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Human spatial navigation deficits after traumatic brain injury shown in the arena maze, a virtual Morris water maze

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Abstract
Objective: Survivors of traumatic brain injury (TBI) often have spatial navigation deficits. This study examined such deficits and conducted a detailed analysis of navigational behaviour in a virtual environment.
Design: TBI survivors were tested in a computer simulation of the Morris water maze task that required them to find and remember the location of an invisible platform that was always in the same location. A follow-up questionnaire assessed everyday spatial ability.
Method: Fourteen survivors of moderate-to-severe TBI were compared to 12 non-injured participants.
Results: TBI survivors navigated to a visible platform but could not learn the location of the invisible platform. The difference between TBI survivors and uninjured participants was best indicated by two new dependent variables, path efficacy and spatial scores.
Conclusion: This study confirms the capacity of virtual environments to reveal spatial navigation deficits after TBI and establishes the best way to identify such deficits.

Keywords: *Topographical disorientation, spatial cognition, cognitive map, place learning, allocentric, closed head injury*

Introduction

Traumatic brain injury (TBI) is caused by a severe blow to the head and leads to widespread anatomical damage and numerous cognitive and functional problems. Although severity and locus vary considerably, there tends to be damage to the orbital frontal cortex and the poles of the temporal lobes [1] and to the hippocampus [2]. Also, diffuse axonal injury may occur [3]. TBI causes a wide range of social, emotional and cognitive changes [4], though the most common cognitive complaint is forgetfulness [5]. Memory problems after TBI manifest on tests of facial recognition, story recall, semantic information, prospective memory and autobiographical memory [6] and these have been linked to hippocampal damage [7, 8]. A deficit which may also be related to hippocampal damage but which has not received much attention is the loss of the ability to navigate from place to place in everyday life. This deficit may relate to the ability to traverse known routes or to learn new ones or to the inability to recognize familiar places or familiar landmarks. These lost functions involve both thinking about space (recognition, memory, planning) and actually moving within space (maintenance of intent, awareness of one's current position and the execution of movements necessary to travel the entire journey) [9].

Deficits in spatial cognition have previously been defined in terms of both recall and recognition, with the terms 'topographical amnesia' and 'topographical agnosia' referring to the inabilities to remember and to know locations according to visual landmarks, respectively [10]. Maguire et al. [11] proposed that topographical disorientation possesses the double aspect of recall and recognition with the possibility

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that these may be impaired either together or selectively. The term 'topographical disorientation' has been used to refer to a selective loss of the ability to 'wayfind' in a locomotor environment [12] or defective orientation and navigation in the real environment [13] or to simply not knowing where one is, i.e. being 'cognitively lost' [14] and has been linked to a small area of the right parahippocampal gyrus [15].

More global deficits in spatial cognition may be the result of damage to various parts of the hippocampal formation. Barrash et al. [16] have demonstrated impairment in route learning with damage to regions including the right hippocampus. Analysis of individuals with surgically placed temporal lobe resections has revealed impairments on a variety of tasks which require acquisition of the location of objects and places relative to each other [11, 17–19] and Spiers et al. [20] report that right temporal lobectomy patients are impaired on tests of topographical memory. Spatial memory deficits have also been described according to the locations of lesions to the hippocampus and parahippocampus [21] and at least one study has concluded that the hippocampal system is required not only for memory consolidation but also for the retrieval of episodic and spatial detail [22].

However, the relationship between real world spatial navigation deficits after TBI and the anatomical damage responsible is not well understood. There have been studies demonstrating deficits in spatial navigation after brain injury, but most have concentrated on ways to measure it, usually within hospital corridors [23] (and see examples in [24, 25]). Some studies have suggested selective impairment of underlying mechanisms (for example [26]), but few have attempted to analyse the cognitive components of the deficit or to draw upon the extensive experimental literature relating anatomical structure to processes of spatial navigation. Further, no standardized methods for objectively assessing real-world spatial deficits have been developed for humans.

Deficits in spatial cognition have been studied extensively in laboratory animals in the context of understanding the functions of the hippocampus [27–29]. One reason for the success in this area is the development of a standardized method for assessing spatial deficits, the Morris water maze (MWM) [30, 31]. This task is important because it can distinguish performance based on spatial learning and memory (i.e. allocentric navigation requiring the hippocampus) from performance based on simple cues or egocentric response patterns that do not require the hippocampus [30–33]. The maze requires laboratory animals to find and escape onto a platform hidden just below the surface of a pool filled with opaque, milky water. Varied start positions and an absence of local landmarks mean that optimal performance requires the formation of a cognitive map of distal extra-maze cues [30, 32]. Although it is clear that rats with hippocampal or frontal lobe damage perform poorly on this task [34, 35], the MWM has also proven valuable in revealing the anatomy, physiology and pharmacology of spatial learning and memory more generally [36–38]. It has also proven to be a useful tool for measuring deficits, treatment and recovery after various forms of brain injury [39–43] and has been used for the development of animal models of TBI [44–47].

In the past 9 years, several studies have extended the research from laboratory animals to humans and have established that the findings apply at both the behavioural and anatomical levels. Reid et al. [48] developed the first virtual MWM (coining the term 'Arenamaze') and showed that Korsakoff's patients were impaired. Jacobs et al. [49] developed a Computer-Generated Arena (C-G Arena) and found that humans learned to locate places from a variety of start positions [30]. Jacobs et al. [50] found that removing large subsets of distal cues did not affect place performance in the C-G Arena, but changing spatial relations among the same cues profoundly disrupted performance ([51], with laboratory animals). Astur et al. [52] and Sandstrom et al. [53] both found large gender differences in spatial navigation abilities in virtual MWMs. Bohbot et al. [54] found rapid learning of a location in a real room using a beeping sensor under the floor to simulate the hidden platform of the MWM. Iaria et al. [55] used a virtual radial arm maze to reveal variability in strategy selection during human place learning (with no gender differences).

The anatomical parallels have been just as strong. In a complex virtual environment, Maguire et al. [56] showed that learning and navigating virtual space activated the right hippocampus (on fMRI), whereas speedy travel through the environment activated the right caudate nucleus. These relative contributions of hippocampus and caudate were also shown by Iaria et al. [55] in a virtual radial arm maze. Using a virtual MWM, Astur et al. [57] found deficits in patients with unilateral temporal lobectomy, which were confirmed by Bohbot et al. [58] using a virtual radial arm maze.

These findings have made it reasonable to investigate the nature of spatial navigation deficits in survivors of TBI. Although this population is not well suited for investigating brain-behaviour relations (given the diverse and diffuse nature of the anatomical damage), they are the ideal population if one is interested in applying laboratory results for the benefit of the entire clinical population and not just a select, scientifically interesting sample.

