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A Randomized Feasibility Trial of a Novel, Integrative, and Intensive Virtual Rehabilitation Program for Service Members Post-Acquired Brain Injury.

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A Randomized Feasibility Trial of a Novel, Integrative, and Intensive Virtual Rehabilitation Program for Service Members Post-Acquired Brain Injury

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ABSTRACT

Introduction

Acquired Brain Injury, whether resulting from Traumatic brain injury (TBI) or Cerebral Vascular Accident (CVA), represent major health concerns for the Department of Defense and the nation. TBI has been referred to as the "signature" injury of recent U.S. military conflicts in Iraq and Afghanistan – affecting approximately 380,000 service members from 2000 to 2017; whereas CVA has been estimated to effect 795,000 individuals each year in the United States. TBI and CVA often present with similar motor, cognitive, and emotional deficits; therefore the treatment interventions for both often overlap. The Defense Health Agency and Veterans Health Administration would benefit from enhanced rehabilitation solutions to treat deficits resulting from acquired brain injuries (ABI), including both TBI and CVA. The purpose of this study was to evaluate the feasibility of implementing a novel, integrative, and intensive virtual rehabilitation system for treating symptoms of ABI in an outpatient clinic. The secondary aim was to evaluate the system's clinical effectiveness.

Materials and Methods

Military healthcare beneficiaries with ABI diagnoses completed a 6-week randomized feasibility study of the Bright-Brainer Virtual Rehabilitation (BBVR) system in an outpatient military hospital clinic. Twenty-six candidates were screened, consented and randomized, 21 of whom completed the study. The BBVR system is an experimental adjunct ABI therapy program which utilizes virtual reality and repetitive bilateral upper extremity training. Four self-report questionnaires measured participant and provider acceptance of the system. Seven clinical outcomes included the Fugl-Meyer Assessment of Upper Extremity, Box and Blocks Test, Jebsen-Taylor Hand Function Test, Automated Neuropsychological Assessment Metrics, Neurobehavioral Symptom Inventory, Quick Inventory of Depressive Symptomatology-Self-Report, and Post Traumatic Stress Disorder Checklist- Civilian Version. The statistical analyses used bootstrapping, non-parametric statistics, and multilevel/hierarchical modeling as appropriate. This research was approved by the Walter Reed National Military Medical Center and Uniformed Services University of the Health Sciences Institutional Review Boards.

Results

All of the participants and providers reported moderate to high levels of utility, ease of use and satisfaction with the BBVR system ($x\bar{x} = 73$–86%). Adjunct therapy with the BBVR system trended towards statistical significance for the measure of cognitive function (ANAM [$x\bar{x} = -1.07$, 95% CI -2.27 to 0.13, $p = 0.074$]); however, none of the other effects approached significance.

Conclusion

This research provides evidence for the feasibility of implementing the BBVR system into an outpatient military setting for treatment of ABI symptoms. It is believed these data justify conducting a larger, randomized trial of the clinical effectiveness of the BBVR system.

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INTRODUCTION

Frequent use of improvised explosive devices (IEDs) in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) resulted in traumatic brain injury (TBI) being called the signature injury of recent conflicts.[1] According to Department of Defense (DoD) reports, 379,519 service members received a TBI diagnosis from 2000 to 2017.[2] Traumatic brain injuries are a subtype of acquired brain injury (ABI), which refers to any post-natal brain injury.[3] Acquired brain injuries commonly present with symptoms of cognitive and motor impairment, and emotional instability that may persist for years and affect performance of activities of daily living (ADLs).[4,5] Though survival rates of mild TBI (mTBI) are high, the resulting diminished quality of life calls for a greater focus on long-term TBI rehabilitative care.[6]

Another category of ABI, Cerebral Vascular Accident (CVA), often presents with similar impairments, such as diminished memory, upper extremity weakness and spasms, and depression.[7–9] Moreover, those who have experienced a TBI are also at higher risk of CVA than those who have not.[10,11] The majority of neurological recovery after TBI and CVA typically occurs within the first 6 months of injury, but training factors such as intensity, repetition, duration, patient motivation, and patient engagement may impact long-term treatment effectiveness on individuals in the chronic phase.[12–16]

Traditional rehabilitation protocols for individual's post-ABI, such as proprioceptive neuromuscular facilitation (PNF), are widely recognized but underutilized by therapists.[17] Additionally, hands-on interventions, while well known, have limited evidence supporting their success with chronic ABI rehabilitation.[18] With technological advancements it may be possible to link the traditional therapies with progressive opportunities, while also increasing patient engagement and decreasing provider burden.

