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Hyperbaric oxygen improves functioning of patients suffering from chronic neurocognitive deficits due to traumatic brain injury- correlations between cognitive functions and brain metabolic imaging

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3 **Hyperbaric oxygen improves functioning of patients suffering from chronic** 1
4 **neurocognitive delicts due to traumatic brain injury- correlations between** 2
5 **cognitive functions and brain metabolic imaging** 3
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3	Abstract	43
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5	<i>Objectives</i>	44
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7	The aim of the study is to evaluate the effect of HBOT in participants suffering from	45
8	chronic neurological deficits of all severities due to TBI in the largest cohort	46
9	evaluated so far with objective cognitive function and metabolic brain imaging.	47
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13	<i>Methods</i>	48
14		
15	A retrospective analysis was conducted of 154 patients suffering from chronic	49
16	neurocognitive damage due to TBI, and had pre- and post-HBOT treatment	50
17	computerized cognitive evaluations.	51
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22	<i>Results</i>	52
23		
24	The average age was 42.7±14.6 years and 58.4% were males. All patients had	53
25	documented traumatic brain injury 0.3-33 years (mean 4.6±5.8, median 2.75 years)	54
26	prior to HBOT. HBOT induced significant improvement in all of the cognitive	55
27	domains where the mean change in global cognitive scores was 4.6±8.5 (p<0.00001).	56
28		
29	The most prominent improvement was in memory index and attention with mean	57
30	changes of 8.1±16.9 (p<0.00001) and 6.8±16.5 (p<0.0001), respectively. The most	58
31	striking changes in brain SPECTs were in the anterior cingulate and the post-central	59
32	cortex, the prefrontal areas and temporal areas.	60
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42	<i>Conclusions</i>	61
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45	HBOT induced significant cognitive improvements in patients suffering from chronic	62
46	deficits in TBI of all severities. The clinical improvement was well correlated with	63
47	increased activity in the relevant brain areas.	64
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3 Keywords: hyperbaric oxygen, HBOT, post concussion, PCS, TBI, traumatic brain 66
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5 injury 67
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7 **Article Summary** 68
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10 • This is a retrospective analysis of the largest cohort of patients suffering from 69
11 TBI related chronic neurocognitive damage, treated by HBOT. Patients 70
12 suffering any degree of TBI injury (mild to severe) were included and 71
13 evaluated with objective computerized cognitive tests. 72
14
15 • HBOT induced significant cognitive improvements in patients who suffer 73
16 from chronic neurocognitive deficits due to mild, moderate and severe TBI. 74
17
18 • The improvement in memory correlated with activation of the perirhinal 75
19 cortex, improvement of executive functions correlated with activation of the 76
20 inferior frontal gyrus and improvement in attention correlated with activation 77
21 of the anterior cingulate gyrus. 78
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32 **Strengths and limitations of the study** 79
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35 • The major limitation relates to its retrospective methodology. This limitation 80
36 should be considered even though this large cohort of patients was treated at 81
37 late chronic stages. The findings presented here are in agreement with the 82
38 findings from previous prospective controlled trials. 83
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40
41 • In regards to strengths, objective cognitive assessments using computerized 84
42 tests were performed to each patient both pre- and post-treatment. Objective 85
43 measures are significantly superior to PCS questionnaires which are 86
44 inaccurate, variable and contain various confounders. Second, most of the 87
45 patients in the study underwent an objective ancillary brain SPECT to confirm 88
46 PCS diagnosis prior to HBOT. This practice is crucial when considering the 89
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differential diagnosis following TBI (PTSD, depression, etc.). Third, the study 90
cohort included a civilian population that does not have any potential 91
secondary gain (such as financial compensation by reporting sick). 92
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3 **Introduction** 94
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5 Traumatic brain injury (TBI) is one of the leading causes of death and disability in the 95
6 general population.(1) Following TBI, patients may experience a set of symptoms 96
7 known as post-concussion syndrome (PCS). PCS symptoms include headaches, 97
8 dizziness, neuropsychiatric symptoms, and cognitive impairments.(2) PCS can 98
9 continue for weeks or months, and up to 25% of all patients experience prolonged 99
10 PCS (PPCS) in which the symptoms last for over six months.(3) 100

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19 In the past years there is growing clinical evidence regarding the effect of hyperbaric 101
20 oxygen therapy (HBOT) on PCS.(4, 5) Unfortunately, the clinical data gathered from 102
21 those studies can be conflicting due to several inherent procedural issues such as the 103
22 use of non-objective end points, the lack of appropriate brain imaging as part of the 104
23 inclusion criteria, the inappropriate placebo of a hyperbaric environment and the 105
24 inclusion of patients that may gain secondary benefits from reporting sick.(4, 5) The 106
25 current study represents the largest cohort evaluated till now of civilian participants 107
26 suffering from PCS treated by HBOT who had objective metabolic brain imaging and 108
27 a computerized neurocognitive test battery before and after the treatment. 109

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40 *Pathophysiology of PCS and HBOT* 110

41 The most common pathological mechanism in TBI is diffuse shearing of axonal 111
42 pathways and small blood vessels, also known as diffuse axonal injury.(6) The 112
43 secondary pathological mechanisms of TBI include ischemia, mild edema, and other 113
44 biochemical and inflammatory processes culminating in impaired regenerative and/or 114
45 healing processes resulting from increasing tissue hypoxia.(7) Due to the diffuse 115
46 nature of injury, affecting multiple brain areas,(8, 9) cognitive impairments are 116
47 usually the predominant symptoms. 117

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3 Global brain hypoperfusion, and its related tissue ischemia, detected in patients 118
4 suffering from TBI, serves as a rate-limiting factor for any regenerative process.(10- 119
5 12) By increasing the oxygen level in blood and body tissues, HBOT can augment the 120
6 repair mechanisms.(13) Various models have strongly suggested that HBOT can 121
7 induce angiogenesis, improve brain plasticity, enhance neurogenesis and 122
8 synaptogenesis and foster functional recovery.(14, 15) 123

