Virtual navigation for memory rehabilitation in a traumatic brain injured patient

M. Caglio[1], L. Latini-Corazzini[1], F. D'Agata[1,2], F. Cauda[1,2], K. Sacco[1,2], S. Monteverdi[3], M. Zettin[1,3], S. Duca[2], and G. Geminiani[1,2]

[1]Department of Psychology, University of Turin, Turin, Italy
[2]CCS-fMRI, Koelliker Hospital, Turin, Italy
[3]Puzzle Rehabilitation Center, Turin, Italy

The use of 3D video games in memory rehabilitation has been explored very little. A virtual navigation task allows participants to encode the spatial layout of the virtual environment and activate areas involved in memory processing. We describe the rehabilitation of a 24-year-old man with traumatic brain injury presenting memory deficits, and evaluate the efficacy of a navigational training program measuring neuropsychological changes and fMRI modification cerebral activations. Memory improvement appears to be present both after navigational training and in follow-up testing. Furthermore, fMRI data suggest that this training may increase activation of the hippocampal and parahippocampal brain regions. The results suggest that intensive training in virtual navigational tasks may result in an enhancement of memory function in brain-damaged adults.

Keywords: Memory rehabilitation; Computer-based training; Virtual reality; Traumatic brain injury; fMRI.

Background

Traumatic brain injury (TBI) can cause a variable range of cognitive impairments usually in the domains of memory, attention, and executive functioning; memory deficit in particular is one of the most common and disabling impairments (Vakil, 2005). The utilization of 3D interactive Virtual Reality (VR) environments in neuropsychological rehabilitation enables ecologically valid and dynamic training to be provided (Rose, Brooks, & Rizzo, 2005).

The crucial role of the hippocampal and parahippocampal cortices in declarative memory has been demonstrated, starting from the seminal report of the H.M. case (Scoville & Milner, 1957); human hippocampal formation is related to different declarative memory subsystems such as declarative learning (Squire & Zola-Morgan, 1991), spatial memory (Maguire et al., 1998), and verbal association (Henke et al., 1999). The hippocampus and related structures are involved in navigation tasks in animals and humans and could be related to the formation of cognitive maps, i.e., mental representations of the spatial (geometric) features of the environment (Delpolvi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007; O'Keefe & Nadel, 1978). The study of the spatial cognition involved in everyday activities in familiar environments suggests that the hippocampus is necessary

for facilitating navigation in places learned long ago (Spiers & Maguire, 2007). It has been shown that navigation of a virtual environment allows participants to encode the spatial layout of the environment and activate a network of areas, such as the hippocampus, which are involved in memory processing (Maguire et al., 1998). Woollett, Glensman, and Maguire (2008) assumed that hippocampal activations are more likely to be observed when the knowledge acquired concerns a complex and detailed large-scale spatial layout.

Aim of the study

The aim of our study was to investigate the effect of navigational training using a 3D VR videogame on both spatial and verbal memory in TBI patient rehabilitation. Our hypothesis is that navigation in a VR environment is an ecological task that is effective in activating hippocampal formation, improving both spatial and verbal memory. The use of functional neuroimaging has been shown to be a useful tool for assessing outcomes in neuropsychological rehabilitation (Laatsch et al., 2007). Therefore, in the present study, we explored the changes in cerebral activation in the medial temporal lobe through functional neuroimaging (fMRI). The assumption is that increased activation in this brain area is associated with improved functions associated with that area as shown by the positive correlations between the number of items retrieved and the signal intensity in the medial temporal lobe linked to the encoding processing (Fernandez et al., 1998).

