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Virtual reality as complementary pain therapy in hospitalized patients with sickle cell disease

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Abstract

Objective: Due to incomplete management of vaso-occlusive pain episodes (VOE) in patients with sickle cell disease (SCD), we sought to determine if immersive VR would be feasible for inpatients. Secondarily, we hypothesized that a single VR session would improve the VOE pain experience.

Procedures: Consecutive patients with SCD eight years and older admitted for VOE were offered one 15-minute VR session, utilizing a relaxing underwater world specifically created for pediatric patients and to minimize potential simulator side effects. Safety and acceptability were evaluated with a brief survey before and after the session. Pain was evaluated utilizing the validated adolescent pediatric pain tool (APPT). Survey data and pain scores were analyzed using Wilcoxon signed-rank test as the data were nonnormally distributed.

Results: Thirty patients, 21 female, with a median age of 16 years were enrolled, the majority having hemoglobin SS disease. The VR session had no reported side effects; all patients requested VR again in the future. Median pain intensity (pre-VR 7.3 [interquartile range, IQR, 6.1, 8.8], post-VR 5.8 [4.7, 7.9]), number of affected body areas (pre-VR 3.0 [2.0, 7.8], post-VR 2.0 [0, 4.8]), and qualitative measures including sensory, affective, evaluative, and temporal pain domains were all statistically reduced (i.e., $P \leq 0.01$).

Conclusions: VR therapy was feasible in a cohort of patients with SCD admitted for VOE. In addition to standard therapies, VR may help reduce the pain experience with SCD VOE. Further study is required to determine the impact of VR therapy on opioid usage and length of stay in hospital.

KEYWORDS

complementary therapies, pain management, sickle cell disease, virtual reality

1 | INTRODUCTION

The management of pain in adult and pediatric patients with sickle cell disease (SCD) remains incomplete and heavily reliant on opioid therapy.[1] Intermittent acute pain due to vaso-occlusion is the principal symptom, often requiring hospitalization.[2–4] Quantity and severity of this pain and its effect on health-related quality of life may be vastly underestimated by healthcare workers.[5] In an analysis of clinical data from the Comprehensive Sickle Cell Centers Clinical Trial Consortium, Dampier et al[6] found that pain in pediatric patients with SCD impacted physical function, sleep, and fatigue as well as school performance. In addition, increasing age in children with SCD has been shown to be associated with a higher frequency of severe pain episodes as well as longer length of stay.[7,8] For patients with SCD, pain syndromes are complex and multifactorial with biologic, psychological, and social factors, and a multidisciplinary approach is required to appropriately manage symptoms.[4,9,10] Complementary and alternative strategies must be utilized in combination with medical therapy to help alleviate pain and suffering in pediatric patients with pain syndromes such as SCD; a holistic multidisciplinary approach such as utilized in palliative care has been suggested.[3,11]

Meta-analyses of psychological interventions in pediatric pain syndromes including cognitive behavioral therapy (CBT), relaxation therapy, and biofeedback have all been shown to provide significant benefit in pain reduction.[12,13] Specifically for pediatric patients with SCD, the utilization of a multidisciplinary pain management team has

Abbreviations: APPT, adolescent pediatric pain tool; CBT, cognitive behavioral therapy; CHO, UCSF Benioff Children's Hospital Oakland; fMRI, functional magnetic resonance imaging; SCD, sickle cell disease; VR, virtual reality

been shown to significantly decrease hospitalizations, with almost all patients being taught nonpharmacologic pain management techniques such as CBT.[14] Use of guided imagery has shown benefit in school-age children with SCD as measured by reductions in pain intensity and utilization of analgesics.[15] However, a Cochrane review of psychological therapies specifically for pain in SCD concluded that there was a paucity of studies to define effectiveness in this population.[16] Patients with SCD welcome the utilization of technology to help manage their disease, and therefore virtual reality (VR), a newer complementary therapy that has not been tested in this population, holds promise.[17–19]

