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Computerized cognitive training during physical inactivity improves executive functioning in older adults

Uros Marusic, Bruno Giordani, Scott D. Moffat, Mojca Petrič, Petra Dolenc, Rado Pišot, and Voyko Kavcic

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ABSTRACT
The hippocampus is closely tied to spatial navigation, a central component in cognitive functioning, and critically involved in age-associated cognitive decline and dementia. This study evaluated a novel, cognitive computerized spatial navigation training (CSNT) program targeting the hippocampus, with expectation of mitigating possible cognitive decline with bed rest (BR). During a 14-day BR study with 16 healthy, older men (mean age = 60 ± 3, range = 55–65 years), half received CSNT for 12 days in 50-min sessions and half were controls (watching documentaries). This design uniquely controlled diet, sleep, and other personal and environmental activities. Although there were no cognitive declines in controls post-BR, CSNT participants demonstrated significant increases in executive/attention ability and processing speed, and continued spatial navigation testing showed improvement to 400 days post-BR. This intervention may prove useful to mitigate cognitive declines known to occur in long periods of immobilization and could have broader implications in protecting against age-related cognitive decline.

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KEYWORDS
Computerized spatial navigation training; virtual maze navigation task; transfer of learning; bed rest immobilization; aging

1. Introduction
The rapid increase in longevity and expansion of the proportion of elderly in the general population, as well as age- and disease-related cognitive declines, have important health and socioeconomic implications (Walter et al., 2012; Wimo, Winblad, Agüero-Torres, & von Strauss, 2003). It has been well documented that accelerated age-related cognitive decline may be prodromal to a neurodegenerative process, among which Alzheimer’s disease is the most prevalent (Bäckman et al., 2004; Cerhan et al., 2007; Johnson, Storrandt, Morris, & Galvin, 2009; Rushing, Sachs-Ericsson, & Steffens, 2014; Wilson, Leurgans, Boyle, & Bennett, 2011). Aging is also associated with increased risk for prolonged hospitalizations that can lead to long periods of inactivity, concomitant sensory-motor declines, and significant changes in body composition, aerobic capacity,
and lower extremity strength and power (Alley et al., 2010; Kortebein et al., 2008). Together, these can lead to substantially impaired mobility functions (Dupui, Montoya, Costessalon, Severac, & Guell, 1992), delayed recovery (Sands et al., 2003), lowered quality of life (Newman et al., 2003; Newman, Haggerty, Kritchevsky, Nevitt, & Simonsick, 2003), significantly increased health care costs (Deary et al., 2009), and even cognitive declines in older adults (c.f., Mathews, Arnold, & Epperson, 2014).

The bed rest (BR) experimental approach has been one of the most widely used methods to study the consequences of periods of physical inactivity (Convertino, Bloomfield, & Greenleaf, 1997; Marusic, Meeusen, Pisot, & Kavcic, 2014), modeling prolonged hospitalizations or extended space flights. In this experimental approach, participants spend a specified number of days in an uninterrupted horizontal position, with strict restriction of their movement, requiring all their daily needs to be performed while laying prone (e.g., eating, daily hygiene). BR studies have shown significant BR-related declines associated with physiological changes, such as impairments in cardiovascular, skeletal, and muscular systems (Pavy-Le Traon, Heer, Narici, Rittweger, & Vernikos, 2007; Pisot et al., 2008; Pisot et al., 2016; Rittweger et al., 2009), even manifesting changes in brain electrocortical activity (Marusic et al., 2014) or negative impacts on brain structure (Li et al., 2015). However, studies examining the effects of BR on cognitive functioning have shown inconsistent results. While some studies reported no effect (Ishizaki et al., 2009; Koppelmans et al., 2015; Seaton, Slack, Sipes, & Bowie, 2009) or even improvement in cognitive performance due to test–retest practice effects (Calamia, Markon, & Tranel, 2012), others suggested detrimental effects on various cognitive domains, including working memory (Lipnicki, Gunga, Belavý, & Felsenberg, 2009; Liu, Zhou, Zhao, & Oei, 2015), executive functioning (Lipnicki et al., 2009; Liu, Zhou, Chen, & Tan 2012), reaction time, and mental arithmetic (Lipnicki & Gunga, 2009; Lipnicki et al., 2009). In addition, BR studies have mainly included only younger adults, usually males, due to potential health risk issues. Since cognitive abilities decline with age, it is possible that older individuals may be particularly sensitive to BR effects. To our knowledge, no study, including preliminary research with appropriate safeguards or potential interventions to mitigate possible cognitive side effects, has so far investigated the effects of prolonged BR on cognitive functioning in healthy older population. This lack of evidence may relate to the challenging nature of such studies when older persons are involved, requiring careful, extensive monitoring, as in the current study.

