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Improvement of Memory Impairments in Poststroke Patients by Hyperbaric Oxygen Therapy

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Objective: Several recent studies have shown that hyperbaric oxygen (HBO_2) therapy carry cognitive and motor therapeutic effects for patients with acquired brain injuries. The goal of this study was to address the specific effects of HBO_2 on memory impairments after stroke at late chronic stages. ***Method:*** A retrospective analysis was conducted on data of 91 stroke patients 18 years or older (mean age ~60 years) who had either ischemic or hemorrhagic stroke 3–180 months before HBO_2 therapy (M = 30–35 months). The HBO_2 protocol included 40 to 60 daily sessions, 5 days per week, 90 min each, 100% oxygen at 2ATA, and memory tests were administered before and after HBO_2 therapy using NeuroTrax's computerized testing battery. Assessments were based on verbal or nonverbal, immediate or delayed memory measures. The cognitive tests were compared with changes in the brain metabolic state measured by single-photon emission computed tomography. ***Results:*** Results revealed statistically significant improvements ($p < .0005$, effect sizes medium to large) in all memory measures after HBO_2 treatments. The clinical improvements were well correlated with improvement in brain metabolism, mainly in temporal areas. ***Conclusions:*** Although further research is needed, the results illustrate the potential of HBO_2 for improving memory impairments in poststroke patients, even years after the acute event.

Keywords: hyperbaric oxygen, memory impairment, stroke

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Stroke is a major cause of adult disability and mortality, giving rise to severe, long-term impairments in the physical, emotional, and cognitive state of the survivors (Zhang, Chapman, Plested, Jackson, & Purroy, 2012). Cognitive impairments after stroke are very common (Edwards, Jacova, Sepehry, Pratt, & Benavente, 2013; Tatemichi et al., 1994); the overall prevalence stands on 22%, 3 months after onset, with no further improvement in most cases (Douiri, Rudd, & Wolfe, 2013). Cognitive impairments commonly involve memory deficits that lead to a decline in everyday functioning and in social functioning, life satisfaction and quality of life of patients and caregivers (Baumann, Couffignal, Le Bihan, & Chau, 2012; Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998; Snaphaan & de Leeuw, 2007; Tatemichi et al., 1994). Therapy and rehabilitation programs are valuable for improving memory deficits early after brain injury, but they usually provide only partial relief (Cicerone et al., 2005; Fish, Manly, Emslie, Evans, & Wilson, 2008; Jennett & Lin-

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coln, 1991; Nair & Lincoln, 2007; Rohling, Faust, Beverly, & Demakis, 2009). There are currently no efficient memory rehabilitation programs available for late chronic stages.

Hyperbaric oxygen (HBO_2) treatment has been recently shown to induce neuroplasticity in brain injured patients, even at chronic stages (Boussi-Gross et al., 2013; Efrati & Ben-Jacob, 2014a, 2014b; Efrati et al., 2013). HBO_2 is the inhalation of 100% oxygen at pressures exceeding 1 atm absolute (ATA) to enhance the amount of oxygen dissolved in the blood and body fluids. As is explained in detail by (Efrati & Ben-Jacob, 2014b), the diverse and powerful innate repair mechanisms activated by HBO_2 are associated both with the elevated level of dissolved oxygen and the elevated pressure.

There is previous evidence for cognitive improvements after HBO_2 in different neurological conditions (Barrett et al., 1998; Boussi-Gross et al., 2013; Hardy et al., 2002; Jacobs, Winter, Alvis, & Small, 1969; Rossignol, Rossignol, James, Melnyk, & Mumper, 2007; Tapeantong & Poungvarin, 2009). However, there is an ongoing debate regarding the efficacy of HBO_2 in victims of traumatic brain injury (TBI) and stroke. Although it is widely agreed, and confirmed by almost all the studies, that HBO_2 treatments lead to significant improvements, the debate is related, mostly to the control group issue and the minimal effective dosages (the minimal pressure that does not have any physiological effect on the central nervous system [CNS]) (Churchill et al., 2013; Efrati & Ben-Jacob, 2014a; Golden, Golden, & Neubauer, 2006; Harch et al., 2012; Mukherjee et al., 2014; Wolf, Cifu, Baugh, Carne, & Profenna, 2012). For detailed assessment of the debate see (Efrati & Ben-Jacob, 2014a, 2014b). Recently, in a prospective randomized trial with mild TBI patients, it was found that HBO_2 could significantly improve cognitive impairments and metabolic brain deficits even at chronic stages of the injury (Boussi-Gross et al., 2013). In addition, in another study with poststroke patients, it was reported that HBO_2 could lead to significant motor function improvements also at the late chronic stage (Efrati et al., 2013). These findings imply that HBO_2 might induce neuroplasticity processes in the injured brain in regions where anatomical or metabolic mismatch is detected using computed tomography (CT) or single-photon emission computed tomography (SPECT). In light of these findings, we decided to investigate whether HBO_2 had beneficial effects on impaired memory function in poststroke patients. The idea was to perform retrospective analysis of the specific effects of HBO_2 on memory impairments in poststroke patients through its effect on metabolic dysfunction in brain regions involved in memory processes. The retrospective analysis was performed on previously chronically disabled poststroke patients who had received HBO_2 at the hyperbaric unit of Assaf Harofeh Medical Center. Notably, to reveal the metabolic changes responsible for the memory functions we compared the changes in the memory functions with changes in the brain metabolic state as inferred by SPECT brain imaging data.

Method

Participants

This study is a retrospective analysis of changes in memory functions and their related brain activity of 91 stroke patients after hyperbaric oxygen therapy. Patients were treated at the hyperbaric unit of Assaf Harofeh Medical Center, Israel, between the years 2008–2012. The study was approved by the local ethics committee. Inclusion criteria: Participants who have completed at least 40 sessions of HBO_2, and two cognitive evaluations, one before and one after HBO_2 treatments.