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16 *Conflicting clinical HBOT data and objective measurements in PCS* 124
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19 Some of the previous studies which evaluated the effect of HBOT on chronic 125
20 neurological and cognitive impairments due to TBI, mainly used self-assessment 126
21 questionnaires as their primary endpoints.(16-18) Such endpoints have several 127
22 inherent disadvantages. First, they lack an objective evaluation that is not biased by 128
23 the patients' perspectives. Second, self-administrated questionnaires are exposed to 129
24 various confounding variables such as litigation and compensation (19). Unlike the 130
25 questionnaires, standardized cognitive tests with high test-retest reliability can and 131
26 should be used as objective evaluations of neurocognitive impairments.(20) In 132
27 addition, novel brain imaging techniques such as single photon emission computed 133
28 tomography (SPECT) and perfusion sequences in magnetic resonance imaging (MRI), 134
29 which evaluate cerebral blood flow and brain metabolism, can shed new light in PCS 135
30 diagnosis and in evaluating therapeutic interventions.(20) In clinical studies which 136
31 utilized objective cognitive assessments, HBOT induced significant improvements in 137
32 patients suffering from PCS due to mild TBI. (13, 15, 21) However, to the best of our 138
33 knowledge, the objective effect of HBOT on chronic neurocognitive impairments 139
34 stemming from moderate or severe TBI (in addition to mild) has not been 140
35 investigated. 141
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3 In addition to objective evaluations, there are inherent ethical and logistic difficulties 142
4 in handling the sham-control in HBOT trials.(4, 5, 20, 22) HBOT includes two active 143
5 ingredients: pressure and oxygen. Pressure is needed to increase plasma oxygen, but 144
6 the pressure change alone may also have significant cellular effects.(5) Additionally, 145
7 the greatest effect of pressure is in human tissues that are under tight autoregulation 146
8 pressure control, such as the brain, where the intracranial pressure is normally 0.0092- 147
9 0.0197atm.(23, 24) To generate a pressure sensation, the chamber pressure must be 148
10 1.2ATA or higher. However, such a significant change in environmental pressure and 149
11 subsequent tissue oxygenation (with an increase of tissue oxygenation by at least 150
12 50%) cannot be referred as a sham-control but rather as a lower dose of the active 151
13 ingredient.(4, 20) 152

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18 Any increase in pressure, even with reduced oxygen percentage, cannot serve as a true 153
19 placebo, but rather as a low dosage of the active ingredient, further supporting the 154
20 need for objective data gathered from large cohorts of patients suffering from PCS 155
21 and treated by HBOT. 156

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The aim of the current study was to evaluate the objective effects of HBOT on TBI 157
patients suffering from chronic neurological deficits stemming from mild, moderate, 158
and severe TBI in the largest cohort evaluated till now. Since all the patients had 159
metabolic brain imaging and a computerized neurocognitive test battery before and 160
after HBOT, correlations between specific cognitive indexes and their related brain 161
region activity were also evaluated. 162

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<i>Materials and Methods</i>	164
<i>Participants</i>	165
A retrospective analysis was conducted on patients suffering from TBI related chronic neurocognitive damage, treated by HBOT between January 2008 and January 2017 at the Sagol Center for Hyperbaric Medicine and Research at the Assaf Harofeh Medical Center, Israel. Patients were included if they had pre- and post-HBOT computerized cognitive evaluations. Patients with a history of potential additional brain insults such as spontaneous subarachnoid hemorrhage, anoxic brain injury or history of prior cognitive impairment, were excluded (Figure-1).	166 167 168 169 170 171 172
The study was approved by the Asaf Harofeh Medical Center's Institutional Review Board.	173 174
<i>Patients and public involvement</i>	175
Patients and public weren't involved in the study due to its retrospective nature.	176
<i>TBI severity</i>	177
TBI severities were rated according to the TBI admission documents. Mild TBI was defined as loss of consciousness (LOC) duration of 0–30 minutes, post traumatic amnesia (PTA) duration of less than a day and a Glasgow coma scale (GCS) grade of 13–15. (25) Moderate TBI was defined as LOC duration of more than 30 minutes up to 24 hours, PTA duration of 1-7 days and GCS grade of 9-12. Severe TBI was defined as LOC duration more than 24 hours, PTA duration more than seven days and GCS less than 9. In addition if there was imaging evidence of an injury such as a hematoma, contusion or hemorrhage, then the TBI was classified as moderate to severe. (25)	178 179 180 181 182 183 184 185 186
<i>Hyperbaric oxygen treatment</i>	187

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3 Patients were treated with 40-70 daily hyperbaric sessions, 5 days a week. Each 188
4 session consisted of 60 minutes of exposure to 100% oxygen at 1.5-2 ATA. 189
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7 *Cognitive assessment* 190
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10 The patients' cognitive functions were assessed by NeuroTrax computerized cognitive 191
11 tests (NeuroTrax Corp., TX).(26) The NeuroTrax tests evaluate various aspects of 192
12 brain functions and include verbal memory (immediate and delayed recognition), non- 193
13 verbal memory (immediate and delayed recognition), go-no-go response inhibition, 194
14 problem solving, Stroop interference, finger tapping, catch game, staged information 195
15 processing speed (single digit, two-digit and three-digit arithmetic), verbal function 196
16 and visual spatial processing. Cognitive index scores were computed from the 197
17 normalized outcome parameters for memory, executive function, attention, 198
18 information processing speed, visual spatial, verbal function and motor skills 199
19 domains.(27) A global cognitive score was computed as the average of all index 200
20 scores for each individual. 201
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34 After administration, the NeuroTrax data were uploaded to the NeuroTrax central 202
35 server, and outcome parameters were automatically calculated using software blind to 203
36 diagnosis or testing site. To account for the well-known effects of age and education 204
37 on cognitive performance, each outcome parameter was normalized and fit to an IQ- 205
38 like scale (mean=100, S.D.=15) according to the patient's age and education. The 206
39 normative data used by NeuroTrax consist of test data from cognitively healthy 207
40 individuals in controlled research studies at more than 10 sites. (28) 208
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50 Specifically, the patients were given two different versions of the NeuroTrax test 209
51 battery before and after HBOT, to allow repeated administrations with minimal 210
52 learning effects. Test-retest reliability for these versions was evaluated and found to 211
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3 be high, with no significant learning effect.(29, 30) Regarding the current study 212
4 cohort, in a previous randomized controlled trial in patients suffering from TBI, the 213
5 NeuroTrax scores were found to be stable in the retest of the control group.(21) 214
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10 *Brain SPECT imaging* 215