Case report

The present study describes the rehabilitation of a 24-year-old right-handed man (W.P.), who had completed his compulsory education and worked as a storeman. His medical history was unremarkable until he was involved in a motor vehicle crash (05/06/2006) and sustained a TBI of moderate severity. He remained in a coma for 27 days and his maximum score on the Glasgow Coma Scale was 5. A Computerized Tomography (CT) scan performed the same day as the TBI showed the presence of hemorrhagic contusions in the bilateral frontal, temporal and parietal lobes (see Figure 8S). Seven months after the TBI, the patient was admitted to the 'Puzzle' Rehabilitation Center in Turin.

Neuropsychological assessment on admission indicated the presence of a severe anterograde (both recall and recognition) and retrograde amnesia and deficits in spatial learning (supraspan on Corsi's test). Before the navigational memory training, the patient underwent standard rehabilitation protocols for 5 months. In particular, he performed a first rehabilitation session, lasting 2 months, during which information processing, sustained attention, and working memory were trained; then, he performed a second rehabilitation session, lasting 3 months, designed to improve the mnestic functions and consisting of learning lists of words. A comparison of the results obtained before and after each of these two standard rehabilitation protocols revealed no significant difference in neuropsychological scores. Thus, the patient entered our experimental navigational memory protocol after 5 months of attention and memory rehabilitation followed by no cognitive improvements.

The selection of this patient for our experimental protocol has therefore been motivated by the fact that general practice effects would not explain post-training improvements; also, spontaneous recovery is implausible as our training started 1 year after the traumatic event and no changes occurred in that lapse of time.

METHODS

Procedures

The participant gave his informed written consent to participate in an experimental computerized program of navigational memory training, in accordance with the requirements of the local medical ethics committee and with the ethical standards laid down in the 1964 Declaration of Helsinki.

The rehabilitation training was based on a navigational task, exploring part of a virtual town (London) from a ground-level perspective, using a computer videogame driving simulator (Midtown Madness 2, Microsoft Game Studios; Figure 1S). The participant had previous experience of playing first-person videogames.

The task was different from the original tasks of the videogame; the instruction to the participant was as follows: 'You must cut down poles and trees that you find all along the way'; the participant did not have access to a city map during the task. The aim of the instruction was to induce the participant to explore the virtual town extensively, avoiding

reuse of the same roads; therefore, the spatial memory task was implicit, while the explicit task was a simple game, one that the participant enjoyed.

The training consisted of a series of 90-minute sessions three times a week (total length of intervention: 5 weeks). In each training session the subject had a 7-minute break after every 20 minutes of navigation.

The patient was evaluated before and immediately after training by means of a standardized neuropsychological assessment. He was retested 2 months after the last memory training session; and once again 1 year after training.

A comparison was then made of the subject's performance before and after intervention and in the follow-ups.

Neuropsychological assessment

The neuropsychological assessment consisted of a battery of cognitive tests assessing: spatial short-term memory, visuo-spatial learning, working memory, verbal learning, frontal executive functions, and general cognitive impairment. Four parallel and equivalent forms were used for all tests.

Corsi Block-Tapping Test (Spinnler & Tognoni, 1987)

The aim of the test is to provide a measure of short-term spatial memory. This task was given according to the procedure suggested by Spinnler and Tognoni (1987). The experimental apparatus consisted of a board measuring 25×35 cm on which 9 blocks (side 4.5 cm) were fixed. A serial number identifying each block was visible only to the examiner. The participants were asked to reproduce a specific sequence of cubes in the same order as the examiner. Performance was defined by the longest sequence at which participants correctly recalled at least two out of three sequences.

Corsi's Supraspan Test (Spinnler & Tognoni, 1987)

This task was given according to the procedure suggested by Spinnler and Tognoni (1987). The experimental apparatus was the same used in the Corsi Block-Tapping Test. A serial number identifying each block was visible only to the examiner. The examiner touched a standard supraspan sequence of 8 blocks at a rate of 1 block every second. Immediately following the presentation, the patient was asked to touch the blocks in the same order (immediate recall). The same sequence of blocks was reproposed by the examiner until the subject could reproduce it correctly three consecutive times or after 18 consecutive trials. Five minutes after the last trial, the subject was again asked to reproduce the sequence of blocks (delayed recall). The response to each presentation was scored on the basis of the probability of giving the correct response (or fragment of it) by chance (Carlesimo, Fadda, Bonci, & Caltagirone, 1993).