Materials and Procedure

Hyperbaric oxygen treatment. The following HBO_2 protocol was practiced: 40–60 daily sessions, 5 days per week, 90 min each, 100% oxygen at 2ATA. The difference in treatments number (40 or 60) were because of the fact that some of the patients had participated in a prospective randomized controlled study on physical and quality of life improvement in stroke patients after HBO_2 (Efrati et al., 2013) and had 40 treatment sessions according to that study's protocol. The rest of the patients had 60 treatment sessions because of later considerations regarding the length and benefit of the treatments, based on our prolonged experience with those patients and the treatment outcome.

Memory evaluation. All patients underwent baseline and posttreatment evaluations 1–3 weeks before and after HBO_2. Memory was assessed using memory test scores of NeuroTrax computerized cognitive testing (previously known as "MindStreams") of NeuroTrax Corp., Houston, TX. A detailed description of the tests in the battery can be found on NeuroTrax Web site (www.neurotrax.com) and in Doniger (2014b). NeuroTrax testing battery has been previously used in several studies of poststroke population (Kliper et al., 2013; Shopin et al., 2013; Weinstein, Goldbourt, & Tanne, 2013), including the Tel Aviv Brain Acute Stroke Cohort (TABASCO) study, which is an ongoing, prospective cohort study with ~1,125 consecutive stroke patients designed to evaluate the association between predefined demographic, psychological, inflammatory, biochemical, neuroimaging, and genetic markers, measured during the acute phase, and the long-term outcome (Ben Assayag et al., 2012).

Although there are several cognitive tests in the battery, the changes in memory functions were evaluated by analysis of the memory tests scores of the following five memory measures:

Immediate verbal memory (IVM): Ten pairs of words were presented, followed by a recognition test in which the first word of a previously presented pair appeared together with a list of four words from which the patient chose the other member of the pair. There were four immediate repetitions and a total score of all four was calculated.

Delayed verbal memory (DVM): Delayed repetition of the same 10 previously learned pairs after 10–15 min.

Immediate nonverbal memory (INVM): Eight pictures of simple geometric objects were presented, followed by a recognition test in which four versions of each object were presented, each oriented in a different direction. There were four immediate repetitions, and a total score of all four was calculated.

Delayed nonverbal memory (DNVM): Delayed repetition of the previously learned eight figures after 10–15 min.

Total memory index (TMI): Calculated mean score of all four scores described above.

Construct validity of the memory tests was reported in several studies (Abramovitch, Dar, Hermesh, & Schweiger, 2012; Doniger & Simon, 2014; Doniger et al., 2006; Dwolatzky et al., 2003; Elstein et al., 2005); for example, verbal memory tests were found to well correlate with several familiar paper-and-pencil verbal memory tests, such as logical memory subtest in Wechsler Memory Scale-Third Edition (WMS-III), California verbal learning test (CVLT), Hopkins verbal learning test (HVLT), and others (*r*s = 0.59–0.73) (Doniger & Simon, 2014). The nonverbal memory had strong psychometric properties, including good reliability (Cronbach's alpha = 0.65–0.71) and was found to correlate with several subtests of the WMS-III, the Rey Auditory Verbal Learning Test, and the Rey Osterreith Complex Figure Test in cohorts of clinical and healthy participants (*r*s = 0.52–0.77) (Abramovitch et al., 2012; Doniger & Simon, 2014).

After administration, NeuroTrax data was automatically and blindly uploaded to the NeuroTrax central server, and outcome parameters were calculated using custom software blind to diagnosis or testing site. To account for the well-known effects of age and education on cognitive performance, each outcome parameter was normalized and fit to an IQ-like scale ($M = 100$, $SD = 15$) according to the patient's age and education. Normative data, provided by NeuroTrax, consisted of test data of cognitively healthy individuals in controlled research studies at more than 10 clinical sites (Doniger, 2014a).

Notably, the patients were given two different tests versions of the NeuroTrax test battery before and after HBO_2 therapy, to allow repeated administrations with minimal learning effect. Test–retest reliability for those versions was evaluated and found high, with no significant learning effect (Dwolatzky et al., 2003; Melton, 2005).

Assessment of brain activity. Brain activity was assessed using SPECT 1–3 weeks before and after HBO_2 therapy. The imaging was conducted using 925–1,110 MBq (25–30 mCi) of technetium-99methyl-cysteinate-dimmer (Tc-99m-ECD) at 40–60 min postinjection. A dual detector γ camera (ECAM or Symbia T, Siemens Medical Systems, Malvern, PA) equipped with high resolution collimators was used and the data was acquired in three-degree steps and reconstructed iteratively with Chang method ($\mu = 0.12$/cm) attenuation correction (Jaszczak, Chang, Stein, & Moore, 1979). Pre- and post-HBO_2 treatments were compared. Brain perfusion analysis was performed first by fusing pre- and posttreatment SPECT studies to pretreatment brain CT. Both SPECT studies were normalized to maximum brain activity in the entire brain. SPECT images were then reoriented into Talairach space using NeuroGam (Segami Corporation) to identify Brodmann cortical areas and to compute the mean perfusion in each Brodmann area (BA). In addition, volume rendered brain perfusion images were reconstructed and normalized to entire brain maximal activity. All SPECT analyses were done by study team members who were blinded to the laboratory and clinical data. SPECT scans were performed at late-morning to mid-day. On the day of the SPECT scan, patients were treated only with their chronic medications and were instructed not to smoke.

Change in perfusion in all BA for each subject was determined by calculating the percentage of difference between postperiod and preperiod divided by the preperiod perfusion. An average of these perfusion changes for each BA was calculated.

Statistical Analysis

The memory tests data was statistically analyzed using SPSS software (version 16.0). Continuous data was expressed as means ± *SD*s or *SE*s.