A previous study [14] employed a virtual water maze, the 'Virtual Arena', to investigate spatial deficits in patients with moderate-to-severe TBI. It was found that most of the sample (eight of 12) had significant deficits in place learning and that these deficits correlated with deficits on the Rivermead Behavioural Memory Task, as well as with self-reports of difficulty with wayfinding and episodic memory. However, there was some question as to whether the deficit was an artefact of the rather primitive graphics available at the time (i.e. a failure of imagination by TBI survivors) or whether the deficits were specific to this relatively small sample. Given the heterogeneous nature of the anatomical damage caused by TBI [59] and the variability between individuals, it seemed crucial to replicate this study, using a different sample of survivors and newer, better graphics.

The long-term objective is to better understand spatial cognition deficits after brain injury. The three specific objectives were: (a) to validate a more realistic MWM simulation, (b) to replicate a previous study with a new sample of survivors and (c) to determine the best dependent variables to identify deficits in spatial navigation in this population.

Methods

Participants

Thirty-three people were recruited for this study, 17 with TBI and 16 comparison participants with no history of brain injury. Five of the participants with brain injury were recruited from a residential facility for individuals with brain injury and behavioural/impulse problems, the Skeleem Village site of the Cedar Lodge Society. The remaining 12 participants were recruited from the community. Comparison participants were screened for history of head injury by being asked if they had ever been hospitalized for a loss of consciousness. Those 18 years or older who had no neurological or psychological diagnoses were included. This study was approved by the research ethics committees of both the University of Victoria and the Capital Health Region. Informed written consent was given by all participants at the outset of the testing session.

Apparatus

Spatial learning and memory were tested in a virtual MWM, the Arena Maze, which was rendered in computerized virtual space using the Unreal® engine (Epic Megagames) and displayed on a 17″ monitor at 800×600 resolution by a 450 MHz Pentium III personal computer. The virtual environment consisted of a round arena centred in a large square room of a two-room building, set in an outdoor landscape. The landscape was visible through large windows on three sides of the large room and was designed to provide the main distal cues for navigation. The arena and room were proportioned to approximate the appearance of a virtual MWM used previously in this laboratory (see [14, 60] for details), except that the arena wall was set low to permit an unobstructed view of the room and windows from any point within the arena. Specifically, the arena appeared to be 40 m in diameter, bounded by a wall 1 m high, set within a room $75 \times 75 \times 17.5$ m with large windows to the outside on three sides (see Figure 1). The walls were arbitrarily designated as North, East, South and West (N, E, S, W). The west wall had a door leading to a second windowed room, from which the outside landscape could also be seen. The landscape featured mountains to the west and an island in a large body of water to the east. The land sloped from the mountains to a beach along the curved shore. The east wall of the arena room had one large window giving a view of the water and island. The north and south walls each had three windows, showing the sloping landscape. Thus, the N–S direction was distinguishable only by the direction in which the land sloped (viz., left-to-right or right-to-left). All surfaces were textured to optimize 'optic flow' [61, 62] and all but the ceiling were textured like marble, to avoid local cues to location (specific features or number of pattern repetitions). The sound of footsteps and a slight 'head bob' during movement were added to heighten the sense of reality or 'presence' in the environment.

Participants navigated the room using a joystick, which allowed them to move only forwards, left and right. The joystick was adapted to prevent movement backwards to simulate real-world walking (and to increase compatibility with the MWM by matching the movement options of a swimming rat). As in the MWM, the task was to learn the location of a hidden platform, located at a fixed location within the room, defined only by its spatial position relative to distal cues. As per standard procedure in the MWM [31, 37], there were three types of trials. 'Invisible platform' trials were used to test spatial learning: the round platform ($\sim$5 m diameter) was kept in a fixed location, invisible until stepped on (triggered), at which point it rose slightly ($\sim$0.2 m) accompanied by an alerting (mechanical) sound and it became visible as a disk $\sim$0.1 m thick. 'Probe' trials were used to test knowledge of the platform location: the platform was set to not respond when stepped on, but to rise automatically after 50 seconds. 'Visible platform' trials were used at the start of sessions to familiarize participants with the procedures and to test for

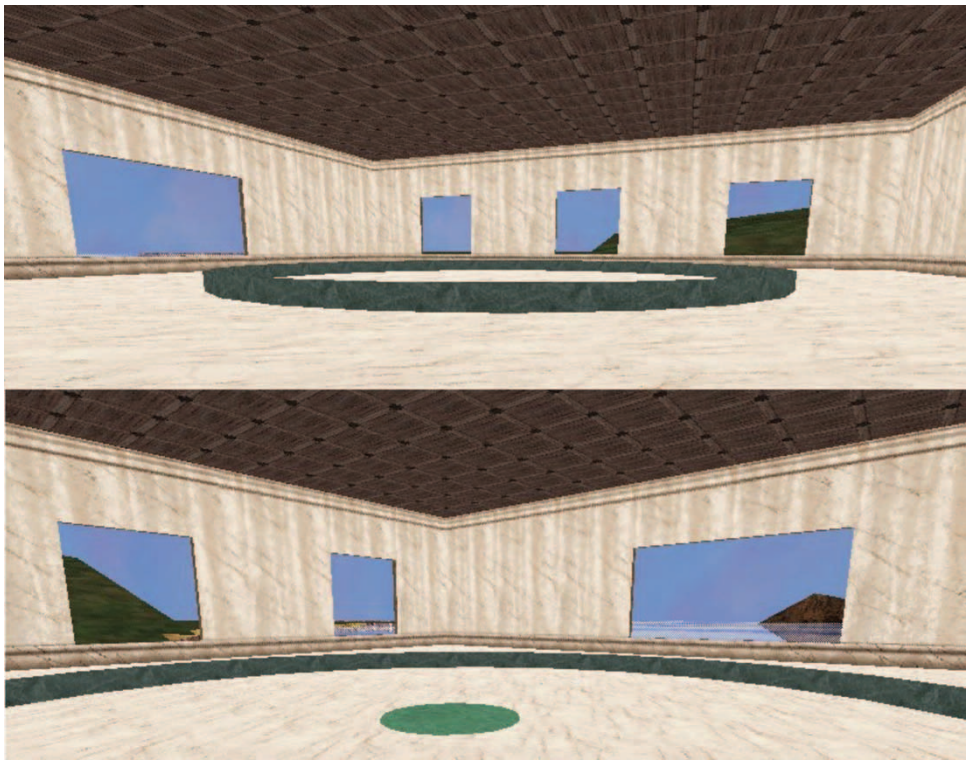

Figure 1. Two views of the Arena Maze. Top panel illustrates the position of the round arena in the centre of the square room and the view of the landscape outside from eye-level view. Lower panel illustrates proportion of platform within arena and provides better view of landscape outside, from higher than normal viewing level.

procedural competency, including sensory and motor ability and sensorimotor co-ordination.