From a neurobiological standpoint, it is hypothesized that VR decreases pain by decreasing both attention to pain and the emotion related to pain sensation.[20] Diversion of attention to pain through use of VR hypothetically decreases the anterior cingulate cortex response to the pain sensation, modulating efferent descending pain fibers.[20] Additionally, emotional response to VR may inhibit activation of the amygdala and subsequent activation of the periaqueductal gray area and the anterior cingulate cortex mitigating pain response.[20] Functional magnetic resonance imaging (fMRI) studies have shown correlative drops in pain-related brain activity with concomitant utilization of VR technology.[21] A study of fMRI in healthy subjects receiving thermal pain stimulation showed significantly decreased pain-related brain activity in the insula and thalamus with either opioids or VR; the combined effect of opioids plus VR was synergistic and correlated with subjective decrease in pain scores.[22]

Utilization of VR has shown benefit in pediatric patients with acute burn injuries as well as distraction for needle sticks and chemotherapy administration with minimal side effects.[23–27] The benefit has been shown to persist with recurrent utilization of the VR technology.[27,28] In addition, totally immersive VR was shown to have greater benefit in pain reduction.[29–31] As immersive VR technology improves, VR is being utilized as a complementary therapy for persistent, chronic pain rather than solely for acute pain.[32–34] On the basis of these data and our recognition that novel complementary therapies are required to improve pain management in patients with SCD, we aimed to conduct a feasibility study of immersive VR therapy in patients hospitalized for vaso-occlusive pain. Secondarily, we hypothesized that a single VR session would improve the pain experience in this group.

2 | METHODS

After institutional review board approval, we identified consecutive patients eight years or older at UCSF Benioff Children's Hospital Oakland (CHO) with SCD including hemoglobin variants SS, SC, and S/β-thalassemia hospitalized for a vaso-occlusive event, with a planned feasibility study of 30 unique patients based on suggested sample size for feasibility assessment.[35]

2.1 | Feasibility and eligibility criteria

Feasibility was defined by our ability to (1) recruit patients during hospitalization for VOE; (2) implement processes and resources to administer VR to all eligible patients during hospitalization; (3) determine safety of the intervention (i.e., no VR simulator sickness); and (4) determine acceptability of the intervention (i.e., willingness to use VR again in future with VOE). Children younger than eight years of age were excluded secondary to the minimal suggested interpupillary diameter to attain binocular vision with Oculus Rift goggles. Patients with previous stroke or other neurologic disorders were not excluded as long as they could comprehend the functioning of the device. Patients were generally identified as eligible in the first 24 hours of admission (except for weekend admissions) to ensure inclusion prior to discharge.

2.2 | Survey data

Patients filled out a validated simulator sickness questionnaire before and after completion of the VR session to ensure safety of the device as either the motion within the VR software or head motion while using the headset can lead to headache, eyestrain, nausea, motion sickness, or vomiting.[36] A simple, nonvalidated Likert scale satisfaction survey was formulated and given to all enrollees after completion of the VR session to determine acceptability (Supporting Information Figure S1). Patients filled out the adolescent pediatric pain tool (APPT), a validated multidimensional measure of pain intensity, location, and quality for pediatric inpatients, prior to and after administration of the single 15-minute VR session (Supporting Information Figure S2).[37] The APPT was selected as the pain assessment tool as it has been widely utilized in SCD with studies showing decrement in body areas marked and pain quality descriptors over hospitalization time, not always concurrent with simple pain intensity scale ratings.[37]

2.3 | VR software utilization

KindVR, an independent VR firm in the Oakland Bay Area, develops VR software specifically for the utilization of pediatric patients, which minimizes significant motion in order to mitigate risk of motion sickness and nausea and provides a relaxing, nonfrightening, age-appropriate, interactive, and immersive environment. The VR software was used in conjunction with the Oculus Rift VR headset, which provides an immersive, 3D experience in which the user can explore a virtual world by moving their head in all directions. For this pilot, KindVR developed an underwater world called Aqua in which participants can explore underwater objects as well as interact with underwater animals (Figure 1). Participants can look for treasure and feed the animals, while still being able to see the sunny surface of the water. Aqua was chosen as the initial environment to test based on prior feedback from children and patients. The 15-minute session time was somewhat arbitrary, as there is no known minimum time to achieve distraction or immersion and no maximum time to reach exhaustion or saturation.[18] Additional time was required to prepare the device as well as clean the device after use.