Preliminary analysis. Analysis of variance (ANOVA) was used to evaluate the effect of HBO_2 therapy on patients' memory performance. The dependant variables were scores in the different memory measures, the independent variables were time of testing (before or after HBO_2) and group. Because most of the initial complaints were regarding motor and physical rather than cognitive disabilities, we subdivided the patients into two groups according to their baseline memory scores (low\high): "low baseline score" (LBS) (baseline score <85, i.e., 1 *SD* below average), and "high baseline score" (HBS) (baseline score >85). Main effects (time) and interactions (Time × Group) were examined and effect sizes were calculated using η^2.

Main analysis. Paired *t* tests were used for intragroup comparisons. Effect sizes for main comparisons were calculated using Cohen's *d* measure. The percentages of relative changes after treatment were also calculated for each memory measure, for the LBS groups only (see results of preliminary analysis), by subtracting the pretreatment score from the posttreatment score, and dividing by the pretreatment score.

In addition, Jacobson and Truax's analysis was performed to determine the clinical significance of the results (Jacobson & Truax, 1991). This is a relative common method used for calculating clinical significance by establishing cutoff scores for participants' classification into one of the four categories: recovered, improved, unchanged, or deteriorated. Reliable change index (RCI) was calculated to assess clinical change significance in the LBS groups. RCI enables to determine whether the magnitude of change from baseline to posttreatment (either positive or negative) is significantly larger than arbitrary changes because of the instrument measurement error (Jacobson & Truax, 1991). An RCI larger than ±1.96 would be unlikely to occur without actual change ($p < .05$). Symbols associated with the derivation of RCI scores are presented in Table 1. The formula

Table 1
Symbols and Explanations of the Jacobson-Truax's Clinical Change Analysis

Symbol	Explanation
X1	Patient's baseline score in one of the memory measures
X2	Patient's posttreatment score in one of the memory measures
S1	*SD* of patients' baseline scores in one of the memory measures
M1	Mean of patients' baseline scores in one of the memory measures
S0	*SD* of normal population scores in one of the memory measures (=15)
M0	Mean of normal population scores in one of the memory measures (=100)
r_{xx}	Test–retest reliability coefficient for NeuroTrax memory index
SE	The *SE* of measurement for memory measures
Sdiff	The *SE* of difference for memory measures

Table 2
Descriptive Statistics of Memory Scores Before and After HBO_2 Therapy and ANOVA Results of All Patients, and Memory Low Baseline Score and High Baseline Score Subgroups

Memory measure	N	Mean (*SD*) Before	Mean (*SD*) After		*F*	*p*-value	Effect size (η^2)	
TMI								
All	91	83.06 (18.71)	89.38 (18.10)	Time	20.93	0.00001	0.19	Medium
Impaired	48	68.66 (13.41)	80.45 (19.62)	Time × Group	19.35	0.00002	0.17	Medium
Unimpaired	43	99.13 (6.90)	99.36 (8.83)					
IVM								
All	91	76.31 (25.80)	88.09 (24.69)	Time	36.51	0.00000	0.29	Large
Impaired	47	55.34 (18.12)	73.84 (25.83)	Time × Group	13.25	0.00045	0.13	Medium
Unimpaired	44	98.72 (6.85)	103.31 (10.66)					
DVM								
All	91	81.74 (26.07)	90.03 (24.78)	Time	14.56	0.00025	0.14	Medium
Impaired	43	58.62 (18.58)	80.59 (27.07)	Time × Group	30.22	0.00000	0.25	Large
Unimpaired	48	102.4 (8.12)	98.49 (19.17)					
INVM								
All	91	87.71 (18.83)	90.16 (16.69)	Time	5.53	0.02089	0.05	Small
Impaired	41	71.10 (11.73)	82.14 (16.14)	Time × Group	32.43	0.00000	0.27	Large
Unimpaired	50	101.33 (10.90)	96.74 (14.19)					
DNVM								
All	91	86.36 (19.39)	89.33 (18.47)	Time	3.15	0.07944	0.03	Small
Impaired	45	70.88 (14.15)	81.04 (19.05)	Time × Group	17.18	0.00008	0.16	Medium
Unimpaired	46	101.51 (9.09)	97.44 (13.84)					

Note. *p* value derived from ANOVAs main and interaction effects. TMI = total memory index; IVM = immediate verbal memory; DVM = delayed verbal memory; INVM = immediate nonverbal memory; DNVM = delayed nonverbal memory.

used in RCI calculations is $RC = \frac{X_2 - X_1}{S_{diff}}$, where S_{diff} is the *SE* of the differences, defined as the spread of distribution of changes because of arbitrary time variability of the score value, and is equal to $\sqrt{2(SE)^2}$. *SE* is the standard error of measurement and is found by $S_1\sqrt{1-r_{xx}}$. The value of r_{xx} used in our study was $r = .84$, a value of a test–retest reliability coefficient for NeuroTrax total memory index in a previous study of 57 healthy volunteers with a median test–retest interval of 4.84 weeks (Schweiger, Doniger, Dwolatzky, Jaffe, & Simon, 2003).

To assess the statistical significance of the patients' clinical changes we calculated, the Jacobson-Truax's RCI and categorized for each patient (positive change, no change, or negative change).

Jacobson and Truax's "cutoff score" was also calculated for each memory measure. The cutoff score is the score in the post-treatment assessment, above which the patient is classified as "recovered," that is, having higher probability to be part of the normal population distribution than of the impaired one. This cutoff score was set with consideration of the means and *SD*s of both the normal and impaired populations: $\frac{S_0M_1 + S_1M_0}{S_0 + S_1}$.