Procedures

The trial sequence consisted of four visible platform trials, 10 invisible platform trials and a probe trial. The visible platforms were located in the centre of the arena and then in the centre of the NE, NW and SE quadrants on successive trials. Trials were started from S, W, E and N cardinal points, in that order, so that participants faced a different wall on each trial (maximizing the chance that they incorporated it into their cognitive map of the room) and had to cross most of the arena to reach the platform. On invisible platform trials, the platform was always in the centre of the NE quadrant (see Figure 2). Starting positions were sequenced such that in each set of four trials the following conditions were satisfied: (a) each cardinal starting point was used once, (b) trials with longer distances to the platform alternated with trials with shorter distances and (c) the direction to the platform from the start position (i.e. right or left) varied in a complex sequence without alternation or repetition more than two trials in a row. Specifically, the starting sequence was SNWE, NWSE, WE. The probe trial (no platform) started from the south and at the maximum distance from the correct quadrant (NE). All trials began with the participant facing into the centre of the arena.

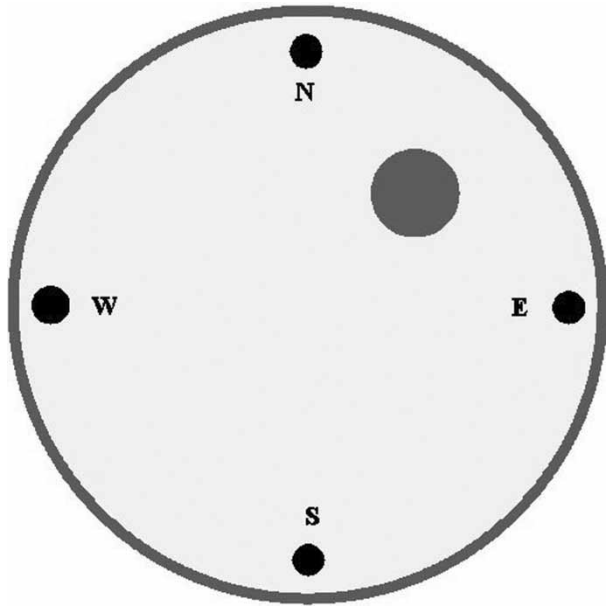

Figure 2. Diagram of arena area showing start positions (black dots) at four cardinal points and platform position (larger circle) within the arena wall.

At the start of each session, experimenters informed the participants of the purpose and general

procedures of the experiment and then obtained written consent to continue. Participants sat in front of the monitor with the joystick centred between them and the monitor and the experimenter sat beside and slightly behind them (i.e. out of their visual field). The experimenter read the instructions from a script and answered any questions about the task procedures. The script (available on request) informed them of the task demands and, in general terms, the sequence of visible and invisible trials. In particular, participants were instructed to familiarize themselves with the room and the position of the platform within it and advised that the position of the invisible platform would always be the same. Questions to the participants confirmed their understanding of the task demands. In regard to the probe trial, participants were informed that there would be a trial in which the platform would be 'difficult to find', though it would not be moved to a different location, and to keep searching in the area where they thought it should be.

Prior to the onset of learning trials, participants had an opportunity to familiarize themselves with the joystick and the room. They were introduced into the room, outside the arena walls and encouraged to explore until comfortable with the joystick and environment, including the view out the windows. The experimenter then verbally guided participants through the door into a second room containing a 'teleporter' – a tall square box with a blue fluid pattern on one side. Participants were told that the experiment would begin as soon as they stepped through this teleporter and that they could step through whenever they felt ready. Participants were encouraged to view the remaining outdoor space through the windows of the second room and were queried to ensure they remembered their task (i.e. go to the visible platform).

Once through the teleporter, participants found themselves inside the arena squarely facing the opposite wall and with the platform visible in the centre of the arena directly in front of them. Once the participant stepped onto the platform they were encouraged to look around the room. When they indicated that they had looked about the room sufficiently and were ready for the next trial, the experimenter 'teleported' them to a new start position for the next trial. Except for a computer voice saying 'hup' softly, no teleporter sounds or visual effects accompanied this teleportation: as far as the participants were concerned (reinforced by instructional information), they were instantly 'teleported' to a different position within the same room, inside the arena, facing inward, with the platform visible in a new location. Trials continued through the sequence of three more visible platform trials. Prior to starting the remaining 10 invisible platform trials and probe trial, participants were reminded that the platform would no longer be visible, but would always be in the same place in the room.

On invisible platform trials, participants had up to 3 minutes to locate the platform. On the first three invisible trials, those who were unable to find the platform were guided to it, using movement-based oral directions (e.g. 'turn left', 'go straight'). On subsequent trials, if the participant had not found the platform within 3 minutes, it rose automatically (making its usual sound) and the participant was told to go stand on it. Once on the platform, participants were encouraged to look around the room and try to remember their current location to be able to return to it. The experimenter initiated the next trial only when the participant indicated they were ready. On the probe trial, the platform could not be triggered by walking over it, so it remained invisible for 50 seconds and then rose. Throughout testing, participants were monitored for dizziness or fatigue and were given as many breaks as they needed. Testing took 35–70 minutes, with TBI participants taking ~10 minutes more than comparison participants.

After the Arena Maze task, the participants were asked for basic demographic information (age, education, sex, aetiology of injury, time since injury, medications, computer experience) and asked to rate how 'real' the computer task felt. They were then given the 'Everyday Spatial Questionnaire' [14], which consists of a set of 13 questions asking about the frequency of various problems in wayfinding (e.g. 'Do you feel disoriented when you come out of an unfamiliar building?') and locating objects left in the environment (e.g. 'Do you have trouble finding your car in a parking lot?'). Responses were made on a 100 mm magnitude-estimation scale anchored at opposite ends by 'Never' and 'Always' or 'Every time' (see [14] for full questionnaire).

After the participants had answered all of the questions, they were debriefed about the study, thanked and paid for their time.