2.4 | VR study implementation

Staff were trained on the utilization of the VR headset and Aqua software as well as how to ensure cleanliness of the headset before and after each VR session. After patient identification, the pilot was introduced to the patient and family (if less than 18 years of age) and

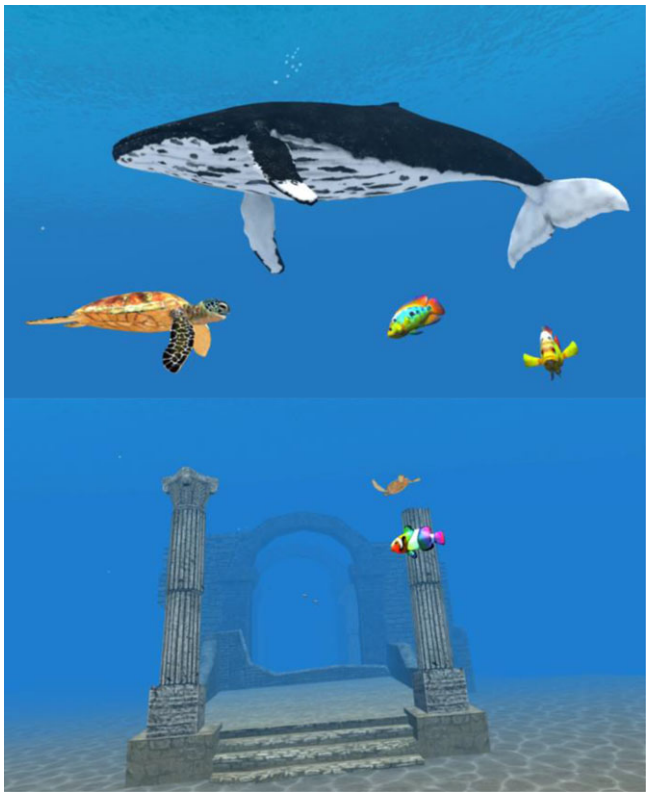

FIGURE 1 Example of underwater imagery during KindVR Aqua VR session

verbal assent and consent obtained. We provided easy-to-read and pictorial instructions to the patient and family on how to utilize the VR headset, in addition to direct explanation of the device (Supporting Information Figure S3). Staff or volunteers supervised the VR session and could help direct patients during the session as needed. Patient demographic information was collected including age, sex, underlying hemoglobin variant, and day of hospitalization when the VR session was administered. We subsequently recorded whether patients had frequent admissions for pain (i.e., ≥2 admissions on average annually over the previous two years) or infrequent admissions (i.e., less than stated above).

2.5 | Data analysis

The administered simulator sickness questionnaire and satisfaction survey were based on a 1–10 Likert scale, with the satisfaction survey used to determine how immersive the Aqua environment felt for the patient, as well as how comfortable and enjoyable the experience was (Supporting Information Figure S3). The APPT was utilized to measure intensity of pain based on a 0–10 word graphic rating scale, location of pain determined based on circling affected body parts, and qualitative assessment of pain domains including affective, evaluative, sensory, and temporal qualities based on the number of descriptors in each of these pain domains circled by the patient (Supporting Information Figure S2).[37] Values collected for the simulator sickness questionnaire and APPT pre- and post-VR session were analyzed using StataCorp 2015 (*Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP). Data were initially determined to be normally or nonnormally distributed based on skewness and kurtosis and histogram plots. Due to pain and survey data being nonnormally distributed, two-tailed Wilcoxon signed-rank testing was performed for nonparametric statistical significance. Median and interquartile range (IQR) were reported based on the data being nonparametric. A descriptive analysis was performed based on the results of the satisfaction survey.

TABLE 1 Basic demographic data of 30 enrolled patients

Number of patients (female; %)	30 (21; 70%)
Median age (IQR; years)	16.0 (13.3, 20.0)
Race (%)	28 African American (93%)
	2 other (7%)
Insurance (%)	21 state (70%); 9 private (30%)
Hemoglobin variant (%)	21 Hb SS (70%); 5 Hb SC (17%)
	4 S/β_+-thalassemia (13%)
Median hospitalization day when VR administered (IQR)	1 (0, 3)
Frequent pain episodes (% within each hemoglobin variant)[a]	16 Hb SS (76%); 4 Hb SC (80%); 0S/β_+-thalassemia (0%)

[a]Frequent defined as ≥2 hospitalizations for pain annually averaged over the two years prior to study enrollment.
IQR, interquartile range.