Results

Preliminary analysis results revealed significant improvement in almost all memory measures after HBO_2 therapy, as well as strong and significant cross time effect (before-after HBO_2 therapy) and cross group effect (LBS-HBS) with medium to large effect sizes in all memory measures (see Table 2). The LBS groups exhibited significantly larger improvement whereas the HBS did not show improvements. Figure 1 represents a visual example of the cross time and cross group in the TMI scores. These observations, along with the distribution of subjects (mean and *SD*, see Table 2) led to the possibility of a ceiling effect in the performance of the HBS patients who were initially less impaired in their memory function. Therefore, in the rest of the analyses we focused on the LBS groups of patients and their potential for improvements after HBO_2 treatments. The number of patients in each group ranged from $n = 41$ to $n = 48$, with an overlap of patients between the different measures (see Figure 2A for the detailed distribution).

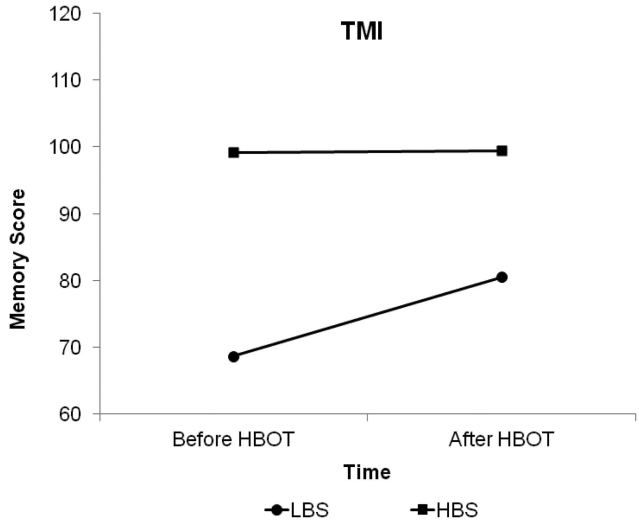

Figure 1. Total memory index scores of all patients, divided to low baseline score (LBS) and high baseline score (HBS) groups. There is a significant improvement in the LBS group after HBO_2 therapy and no change in the HBS group.

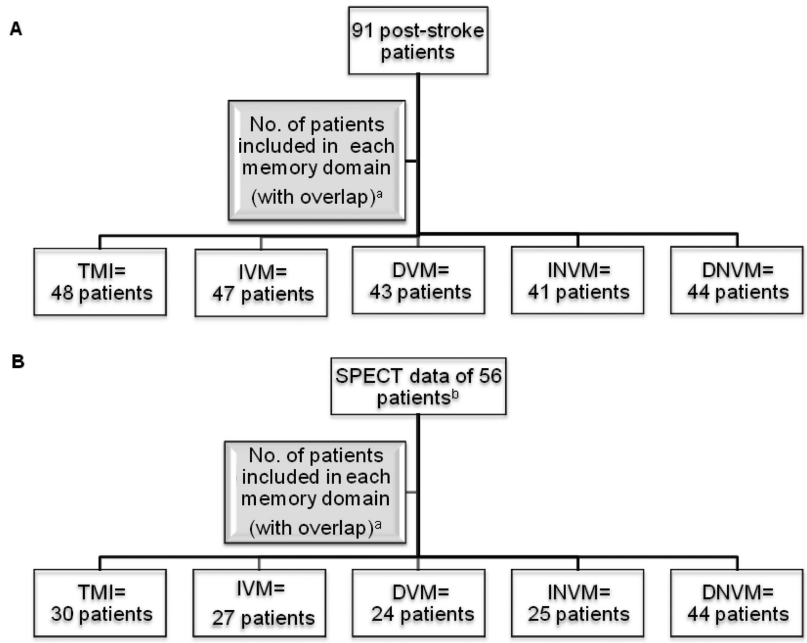

Figure 2. (A) Number of poststroke patients analyzed in this study, assort to the different memory measures (TMI = total memory index; IVM = immediate verbal memory; DVM = delayed verbal memory; INVM = immediate nonverbal memory; DNVM = delayed nonverbal memory). (B) Number of patients with available SPECT data, assorted to the different memory measures. [a]Patients assorted to the different memory measures according to their baseline performance; only patients with low baseline scores (<85, i.e., 2 *SD* below normal average) were included in the main analysis of the different memory measures, with an overlap of patients between the measures. [b]SPECT data of 56 out of 91 patients was available (61% of the patients).

Participants' Profile

Patients were 18 years or older (mean age ~60 years) who had either ischemic or hemorrhagic stroke 3–180 months before HBO_2 (M = 30–35 months, median = 19–23 months). Basic demographics and injury characteristics of all patients in the different groups are presented in Table 3.

Memory Improvement Evaluation

Statistical significance. There was a significant improvement in all memory scores of LBS patients after HBO_2 therapy compared with baseline (TMI: $t_{(47)} = 5.47$, $p < .000005$; IVM: $t_{(46)} = 5.42$, $p < .000005$; DVM: $t_{(42)} = 5.31$, $p < .000005$; INVM: $t(40) = 4.98$, $p < .00005$; DNVM: $t_{(43)} = 3.99$, $p <$

Table 3
Basic Demographic and Injury Characteristics of Low Baseline Score (LBS) Groups (Baseline Score <85)

	TMI	IVM	DVM	INVM	DNVM
N[a]	48	47	43	41	45
Age	60.6	60.4	60.5	62.4	62.1
Months since injury (mean/median)	35.2/19.2	32.4/18.9	34.8/24	30.0/23.0	31.2/23.0
Years of education	14.1	14.4	14.3	13.9	14.1
Gender–male	42 (87.5%)	42 (89.3%)	38 (88.3%)	36 (87.8%)	38 (84.4%)
Side of injury					
Right	15 (34.9%)	15 (31.9%)	13 (30.3%)	14 (34.1%)	14 (31.1%)
Left	29 (60.4%)	28 (53.1%)	26 (60.4%)	24 (58.5%)	27 (60%)
Both	4 (8.3%)	4 (8.5%)	4 (9.3%)	3 (7.4%)	4 (8.9%)
Etiology					
Ischemic	35 (72.9%)	33 (70.3%)	31 (72.1%)	31 (75.7%)	34 (75.5%)
Hemorragic	12 (27.1%)	14 (29.7%)	12 (27.9%)	10 (24.3%)	11 (24.5%)
No. of treatments					
60	25 (52.1%)	27 (57.5%)	25 (58.1%)	19 (46.3%)	22 (48.8%)
40	23 (47.9)	20 (42.5%)	18 (41.9%)	22 (53.7%)	23 (51.2%)

Note. TMI = total memory index; IVM = immediate verbal memory; DVM = delayed verbal memory; INVM = immediate nonverbal memory; DNVM = delayed nonverbal memory.
[a] With overlap between patients in the different memory measures groups.