Backward digit span (Spinnler & Tognoni, 1987)

The participant had to remember lists of increasing length of single-digit numbers and recall them in the opposite order. Performance was defined by the longest sequence at which participants correctly recalled at least two out of three sequences.

Rey Auditory Verbal Learning Test – RAVLT (Lezak, 1995)

This test measures verbal learning and consists of five learning trials of a 15-word list. The participant was asked to repeat as many items as possible after each trial, and then to recall as many items as possible from the original list (immediate recall). Delayed recall of the same list was assessed after 15 minutes (delayed recall).

Trail Making Test TMT A-B (Lezak, 1995)

The aim of the test is to provide a measure of attentional-executive functioning. The participants were instructed to sequentially connect on a sheet 25 circles that in part A contained the numbers 1–25, and in part B the numbers 1–13 and the letters A–N. Part A required the participants to connect the circles in ascending sequence from 1 to 25; part B required them to connect the circles in an ascending sequence of alternating numbers and letters (1, A, 2, B, etc.). The total number of seconds required to complete parts A and B was measured separately.

Phonemic fluency (Lezak, 1995)

The participant was asked to produce in 1 minute as many words as possible beginning with F, A, and S. All results were compared considering the equivalent scores obtained in the different assessments. The equivalent score is a 5-point scale (0–4), where 0 indicates a score that lies below the external

nonparametric tolerance limit of adjusted scores (under 95% of the population with 95% confidence), and 4 indicates A performance equal to or greater than the mean of the adjusted scores, thus no longer distinguishing between scores found in the upper half of the distribution. Equivalent scores of 1, 2, and 3 are intermediate between 0 and 4 on a quasi-interval scale. An equivalent score of 0 will be considered below the normal range, with a controlled error risk (Capitani & Laiacona, 1988, 1997).

Alzheimer's Disease Assessment Scale (ADAS) (Rosen, Mohs, & Davis, 1996)

This global rating scale is used to summarize whether an individual has cognitive impairments consistent with Alzheimer's disease. Test items assess various functions including language ability, memory, ability to copy geometric figures, and orientation to current time and place. Patients are given a score for each area, with higher scores indicating more dysfunction.

The Rivermead Behavioural Memory Test (RBMT) (Wilson & Baddeley, 1985)

This test was used to assess impairments in everyday memory functioning. We turned to the RBMT, a reliable instrument for detecting everyday memory impairments that reflect difficulties in 'real life'. In the RBMT, two tasks (Story Recall and Route Recall subtests) assess everyday memory demands, respectively, in verbal and in spatial learning domain.

Story recall subtest. The experimenter read the short story only once and is then asked to recall as much as they can immediately upon finishing the paragraph. After 10 minutes have passed the patient is reminded of the story and asked to repeat it again. Scoring of the Story: a point is awarded for each event recalled. Maximum score = 21.

Route recall subtest. The experimenter walks a route round the room that includes explicitly visiting five separate locations. The final stage of the route is the experimenter's starting position (therefore, location 5 is the same as location 1). Before they start, the experimenter tells the participant that they will be asked to do 'the same thing' once the experimenter has finished. The experimenter verbalizes what they are doing throughout the route. When the experimenter is finished, he asks the participant to repeat the same path, starting from the same position (Immediate condition). Approximately 15 minutes later the participant is asked to repeat the route (Delayed condition). Scoring of the Route: a point is awarded for each stage visited in the correct order. Any stage that is erroneously added is considered a false positive and a point is deducted. Maximum score = 5.

