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Hyperbaric oxygen can induce neuroplasticity and improve cognitive functions of patients suffering from anoxic brain damage

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Abstract.
Purpose: Cognitive impairment may occur in 42–50% of cardiac arrest survivors. Hyperbaric oxygen therapy (HBO_2) has recently been shown to have neurotherapeutic effects in patients suffering from chronic cognitive impairments (CCI) consequent to stroke and mild traumatic brain injury.

The objective of this study was to assess the neurotherapeutic effect of HBO_2 in patients suffering from CCI due to cardiac arrest.

Methods: Retrospective analysis of patients with CCI caused by cardiac arrest, treated with 60 daily sessions of HBO_2. Evaluation included objective computerized cognitive tests (NeuroTrax), Activity of Daily Living (ADL) and Quality of life questionnaires. The results of these tests were compared with changes in brain activity as assessed by single photon emission computed tomography (SPECT) brain imaging.

Results: The study included 11 cases of CCI patients. Patients were treated with HBO_2, 0.5–7.5 years (mean 2.6 ± 0.6 years) after the cardiac arrest. HBO_2 was found to induce modest, but statistically significant improvement in memory, attention and executive function (mean scores) of 12%, 20% and 24% respectively. The clinical improvements were found to be well correlated with increased brain activity in relevant brain areas as assessed by computerized analysis of the SPECT imaging.

Conclusions: Although further research is needed, the results demonstrate the beneficial effects of HBO_2 on CCI in patients after cardiac arrest, even months to years after the acute event.

Keywords: Anoxic brain damage, rehabilitation, cognitive symptoms, hyperbaric oxygen therapy, SPECT

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1. Introduction

Despite advanced cardiac life support (ACLS), the mortality rate from sudden death after cardiac arrest is 85–95% (Nichol et al., 2008). Moreover, 33–50% of ACLS survivors develop significant neurological dysfunction with variable extent, and these percentages rise to nearly 100% in the rare survivors of non-witnessed arrests (Allen & Buckberg, 2012).

The neuropathology of anoxic brain injury (ABI) includes neural toxicity, intracellular calcium accumulation, oxygen free radicals, neurotransmitters and excitatory amino acid release, reperfusion injury and endothelial injury (Guo, Yu, & Ma, 2011). The hippocampus, basal ganglia (especially the globus pallidum, thalamus) and deep central white matter regions are the first to suffer damage due to their high metabolic requirements (Hopkins & Bigler, 2012). As the duration of anoxia increases, global nonspecific damage in other parts of the brain develops. Accordingly, the clinical presentation includes impairments in visual perception, expression, cognition and motor coordination (Fitzgerald, Aditya, Prior, McNeill, & Pentland, 2010; Hopkins & Bigler, 2012). Cognitive impairment is common and may occur in 42–50% of the survivors (Moulaert, Verbunt, van Heugten, & Wade, 2009; van Alem, de Vos, Schmand, & Koster, 2004). Memory, attention and executive function impairments are the most common (van Alem et al., 2004).

Unfortunately, to date, there is no effective therapy that can induce neuroplasticity with significant cognitive improvement in these survivors. While neurorehabilitation starting in the first 3 months may result in modest improvement (Fertl, Vass, Sterz, Gabriel, & Auff, 2000), significant cognitive improvement later than 3 months is considered to be very rare (Lim, Verfaellie, Schnyer, Lafleche, & Alexander, 2014). In general, in comparison to the recovery from traumatic brain injury (TBI), ABI patients are left with more severe cognitive impairments and worse functional debilitation (Shah, Al-Adawi, Dorvlo, & Burke, 2004).

The neuroplasticity effects of hyperbaric oxygen therapy (HBO_2) on the chronic damaged neuronal tissue have recently been evaluated in patients with chronic neurological deficiencies due to stroke or TBI (Boussi-Gross et al., 2013, 2014; Efrati et al., 2013). HBO_2 includes the inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA) in order to enhance the amount of oxygen dissolved in the body tissues. As explained in detail by Efrati and Ben-Jacob (2014), the diverse and powerful innate repair mechanisms activated by HBO_2 are associated both with the elevated level of dissolved oxygen and with the elevated pressure. The beneficial physiological effects of HBO_2 on the injured brain and cognitive function have been demonstrated in several animal models (Boussi-Gross et al., 2014; Palzur et al., 2004; Palzur, Zaaroor, Vlodavsky, Milman, & Soustiel, 2008).

There is previous evidence for cognitive improvements after HBO_2 in various neurological conditions (Barrett et al., 1998; Boussi-Gross et al., 2013, 2014; Jacobs, Winter, Alvis, & Small, 1969; Mukherjee et al., 2014; Rossignol, Rossignol, James, Melnyk, & Mumper, 2007; Tapeantong & Poungvarin, 2009); however, the neuroplasticity effects of HBO_2 on patients suffering from ABI have not yet been investigated.

The purpose of the current study was to present the first series of cases of ABI patients suffering from chronic cognitive impairments after cardiac arrest treated by HBO_2.

2. Methods

2.1. Participants

Retrospective analysis of patients with CCI caused by cardiac arrest, treated at the institute of Hyperbaric Medicine, Assaf Harofeh Medical Center, Israel, between January 2008 and December 2014. The study was approved by the institutional review board of the hospital.

Inclusion criteria: patients who have completed two cognitive evaluations and assessments of SPECT brain imaging, before and after HBO_2.

All patients applied for HBO_2 on their own interest and funded the sessions. Imaging and functional tests were funded by Assaf Harofe Hyperbaric institute. This were not informed on a research trial before or after their sessions.

2.2. Hyperbaric oxygen treatment

Patients were treated in a multiplace hypberbaric chamber (HAUX-Life-Support GmbH.) for 60 daily sessions, 5 days per week. Each session consisted of 60 minutes exposure to 100% oxygen at 1.5 ATA with 5 minutes air breaks every 30 minute. Acceptable compression and decompression rates of

0.8 meter per minute were used. Oxygen was supplied by tight masks.

2.3. Cognitive assessment

Patients' cognitive functions were assessed by NeuroTrax computerized cognitive tests (NeuroTrax Corp., TX) (Dwolatzky et al., 2003). NeuroTrax tests evaluate various aspects of brain functions and include: Verbal Memory (immediate and delayed recognition), Non-Verbal Memory (immediate and delayed recognition), Go-No-Go Response Inhibition, Problem Solving, Stroop Interference, Finger Tapping, Catch Game, Staged Information Processing Speed (single digit, two-digit and three-digit arithmetic), Verbal Function and Visual Spatial Processing. Cognitive index scores were computed from normalized outcome parameters for these tests for memory, executive function, attention, information processing speed, visual spatial, verbal function and motor skills domains (Achiron et al., 2013; Thaler et al., 2012; Zur, Naftaliev, & Kesler, 2014). A global cognitive score was computed as the average of all index scores for each individual.

After administration, NeuroTrax data were uploaded to the NeuroTrax central server, and outcome parameters were automatically calculated using 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 (mean = 100, S.D. = 15) according to the patient's age and education. The normative data used by NeuroTrax consists of test data from cognitively healthy individuals in controlled research studies at more than 10 sites (Doniger, 2014).

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

2.4. Activities of Daily Living assessment

The Activities of Daily Living (ADL) were evaluated by a questionnaire covering the following functions: bathing, dressing, grooming, oral care, toileting, walking, climbing stairs, eating, shopping, cooking, managing medications, using phone, housework, doing laundry, driving and managing finances (Katz, 1983). For each function, the patient made a dependency rating ranging from independent, needs help, dependent or does not do at all, with a total score ranging from 0 (worst) to 51 (best).

2.5. Quality of Life assessment

Quality of Life (QOL) was evaluated by the EQ-5D questionnaire (Rabin & de Charro, 2001). EQ-5D essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system covers mobility, self-care, usual activities, pain/discomfort and anxiety/depression [range: 5 (best) –15 (worst)]. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale [range: 0 (worst) −100 (best)].

2.6. Brain functional imaging

Brain activity was assessed using single photon emission computed tomography (SPECT) 1-2 weeks prior to and after the HBO_2 period. The imaging was conducted using 925–1,110 MBq (25–30 mCi) of technetium-99m-methyl-cysteinate-dimmer (Tc-99m-ECD) at 40–60 min post injection using a dual detector gamma camera (ECAM or Symbia T, Siemens Medical Systems) equipped with high resolution collimators. Data were acquired in 3-degree steps and reconstructed iteratively with Chang method ($\mu = 0.12$/cm) attenuation correction (Jaszczak, Chang, Stein, & Moore, 1979).