One method of post-ABI rehabilitation with growing clinical acceptance is virtual reality (VR). Virtual reality is defined as a synthetic world that responds in real time to changes in user input, creating a constantly-engaging environment in which users participate.[19] Virtual rehabilitation utilizes VR in a variety of clinically relevant domains,[20] and offers a unique platform for ABI rehabilitation by engaging patients in appropriately challenging tasks.[21] It provides the needed intensity of care, can unify treatment in an integrative rehabilitation, and can involve bimanual interactions engaging both hemispheres.[22] A review of studies evaluating improvements in cognitive domains (e.g., executive function) indicates that computer-based cognitive rehabilitation programs which are tailored to the participant's abilities often produce greater results compared to non-personalized cognitive rehabilitation computer programs.[23]

BrightBrainer Virtual Rehabilitation System

The BrightBrainer Virtual Rehabilitation (BBVR) program is a computer-based VR platform that utilizes real-time bimanual interaction for the purpose of increasing cognitive engagement compared to simple mouse, or single finger touch interaction. Bilateral training has been found to promote improved motor functioning for people who have experienced ABI, above and beyond unilateral training.[24,25] This system facilitates split attention training (focusing), task sequencing (alternating actions between arms), hand-eye coordination, and dual tasking through use of simultaneous cognitive and motor challenges. Though the BBVR system was originally developed for geriatric patients with CVA, the use of adaptable games, bimanual tasks, and repetition may make it translatable as a tool for ABI treatment in a military population.[26]

While literature on VR therapy post-ABI is abundant, many of the systems either focus only on rehabilitation of one aspect of post-ABI deficits,[27] or are too physically large to implement in most clinics.[28] The BBVR system is unique because it combines cognitive and physical training in a compact, adaptive VR system which can be implemented largely unobtrusively into clinical space. This pilot study implemented the BBVR system within a Military Treatment Facility's (MTF) outpatient occupational therapy clinic as a 6-week intervention for participants with ABI. The primary aim was to evaluate the feasibility of integrating the BBVR system into the clinic for both 1-on-1 provider-participant interaction and concurrent treatment in which 1 provider oversees 2 participants at a time. The 3 secondary aims were: (1) to evaluate the preliminary clinical effectiveness of the BBVR system in terms of motor function, cognitive performance, and behavioral/emotional symptoms; (2) to evaluate the dose-response effect of the BBVR system; and (3) to evaluate the correlation between participant-level BBVR game performance and longitudinal change in clinical outcomes.

METHODS

Subjects

Potential candidates were identified through clinician referral. Eligible participants were defined as adult (≥18 years of age) military healthcare beneficiaries ABI endorsing symptoms of cognitive, emotional, or physical dysfunction. Presence of ABI diagnosis was confirmed through the participant's electronic health records upon consent. Exclusion criteria were: (i) inability to comprehend written consent documents, (ii) visual impairment that might prevent system use, (iii) insufficient dexterity to operate BBVR system controllers, and (iv) concurrent enrollment in another cognitive rehabilitation study. This study was approved to consent up to 30 participants and aimed to complete at least 20 (accounting for attrition), which was determined via clinical judgement to be a sufficient number for assessing feasibility. All study procedures were completed in an outpatient occupational therapy clinic. Institutional review board approval was granted through the Walter Reed National Military Medical Center and Uniformed Services University of the Health Sciences.

Outcomes

Four self-report questionnaires measured participant and provider acceptance of the BBVR program. (Appendices 1–4)[29,30] Two of these measures were completed by the participant, and the remaining 2 by the provider. These questionnaires were used as the primary outcome measures in order to assess the feasibility of using this system in an outpatient clinic setting. Since the providers were involved in all assessment time points, including initial and final assessments, blinding was not possible.

Seven clinical outcomes were used to assess cognitive, behavioral, and motor functioning. Three of these assessments measured upper-extremity motor functioning: the Fugl-Meyer Assessment of Upper Extremity (FMA-UE),[31] Box and Blocks Test (BBT),[32] and Jebsen-Taylor Hand Function Test (JHFT).[33] Cognitive function was measured using the Automated Neuropsychological Assessment Metrics (ANAM).[34] Three behavioral self-report questionnaires were used: the Neurobehavioral Symptom Inventory (NSI),[35] the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR),[36] and the Post Traumatic Stress Disorder (PTSD) Checklist-Civilian Version (PCL-C).[37] A more detailed description of each of the outcomes is featured in Figure S1.