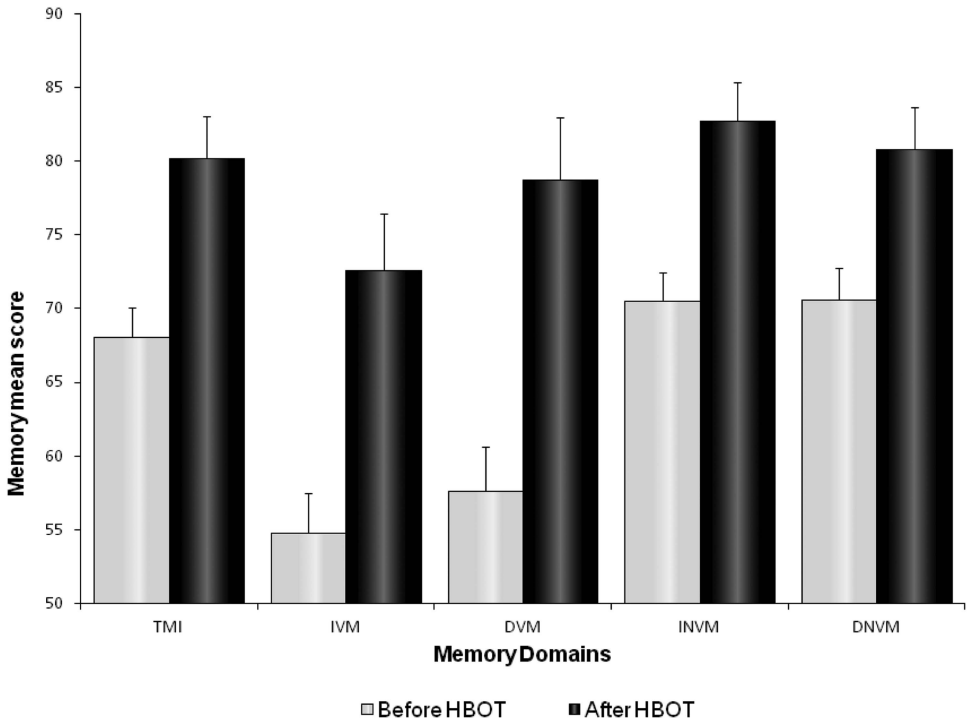

Figure 3. Memory scores (mean + *SE*) before and after HBO_2 therapy. All improvements are significant at a level of $p < .0005$.

.0005). Effect sizes of all results were medium to large (Cohen's $d = 0.69$, 0.82, 0.94, 0.78, and 0.61, respectively). The results are presented in Figure 3 and in Table 4.

Relative changes. The percentages of relative change for each memory measure are presented in Figure 4. The change percentages were found to be as follows: 18% for the TMI measure, 43.5% for IVM, 48.6% for DVM, 17.5% for INVM and 18% for DNVM.

Clinical significance. There were 35–46% of the patients who achieved significant clinical improvement in the different memory measures, out of which a very high percentage (78.9–100%) recovered, that is, passed the cutoff score differentiating between impaired and unimpaired populations in their posttreatment assessment. More specifically, as summarized in Table 4 and in Figure 5, in the TMI, 35% of the patients fell in the positive change category after HBO_2 (out of which 94% passed the recovery cut-off score), 60% remained with no change, and 4% were in the negative change category; in the IVM, 38% demonstrated positive change (out of which 100% passed the recovery cut-off score), 57% had no change and 4% with negative change; in the DVM, 44% demonstrated positive change (out of which 94% passed the recovery cut-off score), 51% had no change and 4.6% had negative change; in the INVM, 46% demonstrated positive change (out of which 79% passed the recovery cut-off score), 49% had no change and 4.5% had negative change; and finally, in the DNVM, 43% demonstrated positive change (out of which 79% passed the recovery cut-off score), 52% had no change and 4.5% had negative change.

Table 4
Mean ± SD of Memory Tests Scores Before and After HBO_2 Therapy

		Mean ± *SD*			%		
Memory measure	*N*	Before HBO_2	After HBO_2	*p* value	Positive change (recovered[a])	Negative change	No change
TMI	48	68.06 ± 13.93	80.2 ± 19.92	<0.000005	35.42 (94.12)	4.17	60.42
IVM	47	54.80 ± 18.56	72.61 ± 26.43	<0.000005	38.33 (100)	4.25	57.40
DVM	43	57.64 ± 19.34	78.71 ± 28.07	<0.000005	44.19 (94.74)	4.65	51.16
INVM	41	70.55 ± 11.96	82.73 ± 16.96	<0.00005	46.34 (78.95)	4.88	48.78
DNVM	45	70.60 ± 14.29	80.78 ± 19.29	<0.0005	43.18 (78.95)	4.55	52.27

Note. *p* value derived from a paired one-tailed *t* test comparison of the means. Percentage of clinical change was calculated according to Jacobson and Truax's reliable change index (RCI) for each memory measure.
[a] Percent of patients out of the positively changed passing the cutoff score, that is, with higher probability to be part of the normal population distribution than the impaired one.