Both SPECT studies were normalized to the median brain activity in the entire brain and were then reoriented into Talairach space using NeuroGam (Segami Corporation) to identify Brodmann cortical areas and in order to compute the mean perfusion in each Brodmann area (BA). In addition, volume rendered brain perfusion images were reconstructed and normalized to entire brain median activity. All SPECT analyses were done by study team members who were blinded to the laboratory and clinical data. SPECT scans were performed late morning to midday. On the day of the SPECT scan, patients were treated with only their chronic medications and were instructed not to smoke. Changes in perfusion in all Brodmann areas for each subject were determined by calculating the percentage of the difference of the normalized activity value between post-treatment and pre-treatment divided by the pre-treatment value.

2.7. Statistical analysis

Continuous data were expressed as means ± standard errors. Relative changes were calculated by subtracting the pre-treatment score from the post-treatment score, and dividing by the pre-treatment score. Normal distribution for all continuous variables was tested using Kolmogorov-Smirnov test. The cognitive index scores and ADL mean differences before and after HBO_2 were analyzed using two tailed paired *t*-test. EQ-VAS mean difference before and after HBO_2 was analyzed using Wilcoxon signed ranks test. Alpha level was set to 0.05. The calculated sample size for 25% change in means was 10 patients. Data were statistically analyzed using SPSS software (version 22.0).

3. Results

3.1. Patients' profile

Of 28 patients suffering from ABI treated at the institute of Hyperbaric Medicine, Assaf Harofeh Medical Center, Israel between January 2008 and December 2014, eleven patients had two neuro-cognitive evaluations before and after HBO_2.

Among these patients, average age was 45.6 ± 4.4 years (29–70), and 9 out of 11 patients (81%) were males. All patients had chronic stable neuro-cognitive impairment, and they began HBO_2 5 months to 7.5 years (mean 2.6 ± 0.6 years) after cardiac arrest. Baseline patients' characteristics are summarized in Table 1.

Table 1
Basic characteristics of patients at baseline

Characteristic	Total patients (11)
Age (years)	45.6 ± 4.4
Males	81%
Time from injury (months)	31.3 ± 7.7
Cardiac ejection fraction	52.2 ± 2.3%
Years of education	13.4 ± 0.5
Chronic Diseases	
Known Ischemic Heart Disease	1/11 (9%)
Known Arrhythmia (Including Long-QT)	2/11 (18%)
Diabetes Mellitus Type II	2/11 (18%)
Hypertension	3/11 (27%)
Dyslipidemia	5/11 (45%)
Smoking history	3/11 (27%)
Medications	
Beta-Blockers	8/11 (72%)
Statins	5/11 (45%)
Anti-Platelets	5/11 (45%)
ACE-Inhibitors	3/11 (27%)
Anti-coagulants	1/11 (9%)

Note the average time of 31 months from cardiac arrest. Data are expressed as means ± standard errors.

3.2. Neuro-cognitive evaluation

High inter-patient variability was present in the baseline cognitive indices. The magnitude of the change in a cognitive score has different implications for patients at low or high baseline levels. Hence, we inspect the effect of HBO_2 on the relative changes, i.e. the change relative to the baseline value. Calculating mean of relative changes is more informative than calculating the changes in mean values, especially in small groups with high patient to patient variability.

One of the patients that had prominent improvement from non-measureable scores, due to insufficient responses prior to treatment, to measureable scores in all cognitive domains after treatment was not included in the means' analysis.

The effect of the hyperbaric oxygen treatment on the patients' cognitive functions, as assessed by the eight cognitive summary scores, is summarized in Table 2. As can be seen, HBO_2 induced significant improvement in the global cognitive scores with a mean relative change of 8% ($p = 0.006$). The most prominent improvement was in executive functions indices, with 24% mean relative change ($p = 0.011$). Attention indices improved by mean relative change of 20% ($p = 0.06$). Memory indices by mean relative change of 12% ($p = 0.08$) (Table 2, Fig. 1).

3.3. Activity of daily living

Two of the patients could not complete the ADL questionnaire before HBO_2. In the nine patients who completed the pre and post HBO_2 questionnaire, ADL score was significantly improved after HBO_2 by an average of 5 points ($p = 0.002$) (Table 3, Fig. 1).

3.4. Quality of life evaluation

Nine patients completed pretreatment quality of life questionnaires. Compared to the pre-treatment score, EQ-VAS and EQ-5D scores after HBO_2 improved significantly ($p = 0.027$ and $p = 0.015$, respectively) (Table 3, Fig. 1).

Table 2
Cognitive indices at baseline, after Hyperbaric Oxygen Therapy (HBO_2). Mean relative change is calculated by mean change divided by the pre HBO_2 mean score. Data are expressed as means ± standard errors

Cognitive function	Pre HBO_2	Post HBO_2	Mean Change	Mean Relative change %	T, df	*P*-value
Global Cognitive Score	70.9 ± 5.9	76.0 ± 5.8	5.0 ± 1.4	8.2 ± 2.7%	3.5, 9	0.006*
Memory	54.9 ± 8.5	59.9 ± 8.3	4.9 ± 2.5	12.3 ± 7.8%	1.9, 9	0.080
Executive	71.3 ± 6.7	82.9 ± 5.0	11.5 ± 3.6	23.8 ± 11.8%	3.5,9	0.011*
Attention	66.13 ± 8.3	72.9 ± 5.7	6.8 ± 3.1	20.3 ± 9.1%	2.1,9	0.060
Information processing speed	67.5 ± 6.4	70.9 ± 7.2	3.4 ± 3.0	5.1 ± .4.8%	1.1,7	0.310
Visual spatial	79.4 ± 8.8	83.8 ± 9.1	4.4 ± 3.3	6.4 ± 4.3%	1.3,9	0.221
Verbal skills	75.4 ± 10.4	78.1 ± 11.1	2,7 ± 4.8	4.1 ± 6.4%	0.563,8	0.589
Motor skills	87.6 ± 6.0	88.0 ± 4.7	0.4 ± 2.7	2.1 ± 3.6%	0.155,9	0.880

One of the patients that had prominent improvement from non-measureable scores due to insufficient responses prior to treatment to measurable scores in all cognitive domains after treatment was not included in this analysis. *significant ($p < 0.05$) by two-tailed paired *t*-test.

3.5. Functional imaging of the brain-SPECT

Five patients had brain SPECT evaluations before and after HBO_2. Six patients refused brain-SPECT imaging due to radiation exposure. The mean relative changes of all patients revealed significant improvement (higher than 10%) in brain activity (reflected by perfusion) following HBO_2 in the cingulate gyrus (BA 31,32,23,24), inferior frontal gyrus (BA 47,44,45), perirhinal cortex (BA 36), primary visual cortex (BA 17) and parietal lobe (BA 7) (Figs. 2 and 3).

3.6. Representative clinical cases

3.6.1. Case 1: 52-year-old male, one year post ventricular fibrillation, suffering from ataxia and significant cognitive decline

Baseline cognitive evaluation showed a very low memory index score and low executive function, verbal function, information processing speed, attention, and motor skills index scores. After 60 HBO_2 sessions, the patient had improvements in verbal function, executive function and attention from scores of 71, 73 and 68 to 106, 90 and 81, respectively. Improvement was also seen in memory from 25 to 43, yet the score was still low. Clinically, with regards to his ADL after HBO_2, the patient was able to participate in housework, managing finances and shopping.

Brain SPECT evaluation showed the that the largest post HBO_2 increase in brain activity was in the perirhinal cortex (BA 36) with over 50% increase, in the primary visual cortex (BA 17,18) with over 30% increase and in the cingulate gyrus (BA 23, 31) with over 20% increase (Fig. 4).

3.6.2. Case 2: 48-year-old male, 2 years post resuscitation, suffering from motor dysphasia, left-right disorientation and significant cognitive dysfunction

Cognitive evaluation at baseline showed low memory, visual spatial and executive function scores in addition to low attention and motor scores. After 60 HBO_2 sessions, the patient had improvement in memory, visual spatial and executive function from scores of 58, 70 and 74 to 68, 76 and 79, respectively. Clinically, he had complete resolution of dysphasia. Improvements were also noticed in ADL abilities such as ability to do laundry and manage finances. Additionally, he was able to return to his previous work.

Brain SPECT evaluation showed the largest post HBO_2 increase in the parietal lobes (BA 5,7), temporal lobe with over 25% increase, in the inferior orbital gyrus (BA 45,47), cingulate gyrus (BA 23,24), in Wernike's area (BA 39) and in the primary visual cortex (BA 17,18) with over 15% increase (Fig. 5). See Appendix for three additional case reports.