Data analysis

Data from the Arena Maze was analysed from 'Demo' files recorded by the UnReal® engine while the participant explored the virtual environment. The co-ordinates of the participant's position every 100 ms were extracted from these files and reformatted by a utility, and analysed using TRAM® (available on request to LN, ludek@equisoft.com). TRAM®, originally designed to analyse data from several traditional Morris water maze video systems, provided a readout of the usual performance variables (e.g. distance, latency) plus several additional variables of interest: namely, (a) path efficacy

(directness of path relative to minimum distance), (b) tortuosity (twists and turns in the path), (c) thigmotaxia (time spent in annulus nearest the wall), (d) average heading and (e) bearing from start position to the platform position. In addition, TRAM® provided measures of time spent in various regions of arena. Time spent in four quadrants, three rings (annuli) that trisected the radius of the circular area and the target vicinity (an area concentric with the platform but double the radius) were examined. Although all these variables were examined, only those which provided new insights into behavioural differences between those with and without brain injury are described in the results.

Data from the Arena Maze, organismic variables (i.e. age, sex, years of education and computer experience (coded as none, low, medium or high)) and the Everyday Spatial Questionnaire were summarized and graphed in Microsoft Excel® then analysed in SPSS. Most pair-wise comparisons between the two groups were analysed using *t*-tests, adjusting for degrees of freedom when assumptions of equal variances were significantly violated (Levine's test). Repeated measures data (trials) were analysed with MANOVA. Sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios [63] were calculated according to formulae found on the internet [64].

Results

Sample selection

Ultimately, 12 of the 16 non-injured participants and 14 of the 17 survivors of TBI were included in this study. The four non-injured participants were excluded because of ongoing psychological disorders ($n = 2$), intentional failure to follow instructions ($n = 1$) or dizziness during testing ($n = 1$). The three TBI survivors were excluded because of inability to find the invisible platform within three trials ($n = 1$) or unclear diagnosis of brain-injury ($n = 2$). The aetiologies were varied: nine were from motor vehicle accidents, three were sports injuries and two were from assaults. The male:female ratios of the remaining 26 participants were 7:5 for non-injured participants and 11:3 for those with TBI. Ages ranged from 19–52 for the non-injured participants (36.2 ± 0.9) and 23–67 for those with TBI (39.3 ± 0.9). Education ranged from 7–17 years (13.8 ± 0.2) for non-injured and 8–16 for those with TBI (12.9 ± 0.2). Neither age nor education was significantly different between groups ($t(24) = 0.79$, 0.82, $p < 0.05$) and none correlated ($p > 0.05$) with any spatial variables, including computer experience. The amount of time that had elapsed since their injuries was diverse among participants, ranging from 0.5–48 years with an average of 15.9 ± 0.9 years. As a variable, time-since-injury correlated only with the Everyday Spatial Questionnaire (ESQ) spatial score ($r(13) = -0.58$, $p < 0.03$), indicating that those participants with TBI who had greater time to recover from their injuries reported fewer problems with wayfinding. However, time-since-injury did not correlate with any measures of Arena Maze performance. Although gender differences were checked, there were no significant effects within either the injured or uninjured participants on performance in the Arena Maze nor in self-reports of spatial ability on the ESQ. This is not surprising, given the small number of female participants (five uninjured, two survivors).

Performance in Arena Maze

In general, those with TBI showed worse performance in the Arena Maze than those without. Although institutionalized TBI survivors tended to perform slightly worse than survivors in the community, their scores were not significantly different from each other on any of the five main dependent variables (see below) ($p < 0.01$, α for five comparisons) and so the results from the two groups were pooled.

Figure 3 shows distances and latencies of participants with and without TBI on visible and invisible platform trials (trials 1–4 and 5–10, respectively). Performances of the two groups were comparable on visible platform trials as measured by both distance and latency. When the platform was invisible, both groups took about the same time to find it on the first trial. Thereafter, those without injuries went to it quickly and directly, but those with brain injuries took more time and longer, more circuitous paths to find it.

There was a significant effect of brain injury on both distance and latency on a repeated measures multivariate analysis of variance (MANOVA) (see Table I for *F*-values and probabilities). There was also a significant effect of trials (i.e. learning), but no Brain Injury × Trials interaction. However, a simple main effects analysis confirmed that those without injury showed significant learning over trials in terms of both distance and latency, but those with brain injury did not show significant change over trials on either measure, indicating that there was learning in non-injured participants, but not in those with brain injuries.

Indeed, those without brain injuries appeared to learn the platform location on the first trial and were able to go to its location thereafter, whereas those with TBI learned slowly, if at all, and never achieved the same level of performance (see Figure 3).

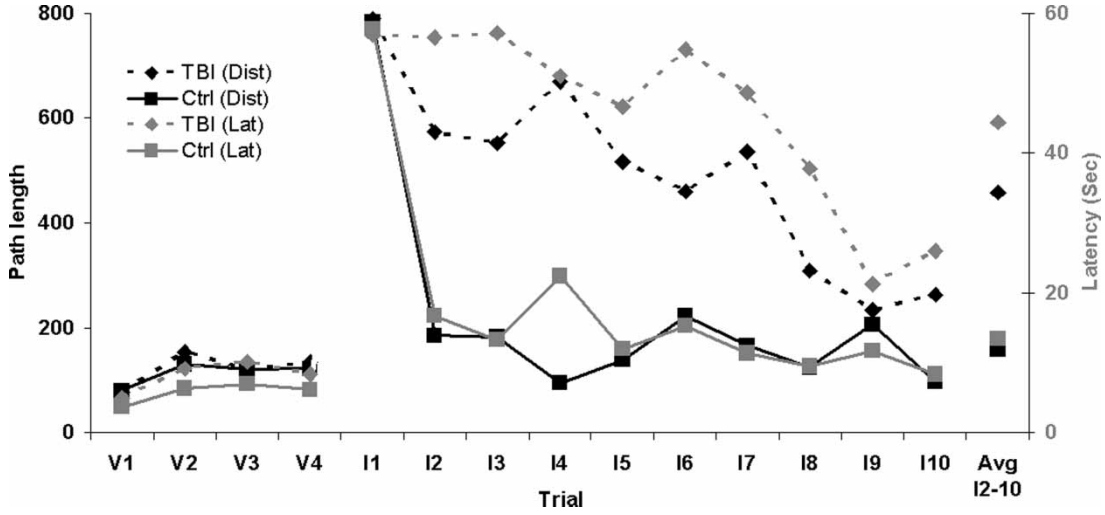

Figure 3. Time taken (latency – Lat) and distance travelled (Dist) to reach the platform by participants with traumatic brain injury (TBI) and without (Ctrl) on Trials V1–V4, when it was visible, and on Trials I1–I10, when it was invisible.

Table I. Results of MANOVA of distance and latency.