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12 Brain activity was assessed using single photon emission computed tomography 216
13 (SPECT) 1-2 weeks prior to and after the HBOT period. The imaging was conducted 217
14 using 925–1,110 MBq (25–30 mCi) of a technetium-99m-methyl-cysteinate-dimer 218
15 (Tc-99m-ECD) at 40–60 min post injection using a dual detector gamma camera 219
16 (ECAM or Symbia T, Siemens Medical Systems) equipped with high resolution 220
17 collimators. Data was acquired in 3-degree steps and reconstructed iteratively using 221
18 the Chang method of ($\mu = 0.12/\text{cm}$) attenuation correction.(31) 222
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29 Both SPECT images were normalized to the median maximal brain activity in the 223
30 entire brain and were then reoriented into Talairach space using NeuroGam (Segami 224
31 Corporation) to identify Brodmann cortical areas and to compute the mean perfusion 225
32 in each Brodmann area (BA). In addition, volume rendered brain perfusion images 226
33 were reconstructed and normalized to the entire brain median maximal activity. All 227
34 SPECT analyses were done by study team members who were blinded to the 228
35 laboratory and clinical data. SPECT scans were performed late morning to midday. 229
36
37 On the day of the SPECT scan, patients were treated with only their chronic 230
38 medications and were instructed not to smoke. Changes in perfusion in all Brodmann 231
39 areas for each subject were determined by calculating the percentage of the difference 232
40 of the normalized activity values between post-period and pre-period divided by the 233
41 pre-period value. 234
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54 *Statistical Analysis* 235

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3 Continuous data were expressed as means \pm standard deviations. The normal 236
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5 distribution for all variables was tested using the Kolmogorov-Smirnov test. The 237
6
7 mean differences between cognitive index scores before and after HBOT were 238
8
9 analyzed using one-way ANOVA with post-hoc Bonferoni tests. Multiple linear 239
10
11 regression models and multivariate logistic regression models were performed to 240
12
13 control for potential confounders and to determine independent predictors for clinical 241
14
15 outcome. The alpha level was set to 0.05. Data were statistically analyzed using SPSS 242
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17 software (version 22.0). 243
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Results*Patient profiles*

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Of the 242 patients suffering from neurocognitive impairment due to TBI treated by HBOT between January 2008 and January 2017, 25 patients had potential additional brain insults and 63 did not have repeat computerized neurocognitive evaluations. Therefore, 154 patients were included in the final analysis, of whom 100 patients completed pre- and post-HBOT SPECT imaging (Figure-1).

The patients' baseline characteristics are summarized in Table 1. The average age was 42.7±14.6 years and 58.4% were males. All patients had documented traumatic brain injury 3 months to 33 years (mean 4.6±5.8, median 2.75 years) prior to HBOT. Sixty-nine (44.8%) had neurocognitive impairments due to mild TBI, 24 (15.6%) from moderate TBI and 61 (39.6%) from severe TBI. Most of the patients (86.2%) complained of cognitive impairment as their main symptom (Table 1).

Patients were treated with 40-70 (mean 52.0±9.9) sessions of hyperbaric oxygen at 1.5-2 ATA with 18 (12%) reporting adverse events which included mild barotrauma of the ears and palpitations/dyspnea while in the chamber.

Severity of TBI

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Patients who suffered severe TBI were younger with higher proportion of males than in the mild and moderate TBI groups ($P<0.0001$, $P=0.002$ respectively, Table 1). As

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3 expected, the severe group had significantly higher proportions of cognitive 279
4 impairment and motor deficits ($p=0.004$ and $p<0.0001$ respectively, Table 1). Mild 280
5 and moderate TBI had higher percentages of tinnitus and/or dizziness ($p<0.0001$, 281
6 $p=0.002$ respectively, Table 1). 282

11 *Severe TBI* 283

13 Sixty-one patients had severe TBI. The main imaging findings at their admission are 284
14 summarized in Figure-2. Of those 61 patients, 36 (59%) had surgical intervention 285
15 during the acute event. 286

22 *Neuro-cognitive evaluation* 288

24
25 The effect of HBOT on the patients' cognitive functions, as assessed by the eight 289
26 cognitive summary scores, is summarized in Table 2 and Figure-3. As can be seen, 290
27 HBOT induced significant improvements in all of the cognitive domains with a mean 291
28 change of 4.6 ± 8.5 ($p<0.00001$). The most prominent improvement was in memory 292
29 index, with 8.1 ± 16.9 ($p<0.00001$) and attention with 6.8 ± 16.5 ($p<0.0001$) (Table 2, 293
30 Figure-3). 294

31
32 The mild TBI subgroup had the largest improvement in attention (8.8 ± 2.1) followed 295
33 by memory (7.9 ± 2.3). Patients following moderate had noticeable improvements in 296
34 memory (11.1 ± 3.1) followed by information processing speed (6.6 ± 3.5) (Figure-4). 297

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36 The magnitude of the change in a cognitive score has different implications for 298
37 patients at low or high baseline levels. Therefore, we further inspected the effect of 299
38 HBOT on the relative changes, i.e. the changes relative to the baseline value, in each 300
39 of the cognitive measured indexes. Marked improvement defined as $>10\%$ increase 301

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3 compared to baseline cognitive index were found with different percentages in all 302
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5 study groups as summarized in Table 3. 303
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9 *Confounders* 305
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11 Relative change higher than 10% from baseline was considered a significant clinical 306
12 improvement. Age, gender, education level, TBI severity, the time from injury to 307
13 HBOT, HBOT protocol and number of sessions had no significant effect on the 308
14 clinical improvement in both general, memory, attention, information processing 309
15 speed and executive functions domains ($p>0.05$). 310
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24 *Metabolic imaging of the brain-SPECT* 312
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27 One hundred patients had brain SPECT evaluations before and after HBOT. When 313
28 calculating the mean relative change in each cortical Brodmann's area for the entire 314
29 cohort, the largest changes were in the anterior temporal tip areas (BA 38, 28, 20) 315
30 and prefrontal cortex (BA 10) (Figure-5). However, these change were minor, in the 316
31 scale of 3-4% relative change. Further analysis per TBI severity group revealed 317
32 several differences in Brodmann areas with involvement of the perirhinal cortex (BA 318
33 36) and the primary visual cortex (BA 18) as seen in the Figure-6. 319
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37 To correlate SPECT imaging and the cognitive changes, analysis was performed on 320
38 the top twenty patients who had the largest cognitive improvement ($>10\%$ relative 321
39 increase from baseline). There was a significantly larger magnitude of metabolism 322
40 increase (5-8%), compared to the entire cohort average increase (2-4%) ($p<0.05$). The 323
41 most striking changes were found in the anterior cingulate (BA 24) and the post- 324
42 central cortex (BA 5), the prefrontal areas (Ba 10,11, 46) and temporal areas (BA 20, 325
43 BA 38, 36). 326
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Discussion

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The present study demonstrates the neurotherapeutic effects of HBOT for chronic TBI of all severities. Even though treatment started during late chronic stages (mean 4.6±5.8 years, median 2.75 years) after the acute insult, HBOT was found to be effective regardless of the TBI severity. The clinical improvements seen in all cognitive domains were well documented by objective computerized neurocognitive tests. The most significant measurable improvements were in memory, attention and executive function. We found the clinical improvement to be well correlated with increased brain activity in relevant brain areas, with significantly higher increases in patients with better cognitive improvements.

