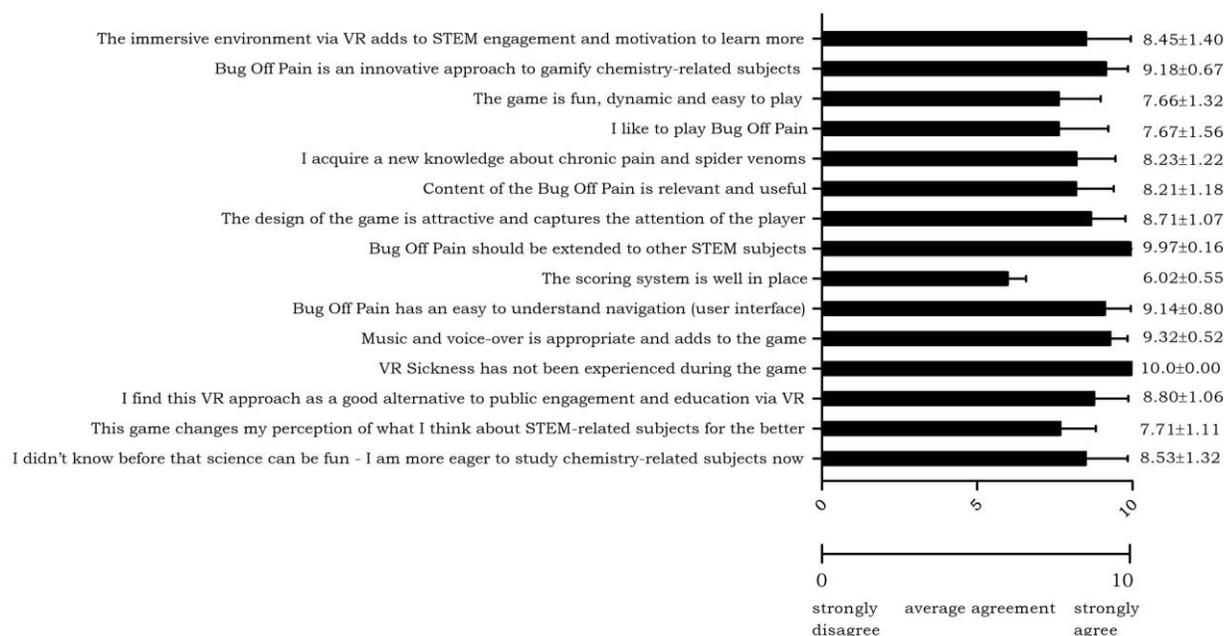


Figure 6. The survey results show the average Likert scores and their standard deviations for evaluators' responses by survey statement

180 The level of agreement with the statements presented a range from 6.02 to 10.0 among evaluators. These statements are closer to "strongly agree" (8-10) than to "neutral" (4-7) or even "strongly disagree" (1-3), so this might reflect an actual trend. With that said, the survey respondents were self-selected, so it might not be evident how accurately this sample represents the total public population. Still, on the basis of these responses, users indicated that the game is fun, dynamic and easy to play, has an

185 attractive design, easy to understand interface and relevant content. The players reported that Bug Off Pain helped them to shift their perception about STEM-related studies. Moreover, it was suggested that extending Bug Off Pain to other STEM-relevant subjects might be useful for engaging and educating the public in other chemistry-related topics. However, the scoring system should be more carefully considered when designing such games, and a better reward system should be in place.

190 The game duration was something we took into serious consideration when designing the game since experiencing VR-related sickness is common among VR gamers. Evaluators reported zero VR-related sickness during the gameplay, probably due to the game duration being between 7-10min. Regan<sup>25</sup> showed that symptoms are most significant at 20 min when almost half of the tested subjects reported VR-related sickness, which seems to be in line with our studies. Therefore, the game Bug Off Pain

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195 might be a good approach to public engagement via VR, and the gamification of chemistry via the  
virtual medium might be considered as an alternative way to STEM outreach activities.

#### Evaluation of VR-based learning by the use of Bug Off Pain among high school students

This evaluation was aimed at finding out whether the educational game Bug Off Pain may achieve  
200 better educational effects in comparison with educational software with no gaming environment. The  
evaluation of Bug Off Pain with respect to the educational impact was conducted by a cohort of 44  
high school students (ages 17-18). This evaluation was a study tested with a controlled pretest-  
posttest design to analyze the effect of the educational role of Bug Off Pain on the learning and  
understanding of the biochemistry behind the venoms in relation to chronic pain. Here, we conducted  
205 an experiment where Bug Off Pain was compared to a similar application (video clips) that had a  
conventional user interface without any VR game. These video clips are also a major part of the VR  
game Bug Off Pain, but in the control group participants were not subjected to the virtual reality  
environment, nor the game elements. The tested hypothesis was: there is a significant difference  
between learning via utilization of our VR-based game as a complementary educational tool compared  
210 to video clips (representative of a traditional lecture -type method where textbooks and slide projections  
are used).