Potential deteriorating effect of BR on cognitive functioning could be challenged by proper (physical and cognitive) interventions, among which cognitive training has demonstrated utility for reducing, stabilizing, or even improving mental performance for healthy older adults (Kueider, Parisi, Gross, & Rebok 2012; Lampit, Hallock, & Valenzuela, 2014; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011; Papp, Walsh, & Snyder, 2009; Tardif & Simard, 2011; Teixeira et al., 2012; Valenzuela & Sachdev, 2009). Most of the reviewed studies, however, used training approaches that were not based on a priori understanding of neural functioning, as well as reporting significant improvements in performance primarily in the specific cognitive functions that were trained [e.g., Ball et al. (2002); Mahncke et al. (2006); Willis et al. (2006)], with only limited transfer to other cognitive functions and/or activities of daily living (Tardif & Simard, 2011). The present study proposes a unique computerized cognitive training approach that targets the hippocampus, using computerized spatial navigation training (CSNT). CSNT was
chosen, because spatial navigation functions have been closely tied to hippocampal integrity (Lövdén et al., 2012). In addition, spatial navigation training involves simulated “walking” through a computer-generated environment, and this imagined walking has been shown to be associated with both hippocampal and frontal brain activation (Allali et al., 2014; Crémers, Dessoulières, & Garraux, 2012; Malouin, Richards, Jackson, Dumas, & Doyon, 2003). Both the hippocampus and frontal lobes have been shown to play a critical role for cognitive functions and are also closely tied to brain areas most affected in aging, mild cognitive impairment, and Alzheimer’s disease (Burgess, Maguire, & O’Keefe, 2002; Kessels, de Haan, Kappelle, & Postma, 2001; Maguire et al., 2000; Maguire, Woollett, & Spiers, 2006; O’Keefe & Nadel, 1978). The use of a spatial navigation-based computerized intervention was, therefore, expected to target multiple network-linked brain areas, subserving critical cognitive skills often found to decline in aging and dementia (e.g., executive function, memory), thereby optimizing the opportunity for generalization of computerized cognitive training (CCT) outcomes.

The first objective of this report was to present data evaluating possible cognitive effects in older participants during 14 days of BR within a well-monitored, safe environment. This model also allowed an initial evaluation of a novel CSNT approach to computerized training that targets the hippocampus and frontal areas critical to age- and dementia-associated cognitive decline. The unique BR setting allowed evaluation of the potential of the CSNT paradigm with older adults in a relatively well-controlled environment (e.g., controlling for possible confounding factors that may affect cognitive training paradigms, such as caloric intake or physical activity). If the CSNT is an effective model, it would improve cognition, including potentially mitigating any evident effects of BR on cognition. Our group has previously reported that CSNT training successfully improved efficiency in return to mobility functions as compared to BR without intervention (Marusic et al., 2015), and we here report the results for cognitive performance.

2. Methods

2.1. Participants

Sixteen men between 55 and 65 years of age (mean = 59.6; SD = 3.4) underwent 14 days of horizontal BR with a supervised 28-day recovery. Eight participants were randomly selected for the CSNT (Intervention group), while the other eight served as controls (Control group). The randomization process was performed with a random-number generator in Microsoft Excel software. Prior to the BR study, participants were medically examined, interviewed, and underwent routine blood and urine analyses and a fitness battery. Exclusion criteria were: regular alcohol consumption; ferromagnetic implants; history of deep vein thrombosis with D-dimer < 500 μg/L; acute or chronic skeletal, neuromuscular, metabolic, and cardiovascular disease condition; pulmonary embolism; a Short Physical Performance Battery score <9; and a VO$_2$max < 21 ml/kg/min-min$^{-1}$. All participants were right-handed; had normal or corrected-to-normal vision; reported no history of cardiovascular disease, neurological, or psychiatric conditions. All procedures were carried out in accordance with the Declaration of Helsinki and were approved by the National Medical Ethics Committee. Written informed consent was obtained from all participants prior to the study. The National Medical Ethics Committee did place two
restrictions on this study that the older participants would be limited in gender to males and only those between 55 and 65 years of age, pending the outcome of this first study. The extremely expensive (approximately $20,000 per participant) and labor-intensive nature of this study required the smaller sample size for the first study.

2.2. Computerized spatial navigation training (CSNT) protocol

Participants in the Intervention group were asked to navigate the mazes with the use of a joystick (Trust Predator Joystick GM-2550) for approximately 50 min for each of 12 days of BR, through several virtual environments of increasing complexity (i.e., titrated for increasing challenge as the participant succeeds through successive levels). At the same time and for the same amount of time, participants in the Control group watched documentaries in separate rooms. During CSNT, participants were lying in bed and their heads were not restrained but comfortably resting on a pillow (Figure 1(a)). The tasks were presented on a 17-inch flat panel LCD monitor situated approximately 60 cm in front of participants. All virtual environments were designed using modified versions of Unreal Tournament 2003 and the Unreal Editor 3.0 (Epic Games, Inc. Cary, North Carolina) software package (Nowak, Diamond, Land, & Moffat, 2014; Nowak & Moffat, 2011).

Figure 1. (a) Photograph depicting a participant during the BR study performing computerized spatial navigation training (CSNT) or computer-based spatial navigation testing (CSNTest) with joystick device. (b–d) Illustrations of training and testing environment. (b) Hallway in virtual maze with two noncritical cues. (c) Decision intersection in virtual maze with three available paths together with two critical cues. (d) The end of virtual maze with a trophy designating the goal.
The CSNT task was presented from a first-person perspective and comprised a series of interconnected hallways and alleys, with three available paths at each intersection or decision point. Some hallways of the maze ultimately led to the goal (designated by a trophy) and others led to dead ends. A pair of verbal or nonverbal cues was displayed at each decision point (i.e., intersection), placed at either opposite corner of the intersection, and in corridors at various nondecision points. Verbal cues (Figures 1(b,c)) consisted of signs with country names, city names, or animal names. Nonverbal cues consisted of animal pictures. Participants were instructed to select the correct path as quickly and efficiently as possible, in order to move toward the goal area. Upon reaching the goal area, participants were “transported” back the starting point to complete another learning trial of the same virtual environment.