3 | RESULTS

Of the 30 enrolled patients, 21 were female with a median age of 16 years, with most patients having hemoglobin SS disease (Table 1). Twenty of the 30 enrolled patients had frequent hospital admission for pain, defined as an average of ≥2 admissions annually over the two years prior to study enrollment. No patient was admitted as his or her first hospitalization. Patients were enrolled in a sequential fashion until 30 patients were enrolled; two patients refused participation in the study, while one initially consented and then refused the study. A picture of a patient with SCD undergoing the VR session is included in Figure 2, and a video link to the project can be found at http://www.childrenshospitaloakland.org/main/videos-podcasts/153.aspx. Informed consent was obtained and properly documented for the included patient.

3.1 | Feasibility

Providing the 15-minute VR session in the hospital by trained staff was feasible, with patients being enrolled soon after admission and no patient being unable to be enrolled prior to discharge (Table 1). No patient reported any sign or symptom of simulator sickness (Table 2); there was no statistical change in any measure of simulator sickness pre- and post-VR. In addition, VR appeared acceptable (Table 3). The Aqua VR software appeared to allow for near-total immersion and thus pain distraction. Both the Aqua VR software and Oculus Rift headset

FIGURE 2 Patient with SCD undergoing a VR session

TABLE 2 Results of simulator sickness questionnaire pre- and post-VR sessions[a]

	Pre-VR	Post-VR	P[b]
Does your head hurt?	2.0 (1.0, 6.0)	1.5 (1.0, 5.0)	NS
Do your eyes hurt?	1.0 (1.0, 1.9)	1.0 (1.0, 1.4)	NS
Do you have an upset stomach?	2.0 (1.0, 5.0)	1.0 (1.0, 5.0)	NS
Do you feel dizzy?	2.0 (1.0, 5.0)	1.5 (1.0, 3.0)	NS

Abbreviations: NS, not significant (i.e., $P > 0.05$); VR, virtual reality.
[a]Median (interquartile range), (1 not at all, 5 somewhat, 10 a lot), adapted from Hoeft et al.[36]
[b]Due to nonnormally distributed data, *P* value calculated by the Wilcoxon signed-rank test (see the text).

were comfortable. Patients had a strong desire to use VR again when in pain. We also collected descriptive data from the enrolled patients: all 30 subjects wanted KindVR Aqua available again to them for future hospital visits while 29 subjects wanted it available at home for pain relief and for other children with SCD (1 participant answered "I don't know" to these two questions). Almost all additional comments regarding the experience were positive and included: "the game was very fun"; "this was a great experience"; "it really relaxed me…it was a beautiful experience"; "the more immersed in Aqua I felt, the less my pain affected me." In regard to future directions, the patients requested additional levels in Aqua, more interactions within Aqua, and more time to use the product. We surveyed which additional VR worlds the patients would like, and the most requested included outer space, jungle, beach, a dream world, and a candy land.

3.2 | APPT results

Patients had significant improvement in all aspects of the APPT after the 15-minute VR session (Table 4). Median pain intensity decreased from 7.3 (IQR 6.1, 8.8) pre-VR to 5.8 (4.7, 7.9) post-VR ($P < 0.001$). The median number of affected body areas decreased from 3.0 (2.0, 7.8) pre-VR to 2.0 (0, 4.8) post-VR ($P < 0.001$). The median percentage of all qualitative measures (adjectives circled out of a total 67 descriptors) as well as individual qualitative pain domains was statistically decreased. Specifically, the median percentage of all qualitative measures decreased from

TABLE 3 Results of VR satisfaction Likert survey

	Median (IQR)[a]
Presence/experience	
1. How much did you feel like you were inside the virtual world? (1 not at all, 10 completely)	10 (8.5, 10)
2. How aware of the real world (e.g., hospital setting) were you? (1 not at all, 10 completely)	5.0 (1.5, 5.0)
3. How did it feel to use the touchpad/controller to shoot bubbles at the fish in Aqua? (1 not difficult at all, 10 extremely difficult)	1.0 (1.0, 1.0)
4. How real did Aqua feel to you? (1 not real at all, 10 completely real)	9.2 (6.0, 10)
5. How much fun did you have while playing Aqua? (1 no fun, 10 extremely fun)	10 (9.6, 10)
6. How much time did you spend thinking about your pain while playing Aqua? (1 none of the time, 10 all of the time)	2.5 (1.0, 5.0)
Comfort/enjoyment	
7. Playing Aqua was comfortable (1 disagree, 10 agree)	10 (10, 10)
8. The headset was comfortable (1 disagree, 10 agree)	10 (8.6, 10)
9. I would play Aqua again when I am in pain (1 disagree, 10 agree)	10 (10, 10)
10. Playing Aqua made me feel better about my hospital stay (1 disagree, 10 agree)	10 (8.0, 10)
11. Playing Aqua made me feel better about my pain (1 disagree, 10 agree)	9.0 (6.6, 10)