Functional neuroimaging assessment

Functional magnetic resonance imaging is employed to record brain activity during the performance on a memory task using Paired Associate Learning (abstract words) as mnemonic content. During scanning, the participant was repeatedly verbally presented with seven pairs of words; then, outside the scanner, the patient was asked to recall the word pairs. The paradigm had a block design with 14 s of rest alternating with 28 s of activation condition. The paradigm consisted of 2 runs of 35 blocks (18 rest conditions, 17 active conditions). During rest, the subject mentally counted from 1 to 10; during learning, he listened to 7 pairs of abstract words.

BOLD imaging data were analyzed using the SPM5 software in the MATLAB 7.0 environment (Math Works Inc., Natick, MA, USA). The subject's functional data underwent the following preprocessing steps: (1) slice scan time correction; (2) 3D motion correction; (3) normalization to the Montreal Neurological Institute (MNI) standard; (4) spatial smoothing using a Gaussian kernel of 8 mm FWHM; and (5) temporal filters – linear trend removal and non-linear trend removal using a temporal high-pass filter (frequency pass = 0.008 Hz) – to remove drifts due to the scanner and other low frequency noises.

The patient underwent three fMRI sessions: pre-VR-training, post-VR-training (after 2 months of navigational memory training), and a follow-up session (2 months after discontinuation of the training).

Statistical analysis was carried out in the context of the General Linear Model (GLM). The resulting SPM{t}s were thresholded at $p < .05$, corrected for multiple comparisons across the whole brain (FWE correction) with a cluster size $k_E > 25$ voxels.

We also used an explicit mask limiting our analysis to the hippocampal and parahippocampal regions in order to study the variation of activity in these areas, guided by our prior hypothesis. The resulting SPM{t}s were thresholded at $q < 0.05$,

corrected for False Discovery Rate (FDR correction, <5% false positive) with a cluster size $k_E > 10$ voxels. The voxel resolution of the functional sequences was $4 \times 4 \times 4$ mm^3.

RESULTS

Neuropsychological data

The scores from the neuropsychological tests performed before and after navigational VR training with video games are shown in Table 1. The effects of the training on performance were evaluated by comparing the scores of the first and later assessments; the raw scores were translated into equivalent scores and compared in this way.

The participant in this study presented a post-VR-training improvement, showing better performance in neuropsychological tests assessing visuo-spatial learning. In particular, improvements from pre-VR-training to post-VR-training were detected in the Corsi's supraspan delayed recall (from 4/8 to 8/8) and in RBMT Route delayed recall (from 0/5 to 4/5), an ecologically valid measured of spatial memory, persisted at follow-ups.

Comparing post-VR-training scores (three observations) vs. pre-VR-training scores (three observations), using the non-parametric Mann–Whitney U-test, the following comparisons showed significant differences: RAVLT immediate recall (z adjusted $= 1.99$, $p = .05$), Corsi's supraspan test, delayed recall (z adjusted $= 1.96$, $p = .05$) and Corsi's supraspan test, immediate recall (z adjusted $= 2.12$, $p = .03$); no significant differences were obtained in the following tests: RAVLT delayed recall, Digit span forward and backward, Corsi's block tapping test.

TABLE 1

Comparison of neuropsychological assessments at baseline, after attention rehabilitation, after memory rehabilitation (pre-VR-training) and after memory training with video game (VR), follow-up at 2 months and at 1 year after the last memory training treatment (post-VR-training)