Participants were trained in environments with three, five, and seven intersections. For each environment, participants were instructed to navigate to the goal area, until successfully completing two consecutive trials with no errors. At this point, participants could then move on to the next environment. Across all training days, participants were to complete 6 three-intersection mazes, 6 five-intersection mazes, and 12 seven-intersection mazes. Although the number of seven-intersection mazes completed by the end of the training period varied depending on how quickly each participant reached criterion, all participants who went through CSNT completed at least four of the seven-intersection mazes. For all levels of maze complexity, alternate forms were used, which contained different spatial layouts and used different cues (i.e., city/country names and images) to minimize practice effects across repeated testing.

To ensure that all participants were equally adept at controlling their movement, the participants were given joystick training prior to cognitive training/testing in the virtual environment. This involved navigating through an environment consisting of a corridor with several turns that was equal in width to those seen in the training mazes. All participants completed the joystick-training environment under the required time of 120 s.

2.3. Outcome measures

2.3.1. Computer-based spatial navigation testing (CSNTTest)
As a direct measure of potential improvement of maze navigation skills, all participants completed five consecutive trials of the same virtual maze. Participants were told to try to locate the goal point as quickly and as accurately as possible and to try to remember the route to the goal. For each maze, the coordinate position and heading bearing was sampled every 20 ms, and this record was used to compute time to completion, distance traveled, and average speed. Due to the different path lengths across multiple mazes, we transformed distance traveled into z-scores. In addition, the number of navigation errors was also calculated. An error was classified as any deviation from the correct route into a dead end corridor. However, during the first trial of the computer-based spatial navigation testing (CSNTTest), participants had no way of knowing which corridors ultimately led to the goal object; thus, the sum of the number of errors of trials 2–5 was used as the dependent measure (Gazova et al., 2013).
2.3.2. Standard Neuropsychological Tests
Tests evaluating several cognitive domains were administered to assess transfer of learning for the CSNT. Simple auditory attention was measured with the Digit Span subtest of the Wechsler Adult Intelligence Scale-III (DSpan) (Wechsler, 1997), and simple visual attention and sequencing was measured with the Trail Making Test, Part A (TMT-A) (Reitan & Wolfson, 1985). Learning/memory was represented by the learning (TL) and delayed recall (DR) subtests from The Rey Auditory Verbal Learning Test (RAVLT) (Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005). Executive functions were measured using the Trail Making Test, Part B (TMT-B) (Reitan & Wolfson, 1985) and Verbal fluency test (VFlue) (Barry, Bates, & Labouvie, 2008). Basic spatial skills were measured with the Mental rotation test (MRot) (Vandenberg & Kuse, 1978) and the Perspective Taking/Spatial Orientation Test (PT/ST) (Hegarty, Kozhevnikov, & Waller, 2008). For the above-listed neuropsychological tests, the primary outcome measures were number of correct responses (RAVLT, DSpan, VFlue, MRot), time of completion (TMT-A and B), and the angular deviation of response (PT/ST).

2.3.3. Computerized CogState battery
The CogState battery was chosen as an additional outcome measure of transfer of learning for this study, because it is brief, uses multiple forms with little or no practice effects, and emphasizes response time and speed of processing (Darby, Maruff, Collie, & McStephen, 2002; Hammers et al., 2012, 2011). Most importantly, CogState could be administered in the supine position, allowing evaluation of the effectiveness of CSNT during actual BR. CogState is a game-like computerized test battery, using playing card stimuli and comprised of tasks covering: simple (Detection, DET) and choice (Identification, IDN) reaction times, working memory (One Back, ONB), and recognition learning (One Card Learning, OCL). An additional measure from the CogState battery was given, the Groton Maze Test (GMT), which is a hidden maze test consisting of a two-dimensional (2D) 10 × 10 grid of gray tiles on the computer screen. Visual psychomotor speed is measured with the Timed Chase subtest (GMT-TC), executive function/planning is measured by with the Groton Maze Learning subtest (GMT-L), and memory is measured by the Groton Maze Learning Test—Delayed Recall subtest (GMT-DR).

For CogState playing card tasks, recommended scoring was used (c.f., Hammers et al. (2012); Hammers et al. (2011) for details), including speed (log of response time in ms) as the primary measure for DET and IDN and accuracy (arc-sine square-root transformation of correct responses in proportion to all responses) for ONB and OCL. For the GMT, GMT-TC used efficiency of performance (i.e., the number of correct moves per second, mps), and GMT-L and GMT-DR used number of errors.

2.3.4. Assessment of subjective workload
The National Aeronautics and Space Administration Task Load Index (NASA-TLX) was used to assess subjective workload (Hart & Staveland, 1988). NASA-TLX is a multidimensional questionnaire, comprising six subscales, using 20-point Likert-type responses. For mental, physical, and temporal demand and frustration, effort, and performance, participants estimated their experience of these burdens by crossing the line between very low (1) and very high (20). Six individual raw subscale ratings (score between 0 and 100)
were analyzed in our study, in addition to the total raw workload (i.e., average of the six subscales) (Hart, 2006; Knaepen et al., 2015).