3.7. Safety

The treatment was well tolerated and all patients completed the treatment protocol. No significant adverse reactions were recorded in any of the patients.

4. Discussion

The neurotherapeutic effects of HBO_2 in patients suffering from CCI caused by cardiac arrest mediated anoxic brain injury, were evaluated by both clinical and brain imaging measures. Even though the acute injury was 5 months to 7.5 years (mean 31.3 ± 7.7 months) prior to treatment, HBO_2 was associated with

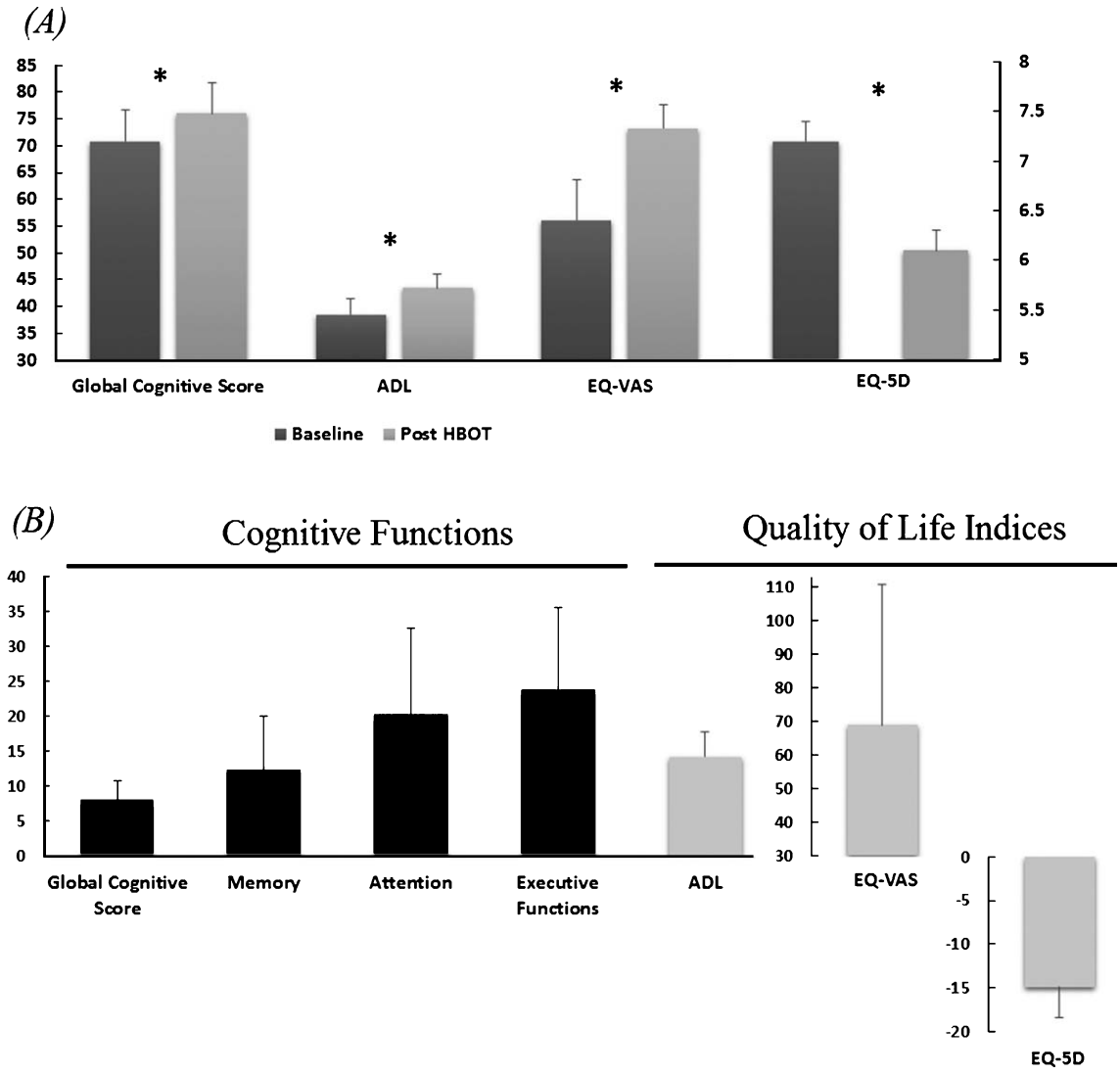

Fig. 1. Improvements in cognitive functions ADL and quality of life (EQ-5D, EQ-VAS). A. Mean changes of the corresponding cognitive indices at baseline and after HBO_2. Statistical significance ($p < 0.05$) is marked by *. Note lower EQ-5D score represents higher quality of life. Bars represent means + standard errors. B. The mean percentage of the relative changes (Post-Pre)/Pre.

Table 3

Activity of Daily Living (ADL) and quality of life (EQ-5D and EQ-VAS) scores before and after Hyperbaric Oxygen Therapy. Mean relative change is calculated by mean change divided by the pre HBO_2 mean score. Data are expressed as means ± standard errors

Score	Pre Treatment ADL	Post HBO_2 ADL	Mean Change	Mean Change %	*P*-Value
ADL	38.6 ± 3.0	43.5 ± 2.5	4.9 ± 1.0	14.3 ± 3.5%	0.002*
EQ-VAS	56.1 ± 7.6	73.3 ± 4.3	17.2 ± 5.0	69 ± 42%	0.027*
EQ-5D	7.2 ± 0.2	6.1 ± 0.2	−1.1 ± 0.2	−14.9 ± 3.5%	0.015*

ADL difference before and after HBO_2 was analyzed using two-tailed paired *t*-test. EQ-VAS and EQ-5D were analyzed using Wilcoxon signed ranks test. *marks statistical significance.

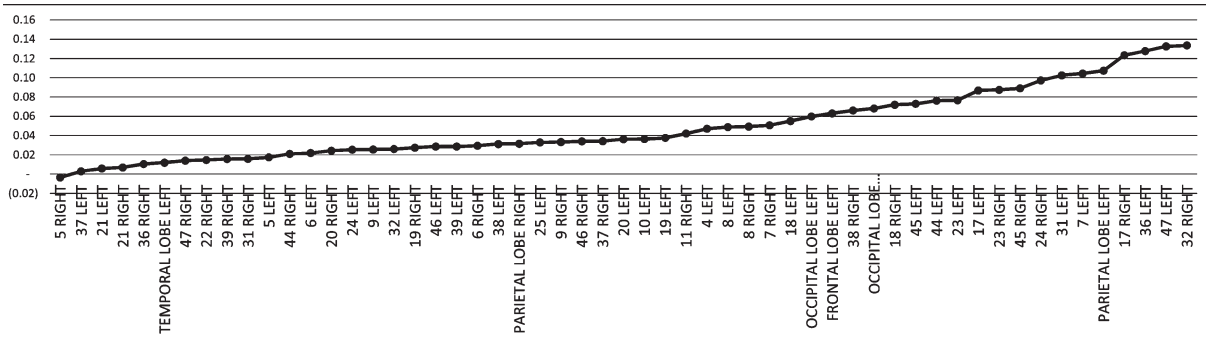

Fig. 2. The mean CBF relative change after hyperbaric oxygen therapy calculated per Brodmann area.