Design

Consented participants were sequentially randomized at a 1:1 ratio into *immediate therapy* or *delayed therapy* groups. Group assignment was generated by a third party prior to the start of research, sealed in envelopes labeled by participant number, and not opened by the researchers until the time of consent. Participants randomized to the immediate therapy group began using the BBVR system at week 0 and continued until week 6, while those randomized to the delayed therapy group began at week 3 and continued until week 9. Participants continued all standard-of-care therapies that they were engaged in pre-consent throughout the duration of their participation and any changes in treatment were tracked by the researchers throughout participation.

The BBVR desktop system consisted of a computer and monitor, wireless headphones, a remote server, and bimanual game controllers ("pendants") that measured the position of the participant's hands in reference to the controller base station, which sat between the participant and the computer. (Figure S2) To ensure safety of the participants, given that dizziness and decreased balance are commonly associated with ABI, games were completed from a seated position. Furthermore, the controllers were wired to a base station on the desk, adjacent to the display. Training while standing would increase the likelihood of entanglement and interference from the controller tethers.

All participants started treatment with access to 6 games (Breakout, Card Island, Kite, Pick & Place, Treasure Hunt, and Towers), which they played uni-manually (i.e., using only 1 arm) the first week to get accustomed to the system. Games trained various motor and cognitive deficits associated with ABI. For example, Card Island tested participants working memory by presenting them with a set of face-down playing cards that they had to flip over 2 at a time to try and match up pictures on the other side. In week 2, participants began working bi-manually and duration and intensity of treatment increased incrementally over time. (Figure S3) Further, the system automatically increased or decreased game difficulty throughout the session based on performance. After 3 weeks of active treatment, participants were scheduled concurrently (i.e., 2 participants at 1 time) to work individually on 2 BBVR systems that were set-up back to back.[38] A summary of the frequency of assessments is featured in Figure S4.

Statistics

The evaluation of clinical effectiveness of the BBVR system on the NSI, QIDS-SR, and PCL-C was conducted using a parallel study design, comparing the 0-to-3-week longitudinal change in outcomes among the immediate therapy group with that of the delayed therapy group. The effect estimate was computed as the difference in the group-level mean longitudinal change from week 0 to week 3 between groups. The corresponding confidence intervals around the 3-week effect estimates were estimated using parametric bootstrapping and false coverage-statement rate adjustment,[39] while the *p*-values were estimated using 2-sample bootstrapped Kolmogorov-Smirnov tests (a non-parametric analog of Student's *t*-test, appropriate for comparing distributions of discrete, ordinal values)[40] and limiting the false discovery rate to 5% among the seven clinical outcomes included in the effectiveness analysis.[41]

The evaluation of the clinical effectiveness of the BBVR system on the ANAM composite score, BBT, JHFT, and FMA-UE was conducted using a crossover study design among only those randomized to the delayed therapy group, comparing the 3-to-9-week longitudinal change in outcomes with the 0-to-3-week longitudinal change in outcomes. For each of these outcomes, the effect estimate was computed as the participant-level difference between the "observed" (linearly interpolated at week 6 from the 3-to-9-week longitudinal change) and "expected" (linearly extrapolated at week 6 from the 0-to-3-week longitudinal change) values. (Note that the values were interpolated/extrapolated at week 6 so that the effect estimate would be in terms of a 3-week effect, comparable to the 3-week effect estimates of the NSI, QIDS-SR, and PCL-C.) The corresponding confidence intervals around the 3-week effect estimates were computed using parametric bootstrapping and false coverage-statement rate adjustment, while the *p*-values were estimated using 1-sample Wilcoxon rank-sum tests of the (interpolated/extrapolated)[42] within-participant differences in outcome values and limiting the false discovery rate to 5% among the 7 clinical outcomes included in the effectiveness analysis.[39] Since the JHFT is relevant only for CVA patients (of whom two CVA patients

TABLE I. Age, Gender, and Diagnoses by Group

Demographics			
	Immediate Therapy (n = 11)	Delayed Therapy (n = 10)	Total (n = 21)
Age (avg years)	42 (SD = 12.01)	39 (SD = 4.93)	41 (SD = 13.38)
Female	18%	40%	29%
CVA	18%	20%	19%
TBI	64%	60%	62%
CVA + TBI	18%	20%	19%

had sufficient data to be included in the analysis), only 2 participants were analyzed, so its corresponding point estimate and confidence interval should not be considered robust or reliable.