Numerous mechanisms of cellular and vascular repair by HBOT have been suggested in addition to tissue oxygenation.(5) These include improved mitochondrial function and cellular metabolism, improved BBB and inflammatory reactions, reduced apoptosis, alleviation of oxidative stress, increased levels of neurotrophins and nitric oxide, and upregulation of axonal guidance agents.(5, 13, 32) Moreover, the effects of HBOT on neurons can be mediated indirectly by glial cells. HBOT may also promote neurogenesis of endogenous neural stem cells.(13, 32) The common denominator underlying all these mechanisms is that they are oxygen-dependent. HBOT may enable the metabolic change simply by supplying the missing energy/oxygen needed for these regeneration processes (32). The induction of angiogenesis and improved brain metabolism, as demonstrated in this study, may

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3 serve as the infrastructure that enables the regenerative process and the preservation 352
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5 of newly generated neuronal functioning. (14, 33) 353
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10 The correlation between specific cognitive function improvements with the metabolic 355
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12 brain imaging changes gives further strength to the study results and serves as an 356
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14 excellent tool for gaining better understanding of brain functionality (Figure-6): 357
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17 - The perirhinal cortex activation after HBOT was most prominent in patients 358
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19 that had significant memory improvement. The perirhinal cortex has a critical 359
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21 role in object recognition memory while interacting with the 360
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23 hippocampus.(34) Since the memory assessments in the cognitive tests were 361
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25 indeed recognition tasks, this area is expected to be involved. 362
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28 -The pre-frontal cortex (BA 10, 11) and more specifically, the inferior frontal 363
29
30 gyrus (BA 46, 47) activation after HBOT were prominent in all patients with 364
31
32 significant executive function improvements. The right frontal gyrus is known 365
33
34 to mediate a go/no go task,(35) which was among the executive function tests 366
35
36 used in the present study. The prefrontal gyrus is presumed to act as a filtering 367
37
38 system that enhances goal directed activities and inhibits irrelevant activations. 368
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40 This filtering mechanism enables executive control.(36) 369
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43 -The anterior cingulate gyrus (BA 24) activation after HBOT was seen in the 370
44
45 subjects with attention improvement. The anterior cingulate gyrus is presumed 371
46
47 to be involved in error detection, especially in a Stroop task,(37) which was 372
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49 used in the attention tests. Lesions in this area can cause inattention to akinetic 373
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51 mutism.(37) 374
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3 This study has several limitations. The major one relates to its retrospective 376
4 methodology. This limitation should be considered even though this large cohort of 377
5 patients was treated at late chronic stages. The findings presented here are in 378
6 agreement and reinforce the findings from previous prospective controlled trials in 379
7 which the neuroplasticity effects of HBOT were demonstrated in chronic stages of 380
8 different types of brain injuries.(15, 21, 38, 39) Moreover, the correlation between the 381
9 changes in cognitive function and the metabolic brain imaging gives further strength 382
10 to the results. 383
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14 Another important limitation relates to the HBOT protocol which was inconsistent in 384
15 the cohort. Although significant neurotherapeutic effects were seen with 60 minutes 385
16 of 1.5 ATA, the optimal protocol needed to induce maximal neuroplasticity for the 386
17 specific individual with minimal side effects has not been specified. 387
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22 The strengths of the study are worth mentioning. First, objective cognitive 389
23 assessments using computerized tests were performed to each patient both pre- and 390
24 post-treatment. Objective measures are significantly superior to PCS questionnaires 391
25 which are inaccurate, variable and contain various confounders rather than reflect the 392
26 true PCS state.(40) Second, most of the patients in the study underwent an objective 393
27 ancillary brain SPECT to confirm PCS diagnosis prior to HBOT. This practice is 394
28 crucial when considering the differential diagnosis following TBI (PTSD, depression, 395
29 etc.). Moreover, post-treatment brain SPECTs enabled an anatomical-functional 396
30 correlation in regards to HBOT's effect in brain neuroplasticity. Third, the study 397
31 cohort included a civilian population that does not have any potential secondary gain 398
32 (such as financial compensation by reporting sick). 399
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Conclusions

HBOT induced significant cognitive improvements in patients who suffer from chronic neurocognitive deficits due to mild, moderate and severe TBI. The improvement in memory correlated with activation of the perirhinal cortex, improvement of executive functions correlated with activation of the inferior frontal gyrus and improvement in attention correlated with activation of the anterior cingulate gyrus.

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Table 1: Baseline patient characteristics.

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Number of patients	154 (100%)	69 (44.8%)	24 (15.6%)	61 (39.6%)	
Age (years)	42.7±14.6	48.8±12.0	41.7±12.7	36.2±15.3	P<0.0001
Sex					
Males	90 (58.4%)	31 (44.9%)	13 (54.2%)	46 (75.4%)	P=0.002
Females	64 (41.6%)	38 (55.1%)	11 (45.8%)	15 (24.6%)	
Education (years)	14.8±3.3	14.9±3.6	14.9±3.3	14.6±3.1	P=0.895
Traumatic event					

Motor Vehicle					
Accident	116 (75.3%)	56 (81.2%)	17 (70.8%)	43 (70.5%)	P=0.048
Fall	21 (13.6%)	8 (11.6%)	1 (4.2%)	12 (57.1%)	
Blow	12 (7.8%)	5 (7.2%)	5 (20.8%)	2 (3.3%)	
Blast	4 (2.6%)	0	1 (4.2%)	3 (4.9%)	
Penetrating	1 (0.6%)	0	0	1 (0.6%)	
Time from trauma (years)	4.6±5.8	4.4±5.9	5.0±5.8	4.6±5.7	P=0.923

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Table 1: Patient characteristics (continued).