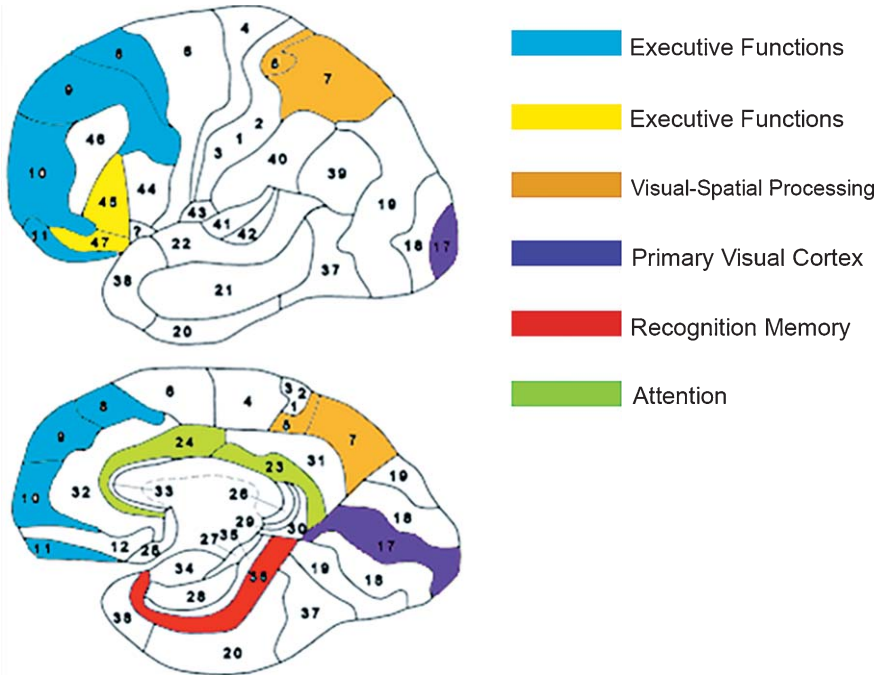

Fig. 3. The Brodmann areas that were most improved after HBO_2; perirhinal cortex (BA36) in red, the pre-frontal cortex (BA 8,9,10,11) in blue, inferior frontal gyrus (BA 45,47) in yellow, the anterior cingulate gyrus (BA 23,24) in green, primary visual cortex (BA 17) in purple and the parietal lobes (BA 5,7) in orange.

significant cognitive improvement in all patients. The clinical improvements were well documented by neurocognitive tests and correlated with improved ability to perform the activities of daily living and quality of life. The most significant measurable improvements were in executive function, attention and memory.

Important validation and clues for future, larger scale studies were provided by the SPECT brain imaging. We found the clinical improvement to be well correlated with increased activity in the relevant brain area. More specifically, the brain areas that had the most significant increase in metabolic activation were in the perirhinal cortex (BA36), the pre-frontal cortex (BA 8,9,10,11), inferior frontal gyrus (BA 45,47), the anterior cingulate gyrus (BA 23,24) and the parietal lobes (BA 5,7). A good correlation was found between the improved neurocognitive functions and the brain areas corresponding to these functions:

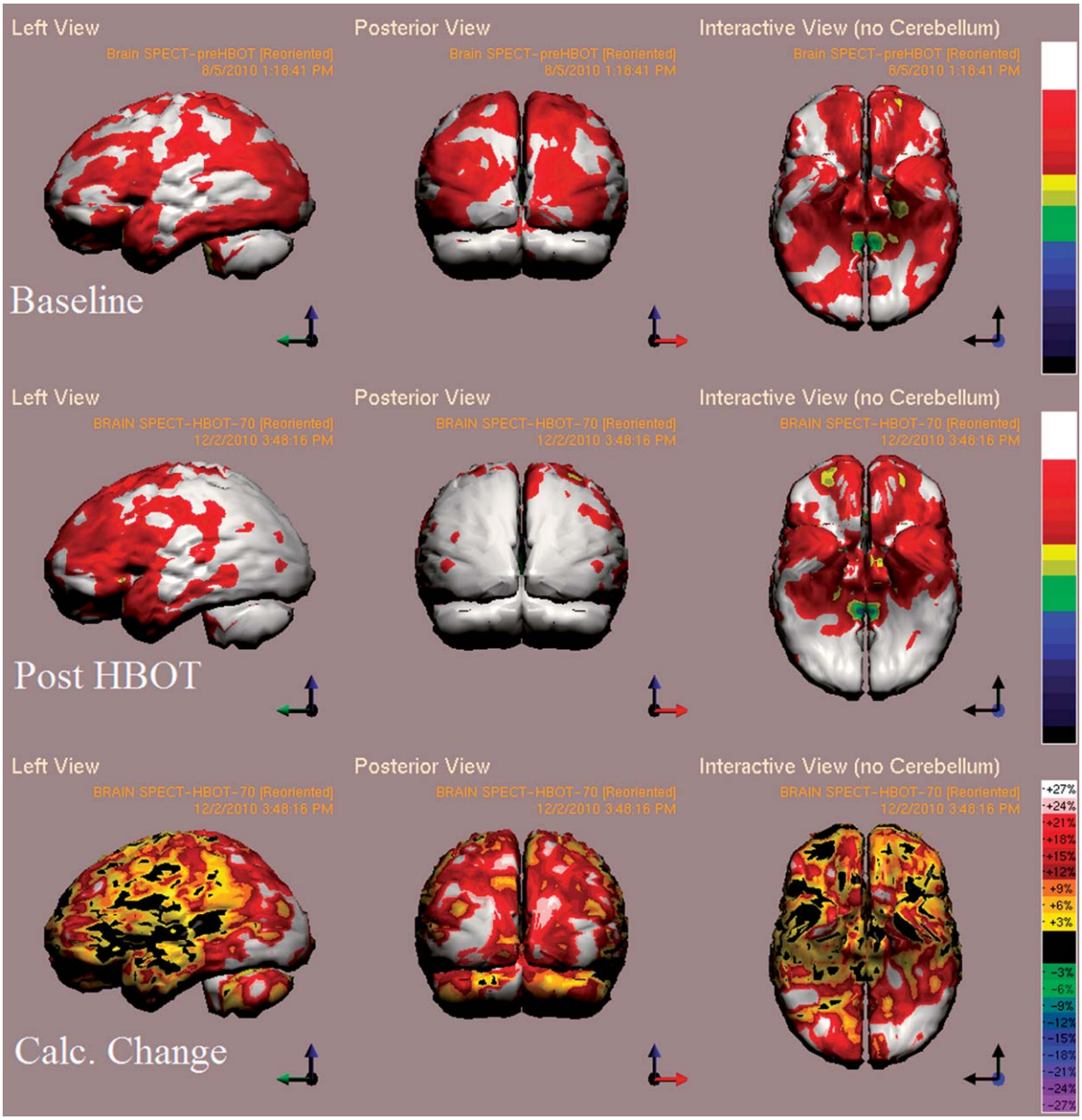

Fig. 4. Case 1 SPECT calculated change after HBO_2 compared to baseline. In the first two rows colors represent maximal functional brain activity relative to brain median activity, where in the bottom row colors represent the regional change in functional brain activity. White and red areas show the highest changes in CBF.

- The perirhinal cortex activation after HBO_2 was most prominent in patients that had significant memory improvement. The perirhinal cortex has a critical role in object recognition memory while interacting with the hippocampus (Brown & Aggleton, 2001). Because the memory assessments in the cognitive tests were indeed recognition tasks, this area might be expected to be involved.
- The pre-frontal cortex (BA 10, 11) and, more specifically, the inferior frontal gyrus (BA 45, 47) activation after HBO_2 were prominent in all patients