The evaluation of the dose-response effect of the BBVR system on the NSI, QIDS-SR, and PCL-C was conducted using a parallel study design, comparing the 0-to-6-week longitudinal change in outcomes among the immediate therapy group with that of the delayed therapy group. For each of these outcomes, the effect estimate was computed as the difference in group-level mean longitudinal change from week 0 to week 6 between the immediate therapy and delayed therapy groups. The corresponding confidence intervals around the dose-response effect estimates were computed using parametric bootstrapping and false coverage-statement rate adjustment, while the p-values were estimated using 2-sample bootstrapped Kolmogorov-Smirnov tests and limiting the false discovery rate to 5% among the three dose-response effects. Note that the difference in group-level means isolates the 6- vs 3-week dose-response effect of the BBVR system by itself, subtracting out the effects of usual care and natural convalescence.

The correlations between participant-level BBVR game performance and longitudinal changes in outcomes (7 clinical outcomes) were evaluated using a 3-step procedure: first, the participant-level longitudinal trend in game performance was estimated for every game within a multilevel/hierarchical modeling framework using a 3-level generalized linear mixed model (GLMM) with participant- and game-level random intercepts and slopes and an identity link function; second, each participant's "observed" 3-week change in clinical outcomes concurrent with the BBVR system was computed, using linear interpolation for the clinical endpoints that were not captured every 3 weeks; and third, Spearman's rank correlation coefficient ρ was used to measure the monotonic association between participant-level game performance and longitudinal change in clinical outcomes. The corresponding confidence intervals CI_ρ were computed analytically per $CI_\rho = \tanh(\operatorname{arctanh}(\rho) \pm 2*(n-3)^{-1/2})$, where n is the number of observations. Spearman's rank correlation was preferred over Pearson's correlation, because the latter assumes linearity while the former has the more relaxed assumption of monotonicity. Note that the correlation estimates did not account for the statistical error associated with the estimated longitudinal trend in game performance, the measurement error of the interpolated-observed 3-week change in clinical outcomes, nor the multiplicity effect of multiple hypothesis testing; so, the confidence intervals CI_ρ are likely overly liberal – that is, the confidence intervals around the correlation coefficient estimates are likely unrealistically tight.[42]

Finally, we used the clinical effectiveness estimates and confidence intervals to conduct post-hoc estimates of minimum sufficient sample sizes to achieve 80% power in order to help inform future randomized controlled trials. This was conducted by using the mean and standard deviations of the estimated effects as the corresponding mean and standard error of a 2-sided t-distributed effect, and then solving for the sample size sufficient to achieve 80% power.

RESULTS

Demographics and clinical characteristics are reported in Table I. A majority of participants were male (71%) and had suffered a TBI (versus a CVA or TBI + CVA; 62%). The largest portion of participants had experienced a mild TBI (33%), with 28% of participants diagnosed with a more severe TBI, 19% having suffered a CVA, and 19% reporting both a TBI and CVA. The most commonly report cause of injury was motor vehicle accident (33%). Blast injuries during deployment accounted for 14% of injuries. The remaining causes of injury were sports-related (14%), unspecified (19%), and other (19%; including carotid artery dissection, sudden cardiac death, fragment wound to the head, and hemorrhage following a fall). Time since ABI varied greatly, with the most recent being 6 weeks prior to participation, and the most distal having occurred over 15 years prior ($x\bar{x}$ = 66 months). Participant's endorsement and electronic medical record review at baseline indicated that 24% of participants suffered from current comorbid psychological symptoms, such as depression and anxiety (including PTSD). Additionally, 38% of participants expressed persisted neurobehavioral symptoms, such as dizziness, poor coordination, light sensitivity, etc., and 42% of participants experienced regular headaches. As expected, a majority of participants (67%) endorsed cognitive deficits at baseline, including slowed processing speeds, speech difficulties, and post-traumatic amnesia.