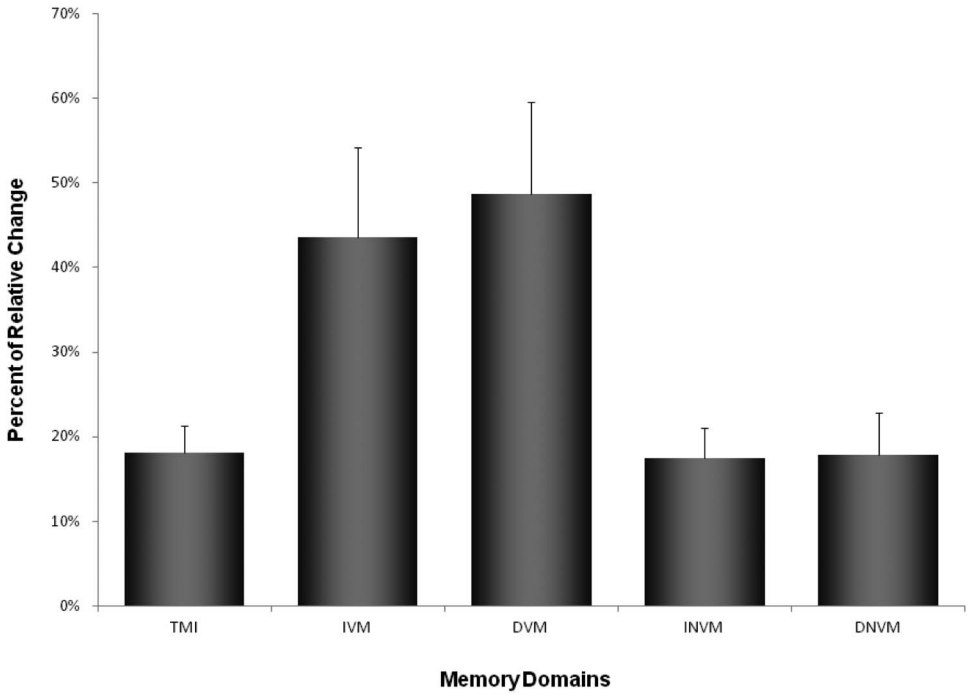

Figure 4. Mean percentages and *SE*s of relative changes in the different memory measures after HBO_2.

SPECT Results

Cortical analysis: BAs. Fifty-six patients had available SPECT imaging before and after HBO_2 therapy (Figure 2B). Patients in the four memory groups were divided into "improved" versus "not improved" according to the clinical significance analysis and RCI score. All patients presenting positive change according to this analysis were considered improved and the rest were classified as not improved. The analysis was conducted specifically for the delayed memory measures (DVM; DNVM), because these are "single-task" scores that describe most accurately episodic memory deficits and have the potential to correlate best with distinct brain area functions. The mean percentages of relative change in activation of cortical BA for clinically improved versus not-improved patients are presented in Figure 6. Several BAs were found to present higher relative change in activation in the improved group versus the not improved. In the DNVM measure, the most significant change in activation was in right BA36 **(**part of the perirhinal cortex in the rhinal sulcus), followed by right BA28 (part of the enthorhinal area in the medial temporal lobe) and other BAs such as right and left BA20 (in the inferior temporal gyrus), BA21 (the middle temporal area), and BA38 (the temporopolar area). In the DVM measure, the most significant change in activation was in left BA36, followed by right BA46 (the middle frontal area) and BA36, left BA23 (the ventral posterior cingulate area), right BA9 (part of the dorsolateral and medial prefrontal cortex), and BA6 (part of the precentral gyrus) and left BA4 (primary motor cortex), BA8 (anterior to the premotor cortex), and BA6 (Figure 7).

Discussion

This study presents analysis of the effects of HBO_2 treatments on memory impairments in poststroke patients during the late chronic, unremitting stage. The analysis revealed statistically significant improvement in memory functions in most patients. More specifically, up to 45% of the patients had positive change in all four measures of memory function up to a level of recovery. These clinical changes were found to be in good agreement with metabolic brain changes assessed by SPECT brain imaging.

The results are consistent with previously reported HBO_2 induced neuroplasticity effects at late chronic stage, months to years after the acute insult (Boussi-Gross et al., 2013; Efrati et al., 2013). Together with reported evidence of significant cognitive improvement in mild TBI patients with HBO_2 (Boussi-Gross et al., 2013), they suggest that HBO_2 may serve as an effective intervention for cognitive impairments in patients presenting brain metabolic dysfunction because of acute damage.

SPECT analysis was used to identify the brain regions associated with the memory impairments and improvements. We found that the perirhinal cortex (BA36) and its activation correlated with clinical improvement in the delayed memory measures. Patients who demonstrated improvement in their verbal and nonverbal delayed memory abilities after HBO_2 had the highest percentage of relative change in activation in the left and right perirhinal cortex (PrC), respectively. The PrC is known to play a crucial role in recognition memory, the PrC and the hippocampus often function as interacting components of an integrated recognition memory system (Brown & Aggleton, 2001; Buffalo, Reber, & Squire, 1998). Because our memory assignments in the cognitive tests were indeed recognition tasks, the involvement of the PrC in this