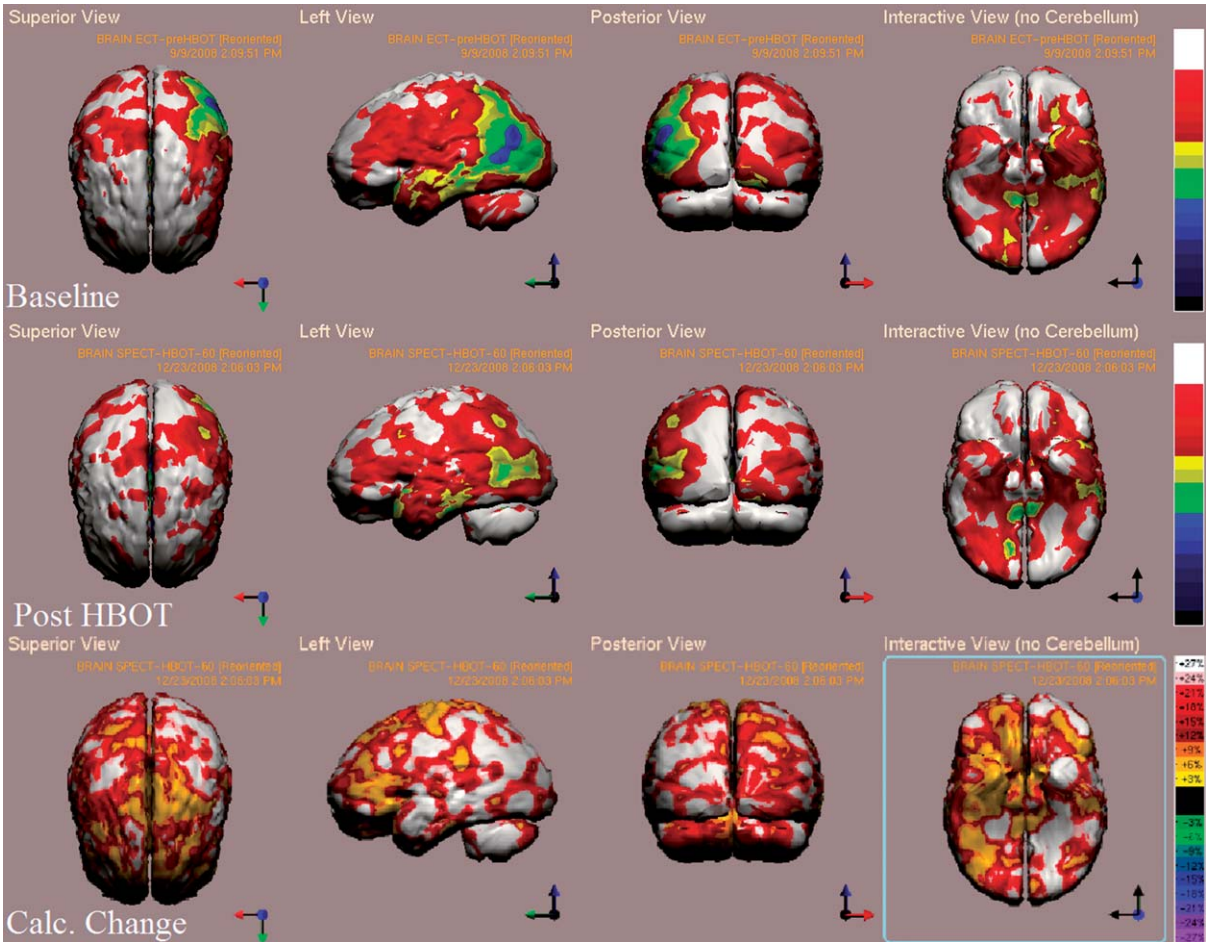

Fig. 5. Case 2 SPECT calculated change after HBO_2 compared to baseline. In the first two rows colors represent maximal functional brain activity relative to brain median activity, where in the bottom row colors represent the regional change in functional brain activity. White and red areas show the highest changes in CBF.

with significant executive function improvements. The right frontal gyrus is known to mediate a go/no go task (Aron, Robbins, & Poldrack, 2004), which was among the executive function tests used in the present study. The prefrontal gyrus is presumed to act as a filtering system that enhances goal directed activities and inhibits irrelevant activations. This filtering mechanism enables executive control (Miller & Cohen, 2001).

- The anterior cingulate gyrus (BA 23, 24) activation after HBO_2 was seen in the subjects with attention improvement. The anterior cingulate gyrus is presumed to be involved in error detection, especially in a Stroop task (Bush, Luu, & Posner, 2000), which was used in the attention tests. Lesions in this area can cause inattention to akinetic mutism (Bush et al., 2000).
- The posterior parietal lobes are involved in visual-spatial processing. Lesions in the right parietal lobe are known to cause visual spatial construction deficits (Mishkin & Ungerleider, 1982). Activations of these areas were seen in the patients with visual-spatial index improvement.

The changes revealed by inspection of the pre and post SPECT images indicate that HBO_2 can induce reactivation of neuronal activity in stunned areas in agreement with earlier studies (Barrett, 1998; Churchill et al., 2013; Jacobs et al., 1969). This implies that increasing the plasma dissolved oxygen with

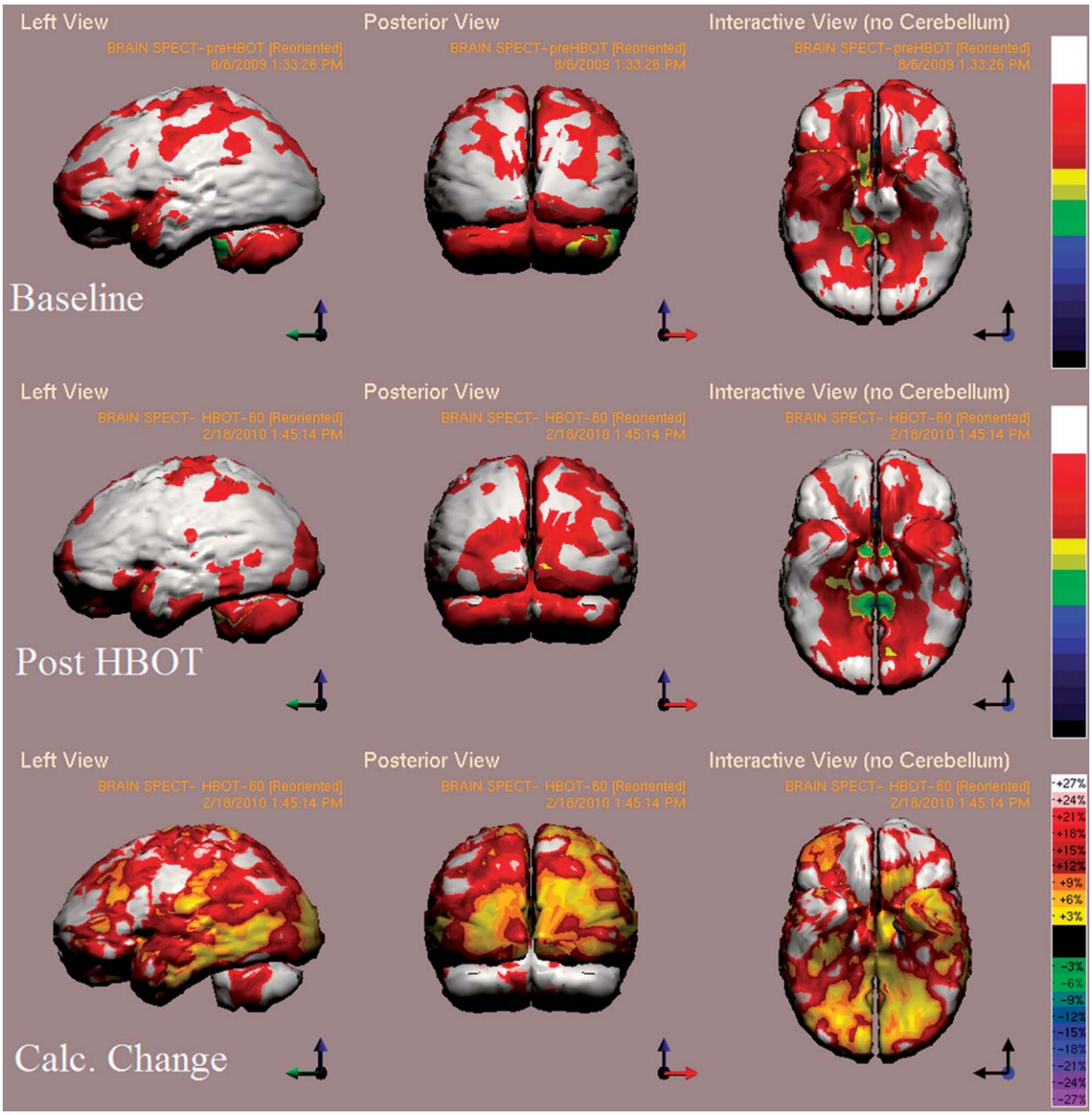

Fig. 6. Case 3 SPECT calculated change after HBO_2 compared to baseline. White and red areas show the highest changes in CBF. In the first two rows color represent metabolic activity, where in third row colors represent the subtraction of the two previous rows, i.e. the change in metabolic activity. Memory, attention, verbal and visual spatial indices improved from non measureable scores to 98, 70, 102, 89 and 89.7 respectively.

hyperbaric oxygenation is a potent mean of delivering sufficient oxygen to the brain for repair processes and induction of neuroplasticity.