	F	df*	*p*<
Distance (10 trials)			
Group	9.625	1,24	0.005
Trials	4.168	3.3, 78.2	0.007
BI × Tr	1.162	3.3, 78.2	0.330
Trials – Within group (simple main effects)			
Comparison	15.48	1.28, 14.1	0.001
BI	1.49	3.0, 39.0	0.232
Latency (10 trials)			
Group	13.1	1,24	0.001
Trials	3.11	4.3, 103.5	0.016
BI × Tr	1.21	4.3, 103.6	0.310
Trials – Within group (simple main effects)			
Comparison	4.95	2.2, 23.9	0.014
BI	1.43	3.8, 48.8	0.240

*Greenhouse-Geisser adjustment to dfs used when Mauchley's test for sphericity was significant.

Analysis of the differences between the first and second invisible platform trials revealed that the comparison participants showed significant changes in distance and latency (*t*-test, $p < 0.02$), whereas participants with TBI showed no change in either variable ($p > 0.30$). Further, there were significant differences between the groups on the second trial in latency ($p < 0.02$), but not distance ($p = 0.15$). On the second trial and thereafter, most trials by participants without brain injury took less than 40 seconds and 200 distance units (99% of trials below 40 seconds, 77% trials below 200 units). In contrast, trials by participants with TBI were below 40 seconds only 65% of the time and below 200 distance units only 33% of the time. The differences between the groups on these trials were significant for both latency ($t(14.4) = -4.05$, $p < 0.001$, Cohen's $d = 1.48$) and distance ($t(14.3) = -3.56$, $p < 0.005$, Cohen's $d = 1.30$).

Although the average latencies and distances of participants with TBI decreased gradually over trials, this gradual decrease was not typical of most individuals (though this discrepancy between individual and average scores is well-established by animal learning studies [60]. Six brain-injury survivors showed very long latencies (150–180 seconds) on one or two trials between trials 2–8 and all generally showed high variability across trials (*t*-test on SD showed significant difference from comparison participants, $t(23) = 3.77$, $p < 0.005$, $d = 1.21$). The gradual decline in distance over trials was attributable to only three individuals who had very long path

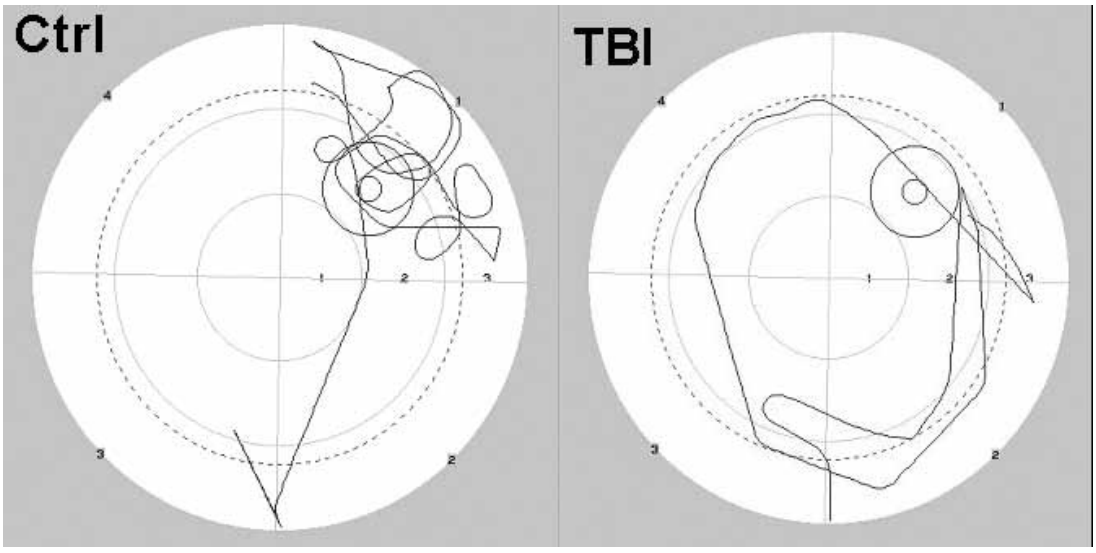

Figure 4. Paths taken during probe trials by representative individuals (median dwell time) from the comparison group (Ctrl) and from those with brain injuries (TBI).

lengths on trials 1–4, 4 and 4–7, respectively. Most other individuals showed poor and variable latencies throughout. The variability of distances (SD) across trials was also different between the groups ($t(23) = 2.87$, $p < 0.01$). Clearly, those with brain injuries never achieved the same ability to go the platform, quickly, directly and consistently.

On Probe Trials, those without brain injuries spent most of the time searching in the correct quadrant of the arena (74% ± 4.3% SEM), suggesting that they knew where the platform was located and were confident in their knowledge. In contrast, those with brain injuries searched the correct quadrant only slightly more than would be expected by chance (33% ± 5.9% SEM *vs.* 25%), suggesting that they either didn't know where it was or had little confidence in their knowledge. The difference between the groups was significant: $t(24) = 5.48$, $p < 0.00001$. Representative samples of paths taken are shown in Figure 4. Note that the control participant tended to concentrate his search in the quadrant that contained the platform and tended to double back quickly once the position had been passed. In contrast, the TBI survivor searched nearly all four quadrants indiscriminately, travelling in an annulus approximating the platform's distance from the wall and not doubling back after the platform position was crossed.

Comparison of dependent variables

One of the objectives of the present study was to determine which measures of Arena Maze performance were best able to differentiate those with and without brain injury. Accordingly, nine variables from the invisible platform trials and eight variables from the probe trial were analysed. Trial data was analysed from trials 2–10, excluding trial 1, which reflected searching ability rather than wayfinding to a previously visited location. In addition to the usual variables of latency, distance and speed, path efficacy, radius, tortuosity, thigmotaxia, heading accuracy and bearing accuracy were analysed. The only variable that showed a greater effect size than latency or distance was path efficacy, a relatively new measure consisting of the ratio of the length of path taken to the shortest possible path. The remaining trial variables provided no new information of value. In case the difference between those with and without injury was related to the variability of performance over trials (i.e. those with injuries were good on some trials but not others), the standard deviation was calculated over trials for each individual on all nine trial variables and then compared the standard deviations between groups. None of these differences were significant or showed an effect size above 0.85. Therefore, the only trial variables to be discussed further are latency, distance, speed and path efficacy.