Pre-tests and post-tests were analyzed, and their results are presented in Table 1 and Table 2.

Table 1 shows that in all groups there was an improvement in the average number of correct answers  
(ANCA) in the post-test when compared to the previous pre-test.

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**Table 1. Comparison of Pupils' average scores by Instructional Method**

Assessment <sup>a</sup>	Mean Scores <sup>a</sup> (SD) by Group, N = 22	
	Control Group: Video Clips	Experimental Group: VR Game
Pretest	3.045 (1.397)	3.818 (0.958)
Post-test	5.773 (1.110)	8.696 (1.093)
Av. Score Differences	2.323	4.878

<sup>a</sup>The scale has a range of 1-10

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By doing the multiple comparison (two-way ANOVA and Wilcoxon test) between the relative differences of the ANCA ( $p < 0.05$ ), we can conclude that there was a significant improvement ( $p = 0.002$ , \*\*\*) in the ANCA in the experimental group (EG) than in the control group (CG). Lastly, the calculation of the effect size (Cohen's  $d$  value) between post-test (video) clips and post-test (VR game) was considered. This assessment showed the effect size to be very large ( $d > 2$ ) based on benchmarks suggestion by Cohen and others.<sup>26-27</sup> This emphasized that the size of the differences between these two groups is substantial. Therefore, the effectiveness of the instructional role of the game in promoting learning about chronic pain and the biochemistry of venoms via a VR medium is demonstrated by these data (Table 2, Figure S2).

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**Table 2. Comparative Student Performance Relative to Instructional Method**

Structure of Analysis	P value <sup>b</sup> ( $N = 22$ )	Cohen's $d$ value
Video clips (pretest vs posttest)	0.0001	2.16
VR Game (pretest vs posttest)	<0.0001	4.76
$\Delta$ video clips <sup>a</sup> vs $\Delta$ VR game <sup>a</sup>	0.0002	NA
Posttest (video clips vs VR game)	0.0001	2.65

<sup>a</sup>Relative difference of right answers between pre- or posttest. <sup>b</sup>All the  $p$  values were found to be significant ( $P < 0.05$ )

## CONCLUSIONS

It is clear that the development of educational games can allow the traditional public engagement process to become more appealing and effective to the general public when permeated with VR tools. One such example is our multi-platform, immersive, engaging and educational VR game, Bug Off Pain. Here, the game's design and implementation are reported. Bug Off Pain is freely available online,<sup>23</sup> and it has been tested and evaluated by the general public and high school students. Results show that public opinions were positive about playing the game, engaged their learning about biochemistry and shifted their perception about spider venoms. The findings of this study demonstrate that the VR game Bug Off Pain is a useful tool for science communication, education and public engagement about

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chronic pain and spider venoms. Possible reasons for its valuable educational benefits include not only correctly using critical thinking skills and problem-solving abilities, but also framing individual creativity and self-direction – all of which stand out as the less-tangible, non-academic benefits, as suggested by Navarrete<sup>28</sup> and others.<sup>29</sup> However, our game is not intended as a total replacement to any current effective pedagogy. Instead, this and similar approaches,<sup>17-18,21</sup> may be valuable additions to the teaching toolbox that educators can leverage to engage the modern learner. It will be interesting to see how these platforms are developed in the not so distant future.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available on the ACS Publications website at DOI:

10.1021/acs.jchemed.

Details on the content, software information, 3D models, programming, pre and post-test, and results of student's survey can be found in "Supporting Information (DOCX)."

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### REFERENCES

1. Wu, J. S.; Lee, J. J., Climate change games as tools for education and engagement. *Nature Climate Change* **2015**, 5 (5), 413.
2. Griep, M. A.; Mikasen, M. L., *ReAction!: chemistry in the movies*. Oxford University Press: New York, NY, 2009.