TABLE II. Estimated Clinical Effectiveness and Dose Response of BBVR

Estimated Clinical Effectiveness			
Clinical Outcome	Design	Three-Week Effect (95% CI)	*p*-value
PCL-C	Parallel	0.86 (−5.11 to 6.83)	0.802
QIDS-SR	Parallel	0.10 (−2.19 to 2.40)	0.317
NSI	Parallel	1.24 (−5.99 to 8.48)	0.396
ANAM	Cross-over	−1.07 (−2.27 to 0.13)	0.074
BBT	Cross-over	−3.99 (−13.14 to 5.17)	0.461
JHFT	Cross-over	−31.61 (−65.04 to 1.82)	0.500
FMA-UE	Cross-over	−0.56 (−4.18 to 3.06)	0.675
PCL-C w/o CVA	Parallel	0.07 (−7.26 to 7.4)	0.649
QIDS-SR w/o CVA	Parallel	0.84 (−1.8 to 3.48)	0.268
NSI w/o CVA	Parallel	3.77 (−4.41 to 11.95)	0.124
ANAM w/o CVA	Cross-over	−0.56 (−1.52 to 0.4)	0.297
BBT w/o CVA	Cross-over	−3.36 (−14.83 to 8.11)	0.688
FMA-UE w/o CVA	Cross-over	0.36 (−3.48 to 4.19)	1.000
Clinical Outcome	Design	Six- vs three-Week Effect (95% CI)	*p*-value
PCL-C	Parallel	0.83 (−3.28 to 4.93)	0.943
QIDS-SR	Parallel	0.11 (−1.47 to 1.7)	0.602
NSI	Parallel	1.29 (−3.62 to 6.2)	0.877

Note that the 3-week effect estimates and confidence intervals (CI) were estimated using parametric bootstrapping with false coverage-statement rate adjustment; *p*-values were estimated using one-sample Wilcoxon rank-sum tests of the within-patient difference (interpolated) for crossover designs, and two-sample bootstrapped Kolmogorov-Smirnov tests of the between-group differences for parallel designs, limiting the false discovery rate at 5% among the seven outcomes.

The dose-response effect estimates and confidence intervals (CI) were estimated using parametric bootstrapping; *p*-values were estimated using two-sample bootstrapped Kolmogorov-Smirnov tests of the between-dose differences. Post Traumatic Stress Disorder (PTSD) Checklist-Civilian Version (PCL-C), Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR), Neurobehavioral Symptom Inventory (NSI), Automated Neuropsychological Assessment Metrics (ANAM), Box and Blocks Test (BBT), Jebsen-Taylor Hand Function Test (JHFT), Fugl-Meyer Assessment of Upper Extremity (FMA-UE).

Participants expressed high system enjoyment and usability through the Participant Feedback Form and USE Questionnaire at both 3 ($x\bar{x}$ = 80% and $x\bar{x}$ = 73% respectively) and 6 weeks ($x\bar{x}$ = 81% and $x\bar{x}$ = 79% respectively) of active treatment with the BBVR system. When reporting positive aspects of BBVR, participants commonly stated the games were fun, and that they perceived improvement in memory, strength, and concentration. A few participants expressed interest in continuing BBVR treatment upon completion of the research. Additionally, the provider who ran the treatment sessions reported that approximately half of the participants stated that they would like to utilize the system if it were available for home-based treatment.

Similar reports were demonstrated through the provider (OT/COTA) Feedback Form and Computer System Usability Questionnaire at 3 ($x\bar{x}$ = 83%, $x\bar{x}$ = 86%) and 6 weeks of active treatment ($x\bar{x}$ = 80, $x\bar{x}$ = 84%). Provider reports stated the activities were engaging and appropriately challenging for the participants. In addition, providers indicated that the system allowed 2 participants to receive therapy simultaneously.

While the overall feedback about the BBVR system was positive, some patients did report headaches, which they associated with the brightness of the computer screen. This was relieved in most cases through the use of tinted glasses, although 1 patient withdrew from the study because of headaches. All other study withdrawals were due to non-research-related circumstances. (Figure S5) In addition, most participants expressed dissatisfaction with the controllers, saying that the magnetic tracking system was easily disrupted by the presence of other nearby magnetic items.[43]