In the past 30 years, there have been several studies on HBO_2 effects in the delayed phase (>1 month) of anoxic brain injury caused by different triggers and in varying ages (Collet et al., 2001; Jain, 2009; Montgomery et al., 1999; van Bever Donker, 1999, 2001). Most studies were focused on children with cerebral palsy (Hardy et al., 2002). Neubauer et al reported on 8 adults with non-cardiac related anoxic enceophalopathy who showed clinical improvement after more than

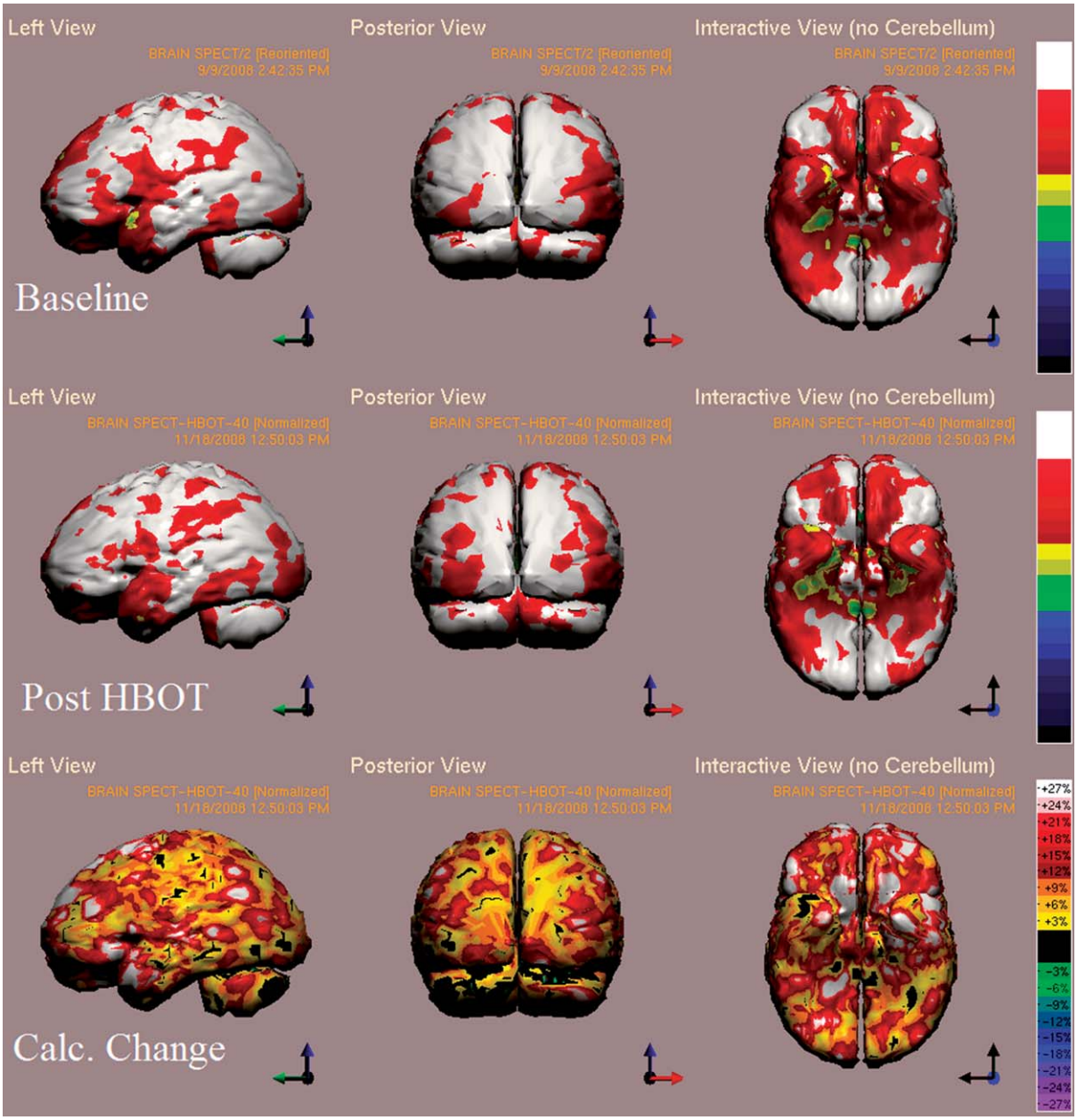

Fig. 7. Case 4 SPECT calculated change after HBO_2 compared to baseline. In the first two rows color represent maximal functional activity relative to brain median activity, where in bottom row colors represent the change in regional brain activity. White and red areas show the highest changes in CBF. Executive function, verbal, visual spatial and memory indices improved from scores of 98, 88, 84, 69 to 111, 104, 104, 79 respectively.

100 sessions of HBO_2 using different hyperbaric protocols (Neubauer & James, 1998). Golden et al. showed improved cognitive functions in 21 adults with chronic brain injury (Golden, Golden, & Neubauer, 2006); however, the causes and extent of the injuries were not reported. As in the current study, the Neubauer and Golden studies showed good correlations with brain activity as evaluated by brain SPECT. In Churchill et al. prospective study, 13 patients with anoxic brain injury had subjective cognitive improvement after HBO_2

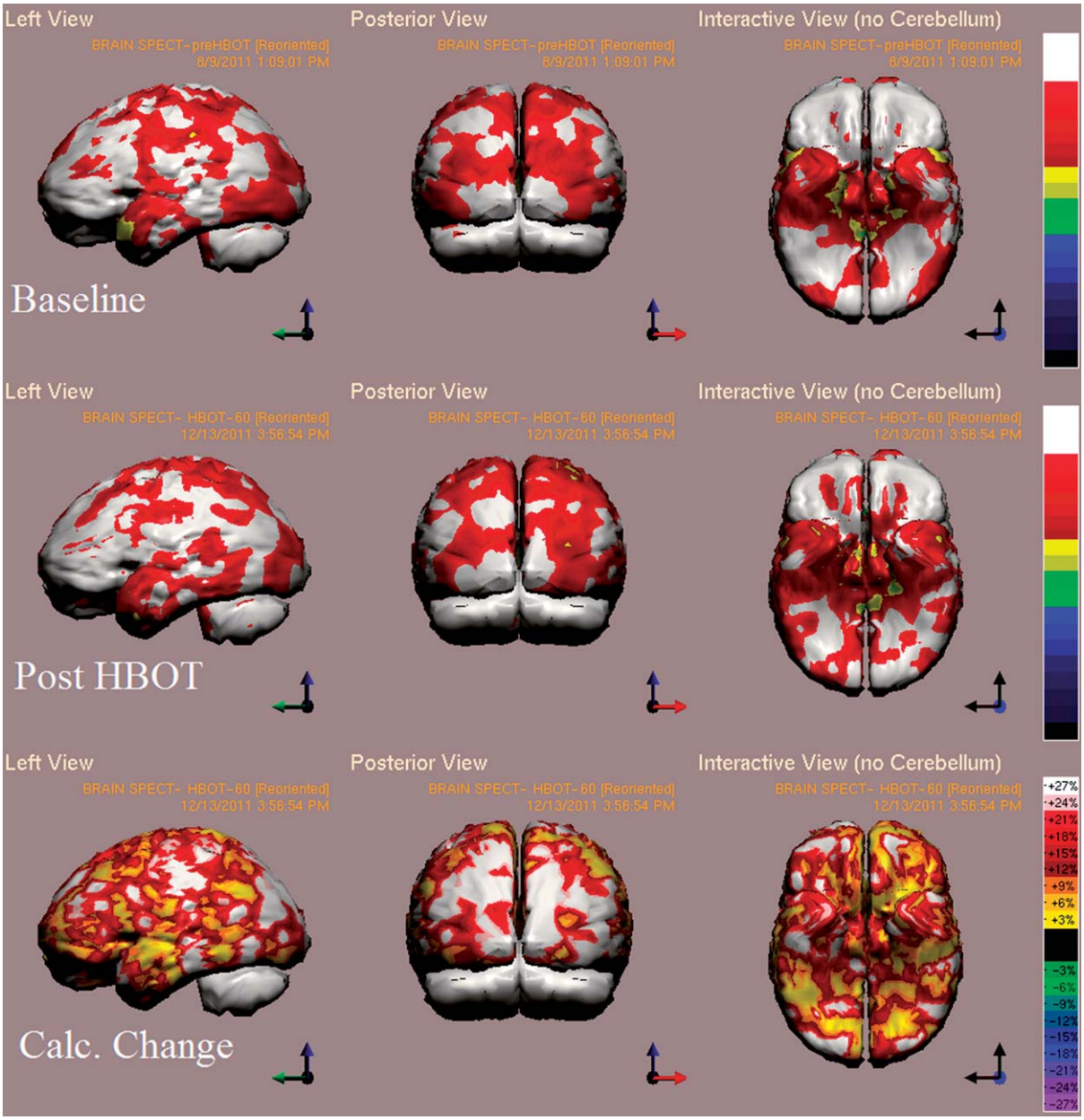

Fig. 8. Case 5 SPECT calculated change after HBO_2 compared to baseline. In the first two rows color represent maximal brain activity relative to brain median activity, where in the bottom row colors represent the change in regional brain function i.e. the change in metabolic activity. A global improvement of brain activity is demonstrated more accentuated in both occipital cortices. White and red areas show the highest changes in CBF. Executive function and attention indices improved from 44 and 38 to 62 and 59, respectively.

however no change was observed in standardized testing (Churchill et al., 2013).