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Symptoms					
Cognitive	100 (86.2%)	38 (74.5%)	19 (90.5%)	43 (97.7%)	P=0.004
Motor	22 (19.0%)	1 (4.8%)	1 (4.8%)	20 (45.5%)	P<0.0001
Sensory	32 (27.6%)	12 (23.5%)	7 (33.3%)	13 (29.5%)	P=0.653
Dizziness/Vertigo	17 (14.7%)	14 (27.5%)	2 (9.5%)	1 (2.3%)	P=0.002
Tinnitus	30 (25.9%)	26 (51.0%)	2 (9.5%)	2 (4.5%)	P<0.0001
Headaches	20 (17.2%)	12 (23.5%)	3 (14.3%)	5 (11.4%)	P=0.272
HBO sessions	52.0±9.9	49.4±10.1	49.0±10.3	56.1±8.2	P=0.0001

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HBO protocol (ATA)	1.5	106 (69.3%)	46 (67.6%)	18 (75.0%)	42 (68.9%)	P=0.795
	2	47 (30.7%)	22 (32.4%)	6 (25.0%)	19 (31.1%)	
Adverse Events		18 (12.0%)	10 (15.2%)	3 (12.5%)	5 (8.3%)	P=0.499

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Table 2: Cognitive indices pre- and post-HBOT of the whole study cohort

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	Baseline	Post HBOT	Mean Change	P-Value
General	88.3±15.2	92.9±14.2	4.6±8.5	P<0.0001
Memory	81.7±23.2	89.9±21.9	8.1±16.9	P<0.0001
Executive Functions	88.3±16.6	94.2±15.1	5.9±12.0	P<0.0001
Attention	84.3±20.5	91.1±18.4	6.8±16.5	P<0.0001
IPS	87.5±17.0	92.4±15.7	4.9±13.1	P<0.0001

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VSP	95.0±18.0	98.5±18.0	3.4±14.6	P=0.005
Motor skills	92.3±17.3	96.2±14.5	3.9±11.7	P<0.0001

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Table 3: Large significant increases (>10% change) in cognitive indices proportions across TBI subgroups.

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	Total	Mild TBI	Moderate TBI	Severe TBI	
General	36 (23.4%)	15 (21.7%)	7(29.2%)	14 (23.0%)	P=0.756
Memory	64 (41.6%)	28 (40.6%)	9 (37.5%)	27 (44.3%)	P=0.830
Executive functions	51 (33.1%)	23 (33.3%)	7 (29.2%)	21 (34.9%)	P=0.897
Attention	62 (40.3%)	27 (39.1%)	8 (33.3%)	27 (44.3%)	P=0.631
Information processing speed	48 (31.2%)	23 (33.3%)	12 (50%)	13 (21.3%)	P=0.032

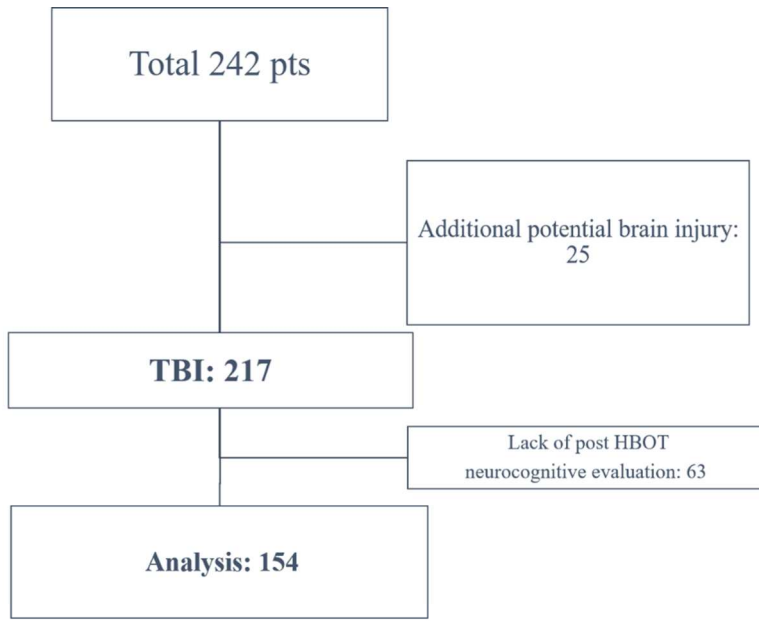
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3	Figures legends	593
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5	Figure-1: Patients flowchart.	594
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7	Figure-2: Imaging findings in the severe TBI subgroup	595
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9	Figure-3: Mean changes of post- compared to pre-HBOT for the entire cohort.	596
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12	After HBOT, all cognitive domains improved significantly, where the most striking	597
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14	changes were seen in memory and attention.	598
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17	*p<0.0001, **p=0.005, IPS=information processing speed	599
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20	Figure-4: Mean changes of post- compared to pre-HBOT across the different TBI	600
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22	severities.	601
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25	Both patients who suffered mild and severe TBI had improvements in general,	602
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27	memory, attention, information processing speed and motor skills scores whereas	603
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29	patients who suffered moderate TBI had significant improvement in memory.	604
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32	*p<0.05, IPS =information processing speed	605
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35	Figure-5: The mean relative change in broadmann areas post HBOT for the entire	606
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37	study cohort.	607
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40	Figure-6: Cognitive functions correlated with Broadmann areas.	608
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43	Each of the TBI severities (mild, moderate and severe) had perfusion/metabolism	609
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45	increase in specific Broadmann areas correlated with improved cognitive function.	610
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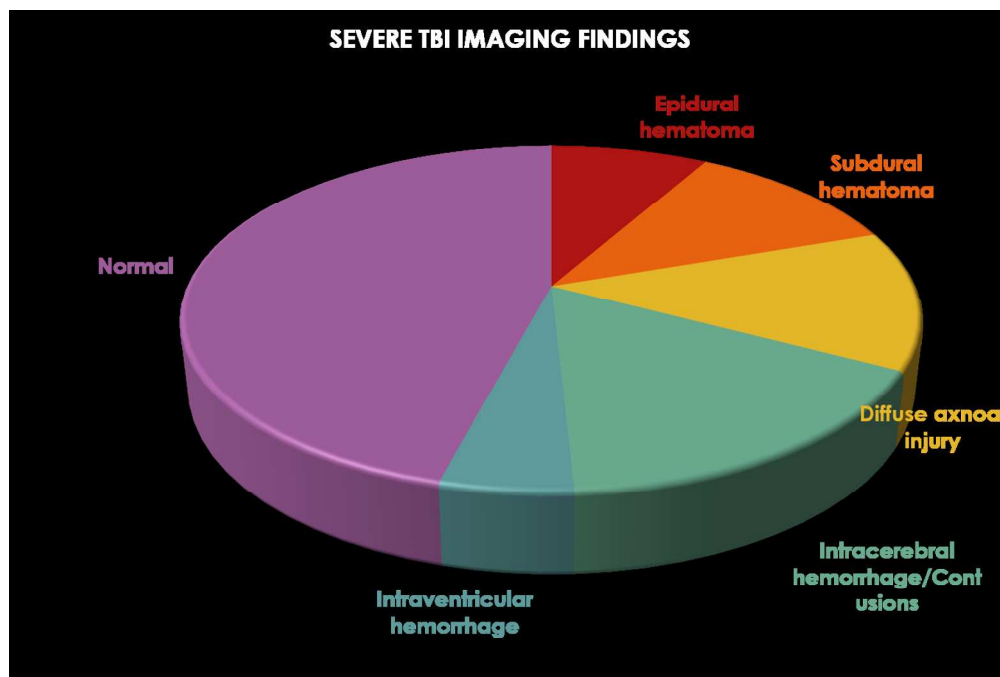
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Patients flowchart