	Pre- VR- training			Post- VR- training		
	Baseline	Attention Rehabilitation	Memory Rehabilitation	Immediate post-training	Follow-up2 months	Follow-up 1 year
Digit span						
Forward	7 (ES: 4)	7 (ES:4)	7 (ES:4)	8 (ES: 4)	NA	5 (ES: 3)
Backward	6	7	7	8	NA	7
Rey AVLT						
IR	32 (ES: 0)	25 (ES: 0)	32 (ES: 0)	39 (ES: 1)	36 (ES: 1)	38 (ES: 1)
DR	4 (ES: 0)	5 (ES: 0)	5 (ES: 0)	4 (ES: 0)	10 (ES: 3)	8 (ES: 1)
RBMT-Story Recall						
IR	NA	NA	7/21	11/21	8/21	8/21
DR	NA	NA	4/21	0/21	5/21	6/21
Corsi's Block Tapping Test	5 (ES: 3)	NA	5 (ES: 3)	7 (ES: 4)	6 (ES: 4)	5 (ES: 3)
Corsi's supraspan						
IR	13.2 (ES:0)	14 (ES:0)	17.2 (ES:1)	17.9 (ES: 1)	25.6 (ES: 3)	18.85 (ES: 2)
DR	4/8	2+2/8	4/8	8/8	8/8	6/8
RBMT Route Recall						
IR	NA	NA	3/5	4/5	4/5	5/5
DR	NA	NA	0/5	4/5	4/5	5/5
Trail making						
Test A	NA	NA	NA	34 (ES: 4)	NA	44 (ES: 3)
Test B	NA	NA	NA	74 (ES:4)	NA	54 (ES: 4)
Phonemic fluency	NA	NA	NA	31 (ES: 3)	35 (ES: 4)	31 (ES: 3)
MMSE	NA	NA	NA	29	29	28
ADAS	NA	NA	NA	7.6	9	8.6

ES, equivalent score; NA, not available; IR, immediate recall; DR, delayed recall.

fMRI data

We compared the post-VR-training session with pre-VR-training (post-VR- > pre-VR-) to explore the neural correlates of the navigational memory rehabilitation and we compared post-VR-training with follow-up to investigate the stability of such changes.

We found a rich pattern of activation in the post-VR-training session (see supplemental content Table 2S, Figure 3S), including principally the superior and middle temporal gyrus (bilaterally), the frontal gyrus (bilaterally; BA 6, 8, 9), the cerebellum (bilaterally), the left and right hippocampus, and the left anterior cingulate.

These activations were more extended compared to the pre-VR-training (Table 2, 1S, 2S, Figure 1, 2S, 3S) and in particular included left ventral tegmental area (VTA) and left hippocampus, the

TABLE 2
Post-VR-training > Pre-VR-training

N	k_E	Area	BA	MNI (x, y, z)	Z_E	R (mm)
1	498	L VTA	*	−4 −24 −12	6.73	2
		L Hippocampus	*	−26 −20 −6	5.34	1
2	69	L Medial Frontal Gyrus	10	−4 52 −8	5.74	0
3	224	L Medial Frontal Gyrus	9	0 54 24	5.47	1
		R Medial Frontal Gyrus	9	6 46 32	4.94	0
4	53	R Parahippocampal Gyrus	30	16 −48 0	4.84	0
5	33	R Cuneus	18	20 −76 30	4.53	0
		R Precuneus	31	10 −74 32	4.49	0