2.4. Procedure

The present study was performed at the Orthopaedic Hospital Valdoltra, University of Primorska, Ankaran, Slovenia. This was a controlled, longitudinal interventional study where participants had to rest in the bed for 14 days. During BR, the participants were only allowed to turn on their sides or put no more than two pillows under their heads. They could not stand up, sit on the bed, or raise their arms above the level of their head. They were allowed to read books or newspapers, use the internet, watch TV and listen to the radio, and freely communicate with each other. During the study, all participants were carefully monitored for medical or other possible significant side effects potentially associated with BR. After BR, all participants underwent a 28-day supervised recovery (physical intervention).

Baseline and post-BR cognitive assessments were performed with three different cognitive batteries at different schedules: The CSNTest assessment was administrated on the first day (BR d1), at the end of the BR (BR d14), and at the end of the physical recovery intervention (REC d28). Additionally, to assess the long-term maintenance of CSNT, a fourth measurement, 400 days after the BR study (REC d400), was also conducted (Figure 2). Traditional paper-and-pencil Standard Neuropsychological Tests were administered in a seated position prior to (BR d1) and following the BR study (REC d1). The computerized CogState battery was given on the first day (BR d1) and at the end of the BR (BR d14) in a supine position. Following the cognitive assessments after the conclusion of BR (REC d1, Figure 2), the NASA-TLX was given to assess participant’s subjective workload over the BR period.

2.5. Statistical procedures

The data were analyzed with IBM SPSS Statistics 22.0 software for Windows (SPSS, Inc., Chicago, IL, USA) and are presented in tables as means ± standard deviations. Homogeneity of variances and normality of the distribution of the parameters were tested with the Levene’s and Shapiro–Wilk’s tests, respectively. Results of Standard Neuropsychological Tests, CogState and NASA-TLX, did not violate any assumptions for parametric statistics, while results for the CSNTest did. Therefore, we used the nonparametric Mann–Whitney U-test for this variable. To maintain a family-wise error rate at 0.05, we used the Holm–Bonferroni method (Holm, 1979). Interactions of Standard Neuropsychological Tests and CogState tests were tested by a two-way analysis of covariance (ANCOVA, pre-BR values as covariates) where Group (Intervention and Control groups) was used as the between-and Time (pre- and post-BR) as the within-subject variable. Additionally, to further interpret the differences between two groups, the Cohen’s $d$ coefficient was calculated, with a value of 0–0.3 being considered a small effect size, 0.4–0.6 being moderate, and above 0.6 being large (Cohen, 1988). Finally, for NASA-TLX measures, the independent sample $t$-test was used to assess the differences between two groups in mental, physical, and temporal demand, frustration, effort, and performance immediately after the completion of BR (REC d1).
3. Results

The Intervention and Control groups did not differ in age (59.4 vs. 59.9 years, \( p = 0.778 \), respectively) or educational level (4.38 vs. 3.75, \( p = 0.403 \), respectively). Subjective evaluation of mental, physical and temporal demand and frustration, effort, performance, and total workload across the BR period are presented in Table 1. Independent sample \( t \)-test analyses showed that there were no statistically significant differences between Intervention and Control groups in any of the measures (all \( p \geq 0.353 \)).

3.1. Baseline CSNTest

At BR d1, a Mann–Whitney U-test showed that the Intervention and Control groups did not differ in the number of errors committed during the CSNTest (7.88 vs. 9.71, \( z = -0.582, \ p = 0.561 \), respectively) (Figure 3) nor on the average distance traveled (z-scores) through the environment (–0.16 vs. 0.18, \( z = -0.347, \ p = 0.728 \), respectively) (Figure 4), demonstrating equivalence between two groups in navigation skills prior to the intervention.
3.2. **CSNTest post CSNT intervention**

The difference in sum of errors in the CSNTest at BR d14, REC d28, and REC d400 between the two groups was tested with Mann–Whitney U-tests, which showed that the Intervention group had significantly fewer errors at BR d14 (Mann–Whitney U-test; Table 1).

### Table 1. Means and standard deviations of The National Aeronautics and Space Administration Task Load Index (NASA-TLX) assessing subjective workload after completion of BR study for Intervention and Control groups together with statistical evaluation of differences between the two groups (t-test p-values are listed in the right column).

<table>
<thead>
<tr>
<th>Demands</th>
<th>NASA-TLX Values</th>
<th>T-test</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td><strong>Mental</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>41.88</td>
<td>14.38</td>
<td>0.98</td>
</tr>
<tr>
<td>Control</td>
<td>41.67</td>
<td>19.15</td>
<td></td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>12.50</td>
<td>9.64</td>
<td>0.72</td>
</tr>
<tr>
<td>Control</td>
<td>15.00</td>
<td>15.81</td>
<td></td>
</tr>
<tr>
<td><strong>Temporal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>50.63</td>
<td>14.74</td>
<td>0.43</td>
</tr>
<tr>
<td>Control</td>
<td>57.50</td>
<td>16.66</td>
<td></td>
</tr>
<tr>
<td><strong>Performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>26.88</td>
<td>18.70</td>
<td>0.93</td>
</tr>
<tr>
<td>Control</td>
<td>25.83</td>
<td>25.58</td>
<td></td>
</tr>
<tr>
<td><strong>Effort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>36.88</td>
<td>16.02</td>
<td>0.35</td>
</tr>
<tr>
<td>Control</td>
<td>47.50</td>
<td>25.25</td>
<td></td>
</tr>
<tr>
<td><strong>Frustration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>21.88</td>
<td>19.63</td>
<td>0.64</td>
</tr>
<tr>
<td>Control</td>
<td>26.67</td>
<td>17.22</td>
<td></td>
</tr>
<tr>
<td><strong>Total workload</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>37.77</td>
<td>8.69</td>
<td>0.47</td>
</tr>
<tr>
<td>Control</td>
<td>35.69</td>
<td>11.15</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 3](image.png)