One was interested to see whether any measure of probe trial performance would be more revealing than the standard quadrant dwell time (%). An area near the platform was defined equal to one third the radius of the arena (see Figure 4) as the 'target vicinity' and examined vicinity dwell time, vicinity entries, as well as target line crossings. Because circling at a fixed distance from the wall is a well-known (non-spatial) response strategy, the arena was also divided into three rings with equal radius (see Figure 4) and examined dwell times in the target's ring, the time in the ring within the correct quadrant and the percentage of time in that quadrant-ring sector compared to the total time in the ring. Interestingly, all variables

Table II. Significance of differences between non-injured and TBI participants on spatial and organismic variables.

Domain	Variable	$t(24)$*	$P<$**	Effect size (Cohen's d)
Arena Maze				
Visible trials	Latency	−2.62*	0.02	1.03
	Distance	−2.13*	0.05	0.84
	Path efficacy	2.64*	0.02	1.04
	Speed	2.61	0.02	1.03
Invisible trials (2–10)	Latency	**−4.05***	**0.001**	**1.48**
	Distance	−3.56*	0.005	1.30
	Path efficacy	**4.16**	**0.0005**	**1.64**
	Speed	0.99*	0.331	0.38
Probe trials	Correct quad dwell %	**5.12**	**0.00001**	**2.01**
	Target vicinity dwell%	**4.09**	**0.0005**	**1.61**
	Target vicinity entries	2.73	0.01	1.07
	Target line xing	2.17	0.05	0.86
	Target ring dwell	1.00	0.33	0.39
	Quad/ring dwell	**3.82**	**0.001**	1.51
	Quad/ring discrimination	**4.84***	**0.0001**	1.85
'Spatial score'	(Dist, lat, Dw%) mean Z	**5.74***	**0.0001**	**2.25**
Everyday Spatial Questionnaire				
	Q 1–9 (spatial)	−2.56	0.02	1.02
	Q 10–13 (object memory)	−3.03	0.01	1.21
	Total	−2.96	0.01	1.16
Organismic variables				
	Sex	0.816	0.42	0.43
	Age	−1.097	0.28	0.31
	Education	−0.795	0.44	0.32

*df = 24 only when equal variances assumed. When this assumption was significantly violated, the corrected t and p values are given.
*Because of the number of comparisons of arena maze behaviour (16), α was adjusted to $p < 0.003$ to protect experimentwise error. Significant comparisons are bolded.

except target-ring dwell time showed effect sizes greater than 0.85, but none were better than the standard dwell time in correct quadrant (see Table II).

When the four variables from the visible platform trials were also considered, performance in the Arena Maze was assessed by a total of 16 dependent variables. Therefore, the per-comparison α was adjusted to $p < 0.003$ to preserve experiment-wise α at $p < 0.05$. With this criterion, there were no significant differences between TBI and non-injured participants on the visible platform trials, indicating that participants with TBI were not significantly impaired in their understanding of the task demands, nor in their ability to navigate to a target location in this virtual environment (see Table II). Although there were large effect sizes on visible platform trials, these appeared to be due to the extremely low variance of data from non-injured participants, which was in turn due to a floor effect on these easy trials.

Figure 5 clearly shows that the measures of performance which best discriminated those with from those without brain injuries were latency and path efficacy on invisible platform trials and quadrant dwell time (%) on probe trials. Examination of data from individual participants revealed that some of those with brain injuries showed poor performance on invisible platform trials but reasonable performance on probe trials, whereas others had poor performance on probe but not on invisible platform trials. In order to best capture individual spatial competence, the two standard measures were combined from the invisible platform trials (latency and distance), with the best measure from the probe trials (dwell time) by converting each individual's score on these measures to z-scores, based on the mean and standard deviation of the control group. Then the scores were combined in a weighted average that equally represented both types of trials and accounted for the fact that latency and distance were negatively related to good performance (lower is better), whereas dwell time is positively related (higher is better) by multiplying latency, distance and dwell time z-scores by −0.25, −0.25 and 0.50, respectively. This new 'Spatial Score' proved to be the best measure of performance in the maze, showing an effect size of 2.25.

Although the number of participants in this study is small, it was still possible to calculate sensitivity and specificity (variables of clinical interest) and to compare the different Arena Maze performance measures for their ability to discriminate those with head injuries from those without. For this purpose, the criterion was set to detect whether an individual score would be significantly different from control (i.e. Mean plus X times SEM where

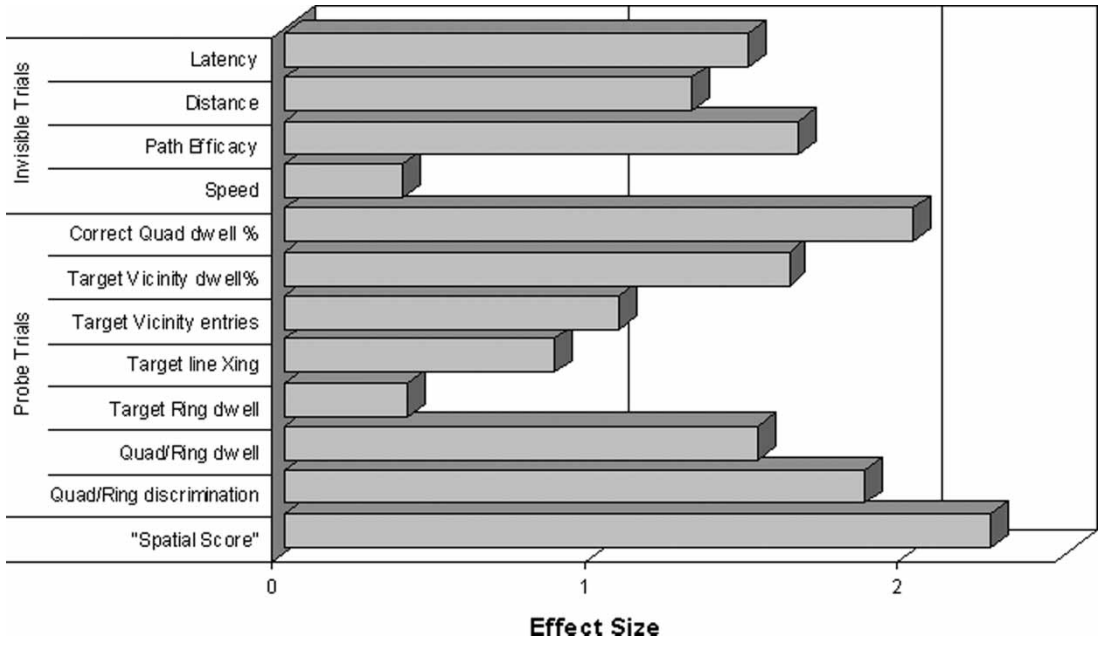

Figure 5. Comparison of effect sizes of pairwise *t*-tests between TBI and comparison groups on the 12 dependent variables of spatial behaviour. Note that an effect size greater than 1.0 is considered a 'large' effect.