Brain activations in the post-VR-training minus pre-VR-training conditions, whole brain. For each cluster of activation, the Brodmann's area (BA) and the local maxima in the Montreal Neurological Institute (MNI) space are reported.
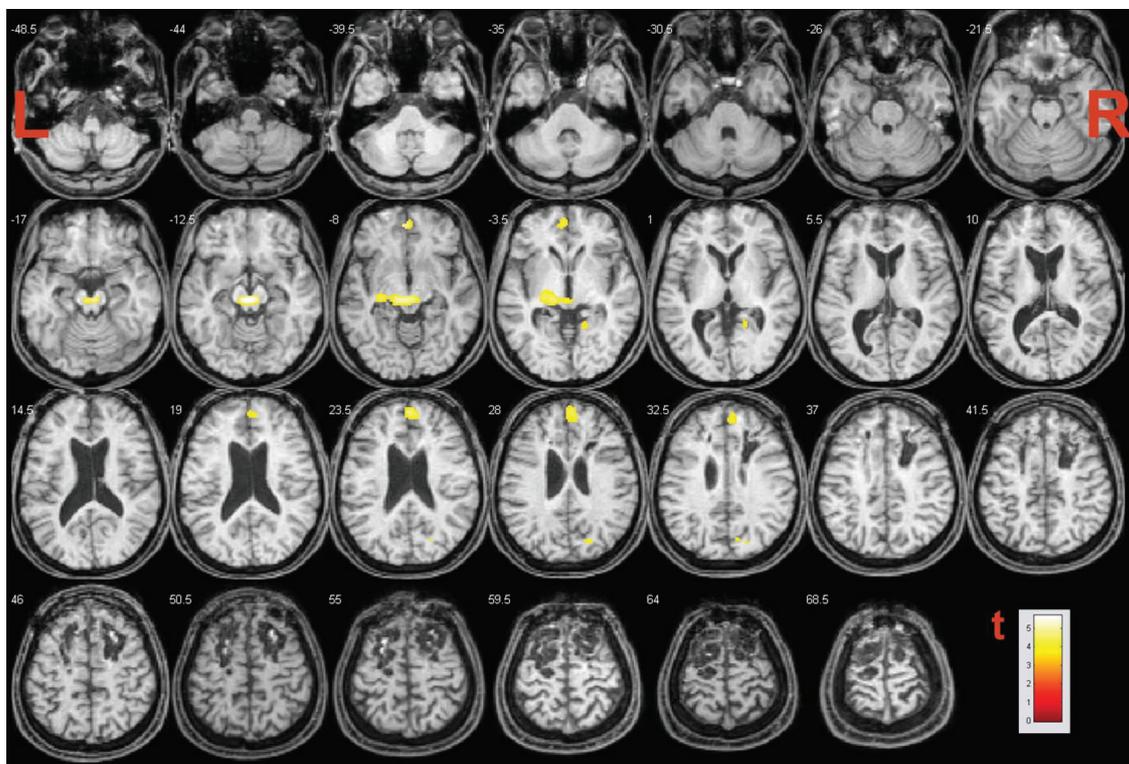Correction for multiple comparison $p < .05$ FWE, cluster size $k_E > 25$ voxels. VTA, Ventral Tegmental Area.

Figure 1. Post-VR-training > Pre-VR-training whole brain. Brain activations in the Post-VR-training minus Pre-VR-training conditions, whole brain. Correction for multiple comparison $p < .05$ FWE, cluster size $k_E > 25$ voxels, neurological convention (L = Left).

left medial frontal gyrus (BA 10), the medial frontal gyrus bilaterally (BA9), the right parahippocampal gyrus region, the right cuneus and precuneus.

The follow-up session did not substantially differ from the post-VR-training (Figure 5S, 6S, 7S, Table 4S, 5S, 6S) except for two small clusters in the left claustrum and in the left middle temporal gyrus (see supplemental content Table 7S).

No clusters of voxels were more activated in the pre-VR-training or follow-up sessions compared to the post-VR-training sessions.

We found similar results for the explicit masked analysis, with more extended activations in the post-VR- compared to the pre-VR-training condition (see supplemental content Table 3S, Figure 4S) and no differences between follow-up and post-VR-training.

We can assume, on the basis of our clinical opinion, neuropsychological retesting and structural MRI images, that the patient was stable enough to not show evident recovery in 1 year. Even though we cannot exclude the presence of subtle changes, we believe that it is improbable that the improvement after the memory navigation training could be the consequence of spontaneous changes (Annoni, Beer, & Kesselring, 1992; Sherer, Madison, & Hannay, 2000).