Regarding clinical effectiveness, adjunct therapy with the BBVR system was associated with positive (i.e., increase) in the 3-week effect estimates for NSI ($x\bar{x}$ = 1.24, 95% CI −5.99 to 8.48, p = 0.396), QIDS-SR ($x\bar{x}$ = 0.10, 95% CI −2.19 to 2.4, p = 0.317), and PCL-C ($x\bar{x}$ = 0.86, 95% CI −5.11 to 6.83, p = 0.802), as well as negative (i.e., decrease) 3-week effect estimates for ANAM ($x\bar{x}$ = −1.07, 95% CI −2.27 to 0.13, p = 0.074), BBT ($x\bar{x}$ = −3.99, 95% CI −13.14 to 5.17, p = 0.461), JHFT ($x\bar{x}$ = −31.61, 95% CI −65.04 to 1.82, p = 0.500), and FMA-UE ($x\bar{x}$ = −0.56, 95% CI −4.18 to 3.06, p = 0.675), albeit none of these clinical effects reached statistical significance at 95% confidence ($p > 0.05$). These results are summarized in Table II. To determine if diagnosis played a role in clinic outcomes, the same analyses were ran excluding participants who had only experienced a CVA. Similar effects were found when participants with just CVA were removed from the analysis, with the notable difference being that, while ANAM scores still showed a negative 3-week effect estimate ($x\bar{x}$ = −0.56, 95% CI −1.52 to 0.40, p = 0.297), the effect was no longer approaching significance.

The 6- vs 3-week dose-response effect estimates were positive (i.e., increase) for NSI ($x\bar{x}$ = 0.83, 95% CI −3.28 to 4.93, p = 0.943), QIDS-SR ($x\bar{x}$ = 0.11, 95% CI −1.47

TABLE III. Spearman's Rank Correlation Estimates (95% Confidence Intervals) Between Participant-Level Average Daily Improvement in Game Performance and BBVR-Associated 3-Week Longitudinal Change in Clinical Outcomes

	Three-Week Clinical Change		
	Three-week effect on PCL	Three-week effect on QIDS	Three-week effect on NSI
Towers	0.595 (0.198 to 0.824)	0.043 (−0.415 to 0.484)	0.395 (−0.054 to 0.711)
Breakout	0.284 (−0.19 to 0.651)	0.023 (−0.432 to 0.468)	−0.055 (−0.483 to 0.394)
Treasure hunt	−0.063 (−0.499 to 0.398)	−0.251 (−0.63 to 0.224)	0.107 (−0.349 to 0.522)
Musical drums	0.306 (−0.215 to 0.691)	−0.268 (−0.68 to 0.273)	0.027 (−0.468 to 0.509)
Submarine rescue	0.534 (0.079 to 0.805)	−0.123 (−0.565 to 0.374)	−0.107 (−0.542 to 0.374)
Card island	−0.01 (−0.458 to 0.442)	−0.117 (−0.539 to 0.351)	−0.239 (−0.614 to 0.224)
Arm slalom	−0.004 (−0.478 to 0.472)	−0.234 (−0.638 to 0.271)	0.279 (−0.211 to 0.656)
Treasure xylophone	0.22 (−0.284 to 0.629)	−0.032 (−0.513 to 0.464)	0.212 (−0.292 to 0.624)
Pick and place	−0.296 (−0.658 to 0.178)	−0.119 (−0.54 to 0.35)	−0.186 (−0.578 to 0.276)
Kite	−0.163 (−0.571 to 0.31)	0.111 (−0.357 to 0.535)	−0.408 (−0.719 to 0.038)
Avalanche	−0.007 (−0.481 to 0.469)	0.471 (−0.024 to 0.78)	−0.001 (−0.476 to 0.474)
	Three-week effect on ANAM	Three-week effect on BBT	Three-week effect on FM
Towers	0.217 (−0.534 to 0.777)	0.12 (−0.649 to 0.768)	−0.131 (−0.739 to 0.595)
Breakout	−0.2 (−0.77 to 0.547)	0.615 (−0.176 to 0.923)	0.122 (−0.601 to 0.735)
Treasure hunt	−0.133 (−0.74 to 0.593)	−0.494 (−0.893 to 0.339)	−0.235 (−0.784 to 0.52)
Musical drums	0.733 (0.119 to 0.942)	0.036 (−0.695 to 0.731)	0.531 (−0.221 to 0.887)
Submarine rescue	0.25 (−0.509 to 0.79)	0.06 (−0.683 to 0.742)	0.583 (−0.148 to 0.902)
Card island	−0.75 (−0.946 to −0.155)	−0.181 (−0.792 to 0.612)	−0.026 (−0.687 to 0.659)
Arm slalom	0.183 (−0.559 to 0.762)	0.277 (−0.544 to 0.827)	−0.331 (−0.821 to 0.44)
Treasure xylophone	0.5 (−0.261 to 0.878)	0.265 (−0.553 to 0.823)	0.287 (−0.478 to 0.805)
Pick and place	0 (−0.673 to 0.673)	−0.374 (−0.858 to 0.464)	0.078 (−0.628 to 0.714)
Kite	0.15 (−0.582 to 0.748)	0.458 (−0.38 to 0.883)	−0.131 (−0.739 to 0.595)
Avalanche	0.317 (−0.453 to 0.816)	−0.024 (−0.725 to 0.702)	−0.461 (−0.866 to 0.307)