The NeuroTrax cognitive tests, used for the cognitive evaluation, are validated for test-retest evaluations. Data from healthy young adults retested with NeuroTrax test battery on the same day, (Doniger, Simon, & Zivotofsky, 2006) demonstrated small mean relative changes (<5%), and intra class correlations provided support for good reliability. Middle age adults retested with an alternate form of the same battery,

(A. Schweiger, 2003) showed stable cognitive scores with small mean relative changes (<5%) except in verbal function (16%) and information processing speed (8%). In the current study, after HBO_2, the patients showed improvement in global cognitive function memory and executive function indices of 14–42%, with retesting more than 3 months after the baseline evaluation.

Our findings are in agreement with the previous studies evaluating the effects of HBO_2 in the chronic phase of ABI (Hardy et al., 2002; Golden et al., 2006). To our knowledge, this is the first case series of HBO_2 application in the chronic phase of brain anoxia focused on patients after cardiac arrest. The use of objective cognitive tests in tandem with objective metabolic brain imaging in the current study, strengthens the conclusion that HBO_2 can induce neuroplasticity even at the late chronic stage of ABI.

This study has several limitations. The major one relates to the retrospective methodology and the relatively small number of patients. Still, the findings presented here are in agreement with and reinforce similar findings from previous prospective controlled trials in which the neuroplasticity effects of HBO_2 were demonstrated in chronic stages of other brain related injuries (Boussi-Gross et al., 2013). These studies provided convincing evidence that HBO_2 can induce neuroplasticity at chronic stages in areas with metabolic dysfunction. Moreover, the natural history of anoxic brain injury implies that maximal recovery is expected during the first 3 months, and no further significant improvement is expected after 3 months (Lim et al., 2014). Accordingly, any significant improvement after 5 months may be attributed to the intervention used. Although significant clinical improvement at a relatively late chronic stage and high correlation with the improved metabolic activity support the validity of the findings, larger randomized prospective controlled trials are needed.

Another important limitation relates to the HBO_2 protocol. Although significant neurotherapeutic effects were achieved with 60 sessions of 1.5 ATA for 60 minutes, the exact protocol needed to induce maximal neuroplasticity with minimal side effects remains unknown. There is cumulative data that even smaller increase in pressure might be as effective (Efrati & Ben-Jacob, 2014).

As stated above, further randomized controlled trials with large patient cohorts are needed to better understand who the best candidates are and what the optimal HBO_2 protocol is for patients suffering from ABI.

5. Conclusions

Hyperbaric oxygen therapy may improve cognitive functions even during the late chronic phase after ABI resulting from cardiac arrest. Due to the growing numbers of cardiac arrest survivors, the application of HBO_2 in this population should be considered. Further prospective randomized clinical studies should be carried out in order to evaluate the patients who can benefit the most from the treatment and the optimal HBO_2 protocol (dose and duration) for this population.

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Declaration of interest

The authors have no financial or personal relationships to disclose regarding this research and data.

References

Achiron, A., Chapman, J., Magalashvili, D., Dolev, M., Lavie, M., Bercovich, E., et al. (2013). Modeling of cognitive impairment by disease duration in multiple sclerosis: A cross-sectional study. *PloS One*, *8*(8), e71058. doi: 10.1371/journal.pone.0071058

Allen, B.S., & Buckberg, G.D. (2012). Studies of isolated global brain ischaemia: I. Overview of irreversible brain injury and evolution of a new concept – redefining the time of brain death. *European Journal of Cardio-Thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic Surgery 41*(5), 1132-1137. doi: 10.1093/ejcts/ezr315

Aron, A.R., Robbins, T.W., & Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. *Trends in Cognitive Sciences*, *8*(4), 170-177. doi: 10.1016/j.tics.2004.02.010

Barrett, K.F., Masel, B.E., Harch, P.G., Ingram, F., Corson, K.P., & Mader, J.T. (1998). Cerebral blood flow changes and cognitive improvement in chronic stable traumatic brain injuries treated with hyperbaric oxygen therapy. *Neurology*, *50*, 178-179.

Barrett, K.F.M.B., Harch, P.G., Ingram, F., Corson, K.P., et al. (1998). Cerebral blood flow changes and cognitive improvement in chronic stable traumatic brain injuries treated with hyperbaric oxygen therapy. *Neurology*, *50*, A178-179.

Boussi-Gross, R., Golan, H., Fishlev, G., Bechor, Y., Volkov, O., Bergan, J., et al. (2013). Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury - randomized prospective trial. *PloS One*, *8*(11), e79995. doi: 10.1371/journal.pone.0079995

Boussi-Gross, R., Golan, H., Volkov, O., Bechor, Y., Hoofien, D., Schnaider Beeri, M., et al. (2014). Improvement of Memory Impairments in Poststroke Patients by Hyperbaric Oxygen Therapy. *Neuropsychology*. doi: 10.1037/neu0000149 [Epub ahead of print]

Brown, M.W., & Aggleton, J.P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? Nature reviews. *Neuroscience*, *2*(1), 51-61. doi: 10.1038/35049064

Bush, G., Luu, P., & Posner, M.I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*(6), 215-222.

Churchill, S., Weaver, L.K., Deru, K., Russo, A.A., Handrahan, D., & Orrison, W.W., Jr., et al. (2013). A prospective trial of hyperbaric oxygen for chronic sequelae after brain injury (HYBOBI). *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc*, *40*(2), 165-193.

Collet, J.P., Vanasse, M., Marois, P., Amar, M., Goldberg, J., Lambert, J., et al. (2001). Hyperbaric oxygen for children with cerebral palsy: A randomised multicentre trial. HBO-CP Research Group. *Lancet*, *357*(9256), 582-586.

Doniger, G.M. (2014). Guide to Normative Data. Retrieved July, 16th, 2014, from http://www1.neurotrax.com/docs/norms_guide.pdf

Doniger, G.M., Simon, E.S., & Zivotofsky, A.Z. (2006). Comprehensive computerized assessment of cognitive sequelae of a complete 12-16 hour fast. *Behavioral Neuroscience*, *120*(4), 804-816. doi: 10.1037/0735-7044.120.4.804

Dwolatzky, T., Whitehead, V., Doniger, G.M., Simon, E.S., Schweiger, A., Jaffe, D., et al. (2003). Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatrics*, *3*, 4. doi: 10.1186/1471-2318-3-4

Efrati, S., & Ben-Jacob, E. (2014a). How and why hyperbaric oxygen therapy can bring new hope for children suffering from cerebral palsy–an editorial perspective. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc*, *41*(2), 71-76.

Efrati, S., & Ben-Jacob, E. (2014b). Reflections on the neurotherapeutic effects of hyperbaric oxygen. *Expert Rev Neurother*, *14*(3), 233-236. doi: 10.1586/14737175.2014.884928

Efrati, S., Fishlev, G., Bechor, Y., Volkov, O., Bergan, J., Kliakhandler, K., et al. (2013). Hyperbaric oxygen induces late neuroplasticity in post stroke patients–randomized, prospective trial. *PloS One*, *8*(1), e53716. doi: 10.1371/journal.pone.0053716

Fertl, E., Vass, K., Sterz, F., Gabriel, H., & Auff, E. (2000). Neurological rehabilitation of severely disabled cardiac arrest survivors. Part I. Course of post-acute inpatient treatment. *Resuscitation*, *47*(3), 231-239.

Fitzgerald, A., Aditya, H., Prior, A., McNeill, E., & Pentland, B. (2010). Anoxic brain injury: Clinical patterns and functional outcomes. A study of 93 cases. *Brain injury: [BI]*, *24*(11), 1311-1323. doi: 10.3109/02699052.2010.506864

Golden, Z., Golden, C.J., & Neubauer, R.A. (2006). Improving neuropsychological function after chronic brain injury with hyperbaric oxygen. *Disability and Rehabilitation*, *28*(22), 1379-1386. doi: 10.1080/09638280600638364

Guo, M.F., Yu, J.Z., & Ma, C.G. (2011). Mechanisms related to neuron injury and death in cerebral hypoxic ischaemia. *Folia Neuropathologica/Association of Polish Neuropathologists and Medical Research Centre, Polish Academy of Sciences*, *49*(2), 78-87.

Hardy, P., Collet, J.P., Goldberg, J., Ducruet, T., Vanasse, M., Lambert, J., et al. (2002). Neuropsychological effects of hyperbaric oxygen therapy in cerebral palsy. *Developmental Medicine and Child Neurology*, *44*(7), 436-446.