DISCUSSION

In this study, we measured, in a stabilized TBI patient, the changes before and after VR navigational training with a 3D videogame in neuropsychological tests (assessing spatial and verbal memory and attentive/executive functions) and fMRI activation of the hippocampal and parahippocampal brain regions involved in memory processing. Our findings showed that a clear improvement in visual-spatial memory learning was observed in our patient after navigational VR training; in particular, enhanced performance was observed in delayed recall. This outcome allowed us to conclude that spatial memory could improve through the exploration of a new and complex environment. A study by Matheis et al. (2007) examined the usefulness of virtual reality to assess learning and memory in individuals with TBI. It demonstrated that data regarding integrated memory abilities can be obtained empirically within a consistent and controllable environment that is similar to the real-world.

Our results showed no clear effect of VR-memory training on immediate recall; only in Corsi's suprasspan task the immediate recall seems to improve, but a trend to improvement was present before VR-memory training. These findings are not surprising, because the immediate recall is only partly related to the function of medial temporal regions; in fact, immediate recalls is related to the working memory fronto-parietal network activation; after repeated exposure of the same materials (as in Corsi's Suprasspan Test), the immediate recall become connected also with the medial temporal regions (Wolk & Dickerson, 2011). This pattern of results provides some considerations. One possible interpretation of the results is that the enhancement in spatial memory could in part be a consequence of spatial implicit learning training on acquiring spatial knowledge during navigation: indeed, the participant did not have to learn a route but rather to conduct an extensive exploration of the virtual town. In other words, the implicit spatial memory involved in the training task increased specific spatial cognitive functions. Our hypothesis was that the navigational task could have activated the medial temporal lobe network involved in both spatial and verbal memory learning.

This supposition is supported by the functional neuroimaging assessment, which shows increased metabolism in the left hippocampus and the right parahippocampal cortex during a verbal task after navigational VR-memory training. Increases in cerebral activity after navigational VR training were also found along the mesolimbic network (VTA and medial prefrontal cortex) involved in the reward. In particular, we assume that the navigational VR training activated a VTA-hippocampal loop that controls the entry of information into long-term memory (Lisman & Grace, 2005).

As suggested by Green and Baveller (2003) in their paper on the effect of videogames on visual attention, it could be speculated that the attentional and executive functions were primarily affected by the training. However, the improvement in memory, in this case, was not associated with a significant improvement in executive and attentional functions. Also the functional neuroimaging, in this case, does not support a significant increase in metabolism in the dorsolateral prefrontal cortex involved in executive functions.

Interestingly, our results pointed out that improvement in spatial but not verbal memory appeared to be sustained after a 1-year no-contact follow-up period. This dissociation suggests that

the long-term effect of rehabilitation training is maintained if daily training is performed; clinical investigation suggests that in daily life the participant of this study performs more spatial than verbal activities.

CONCLUSION

In conclusion, our findings suggest that virtual navigational training might support an enhancement of memory functions in brain-damaged adults. According to Brooks and McNeil (1999), we showed that VR can be a useful tool in cognitive rehabilitation and that training in a virtual environment can transfer to improve real world performance.

We hope that this tool can be applied not only to individuals with TBI but also to other patients with memory deficits. Our study showed that navigational memory training was associated with an increased activation of hippocampal and parahippocampal brain regions involved in memory processing.

REFERENCES

Annoni, J. M., Beer, S., & Kesselring, J. (1992). Severe traumatic brain injury: Epidemiology and outcome after 3 years. *Disability and Rehabilitation*, *14* (1), 23–26.

Brooks, B. M., & McNeil, J. E. (1999). Route learning in a case of amnesia: A preliminary investigation into the efficacy of training in a virtual environment. *Neuropsychological Rehabilitation*, *9* (1), 63–76.

Capitani, E., & Laiacona, M. (1988). Aging and psychometric diagnosis of intellectual impairment: Some considerations on test scores and their use. *Developmental Neuropsychology*, *4*, 325–330.

Capitani, E., & Laiacona, M. (1997). Composite neuropsychological batteries and demographic correction: Standardization based on equivalent scores, with a review of published data. *Journal of Clinical and Experimental Neuropsychology*, *19* (6), 795–809.