**Figure 3.** Line graph representing performance on virtual maze navigation task in terms of summed errors (y-axis) before CSNT (BR d1), at the end of CSNT (BR d14), at the end of recovery period (REC d28), and 400 days after the CSNT (REC d400) (x-axis) for the Intervention (squares) and Control groups (triangles). *Marks a significant difference between both groups.
Results for average traveled distances, represented in $z$-scores (Figure 4), showed that the Intervention group traveled a significantly shorter distance than the Intervention at BR d14 (Mann–Whitney U-test; $z = -3.009$, $p = 0.001$), at REC d28 (Mann–Whitney U-test; $z = -2.083$, $p = 0.020$), but at REC d400 there was a trend toward shorter distances (Mann–Whitney U-test; $z = -1.504$, $p = 0.076$) (Figure 4).

### 3.3. CSNT transfer of learning

We evaluated transfer of learning based on CSNT to cognitive domains represented by traditional paper-and-pencil Standard Neuropsychological Test measures and the computerized CogState battery. Results from Standard Neuropsychological Tests and CogState tests are presented in Tables 2 and 3, respectively. ANCOVA showed that there was a significant interaction effect between time and group for TMT-B, Part B [$F(1,13) = 4.83$, $p = 0.047$, $\eta^2 = 0.271$]. Post hoc analysis showed that this effect was driven by Intervention group: While there was no significant difference ($p = 0.865$) in the Control group between pre- (98.13; 95% CI, 62.4–133.9) and post-BR (96.13; 95% CI, 57.6–134.7), participants in the Intervention group showed a significant improvement ($p = 0.022$) at post-BR (pre-BR: 90.13, 95% CI, 57.8–122.4; post-BR: 62.75, 95% CI, 47.0–78.5). In addition to faster completion times, participants in the Intervention group showed improved consistency by halving their standard deviation at BR d14 as compared to BR d1 (18.8 vs. 38.7, respectively) (Figure 5). Similarly, for GMT-TC, there was a significant interaction effect between time and group [$F(1,13) = 5.74$, $p = 0.032$,
\[ \eta^2 = 0.307 \]. Post hoc analysis showed that this effect was driven by the Intervention group: while there was no significant difference \((p = 0.807)\) in the Control group between pre-\((1.16; 95\% \text{ CI}, 0.95–1.37)\) and post-BR \((1.14; 95\% \text{ CI}, 0.81–1.46)\), participants in the Intervention group showed a significant improvement \((p = 0.005)\) at post-BR \((pre-BR: 1.03, 95\% \text{ CI}, 0.82–1.24; post-BR: 1.26, 95\% \text{ CI}, 1.04–1.48)\).

Additionally, to graphically compare the effect sizes across all the Standard Neuropsychological and CogState tests, we computed Cohen’s \(d\) values (Tables 1, 2 and Figure 6), even for nonsignificant \(F\)-tests. Figure 6 illustrates that across all the tests, the Intervention group obtained better results than the Control group. A sign test for direction of change demonstrates strong significance \((p < 0.001)\), as all measures of change are in the same direction of improved performance for the Intervention group. It is also noteworthy that there are four tests with moderate effect sizes \((d > 0.50)\): MRot, VFlue, RAVLT-DR, and ONB.

### 4. Discussion

Our first aim was to look at the possible cognitive declines which could occur after 14 days of BR in the healthy participants in an age group \((55–65\) years) that has not been previously studied in this paradigm. As a part of this protocol, we also aimed to study whether a novel

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**Table 2.** Means and standard deviations for paper-pencil Standard Neuropsychological Tests for Intervention and Control groups from pre- and post-BR (see Figure 2) with statistical evaluations of transfer of CSNT as indicated by interaction effects.  