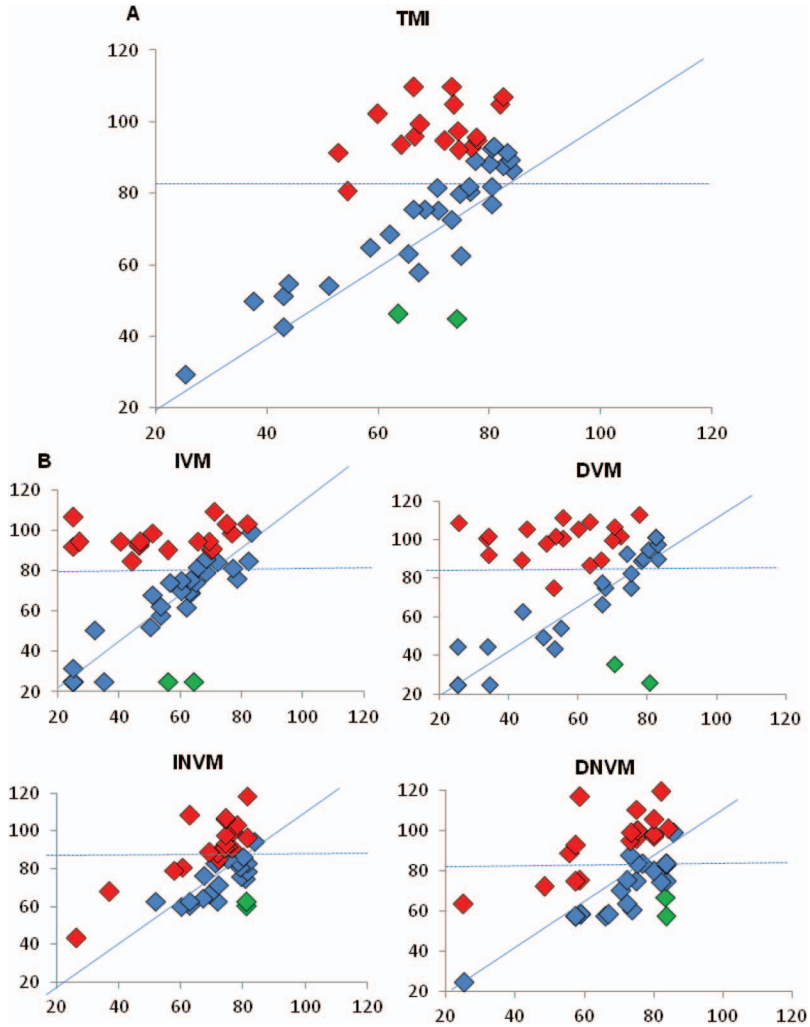

Figure 5. Patients scores before (X axis) and after (Y axis) HBO_2 in: (A) total memory index (TMI) and (B) other four memory measures. The colors represent the clinical change of each patient according to RCI (red = improved, blue = no change, green = deteriorated). The horizontal line represents the cut-off score; improved patients above this score are considered "recovered" according to the explanation in the method part in the text.

process was quite predictable. Other brain areas that showed significant change in activation in the clinically improved group were part of the enthorinal cortex (BA28), which has been found to be affected in Alzheimer's disease and to play a role in the process of spatial memory (Khan et al., 2014; Suthana et al., 2012). The temporal pole (BA38), is among the earliest affected by Alzheimer's disease and the earliest involved at the start of temporal lobe seizures (Ding, Van Hoesen, Cassell, & Poremba, 2009). Studies in monkeys revealed a role for the temporal pole in a variety of functions, visual discrimination of two-dimensional pictures, and the mnemonic functions of matching and learning (Dupont, 2002).

More important, the main lesion area, the "chronic penumbra" or "stunned brain" was identified, an area characterized by critically reduced cerebral blood flow (CBF), abolished synaptic activity but preserved structural integrity (Furlan, Marchal, Viader, Derlon, & Baron, 1996). These areas of the brain that are damaged but not dead after stroke offer the promise that, with proper therapy, their function could be restored (Lo, 2008). HBO_2 is expected to induce improvement of recognition memory deficits mainly in patients who had the potential for improvement of the PrC activation (i.e., this area was not anatomically disrupted, only dysfunctional, as in the case of penumbra tissue). The above possibilities require further investigation and research as well as investigation of the anatomical damage localization and volume. A detailed discussion of the metabolic processes, possible innate repair mechanisms and neuroplasticity activated by HBO_2 treatments at late chronic stages of stroke in the injured brain is presented in (Efrati & Ben-Jacob, 2014b; Efrati et al., 2013).

Being a retrospective analysis of previously published data, the analysis lacks a control group. However, the findings presented here are in agreement with and reinforce similar findings from previous prospective controlled trials in which the neurotherapeutic effects of HBO_2 in stroke and TBI patients were tested (Boussi-