Correlations with JHFT could not be computed due to lack of data. Exact *p*-values could not be computed because of the presence of ties, and so they were omitted.

to 1.70, $p = 0.602$), and PCL-C ($x\bar{x} = 1.29$, 95% CI –3.62 to 6.20, $p = 0.877$), yet, again none of these effects were statistically significant ($p > 0.05$). Again, similar results were found when looking only at participant who had experienced a TBI (including TBI + CVA participants). The results of the dose-response analyses are summarized in Table II.

Due to insufficient data, correlations between game performance and longitudinal changes in JHFT could not be computed, so we report the pairwise correlations between the 11 games and remaining 6 clinical outcomes yielded 66 total correlation estimates. The results of the correlation analyses were mixed and inconsistent: some correlations were positive and others were negative, but without any consistent trend (i.e., correlation coefficient estimates with congruent signs across BBVR games) for any of the clinical outcomes. Among the 66 correlations computed, 4 were statistically significant; however, we choose not to emphasize their confidence intervals here, because they did not account for measurement error or multiple hypothesis testing, and thus are overly liberal. The results of the correlation analyses are summarized in Table III.

The post-hoc calculations of minimum sufficient sample sizes to achieve 80% power for each of the clinical outcomes are reported in Table IV. These estimates were based on reported effect size, using a 2-sided 1-sample *t*-test where the standard errors (*SE*) were derived such that $SE = (UL - \beta)/1.96$, where *UL* is the upper limit of the corresponding effect size's 95% confidence interval.[44]

To achieve 80% power in a parallel-design randomized controlled trial of the effectiveness of the BBVR system on the ANAM and JHFT, at least 10 participants should be enrolled

TABLE IV. Results of Post-hoc Calculation of Minimum Sufficient Sample Sizes to Achieve 80% Power, Based Effect Size Estimates of Clinical Effectiveness of the BrightBrainer Virtual Rehabilitation (BBVR) System, Using a Two-Sided, One-Sample *t*-Test of the Mean Effect Being Non-zero at 5% Significance

	Sample Size Estimate		
Outcome	Effect Size (β)	*SE*	*N*
NSI	1.24	3.7	144
QIDS-SR	0.1	1.2	2266
PCL-C	0.86	3.1	208
ANAM	−1.07	0.62	10
BBT	−3.99	4.7	26
JHFT	−31.6	17	10
FMA-UE	−0.56	1.9	186

The standard errors (*SE*) were derived from the effect sizes (β) and 95% confidence intervals in Table IV, such that $SE = (UL - \beta)/1.96$, where *UL* is the upper limit of the 95% confidence interval. Here, the minimum sufficient sample size *N* corresponds to the total sample size for randomization into both arms of a subsequent randomized clinical trial.

in total. The careful reader will notice that the minimum sufficient sample size in each arm for the ANAM (n = 10) is the same as that which was observed in the current study. The apparent discordance is the result of limiting the false discovery rate among the 7 clinical effectiveness analyses, while each of the post-hoc power analyses were conducted independently of the others.

DISCUSSION

Overall the provider and patient reports indicated that the system demonstrated high levels of technical usability and patient engagement. Participants expressed enjoyment in using the system, maintaining such reports from three to six weeks of treatment, and some noted that they believed the system would be a good resource for home-based therapy. Moreover, as providers and patients became more familiar with the technology, this study demonstrated the feasibility for providers to simultaneously supervise more than 1 patient at a time, improving clinic efficiency and access to care. This scheduling was possible when sessions were offset by 15 minutes, allowing for setup prior to the second participant's arrival.