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-BR (BR d-1)</th>
<th>Post-BR (REC d1)</th>
<th>Change scores</th>
<th>ANCOVA F-value</th>
<th>P-value</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
<td>F-value</td>
<td>P-value</td>
</tr>
<tr>
<td>MRot Intervention</td>
<td>19.25</td>
<td>6.84</td>
<td>19.63</td>
<td>6.41</td>
<td>0.38</td>
<td>4.98</td>
</tr>
<tr>
<td>Control</td>
<td>17.25</td>
<td>7.85</td>
<td>18.50</td>
<td>5.83</td>
<td>1.25</td>
<td>3.62</td>
</tr>
<tr>
<td>TMT-A Intervention</td>
<td>32.75</td>
<td>12.93</td>
<td>28.38</td>
<td>8.83</td>
<td>-4.38</td>
<td>9.88</td>
</tr>
<tr>
<td>Control</td>
<td>43.00</td>
<td>26.61</td>
<td>38.37</td>
<td>18.10</td>
<td>-4.63</td>
<td>24.88</td>
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<tr>
<td>TMT-B Intervention</td>
<td>90.13</td>
<td>38.65</td>
<td>62.75</td>
<td>18.84</td>
<td>-27.38</td>
<td>26.51</td>
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<tr>
<td>Control</td>
<td>98.13</td>
<td>42.73</td>
<td>96.13</td>
<td>46.10</td>
<td>-2.00</td>
<td>32.03</td>
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<tr>
<td>DSpan Intervention</td>
<td>5.44</td>
<td>0.68</td>
<td>5.25</td>
<td>1.01</td>
<td>-0.19</td>
<td>0.92</td>
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<tr>
<td>Control</td>
<td>5.56</td>
<td>1.29</td>
<td>5.19</td>
<td>1.36</td>
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<td>0.92</td>
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<tr>
<td>VFlue Intervention</td>
<td>7.92</td>
<td>1.58</td>
<td>10.17</td>
<td>1.74</td>
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<tr>
<td>Control</td>
<td>8.54</td>
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<td>9.75</td>
<td>2.31</td>
<td>1.21</td>
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<tr>
<td>RAVLT-TL Intervention</td>
<td>9.18</td>
<td>0.91</td>
<td>9.43</td>
<td>1.97</td>
<td>0.25</td>
<td>1.47</td>
</tr>
<tr>
<td>Control</td>
<td>8.86</td>
<td>0.72</td>
<td>8.98</td>
<td>1.09</td>
<td>0.10</td>
<td>0.91</td>
</tr>
<tr>
<td>RAVLT-DR Intervention</td>
<td>8.88</td>
<td>2.80</td>
<td>9.38</td>
<td>2.92</td>
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<td>3.21</td>
</tr>
<tr>
<td>Control</td>
<td>8.50</td>
<td>2.14</td>
<td>7.13</td>
<td>2.30</td>
<td>-1.38</td>
<td>1.69</td>
</tr>
<tr>
<td>PT/ST Intervention</td>
<td>90.13</td>
<td>54.50</td>
<td>62.88</td>
<td>17.82</td>
<td>-27.25</td>
<td>46.72</td>
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<tr>
<td>Control</td>
<td>77.63</td>
<td>52.91</td>
<td>67.00</td>
<td>54.27</td>
<td>-10.63</td>
<td>42.37</td>
</tr>
</tbody>
</table>

Bold numbers signify significant effects \((p < 0.05)\).  
Primary outcome measures were (i) number of correct responses (RAVLT-TL: Rey Auditory Verbal Learning Test—Total learning, RAVLT-DR: Rey Auditory Verbal Learning Test—Delayed recall, DSpan: Digit Span, VFlue: Verbal fluency test, MRot: Mental Rotation test); (ii) time of completion (TMT-A and B: Trail Making Test, Parts A and B); and (iii) the angular deviation of response (PT/ST: Perspective Taking/Spatial Orientation Test).
Table 3. Means and standard deviations for tests on CogState battery for Intervention and Control groups prior to (BR d1) and after (BR d14) CSNT with statistical evaluations of transfer of CSNT as indicated by interaction effects. Bold numbers signify significant effects ($p < 0.05$).

<table>
<thead>
<tr>
<th>Test</th>
<th>BR d1 M</th>
<th>SD</th>
<th>BR d14 M</th>
<th>SD</th>
<th>Change scores M</th>
<th>SD</th>
<th>ANCOVA F-value</th>
<th>P-value</th>
<th>Cohen's d</th>
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<tr>
<td><strong>Playing card-based tests</strong></td>
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<tr>
<td>IDN (ms)</td>
<td></td>
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<td></td>
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<tr>
<td>Intervention</td>
<td>2.72</td>
<td>0.03</td>
<td>2.71</td>
<td>0.07</td>
<td>−0.01</td>
<td>0.06</td>
<td>0.043</td>
<td>0.838</td>
<td>0.010</td>
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<tr>
<td>Control</td>
<td>2.71</td>
<td>0.08</td>
<td>2.71</td>
<td>0.07</td>
<td>−0.00</td>
<td>0.03</td>
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<tr>
<td>DET (ms)</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>2.49</td>
<td>0.07</td>
<td>2.51</td>
<td>0.06</td>
<td>0.02</td>
<td>0.05</td>
<td>3.108</td>
<td>0.103</td>
<td>0.278</td>
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<tr>
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<td>0.11</td>
<td>2.44</td>
<td>0.09</td>
<td>0.00</td>
<td>0.05</td>
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<tr>
<td>Intervention</td>
<td>0.97</td>
<td>0.08</td>
<td>0.99</td>
<td>0.09</td>
<td>0.02</td>
<td>0.07</td>
<td>0.009</td>
<td>0.925</td>
<td>0.088</td>
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<tr>
<td>Control</td>
<td>0.96</td>
<td>0.04</td>
<td>0.97</td>
<td>0.11</td>
<td>0.01</td>
<td>0.10</td>
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<td>ONB (acc)</td>
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<tr>
<td>Intervention</td>
<td>1.24</td>
<td>0.13</td>
<td>1.34</td>
<td>0.05</td>
<td>0.09</td>
<td>0.10</td>
<td>0.453</td>
<td>0.513</td>
<td>0.518</td>
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<td>1.33</td>
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<td>0.23</td>
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<tr>
<td><strong>GMTs</strong></td>
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<tr>
<td>GMT-TC (mps)</td>
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<tr>
<td>Intervention</td>
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<td>0.26</td>
<td>1.26</td>
<td>0.26</td>
<td>0.23</td>
<td>0.16</td>
<td>5.749</td>
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<tr>
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<td>1.14</td>
<td>0.39</td>
<td>−0.02</td>
<td>0.23</td>
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<tr>
<td>GMT-DR (err)</td>
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<tr>
<td>Intervention</td>
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<td>3.27</td>
<td>6.63</td>
<td>3.50</td>
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<td>4.20</td>
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<tr>
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<td>6.75</td>
<td>3.85</td>
<td>−0.88</td>
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<tr>
<td>GMT-L (err)</td>
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</tr>
<tr>
<td>Intervention</td>
<td>66.75</td>
<td>14.50</td>
<td>52.00</td>
<td>14.87</td>
<td>−15.75</td>
<td>11.85</td>
<td>0.325</td>
<td>0.578</td>
<td>0.031</td>
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<tr>
<td>Control</td>
<td>64.38</td>
<td>15.68</td>
<td>47.13</td>
<td>11.09</td>
<td>−17.25</td>
<td>15.06</td>
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</tr>
</tbody>
</table>