- 
3. Frey, C. A.; Mikasen, M. L.; Griep, M. A., Put some movie wow! in your chemistry teaching. *Journal of Chemical Education* **2012**, 89 (9), 1138-1143.
4. Beeken, M.; Budke, M., "PubScience—The Long Night of Experiments": Students Present  
270 Chemical Experiments in Dining Facilities. *Journal of Chemical Education* **2018**, 95 (8), 1323-1330.
5. Burks, R.; Deards, K.; DeFrain, E., Where Science Intersects Pop Culture: An Informal Science  
Education Outreach Program. *Journal of Chemical Education* **2017**, 94 (12), 1918-1924.
6. Papastergiou, M., Digital game-based learning in high school computer science education:  
275 Impact on educational effectiveness and student motivation. *Computers & Education* **2009**, 52 (1), 1-  
12.
7. Winter, J.; Wentzel, M.; Ahluwalia, S., Chairs!: A mobile game for organic chemistry students to  
learn the ring flip of cyclohexane. *Journal of Chemical Education* **2016**, 93 (9), 1657-1659.
8. Jones, O. A.; Spichkova, M.; Spencer, M. J., Chirality-2: Development of a Multilevel Mobile  
Gaming App To Support the Teaching of Introductory Undergraduate -Level Organic Chemistry.  
280 *Journal of Chemical Education* **2018**, 95 (7), 1216-1220.
9. da Silva Júnior, J. N.; Nobre, D. J.; do Nascimento, R. S.; Torres Jr, G. S.; Leite Jr, A. J. M.;  
Monteiro, A. J.; Alexandre, F. S. O.; Rodríguez, M. T.; Rojo, M. J., Interactive Computer Game That  
Engages Students in Reviewing Organic Compound Nomenclature. *Journal of Chemical Education*  
**2018**, 95 (5), 899-902.
- 285 10. Feng, Z.; González, V. A.; Amor, R.; Lovreglio, R.; Cabrera-Guerrero, G. Immersive Virtual  
Reality Serious Games for Evacuation Training and Research: A Systematic Literature Review. *Comput.  
Educ.* **2018**, 127, 252-266; DOI: 10.1016/j.compedu.2018.09.002.
11. Ibáñez, M.-B.; Delgado-Kloos, C., Augmented reality for STEM learning: A systematic review.  
*Computers & Education* **2018**, 123, 109-123.
- 290 12. Bailenson, J., *Experience on Demand: What Virtual Reality Is, how it Works, and what it Can Do*.  
WW Norton & Company: New York, NY, 2018.
13. KZero. (n.d.). Number of active virtual reality users worldwide from 2014 to 2018 (in millions).  
In *Statista - The Statistics Portal*. Retrieved April 16, 2019, from  
<https://www.statista.com/statistics/426469/active-virtual-reality-users-worldwide/>.
- 295 14. Illes, J.; Moser, M. A.; McCormick, J. B.; Racine, E.; Blakeslee, S.; Caplan, A.; Hayden, E. C.;  
Ingram, J.; Lohwater, T.; McKnight, P., Neurotalk: improving the communication of neuroscience  
research. *Nature Reviews Neuroscience* **2010**, 11 (1), 61.
15. Mayo, M. J., Video games: A route to large-scale STEM education? *Science* **2009**, 323 (5910),  
79-82.
- 300 16. Pham, D., Public engagement is key for the future of science research. *NPJ Science of Learning*  
**2016**, 1, 16010.
17. EduChemVR Improving Chemistry Learning with Virtual Reality. Accessed April, 2019 from  
<http://educhem-vr.com/>.
18. Virvou, M.; Katsionis, G., On the usability and likeability of virtual reality games for education:  
305 The case of VR-ENGAGE. *Computers & Education* **2008**, 50 (1), 154-178.
19. Tee, N. Y. K.; Gan, H. S.; Li, J.; Cheong, B. H.-P.; Tan, H. Y.; Liew, O. W.; Ng, T. W., Developing  
and demonstrating an augmented reality colorimetric titration tool. *Journal of Chemical Education*  
**2018**, 95 (3), 393-399.
20. Virtual Reality at UCSF. Retrieved April 16, 2019, from <http://vr.ucsf.edu/>.
- 310 21. Barrett, R.; Gandhi, H. A.; Naganathan, A.; Daniels, D.; Zhang, Y.; Onwunaka, C.; Luehmann,  
A.; White, A. D., Social and Tactile Mixed Reality Increases Student Engagement in Undergraduate Lab  
Activities. *Journal of Chemical Education* **2018**, 95 (10), 1755-1762.
22. Schmidtko, A.; Lötsch, J.; Freynhagen, R.; Geisslinger, G., Ziconotide for treatment of severe  
chronic pain. *The Lancet* **2010**, 375 (9725), 1569-1577.
- 315 23. Bibic, L., Druskis J., VR game Bug Off Pain. Accessed April, 2019 from  
<http://www.bugoffpain.com/>.
24. Schulz, S., The chemistry of spider toxins and spider silk. *Angewandte Chemie International  
Edition in English* **1997**, 36 (4), 314-326.
- 320 25. Regan, C., An investigation into nausea and other side-effects of head-coupled immersive  
virtual reality. *Virtual Real-London* **1995**, 1 (1), 17-31.

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26. Cohen, J., *Statistical power analysis for the behavioral sciences*. 1988, Hillsdale, NJ: L. Lawrence Earlbaum Associates **1988**, 2.

27. Lakens, D., Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in psychology* **2013**, 4, 863.

325 28. Navarrete, C. C., Creative thinking in digital game design and development: A case study. *Computers & Education* **2013**, 69, 320-331.

29. de Souza Sombrio, G.; Ulbricht, V. R.; Haeming, W. K., Games and gamification: A proposal for a creative learning process in education. *Journal of Education and Human Development* **2014**, 3 (4), 117-129.

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