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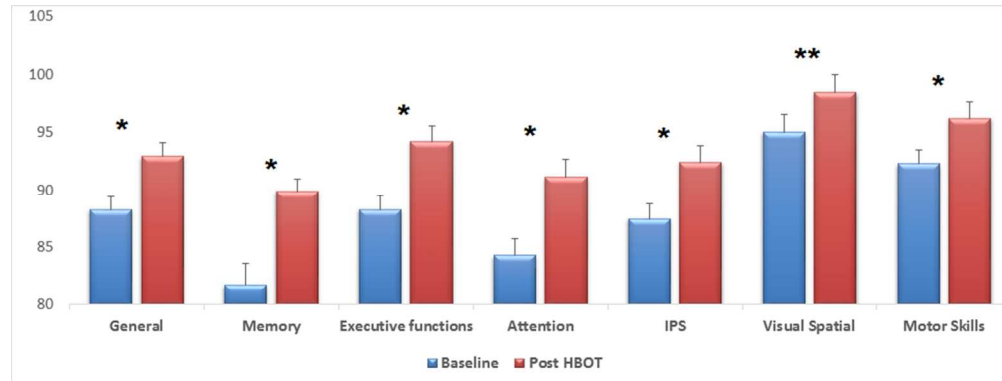
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Imaging findings in the severe TBI subgroup

230x154mm (300 x 300 DPI)

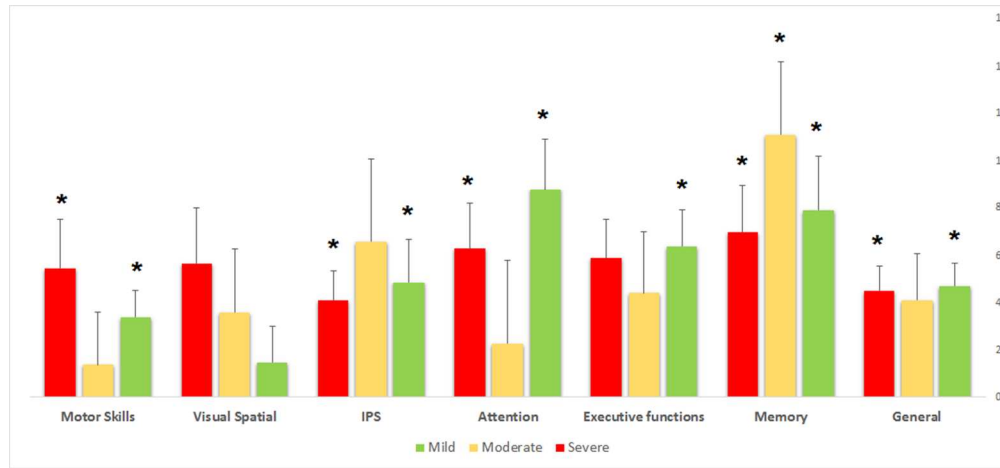
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Mean changes of post- compared to pre-HBOT for the entire cohort.
After HBOT, all cognitive domains improved significantly, where the most striking changes were seen in memory and attention.

* $p < 0.0001$, ** $p = 0.005$, IPS=information processing speed

204x77mm (300 x 300 DPI)

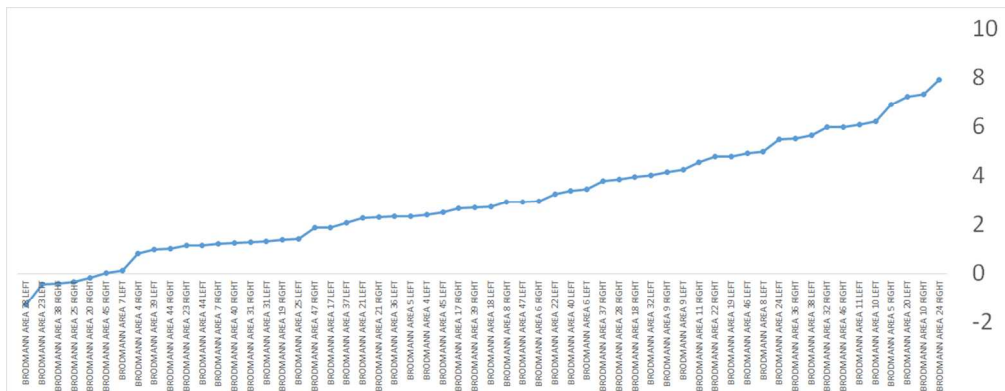


Mean changes of post- compared to pre-HBOT across the different TBI severities. Both patients who suffered mild and severe TBI had improvements in general, memory, attention, information processing speed and motor skills scores whereas patients who suffered moderate TBI had significant improvement in memory. *p<0.05, IPS =information processing speed

225x104mm (300 x 300 DPI)

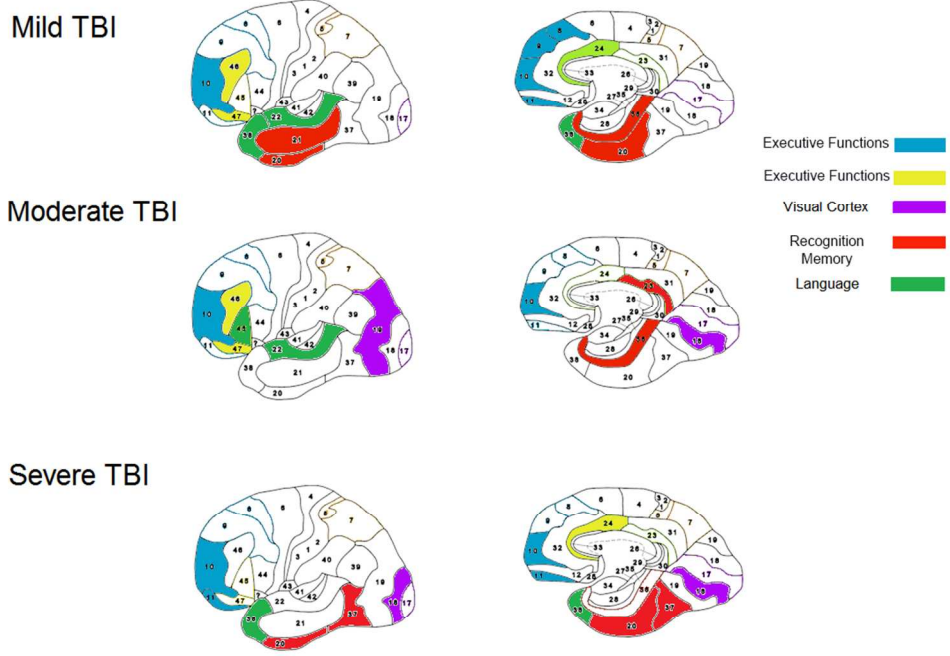
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The mean relative change in broadmann areas post HBOT for the entire study cohort
 261x101mm (300 x 300 DPI)