Abbreviation: IQR, interquartile range.
[a]For questions 3 and 6, a lower score signified a better result; for question 2, neither a low or high score was ideal, as low would indicate too much dissociation and high a lack of immersion; for the rest of the questions, a high score signified a better result.

TABLE 4 Results of APPT pre- and post-VR sessions

	Pre-VR	Post-VR	P[a]
Pain intensity (1–10) (median [IQR])	7.3 (6.1, 8.8)	5.8 (4.7, 7.9)	<0.001
Number of affected areas (median [IQR])	3.0 (2.0, 7.8)	2.0 (0, 4.8)	<0.001
Total qualitative measures (% median [IQR])[b]	20.1 (12.7, 32.1)	12.7 (4.9, 25.0)	<0.001
Sensory (% median [IQR])[b]	18.9 (10.8, 27.0)	13.5 (3.4, 21.6)	<0.001
Affective (% median [IQR])[b]	9.1 (2.3, 27.3)	0 (0, 18.2)	<0.001
Evaluative (% median [IQR])[b]	37.5 (25.0, 50.0)	25.0 (12.5, 37.5)	0.001
Temporal (% median [IQR])[b]	18.2 (9.1, 36.3)	13.6 (9.1, 25.0)	0.01

Abbreviations: IQR, interquartile range; VR, virtual reality.
[a]Due to nonnormally distributed data, *P* value was calculated by the Wilcoxon signed-rank test (see the text).
[b]Measured based on the percentage of descriptors circled within each qualitative category out of a total of 67 descriptors.

20.1% (IQR 12.7%, 32.1%) pre-VR to 12.7% (IQR 4.9%, 25.0%) post-VR ($P < 0.001$).

4 | DISCUSSION

Utilization of immersive VR technology was feasible for a cohort of patients with SCD admitted for vaso-occlusive pain. We were able to train staff who could then provide instruction and supervise administration of the VR session without issues. There were no negative side effects of the VR sessions, and all subjects desired to use VR again in the future with painful episodes. The KindVR Aqua software was able to provide distraction through total immersion, though the patients were still able to retain a sense of their actual surroundings, implying the session was not negatively dissociative. One 15-minute VR session had benefit in subjective multidimensional self-assessment of pain in terms of pain intensity, body areas affected, and qualitative measures of pain in all studied pain domains. As the first study utilizing immersive VR therapy for vaso-occlusive pain in pediatric patients with SCD, this provides an additional, potentially effective complementary therapy to manage pain for hospitalized patients.

It has been reported previously that most frequently hospitalized pediatric patients with SCD are largely adolescent females, as was seen in our patient cohort (Table 1).[14] Females have also been reported to have significantly higher pain intensity in addition to the number of body areas affected in comparison with their male counterparts, with older patients reporting more body areas affected and more qualitative descriptors in comparison with younger patients.[38] Exploration into the nature of SCD-related pain has found that the pain cannot be described simply and instead patients characterize it as "unimaginable, agonizing, continuous, inescapable and limitless pain."[39] For this reason, the APPT is a more global measure of pain in patients with SCD than the visual analog scale.[37] Studies attempting to define clinically meaningful pain reduction are limited. Generally, a 30%–50% decrement in pain scores is considered clinically meaningful, though it cannot be generalized to the individual patient.[40] In studies in both acute, postoperative pain and chronic pain, a decrement in the visual analog scale of 20% corresponded to minimal improvement, while a 30%–35% decrement corresponded to much improvement.[41,42] Myrvik et al[43] note in a small pediatric SCD cohort that a decrement in the visual analog scale of 0.97 cm and 0.9 in the numeric rating scale was the minimum clinically significant improvement. In our study, the median decrease in the visual analog scale was 20%; however, the median decline in body areas affected was 33% and qualitative measures of pain declined by a median 37%. Given that qualitative measures of pain may more accurately reflect the global pain experience for SCD patients with VOE, the median reduction of body areas affected and qualitative measures of pain does appear clinically meaningful, at least immediately after the completion of the VR session. On the other hand, it can be argued that the decrease in the visual analog scale represented minimal improvement, though it is difficult to extrapolate from patients with acute and chronic pain different from the SCD VOE experience. In addition, because the data were nonnormally distributed, the reductions noted were based on nonparametric testing of significance. Effect size (i.e., absolute median difference pre- and post-VR) remains statistically relevant regarding benefit of the intervention for the entire patient cohort, though is not generalizable for each individual patient due to the nonnormal distribution.