While the overall effects on clinical outcomes using the BBVR system did not reach statistical significance, its use as an adjunct to traditional therapy showed effectiveness in improving upper extremity physical function on the JHFT. As JHFT is a timed test of ADLs, this is indicative of increased independence in daily life. Performance on other measures of physical functioning (i.e., BBT and FMA-UE), however showed some worsening, albeit not statistically significant. In addition, subjects also seemed to have an increase in their symptom reporting from pre- to post-BBVR treatment, just after completion of the 6-week active training period, as demonstrated by the NSI, QIDS-SR, and PCL-C, which may be due to increased awareness of their symptoms gained through participation in this research. While awareness of ABI-related deficits is generally considered important for neuropsychological rehabilitation, long-term follow-up would be required in order to determine if there were any lasting beneficial or detrimental effects post-BBVR treatment.[45] Because this study used each individual as their own control, this study was not designed to compare the results of subjects who did or did not use the BBVR system, which has to be noted when interpreting this data. Similarly, it was noted that ANAM composite scores actually improved during the pre-therapy waiting period more than after completion of the BBVR treatment. While again, this was not statistically significant, it may have been because of the potential learning effect with re-administering the ANAM in a shorter period of time for this group as compared to those completing the BBVR therapy. These factors should be taken into account when designing future studies, particularly when using tools that rely on patient subjective symptom reporting and the ANAM as outcome measures.

Previous studies using VR as a rehabilitation intervention have shown significant improvements in cognition and upper extremity function above and beyond that of traditional therapies.[46,47] This pilot study, while not showing statistically significant improvement in patients using the BBVR system, does show potential for improvements in clinical domains. More importantly, it adds to the body of rehabilitation literature that VR systems, like the BBVR, can be used to concurrently treat 2 participants with 1 supervising provider, which has the potential for increased access to care and decreased personnel resources needed to treat multiple patients with ABI. Study results also support previous findings of high levels of participant enjoyment and perceived clinical benefits gained from use of virtual rehabilitation.[48] This is important, because a 2011 survey of healthcare providers in the rehabilitation field noted that patient acceptance is 1 of the most important factors in determining whether or not a provider will introduce new technology into treatment.[49] Therefore, patient acceptance and enjoyment are important not only for a participant's motivation to continue treatment, but also for providers who are considering implementing novel technology in their treatment protocol.

Study Limitations

All participants included in this research study were beyond the sub-acute stage post-injury, with the average time since injury in this sample being 66 months.[14] In general, subacute patients will benefit more from VR than the chronic population in this study. This is because of brain hyper plasticity coupled with the large intensity of training (and large number of task-induced repetitions) that VR provides. In fact, a previous study using VR for individuals with severe TBI during the acute recovery period, demonstrated significant improvements in sustained attention tasks.[50] If improvements did occur, the small sample size limits the ability of this research to determine whether or not BBVR system had an effect on clinical symptom improvement above and beyond the control period. Therefore, future research utilizing the BBVR system would benefit from assessing its comparative effectiveness with other more standard therapies during the acute/subacute stages of rehabilitation using a larger sample size.

CONCLUSION

The current study demonstrated the feasibility of implementing the BBVR system into the outpatient rehabilitation of individuals with ABI in a military Occupational Therapy setting. Provider and patient reports indicated that the system demonstrated moderate to high levels of technical usability, patient engagement, and perceived usefulness. Participants expressed enjoyment in using the system and endorsement of improved cognitive and motor function, maintaining such reports from 3 to 6 weeks of treatment. The post-hoc power

analyses suggest that clinical effectiveness could be demonstrated with reasonable sample sizes for all seven outcomes except QIDS-SR. We believe these data provide sufficient evidence to justify conducting a follow-up, randomized trial of the clinical effectiveness of the BBVR system.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Military Medicine* online.

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Grigore Burdea, PhD is a majority owner of Bright Cloud International, the company which developed the BrightBrainer Rehabilitation System

Gregory House was previously the Chief Technical Officer of Bright Cloud International, the company which developed the BrightBrainer Rehabilitation System. Dr. House no longer retains that title.

PRESENTATIONS

Posters describing preliminary results of this research were presented at the Military Health System Research Symposium (MHSRS) from 27–30 August, 2017 Kissimmee, FL; American Congress of Rehabilitation Medicine (ACRM) from 23–28 October, 2017, Atlanta, GA; DCoE Summit from 19–21 September, 2017, Silver Spring, MD; 4th Federal Interagency Conference on Traumatic Brain Injury (FICTBI) from 11–13 June, 2018 Washington, DC. A conference paper describing gameplay performance during concurrent (two participants at once) training was presented at the 12th International Conference on Disability Virtual Reality and Associated Technologies from 4–6 September, 2018 University of Nottingham, England.

SUPPLIERS

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