The last column represents the Cohen’s $d$ coefficient.

ms: log of response time in milliseconds (higher scores indicate slower reaction time); acc: Arc-sine square-root transformation of correct responses in proportion to all responses (higher scores indicate more accurate performance); mps: number of correct moves per second; err: total number of errors. Playing card-based tests (IDN: Identification, DET: Detection, OCL: One Card Learning, ONB: One Back). GMTs (GMT-TC: Timed Chase subtest, GMT-DR: Groton Maze Learning Test—Delayed Recall subtest, GMT-L: Groton Maze Learning subtest).

Figure 5. Line graph representing performance on the Trial Making Test, Part B, with average completion time and standard errors of the mean (y-axis) before (BR d-1) and at the end of BR (REC d1) (x-axis), for the Intervention (squares) and Control groups (triangles). Note a significant decrease of standard error of the mean at post as compared to pre-CSNT intervention.
spatial navigation-based computerized training intervention, developed from an underlying brain-based model, could improve cognitive functioning and mitigate possible BR-associated cognitive declines within a setting that controlled for possible physical or environmental confounding factors that can affect cognitive training paradigms.

First, the results of this study did not show any detrimental effects on cognitive functioning in our participants. The small sample size and relatively short two-week duration, due to the use of relatively older participants with the need for careful, complex, high-cost health monitoring, could possibly have concealed potential detrimental effects on neuropsychological functioning, though further studies will now expand on these findings.

Second, the fidelity of the CSNT intervention was demonstrated through a significant positive effect on the CSNTest, which used a testing environment identical to the training environment. The improved performance of the Intervention group (reduced number of errors) was evident up to 400 days after the study was conducted. This finding is consistent with several previous research studies in which CCT significantly increased performance in tested outcomes directly related to the training paradigm (Ball et al., 2002; Mahncke et al. (2006); Willis et al. (2006)), emphasizing the fidelity of training. It is also important to emphasize that these positive results were found with older individuals even in a negative environment, such as prolonged BR.
Third, in this study, the CSNT paradigm also demonstrated transfer of learning through increased performance for the Intervention group on tests not directly related to the training experience, specifically on measures of executive functioning (TMT-B) and psychomotor speed (GMT-TC), with other tasks not showing significant relative improvement for the Intervention group, though moderate effect sizes were also evident on other measures reflecting executive functioning and working memory, along with spatial ability and memory, consistent with task areas subserved by the hippocampus and its brain interconnections. We demonstrated previously that the CSNT intervention can lead to transfer to a testing paradigm very different from traditional paper-and-pencil testing and not necessarily expected to be subserved by the hippocampus, specifically fast-paced dual task walking performance (Marusic et al., 2015), though mobility tasks requiring divided attention or dual tasking also have been associated with efficiency in executive functioning (Giordani & Persad, 2005). It is also important to note that the nature of the BR study allows for control of other potential confounding factors that could occur in other less-structured training experiences in which participants in intervention groups might also increase other health benefitting habits (e.g., diet, exercise, breadth of social activities).

To our knowledge, there are two previous studies using some aspect of spatial navigation for cognitive training purposes. Lövdén and colleagues (2012) reported that spatial navigation training, with participants on treadmills navigating in virtual reality (every other day for 4 months), improved subsequent spatial navigation performance. Moreover, the intervention group maintained stable hippocampal volumes during and after 4 months of training, while the control group showed small age-related volume declines. Hötting and colleagues (2013) conducted a 6-month-long aerobic endurance training study with 40–55-year-old sedentary adults. In the last month of the physical intervention, participants were also exposed to one of two computerized spatial navigation modules (spatial navigation or perceptual training). Their results showed that only the spatial navigation intervention improved spatial navigation performance following aerobic training. Moreover, spatial navigation training resulted in lower brain activations (presumed to be more efficient neural processing) in the hippocampus and parahippocampal gyrus, as well in frontal and temporal brain areas, a network of brain areas associated with spatial navigation.

Transfer of cognitive training to specifically untrained testing situations has been conceptualized as resulting from some form of plasticity or change in overlapping brain regions or networks important for the untrained task (Berry et al., 2010; Pressler et al., 2011; Smith et al., 2009). In the case of better performance on CogState Chase test (e.g., faster moves), overlap in training through preparation, execution, and control gained in motor control by the Intervention group, after practicing with the joystick across sessions and transferring to use of a joystick for the Groton Maze board. However, we also observed significant transfer on the TMT-B test (d = 1.54) measuring executive ability. Seven of eight participants who underwent CSNT improved their TMT-B completion time by almost one-third (pre-training = 90.1 s vs. post-training = 62.8 s, respectively). Furthermore, although the standard deviations between the two participant groups were similar at baseline, the variability of completion time was halved in the Intervention group (pre-training = 38.7 s vs. post-training = 18.8 s, respectively). This marked improvement was not evident on the simpler, speeded motor sequencing TMT-
A subtest. This finding of transfer effect on executive functioning was additionally supported by the transfer effects, as shown by at least moderate Cohen’s $d > 0.4$ effect sizes observed on tests also related to executive functioning, such as spatial cognition (MRot test), executive functions (VFlue), working memory (ONB), and memory recall (RAVLT-DR) (Tables 2 and 3). Transfer to these cognitive functions is in agreement with the notion that spatial navigation is a complex cognitive skill that likely depends on a wide range of cognitive domains (Allain et al., 2005; Klencklen, Després, & Dufour, 2012).