Hopkins, R.O., & Bigler, E.D. (2012). Neuroimaging of anoxic injury: Implications for neurorehabilitation. *NeuroRehabilitation*, *31*(3), 319-329. doi: 10.3233/NRE-2012-0799

Jacobs, E.A., Winter, P.M., Alvis, H.J., & Small, S.M. (1969). Hyperoxygenation effect on cognitive functioning in the aged. *The New England Journal of Medicine*, *281*(14), 753-757. doi: 10.1056/NEJM196910022811402

Jain, K.K. (2009). Textbook of Hyperbaric Medicine.

Jaszczak, R.J., Chang, L.T., Stein, N.A., & Moore, F.E. (1979). Whole-body single-photon emission computed tomography using dual, large-field-of-view scintillation cameras. *Physics in Medicine and Biology*, *24*(6), 1123-1143.

Katz, S. (1983). Assessing self-maintenance: Activities of daily living, mobility, and instrumental activities of daily living. *Journal of the American Geriatrics Society*, *31*(12), 721-727.

Lim, C., Verfaellie, M., Schnyer, D., Lafleche, G., & Alexander, M.P. (2014). Recovery, long-term cognitive outcome and quality of life following out-of-hospital cardiac arrest. *Journal of rehabilitation medicine: Official Journal of the UEMS European Board of Physical and Rehabilitation Medicine*, *46*, 691-697. doi: 10.2340/16501977-1816

Melton, J.L. (2005). Psychometric evaluation of the Mindstreams neuropsychological screening tool (pp. 06-10). Panama City (FL): Navy Experimental Diving Unit (US).

Miller, E.K., & Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167-202. doi: 10.1146/annurev.neuro.24.1.167

Mishkin, M., & Ungerleider, L.G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioural Brain Research*, *6*(1), 57-77.

Montgomery, D., Goldberg, J., Amar, M., Lacroix, V., Lecomte, J., Lambert, J., et al. (1999). Effects of hyperbaric oxygen therapy on children with spastic diplegic cerebral palsy: A pilot project. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc*, *26*(4), 235-242.

Moulaert, V.R., Verbunt, J.A., van Heugten, C.M., & Wade, D.T. (2009). Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. *Resuscitation*, *80*(3), 297-305. doi: 10.1016/j.resuscitation.2008.10.034

Mukherjee, A., Raison, M., Sahni, T., Arya, A., Lambert, J., Marois, P., et al. (2014). Intensive rehabilitation combined with HBO_2 therapy in children with cerebral palsy: A controlled longitudinal study. *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc*, *41*(2), 77-85.

Neubauer, R.A., & James, P. (1998). Cerebral oxygenation and the recoverable brain. *Neurological Research*, *20*(Suppl 1), S33-S36.

Nichol, G., Thomas, E., Callaway, C.W., Hedges, J., Powell, J.L., Aufderheide, T.P., et al. (2008). Regional variation in out-of-hospital cardiac arrest incidence and outcome. *Jama*, *300*(12), 1423-1431. doi: 10.1001/jama.300.12.1423

Palzur, E., Vlodavsky, E., Mulla, H., Arieli, R., Feinsod, M., & Soustiel, J.F. (2004). Hyperbaric oxygen therapy for reduction of secondary brain damage in head injury: An animal model of brain contusion. *Journal of Neurotrauma*, *21*(1), 41-48. doi: 10.1089/089771504772695931

Palzur, E., Zaaroor, M., Vlodavsky, E., Milman, F., & Soustiel, J.F. (2008). Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties. *Brain Research*, *1221*, 126-133. doi: 10.1016/j.brainres.2008.04.078

Rabin, R., & de Charro, F. (2001). EQ-5D: A measure of health status from the EuroQol Group. *Annals of Medicine*, *33*(5), 337-343.

Rossignol, D.A., Rossignol, L.W., James, S.J., Melnyk, S., & Mumper, E. (2007). The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: An open-label pilot study. *BMC Pediatrics*, *7*, 36. doi: 10.1186/1471-2431-7-36

Schweiger, A., G. M. D., Dwolatzky, T., Jaffe, D., & Simon, E.S. (2003). Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. *Acta Neuropsychologica*, *1*(4), 407-413.

Shah, M.K., Al-Adawi, S., Dorvlo, A.S., & Burke, D.T. (2004). Functional outcomes following anoxic brain injury: A comparison with traumatic brain injury. *Brain Injury: [BI]*, *18*(2), 111-117. doi: 10.1080/0269905031000149551

Tapeantong, T., & Poungvarin, N. (2009). Delayed encephalopathy and cognitive sequelae after acute carbon monoxide poisoning: Report of a case and review of the literature. *J Med Assoc Thai*, *92*(10), 1374-1379.

Thaler, A., Mirelman, A., Gurevich, T., Simon, E., Orr-Urtreger, A., Marder, K., et al. (2012). Lower cognitive performance in healthy G2019S LRRK2 mutation carriers. *Neurology*, *79*(10), 1027-1032. doi: 10.1212/WNL.0b013e3182684646

van Alem, A.P., de Vos, R., Schmand, B., & Koster, R.W. (2004). Cognitive impairment in survivors of out-of-hospital cardiac arrest. *American Heart Journal*, *148*(3), 416-421. doi: 10.1016/j.ahj.2004.01.031

van Bever Donker, S.C. (1999). Hyperbaric oxygen therapy for children with cerebral palsy. *South African Medical Journal=Suid-Afrikaanse Tydskrif vir Geneeskunde*, *89*(4), 360-361.

van Bever Donker, S.C. (2001). Hyperbaric oxygen therapy for children with cerebral palsy. *South African Medical Journal=Suid-Afrikaanse Tydskrif vir Geneeskunde*, *91*(11), 909.

Zur, D., Naftaliev, E., & Kesler, A. (2014). Evidence of multidomain mild cognitive impairment in idiopathic intracranial hypertension. *Journal of Neuro-Ophthalmology: The Official Journal of the North American Neuro-Ophthalmology Society*, *35*(1), 26-30. doi: 10.1097/WNO.0000000000000199

Appendix

Case 3: 70 years old male, 5 years post cardiac arrest, suffering from motor dysphasia, 4 limbs spasticity with no ability to walk, swallowing difficulties and incontinence.

At baseline, the patient could not complete the cognitive evaluation due to very low communication and cognitive skills. After 60 HBO_2 sessions, clinically, he had considerable improvement in speech, controlled continence, swallowing and walking capabilities. In addition, in the neuro-cognitive test he had significant improvement in memory, attention, verbal and visual spatial indices from unmeasurables to scores of 98, 70, 102, 89 and 89.7 respectively.

In brain SPECT evaluation, the greatest improvement in brain perfusion (higher than 20%) following HBO_2 was seen in the frontal lobes – pre frontal gyrus (BA 10) orbito-frontal gyrus (BA 11) inferior frontal gyrus (BA 45,47), pre motor cortex (BA 6). Improvement (higher than 10%) was also seen in the parietal lobes (BA 7), temporal lobes (BA 20,38) and cingulate gyrus (BA 24,32) (Fig. 6).

Case 4: 57 years old male, 2.5 years post ventricular fibrillation, suffered from dysarthria and significant cognitive dysfunction.

Cognitive evaluation showed low memory, verbal and visual spatial, executive function, information processing speed and attention index scores. Motor skills were high at baseline. After 60 HBO_2 daily sessions, cognitive evaluation revealed improvement to in executive function, verbal, visual spatial and memory indices from scores of 98, 88, 84, 69 to 111, 104, 104, 79 respectively.

Clinically, in addition to cognitive improvement, the patient had considerable improvement in speech and daily function – he returned to work and drive by himself.

SPECT evaluation demonstrated the greatest improvement in brain perfusion after HBO_2 in the inferior frontal gyrus (BA 45,47), posterior cingulate gyrus (BA 31,32) with over 20% change. Over 10% changes in prefrontal gyrus (BA 8,9), Broca's and Wernike's areas (BA 22,39,44) (Fig. 7).

Case 5: 30 years old male, 5 months post ventricular fibrillation suffered from ataxia and significant cognitive decline.

Cognitive evaluation at baseline showed very low memory, attention and executive function scores, and low information processing speed, motor skills, visual spatial and verbal scores. After 60 HBO_2 sessions, cognitive evaluation showed improvement in executive function and attention from scores of 44, 38 to 62 and 59 respectively.

SPECT evaluation revealed the greatest improvement in brain perfusion after HBO_2 in the perirhinal cortex (BA 36) with over 20% change, inferior frontal gyrus (BA 47), cingulate gyrus (BA 24), primary visual gyrus (BA 17), prefrontal gyrus (BA 10), and inferior temporal gyrus (BA 20) with over 15% change (Fig. 8).