A systematic review by Malloy and Milling[29] regarding effectiveness of VR in pain reduction reported that there are limited data, but these data show that VR distraction is effective in burn injuries, with immersive VR being more efficacious. Additional studies after this review in 2010 have shown similar results, as well as reporting the benefit of ongoing immersive VR sessions. In a crossover design, Schmitt et al[27] studied the benefit of immersive VR in pediatric burn patients utilizing VR during rehabilitation and found a meaningful reduction in pain ratings with the addition of VR, which was sustained with repeated usage. Faber et al[28] similarly showed a statistical reduction in pain scores for pediatric and adult burn patients with daily wound dressing changes that persisted with daily utilization of VR therapy. None of these studies reported any notable side effects, especially simulator sickness. VR therapy as a distraction for pediatric patients receiving chemotherapy has also appeared beneficial in a small cohort, with 82% of patients reporting benefit and all wanting to receiving the intervention again.[25] Similarly, a small cohort of pediatric patients who utilized VR during intravenous line placement reported improved pain management without side effects.[24]

Data regarding utilization of complementary therapies in pediatric patients with SCD are also quite limited. Dobson and Byrne[15] reported benefit of CBT in a cohort of 20 patients; two months after guided imagery training, use of analgesics and self-reported pain intensity decreased. On the other hand, Barakat et al[44] showed no benefit of a family-based CBT pain management intervention in adolescent patients with SCD, though the study was underpowered to address efficacy. A randomized controlled study by Lemanek et al[45] regarding utilization of home-based massage in pediatric patients with SCD reported significant improvement in depression, anxiety, and pain, though no change in health service utilization rates. In a review of nonpharmacological approaches to pain in adult and pediatric patients with SCD, Williams and Tanabe[46] note a significant reduction in pain with CBT in only a subset of trials. Massage and acupuncture generally reduced pain scores, though not always to statistically significant levels.[46] Further study is required to determine if complementary therapies such as VR can be systematically utilized to improve the pain experience in SCD VOE.

Our study was limited as the primary aim was feasibility rather than efficacy. Although there was a potentially clinically meaningful reduction in body areas affected and qualitative measures of pain as assessed by the APPT, this assessment was limited to the immediate time period after the VR session and was not subsequently assessed. Additionally, the study did not assess the benefit of daily VR sessions in terms of impact on opioid usage or length of hospitalization, which merits further future study.[27,28] Past utilization of VR technology has been limited by expense as well as the cumbersome nature of the VR products. Availability of inexpensive and portable VR headsets such as the Oculus Rift allows for much wider dissemination of this complementary therapy.[47] Child-life specialists play an important role in the management of pediatric pain, and child-life specialists should be

enlisted to help administer VR sessions with the assistance of hospital volunteers.[48] In addition to the 15 minutes for the VR session, preparation time and cleaning of the equipment takes approximately 10 minutes. Efficacy studies are needed to further assess the potential benefit of VR. There is also the potential to develop VR systems which can provide biofeedback and thus provide CBT as well as distraction. Our study highlights the feasibility of inpatient VR for pediatric patients with SCD as a first step to further utilization and study.

CONFLICTS OF INTEREST

S.R. is the CEO of KindVR. He participated in training the other authors on use of the KindVR software in conjunction with the Oculus Rift headset and was involved with data collection. He did not participate in data analysis or manuscript writing, though he did have an opportunity to review and suggest changes to the final manuscript as submitted. The other authors have no financial or other conflicts of interest relevant to this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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