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Cognitive functions correlated with Brodmann areas.
 Each of the TBI severities (mild, moderate and severe) had perfusion/metabolism increase in specific Brodmann areas correlated with improved cognitive function

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The effect of hyperbaric oxygen therapy on chronic neurocognitive function of deficits post traumatic brain injury patients – retrospective analysis

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Manuscripts

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3 **The effect of hyperbaric oxygen therapy on chronic neurocognitive function of** 1
4
5 **deficits post traumatic brain injury patients – retrospective analysis** 2

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3	Abstract	44
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5	<i>Objectives</i>	45
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7	The aim of the study is to evaluate the effect of hyperbaric oxygen therapy (HBOT) in	46
8	participants suffering from chronic neurological deficits due to traumatic brain injury	47
9	(TBI) of all severities in the largest cohort evaluated so far with objective cognitive	48
10	function tests and metabolic brain imaging.	49
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15	<i>Methods</i>	50
16		
17	A retrospective analysis was conducted of 154 patients suffering from chronic	51
18	neurocognitive damage due to TBI, who had undergone computerized cognitive	52
19	evaluations pre- and post-HBOT treatment.	53
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24	<i>Results</i>	54
25		
26	The average age was 42.7±14.6 years and 58.4% were males. All patients had	55
27	documented traumatic brain injury 0.3-33 years (mean 4.6±5.8, median 2.75 years)	56
28	prior to HBOT. HBOT induced significant improvement in all of the cognitive	57
29	domains, with mean change in global cognitive scores of 4.6±8.5 (p<0.00001). The	58
30	most prominent improvements were in memory index and attention, with mean	59
31	changes of 8.1±16.9 (p<0.00001) and 6.8±16.5 (p<0.0001), respectively. The most	60
32	striking changes observed in brain single photon emission computed tomography	61
33	(SPECT) images were in the anterior cingulate and the post-central cortex, in the	62
34	prefrontal areas and in the temporal areas.	63
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47	<i>Conclusions</i>	64
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50	In the largest published cohort of patients suffering from chronic deficits post TBI of	65
51	all severities, HBOT induced significant cognitive improvements. The clinical	66
52	improvements were well correlated with increased activity in the relevant brain areas.	67
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5	Keywords: hyperbaric oxygen, HBOT, post-concussion, PCS, TBI, traumatic brain	69
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7	injury	70
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9	Article Summary	71
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12	<i>Strengths and limitations of the study</i>	72
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15	• The major limitation relates to its retrospective methodology, however this	73
16		
17	limitation is diminished by the fact that all patients of the study large cohort	74
18		
19	were treated at late chronic stages.	75
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21		
22	• In regards to strengths, objective cognitive assessments using computerized	76
23		
24	tests (which are superior to any clinical questionnaire), were performed on	77
25		
26	each patient both pre- and post-treatment.	78
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29	• The study cohort consisted of a civilian population that does not have any	79
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31	potential secondary gain (such as financial compensation by reporting sick).	80
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3	<i>Introduction</i>	82
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6	Traumatic brain injury (TBI) is one of the leading causes of death and disability in the	83
7	general population.(1) Following TBI, patients may experience a set of symptoms	84
8	known as post-concussion syndrome (PCS). PCS symptoms include headaches,	85
9	dizziness, neuropsychiatric symptoms, and cognitive impairments.(2) PCS can	86
10	continue for weeks or months, and up to 25% of all patients experience prolonged	87
11	PCS (PPCS) in which the symptoms last for over six months.(3)	88
12		
13		
14	In the past years there is growing clinical evidence regarding the effect of hyperbaric	89
15	oxygen therapy (HBOT) on PCS.(4, 5) Unfortunately, the clinical data gathered from	90
16	those studies can be conflicting due to several inherent procedural issues, such as the	91
17	use of non-objective end points, the lack of appropriate brain imaging as part of the	92
18	inclusion criteria, the inappropriate placebo of a hyperbaric environment, and the	93
19	inclusion of patients that may gain secondary benefits from reporting sick.(4, 5) The	94
20	current study represents the largest cohort evaluated until now of civilian participants	95
21	suffering from PCS treated by HBOT, who had undergone objective metabolic brain	96
22	imaging and a computerized neurocognitive test battery before and after the treatment.	97
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40	<i>Pathophysiology of PCS and HBOT</i>	98
41		
42	The most common pathological mechanism in TBI is diffuse shearing of axonal	99
43	pathways and small blood vessels, also known as diffuse axonal injury.(6) Secondary	100
44	pathological mechanisms of TBI include ischemia, mild edema, and other	101
45	biochemical and inflammatory processes culminating in impaired regenerative and/or	102
46	healing processes resulting from increasing tissue hypoxia.(7) Due to the diffuse	103
47	nature of injury, affecting multiple brain areas,(8, 9) cognitive impairments are	104
48	usually the predominant symptoms.	105
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3 Global brain hypoperfusion, and its related tissue ischemia, detected in patients 106
4 suffering from TBI, serves as a rate-limiting factor for any regenerative process.(10- 107
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7 12) By increasing the oxygen level in blood and body tissues, HBOT can augment the 108
8
9 repair mechanisms.(13) Various models have strongly suggested that HBOT can 109
10 induce angiogenesis, improve brain plasticity, enhance neurogenesis and 110
11
12 synaptogenesis and foster functional recovery.(14, 15) 111
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16 *Conflicting clinical HBOT data and objective measurements in PCS* 112