Transfer of CSNT on executive functioning also can be supported by several lines of converging evidence: (i) correlation of performance on spatial navigation with executive functioning (Jebara, Orriols, Zaoui, Berthoz, & Piolino, 2014; Taillade et al., 2013); (ii) spatial navigation imaging findings showing the engagement of cortical cortices (Hötting et al., 2013; Moffat, 2009; Nemmi et al., 2013); and (iii) correlation of hippocampal activity with executive functioning tests (Leirer et al., 2010). It also has been well documented that gait and mobility imagery (imagined walking) engages executive/frontal, as well as hippocampal processes especially in demanding situations (Allali et al., 2014; Yogev-Seligmann, Hausdorff, & Giladi, 2008).

The lack of transfer to GMT performance is somewhat unexpected, as this is another maze-type task. Our spatial navigation task, however, could best be described as a route learning process in which participants rely primarily on an egocentric strategy. That is, learning a route with multiple decision points requires memory for landmarks along the routes, associations of directional information with these landmarks, memory about the order of landmarks, and consolidation of information about a maze (Tom & Tversky, 2012). The Groton Maze task does not include landmarks to be learned along the route, as it is a hidden maze task in which the participants move across a simple grid of squares, attempting to discern the maze path based on correct or incorrect moves and hidden “blocks” along their path. The lack of transfer from our CSNT, which used a 3D virtual maze navigation environment, to 2D Groton Maze could be explained by significant difference between the two mazes. Learning of 2D maze test requires route memorization of the proper sequence of correct tiles, while 3D maze navigation is based on stimulus-response associative learning (e.g., turn left at specific town name).

While contributing to the study of the cognitive training and spatial navigation, our study has methodological limitations. A limiting factor in the BR paradigm is that it imposes very specific demands on cognitive training: (i) training has to be accomplished within the time frame of the BR, which is, in most cases, of relatively short duration and thus requires training to be “massed” rather than distributed over time to increase the opportunity for learning and practice and (ii) the training, itself, has to be conducted in a supine position. However, the CSNT task used lends itself easily to work within a BR setting and can be operated on both laptops and tablet computers. It also is necessary to keep in mind that BR studies are very costly, labor-intensive, and limited by hospital/institutional capacity, and in this case additional care and monitoring for relatively older participants. Consequently, our study included only a relatively small sample size—16 men—and has thus limited power to detect effects and generalizability across older individuals. Furthermore, due to limited resources, we did not closely monitor and assess all activities that participants could engage in, such as reading or chatting between participants, which could have possibly affected outcomes. Our study also included only male participants, though this is consistent with the restrictions of the National Medical
Ethics Committee, as well as to reduce any potential gender differences in navigation performance that have been previously observed (Gron, Wunderlich, Spitzer, Tomczak, & Riepe, 2000; Moffat, Hampson, & Hatzipantelis, 1998; Sandstrom, Kaufman, & Huettel, 1998). Finally, although spatial navigation testing was completed out past the immediate post-BR time frame, we did not have the resources to continue to use paper-and-pencil or CogState measures for the longer intervals, so further studies will be needed to assess the long-term retention of any transfer of learning effects with this intervention among older individuals.

Overall, this study provides initial support for the ability to complete BR studies in older individuals without evident cognitive effects, at least in this first sample. Empirical evidence also was presented that CSNT results not only in improved spatial navigation performance (fidelity), but also in improvements across other cognitive domains known to be associated with brain areas subserved by those that involve spatial navigation (transfer of learning). Most importantly, the results of this study clearly call for further and larger investigations using the spatial navigation-based CCT paradigm with older individuals, in order to more closely explore the domains of cognitive improvement. This is particularly true, given the fact that the brain areas involved in spatial navigation are those most often seen affected early in the course of cognitive loss with aging and dementia (e.g., hippocampus, frontal lobes).

Development of reasonable, economically viable, and culturally acceptable interventions to maintain cognitive function in later life can promote health, social, and economic benefits. Such interventions are particularly needed nowadays, when no clear pharmacological treatment for slowing cognitive decline is yet available. A successful approach to slow age- or dementia-associated cognitive decline or mitigate possible cognitive effects due to longer hospitalizations will allow persons to maintain successful aging and remain in their own home longer. This can result in significant local, regional, and federal savings in health expenses, as well as in maintaining quality of life. More directly, our study showed the feasibility of the CSNT intervention in the specific environment and age group that could possibly serve as a new therapeutic tool in hospital settings. If the CSNT paradigm proposed for this study is successful, it could serve as a model for the development of new intervention programs, as well as rehabilitation protocols that could be used in situations of inactivity or immobilization caused by illness, injuries, sedentary jobs, or even space flight.

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Disclosure statement

No potential conflict of interest was reported by the authors.
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