Carlesimo, G. A., Fadda, L., Bonci, A., & Caltagirone, C. (1993). Differential rates of forgetting from long-term memory in Alzheimer's and multi-infarct dementia. *International Journal of Neuroscience*, *73*, 1–11.

Delpolvi, A. R., Rankin, K. P., Mucke, L., Miller, B. L., & Gorno-Tempini, M. L. (2007). Spatial cognition and the Human navigation network in AD and MCI. *Neurology*, *69* (10), 986–987.

Fernandez, G., Weyerts, H., Schrader-Bolsche, M., Tendolkar, I., Smid, H. G., Tempelmann, C., et al. (1998). Successful verbal encoding into episodic memory engages the posterior hippocampus: A parametrically analyzed functional magnetic resonance images study. *Journal of Neuroscience*, *18* (5), 1841–1847.

Green, C. S., & Baveller, D. (2003). Action video game modifies visual selective attention. *Nature*, *423*, 534–537.

Henke, K., Kroll, N. E., Behniea, H., Amaral, D. G., Milner, M. B., Rafal, R., et al. (1999). Memory lost and regained following bilateral hippocampal damage. *Journal of Cognitive Neuroscience*, *11* (6), 682–697.

Laatsch, L., Harrington, D., Hotz, G., Marcantuono, J., Mozzini, M. P., Walsh, V., & Hersey, K. P. (2007). An evidence-based review of cognitive and behavioral rehabilitation treatment studies in children with acquired brain injury. *The Journal of Head Trauma Rehabilitation*, *22* (4), 248–256.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York, NY: Oxford University Press.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA Loop: Controlling the entry of information into long-term memory. *Neuron*, *46*, 703–713.

Maguire, E. A., Burgess, N., Donnett, J. D., Frackowiak, R. S. J., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: A human navigation network. *Science*, *280*, 921–924.

Matheis, R. J., Schultheis, M. T., Tiersky, L. A., DeLuca, J., Millis, S. R., & Rizzo, A. (2007). Is learning and memory different in a virtual environment? *Clinical Neuropsychology*, *21*, 146–161.

O'Keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford, UK: Clarendon Press.

Rose, F. D., Brooks, B. M., & Rizzo, A. A. (2005). Virtual reality in brain damage rehabilitation: Review. *CyberPsychology & Behaviour*, *8* (3), 241–261.

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1996). *ADAS Alzheimer's Disease Assessment Scale*. Versione Italiana. O.S. Organizzazioni Speciali: Giunti.

Sherer, M., Madison, C., & Hannay, H. J. (2000). A review of outcome after moderate and severe closed head injury with an introduction to life care planning. *Journal of Head Trauma Rehabilitation*, *15* (2), 767–782.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, *20*, 11–21.

Spiers, H. J., & Maguire, E. A. (2007). The Neuroscience of remote spatial memory: A tale of two cities. *Neuroscience*, *149*, 7–27.

Spinnler, H. A., & Rognoni, G. (1987). Standardizzazione e taratura italiana di test neuropsicologici. *Italian Journal of Environmental Psychology*, *9*, 233–239.

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253* (5026), 1380–1386.

Vakil, E. (2005). The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: A selective review. *Journal of Clinical and Experimental Neuropsychology*, *27* (8), 977–1021.

Wilson, B. A. C., & Baddeley, A. D. (1985). The Rivermead Behavioural Memory Test. Titchfield, UK: Thames Valley Test Company.

Wolk, D. A., & Dickerson, B. C. (2011). Alzheimer's disease neuroimaging initiative: Fractionating verbal episodic memory in Alzheimer's disease. *Neuroimage*, *54* (2), 1530–1539.

Woollett, K., Glensman, J., & Maguire, E. A. (2008). Non-spatial expertise and hippocampal gray matter volume in humans. *Hippocampus*, *18* (10), 981–984.