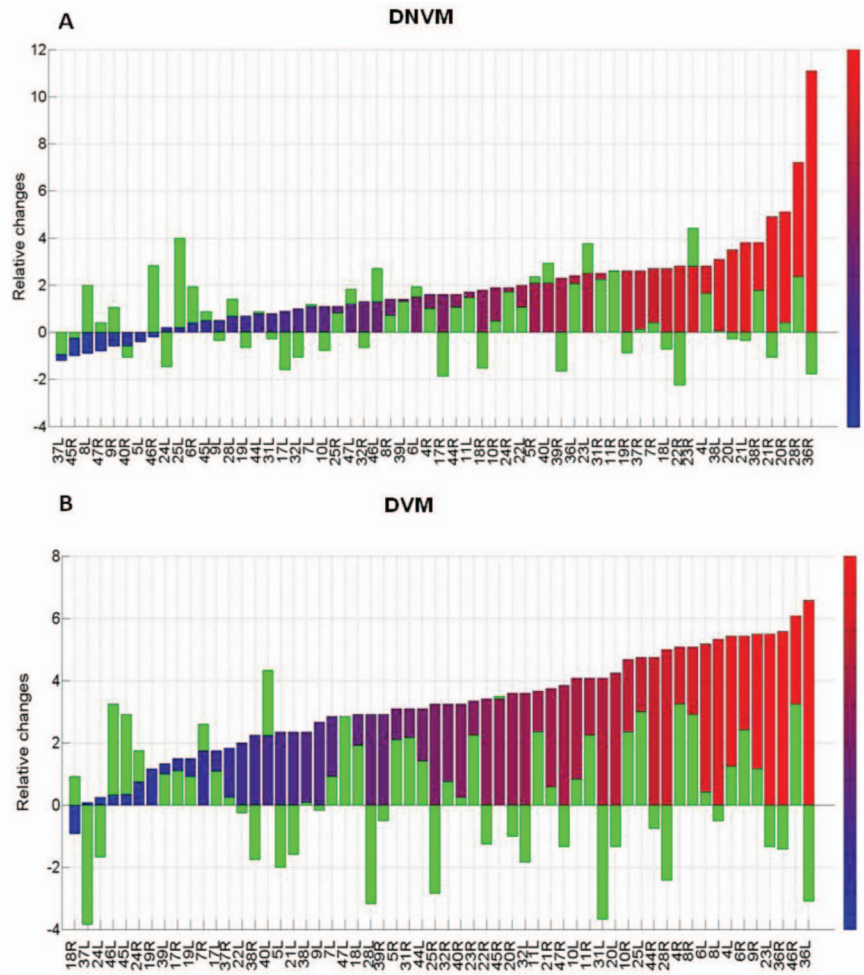

Figure 6. Mean percent of relative change in SPECT activation. This figure presents the mean relative change in SPECT activation in (A) the delayed nonverbal memory (DNVM) group, and (B) the delayed verbal memory (DVM) group. In each group, the mean percent of relative change is presented for both the clinically improved group (blue-to-red bars) and the not-improved group (green bars). In (A), improved group: $n = 10$; not-improved group: $n = 17$; in (B), improved group: $n = 12$; not-improved group: $n = 12$.

Gross et al., 2013; Efrati et al., 2013). These studies provided convincing evidence that HBO_2 can induce neuroplasticity at chronic stages in areas with metabolic dysfunction. If an area of metabolic dysfunction relevant to memory function in the brain is such that can improve after HBO_2, one can expect clinical improvement in memory, as was demonstrated in this study. In addition, the correlation found between the clinical measures of memory improvement and brain imaging in areas relevant to the same clinical improvement also strengthens the findings. Finally, most of the patients in this study were in the chronic stage where no spontaneous improvement was expected. Clearly, further, larger prospective randomized trials on the effect of HBO_2 on cognitive impairment in poststroke patients should be conducted.

The study has several limitations: the first is that the data analyzed was done retrospectively so there is a lack of follow-up data or data regarding long-term effects of the treatments. The significant improvements found in this study mean that it is important to perform future studies to replicate these findings as well as study whether the effects persist over time.

Another study limitation relates to the focus on recognition memory in the selected tests. There is a differentiation between recall and recognition memory abilities, as well as evidence for different brain structures and networks (Cabeza et al., 1997; Eichenbaum, Yonelinas, & Ranganath, 2007; Staresina & Davachi, 2006). The current research deals only with recognition abilities because of the limitation of the test battery used, although these were shown to highly correlate with other recall paper based memory tests (Doniger et al., 2006; Dwolatzky et al., 2003; Elstein et al., 2005). However, future studies should widen the exploration of HBO_2 effect on the different memory abilities, including recall memory, as well as other cognitive impairments.

Additional study limitation relates to the HBO_2 treatment protocol. Even though a significant beneficial effect is notice with HBO_2 treatment, the exact HBO_2 protocol needed to induce maximal neuroplasticity with minimal side effects was behind the scope of this study. It is well recognized that HBO_2 can induce significant neurophysiological effect even at lower pressures and it is also possible that additional HBO_2 sessions could have bring

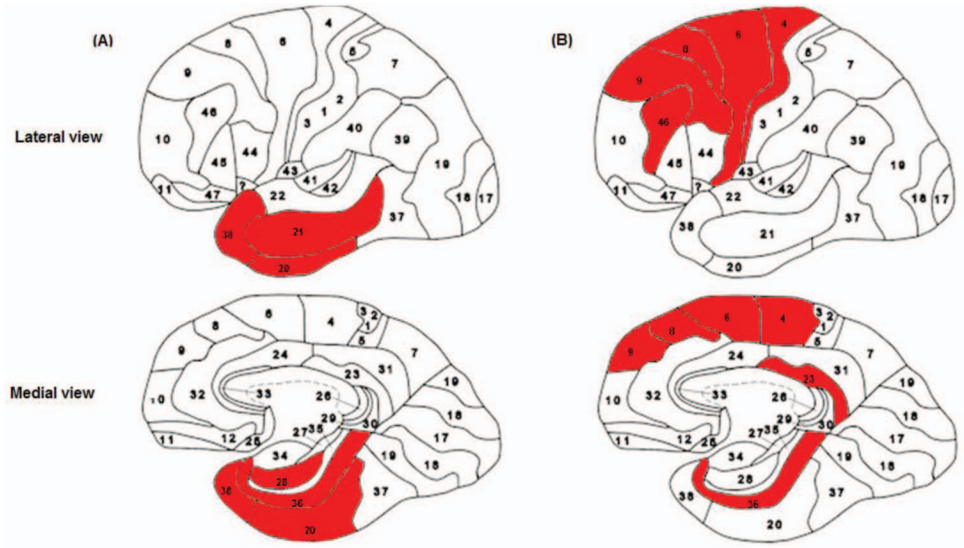

Figure 7. Activated Brodmann areas (BAs) of patients that had cognitive improvement after HBO_2 treatment. The colored BAs represent areas with significant increase metabolism in the cognitive improved patients: (A) the delayed nonverbal memory (DNVM) group, and (B) the delayed verbal memory (DVM) group.

further improvement (Efrati & Ben-Jacob, 2014a, 2014b; Efrati et al., 2013). Future pharmacodynamics studies, using different HBO_2 protocols, are needed to optimization of the HBO_2 treatment protocol.

In conclusion, this study demonstrates, for the first time, significant improvements in memory functions of poststroke patients after HBO_2 at the late chronic stage. Further prospective, randomized controlled trials, including more extensive cognitive examinations, are needed to specify the patients who might benefit the most from this treatment.

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