Table III. Comparison of the clinical utility of Arena Maze variables using Bayesian statistics.*

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio (+)	Likelihood ratio (−)
Latency	64%	92%	90%	69%	7.71	0.39
Distance	79%	83%	85%	77%	4.71	0.26
Path efficacy	71%	83%	83%	71%	4.29	0.34
Dwell time (% correct)	79%	83%	85%	77%	4.71	0.26
Spatial score	93%	92%	93%	92%	11.14	0.08

*from http://www.intmed.mcw.edu/clincalc/bayes.html

$X = t(24,\ p < 0.003)$, α as above). In terms of distinguishing members of the injured group from those of the comparison group, most measures did quite well, but the Spatial Score did very well, with a sensitivity of 92% and specificity of 93% and (surprisingly) equal values for positive and negative predictive values. Perhaps most importantly, the likelihood ratios indicated that those given a positive score for brain injury had an odds ratio of 11:1 of being correct, whereas those given a negative score had a 12:1 chance of being correct (see Table III). In the present results, 13 of 14 participants with brain injury were significantly different from the comparison group and only one of the 12 comparison participants did not meet the criterion cut-off.

The differences in performance in the Unreal® Arena Maze between those with and without brain injuries were comparable to those reported previously in the Virtual Arena. In fact, the effect sizes seen here were larger than those reported earlier (see Table IV), suggesting that the previous results were not confined to primitive graphical displays with a less life-like virtual environment.

Table IV. Comparison of effect sizes between current paper and previous report [14].

Variable	Previous study	Current study
Latency	1.04	1.48
Distance	0.74	1.30
Probes	0.92	2.15
Spatial score	1.24	2.41

As in the previous study, participants were asked to rate their spatial functioning in their everyday life using the Everyday Spatial Questionnaire [14]. Once again there was a significant difference between those with and without brain injury ($t(24) = -2.96$, $p < 0.01$, Cohen's $d = 1.16$), but this time there was

no strong correlation with measures of Arena Maze performance. Those with brain injuries reported having more frequent spatial problems than those without brain injury on the ESQ questions related to wayfinding (questions 1–9, $t(24) = 2.63$, $p < 0.015$, $d = 1.01$) and on remembering object locations (questions 10–13, $t(24) = 3.11$, $p < 0.005$, $d = 1.19$). The question that most differentiated those with and without TBI was how often they had trouble finding their car in a parking lot ($t(24) = 3.27$, $p < 0.003$, $d = 1.34$). There were also significant differences ($p < 0.005$) and large effect sizes (>0.80) on five of the six questions about frequency of getting lost or disoriented, be it in familiar or unfamiliar buildings or parts of town. There were no significant group differences on the five questions about compensatory activities like asking directions or putting objects in special places. Among participants with brain injury, there was a significant correlation between dwell time in the correct quadrant and object location memory (ESQ questions 10–13, $r(24) = 0.62$, $p < 0.02$). The reliability of these findings is substantiated by Cronbach's α, which was 0.90 for all participants and 0.76 and 0.91 for comparison and TBI groups, respectively.

The differences between participants with and without brain injury could not be accounted for by differences in any of the demographic variables collected. There were no significant differences between the groups and no correlations with any Arena Maze variables in age, gender, time-since-injury or computer experience.

Discussion

The present results confirm that, as expected, survivors of TBI show severe impairments in spatial navigation in a virtual version of the MWM. These findings extend the previous study [14] in four important ways. First, they confirm that community living survivors of brain injury tend not to have trouble with desktop virtual environments *per se*. Secondly, they verify that the deficits observed in the previous study were not due to the primitive graphics available at the time, but persist in a much more realistic environment. Thirdly, they identify which of the many possible measures of behaviour in the maze are practical, sensitive and specific. Fourthly, they derive from a different population of TBI survivors, namely institutionalized and community-living survivors rather than those in a rehabilitation programme, thereby indicating that the deficits reported earlier were not idiosyncratic to the particular sample of brain injury survivors that were tested.

The procedural demands of the task were not beyond most of the target population. None of the five of the sample institutionalized for severe impairments in executive and social functioning had trouble with the procedural demands and the one community-living survivor who had trouble (becoming 'trapped' by the wall of the arena), had a visual deficit; his binocular images did not fuse. The other 14 participants with brain injury were able to maintain their performance throughout the session. They had no trouble moving to the platform when it was visible, indicating that they understood the demands of the task and had the sensory, motor and sensorimotor abilities necessary to move to a target location in virtual space. Furthermore, on the first invisible platform trial, those with brain injuries took no longer than comparison participants to find the platform, indicating that their ability to search the arena was normal. In other words, they were able to cover the required areas of the arena and did not tend to perseverate in one area of the arena.

However, brain injury survivors had serious difficulty finding the platform quickly and consistently when it was invisible. Non-injured participants, once they found the platform the first time, went to it quickly and directly on every trial thereafter and spent 74% of the probe trial searching for it in the correct quadrant. In contrast, brain injury survivors were unable to find it consistently, often taking circuitous routes and long times to find it on the remaining trials and spending little more time in the correct quadrant than would be expected by chance.

These results replicate the previous finding [14] that survivors of TBI have difficulty navigating in virtual space. The difference is that the new virtual environment is much more realistic, providing better optic flow and greater ease in calculating distances [62]. In the previous study, the floor and ceiling were monochromatic and the arena wall was not textured and the screen resolution was 320×200 pixels. This made judging distances, angular displacements and travel velocity much more difficult and, in fact, it sometimes took participants a minute or so to recognize the three-dimensionality of the environment. In addition, the Virtual Arena of the previous study had pictures on the wall, rather than windows with a view to a three-dimensional landscape outside that provided distinct features at each compass direction. In the current study the screen resolution was 800×600 pixels (an increase of 7.5 times) and participants seemed impressed with the environment, rather than puzzled. The replication of spatial deficits, therefore, confirms that the previously observed deficits were not due to a failure of imagination (visuospatial visualization). Indeed, despite the improvement in three-dimensionality, the difference between those with and without brain injuries was clearer in this study than it was in the

first one. Although it is difficult to know whether the larger effect sizes observed in the present study were due to differences in the virtual environment tasks or to differences in the degree of underlying impairments, the fact remains that the impairments did not disappear when the environment became more realistic. This is important because a more realistic environment is presumably more amenable to path integration [61] and other processes necessary to the development of allocentric representations [65].

The third objective of the present study was to determine which dependent variables best identify deficits in spatial ability based on the effect size. The two variables which best discriminated the spatial memory and navigational ability of TBI from the comparison participants on invisible platform trials were latency and path efficacy. Latency is very commonly used in the MWM and is easy to understand and simple to collect (e.g. with a stopwatch). However, latency is a heterogeneous variable reflecting spatial ability, sensorimotor processing speed, distractibility and level of computer experience. Distance, another commonly used variable, was also a good measure in the present study because it had a large effect size. Distance is a more homogeneous (easier to interpret) variable than latency, as it is less affected by non-spatial factors such as slowing of cognition or motor processes. However, path efficacy (the directness of the path to the target in comparison to the shortest route) seemed to be a better measure of spatial memory and navigational ability than distance or latency.

Dependent variables derived from the probe trials proved to be good at discriminating those with brain injury from those without. The time spent near the platform location is generally felt to reflect their knowledge of the location [30, 66], their ability to go to that location and, presumably, their confidence in their ability to find the platform (leading them to continue searching in the expected location). This interpretation was validated by end-of-session discussions with the participants. Dwell time in the correct quadrant, the traditional measure of performance on probe trials, turned out to be the best probe trial measure for distinguishing injured and non-injured participants, with an effect size of 2.0. Three of the other six measures were also significant with very large effect sizes ($d > 1.5$), but none was as high as quadrant dwell time.

The new 'Spatial Score', introduced in this paper, was the best measure for discriminating brain injury deficits. This measure incorporates all three common measures (distance, latency and dwell time) from both the invisible trials and the probe trials into a single variable based on standard scores. This score incorporates the assessment of the participant's ability to find the platform with their knowledge of the platform's location and their confidence in being in the right place.

Another contribution of the reported research is the new and more realistic environment used in this experiment. Other researchers have developed virtual maze environments using game platforms [52, 68], but few have simulated the MWM and none have used a more realistic environment than Unreal®.

The Arena Maze has several key features. First, there is a world outside the room, which allows people to set cardinal directions (north, east, etc.), for example, by using mountains as navigational beacons, thereby providing an external axis against which to align their egocentric axis (as per O'Keefe and Nadel's [29] 'orientation'). Secondly, two of the room walls can only be discriminated from each other by the view of the world outside or by the spatial relations between one of them and another wall. The outside world and its value for orientation encourage participants to rely on a configuration of distal and proximal cues (e.g. the view out one window plus the distance from arena wall) to find the platform. Thirdly, the realism of the surroundings should encourage the use of spatial cognition normally used in the real world.

If the primary interest is in how TBI survivors navigate in the real world, why test in virtual environments? First, the environment is the same from one lab to another and is free from distractions like the weather or pedestrian or vehicular traffic and it is safe for participants (no cars, no falls). Secondly, the environment can have stimuli and contingencies difficult to find in real world situations, thus providing exquisite control over characteristics of the environment such as geometry and size of the space and location of objects and features (like windows) within it. This ability to systematically vary environmental stimuli and contingencies should improve the analysis of spatial cognition [67] and spatial deficits. Thirdly, it is possible to test in virtual space multiple times for purposes of periodic assessment or practice and rehabilitation [23], a feature important for TBI survivors. Fourthly, virtual environments provide a means to engage anatomical structures underlying spatial cognition while participants are in an fMRI scanner. This approach has been used successfully with uninjured participants [58, 68] and with participants who have unilateral medial temporal lobe resections [58] and, in a preliminary study, with TBI survivors [60].

The software in which this environment is built also offers several advantages. First, it is based in the Unreal® engine, which provides a much more realistic experience to encourage acquisition of allocentric representations and the use of path integration. Secondly it is very flexible in the stimuli and contingencies available and is accompanied by a

commercial-grade three dimensional editor. Thirdly, more recent versions of Unreal® are available, if the realism of the environment is a primary issue. Fourthly, the game environment has been interfaced to a sophisticated program for analysing performance in the maze, namely TRAM®. This program is capable of providing nearly every measure of performance used in the MWM. Fifthly, the virtual environment is available from the authors upon request.

At this point, the full significance of the spatial cognition impairments described here is not clear. They may indicate that damage to the hippocampus, observed to be common on post-mortem exams [7], is also common in community-living survivors of TBI. The vulnerability of the hippocampus to TBI [2] may account for why TBI so often leads to spatial deficits [24] and suggests that loss of spatial ability could in turn be a sensitive indicator of TBI. Furthermore, the anterograde amnesia that often accompanies TBI [69, 70] might also be due to hippocampal dysfunction [71] and further investigation of the co-occurrence of memory and spatial deficits might elucidate the anatomical relation between these two cognitive functions.

Although the deficits observed could have been due to frontal lobe damage (also commonly observed in TBI [59], other 'frontal lobe' deficits [72] such as impulsivity, perseveration and failure to maintain intent were noted in only one participant, who was subsequently excluded from the analysis.

The observation that most participants with brain injury had difficulties with spatial navigation suggests that this impairment should be investigated further, both for the functional problems it might cause and for the proportion of survivors who face this problem. The present results confirm that there is an effect worth studying. Research with laboratory animals suggests that the ability to navigate by landmarks or by memorized response patterns, may be spared [73]. If this is the case, then compensatory strategies could be built around commonly unaffected abilities and this possibility should be studied further. The present findings suggest the need for more studies to determine the nature of the cognitive deficit and the degree of residual ability and possibly more imaging studies relating hippocampal (and frontal lobe) anatomy to spatial navigation in humans.

Although many developmental steps remain, the Arena Maze holds promise as a clinical tool for assessing anterograde topographical disorientation and persistent deficits in allocentric navigation. First, it is easy to implement with ordinary desktop computers and game controllers. Secondly, because it studies navigation in a three dimensional environment, it is more ecologically valid than paper-and-pencil tests. Thirdly, because it is a completely novel task, participants experience no sense of failure, even when they are quite poor at finding the platform; they have no sense of the expected standard of performance and, as a last resort, blame the computer (observations within this study).

It is recognized that the Arena Maze is not yet ready for the clinic: 30 minutes is generally too much assessment time to take to evaluate a single cognitive function like spatial cognition and the data analysis is cumbersome. Furthermore, the need to test for topographical disorientation has not yet been demonstrated; further studies of incidence among TBI survivors and impact on their lives is needed. Nevertheless, it is expected that further research will refine (and shorten) the test procedure, enhance its ability to reveal other deficits and establish the prevalence and impact of topographical disorientation among TBI survivors. More generally, neuroimaging studies should reveal the association between hippocampal damage and cognitive deficits and provide new insights into human spatial processing and functional anatomy.

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