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18
19 Some of the previous studies which evaluated the effect of HBOT on chronic 113
20 neurological and cognitive impairments due to TBI, mainly used self-assessment 114
21 questionnaires as their primary endpoints.(16-18) Such endpoints have several 115
22 inherent disadvantages. First, they lack an objective evaluation that is not biased by 116
23 the patients' perspectives. Second, self-administrated questionnaires are exposed to 117
24 various confounding variables such as litigation and compensation.(19). Unlike the 118
25 questionnaires, standardized cognitive tests with high test-retest reliability can and 119
26 should be used as objective evaluations of neurocognitive impairments.(20) In 120
27 addition, novel brain imaging techniques such as single photon emission computed 121
28 tomography (SPECT) and perfusion sequences in magnetic resonance imaging (MRI), 122
29 which evaluate cerebral blood flow and brain metabolism, can shed new light in PCS 123
30 diagnosis and in evaluating therapeutic interventions.(20) In clinical studies which 124
31 utilized objective cognitive assessments, HBOT was found to induce significant 125
32 improvements in patients suffering from PCS due to mild TBI. (13, 15, 21) However, 126
33 to the best of our knowledge, the objective effect of HBOT on chronic neurocognitive 127
34 impairments stemming from moderate to severe TBI (in addition to mild) has not been 128
35 investigated. 129
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3 In addition to objective evaluations, there are inherent ethical and logistic difficulties 130
4 in handling the sham control in HBOT trials.(4, 5, 20, 22) HBOT includes two active 131
5 ingredients: pressure and oxygen. Pressure is needed to increase plasma oxygen, but 132
6 the pressure change alone may also have significant cellular effects.(5) Additionally, 133
7 the greatest effect of pressure is in human tissues that are under tight autoregulation 134
8 pressure control, such as the brain, where the intracranial pressure is normally 0.0092- 135
9 0.0197atm.(23, 24) To generate a pressure sensation, the chamber pressure must be 136
10 1.2ATA or higher. However, such a change in environmental pressure (from 1ATA 137
11 to 1.2 ATA) and subsequent tissue oxygenation (with an increase of tissue 138
12 oxygenation by at least 50%) has a significant biologic effect (25, 26) Thus, sham 139
13 therapy in previous studies using 1.2 ATA on 21% inhaled oxygen (i.e., air) cannot be 140
14 regarded as an inert or sham control but rather as a lower dose of the active 141
15 ingredient.(4, 20) In regards to a possible effect of vasoconstriction of the large blood 142
16 vessels induced by hyperbaric oxygen - it has been well established that the tissues 143
17 are saturated by hyperoxia and do not suffer from hypoxia, as the vasoconstriction 144
18 effect is compensated by increased plasma oxygen content and microvascular blood 145
19 flow. (27) 146

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21
22 Any increase in pressure, even with reduced oxygen percentage, cannot serve as a true 147
23 placebo, but rather as a low dosage of the active ingredient, further supporting the 148
24 need for objective data gathered from large cohorts of patients suffering from PCS 149
25 and treated by HBOT. 150

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27
28 The aim of the current study was to evaluate the objective effects of HBOT on TBI 151
29 patients suffering from chronic neurological deficits stemming from mild, moderate, 152
30 and severe TBI, in the largest cohort evaluated until now. Since all the patients had 153
31 metabolic brain imaging and a computerized neurocognitive test battery before and 154

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3 after HBOT, correlations between specific cognitive indexes and their related brain 155
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5 regions activity were also evaluated. 156
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3	<i>Materials and Methods</i>	158
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6	<i>Participants</i>	159
7		
8	A retrospective analysis was conducted on patients suffering from TBI-related chronic	160
9	neurocognitive damage (more than 3 months from injury), treated by HBOT between	161
10	January 2008 and January 2017 at the Sagol Center for Hyperbaric Medicine and	162
11	Research, Assaf Harofeh Medical Center, Israel. Patients were included if they had	163
12	pre- and post-HBOT computerized cognitive evaluations. Patients with a history of	164
13	potential additional brain insults, such as spontaneous subarachnoid hemorrhage,	165
14	anoxic brain injury, or history of prior cognitive impairment, were excluded (Figure-	166
15	1).	167
16		
17	The study was approved by the Institutional Review Board of Asaf Harfoeh Medical	168
18	Center.	169
19		
20	<i>Patients and public involvement</i>	170
21		
22	Patients and public weren't involved in the study due to its retrospective nature.	171
23		
24	<i>TBI severity</i>	172
25		
26	TBI severities were rated according to the TBI admission documents. Mild TBI was	173
27	defined as loss of consciousness (LOC) with duration of 0–30 minutes, post traumatic	174
28	amnesia (PTA) with duration of less than a day and a Glasgow coma scale (GCS)	175
29	grade of 13–15. (28) Moderate TBI was defined as LOC with duration of more than	176
30	30 minutes and up to 24 hours, PTA with duration of 1-7 days and GCS grade of 9-	177
31	12. Severe TBI was defined as LOC with duration of more than 24 hours, PTA with	178
32	duration of more than seven days, and GCS less than 9. In addition, if there was	179
33	imaging evidence of an injury such as a hematoma, contusion or hemorrhage, then the	180
34	TBI was classified as moderate to severe. (28)	181
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36	<i>Hyperbaric oxygen treatment</i>	182
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3 Patients were treated with 40-70 daily hyperbaric sessions, 5 days a week. Each 183
4 session consisted of 60 minutes of exposure to 100% oxygen at 1.5-2 ATA. 184

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7 *Cognitive assessment* 185

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10 The patients' cognitive functions were assessed by NeuroTrax computerized cognitive 186
11 tests (NeuroTrax Corp., NY).(29) The NeuroTrax tests evaluate various aspects of 187
12 brain functions and include verbal memory (immediate and delayed recognition), non- 188
13 verbal memory (immediate and delayed recognition), go/no go response inhibition, 189
14 problem solving, Stroop interference, finger tapping, catch game, staged information 190
15 processing speed (single digit, two-digit and three-digit arithmetic), verbal function 191
16 and visual spatial processing. Cognitive index scores were computed from the 192
17 normalized outcome parameters for memory, executive function, attention, 193
18 information processing speed, visual spatial, verbal function and motor skills 194
19 domains.(30) A global cognitive score was computed as the average of all index 195
20 scores for each individual. 196

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23 After administration, the NeuroTrax data were uploaded to the NeuroTrax central 197
24 server, and outcome parameters were automatically calculated using software blind to 198
25 diagnosis or testing site. To account for the well-known effects of age and education 199
26 on cognitive performance, each outcome parameter was normalized and fit to an IQ- 200
27 like scale (mean=100, S.D.=15) according to the patient's age and education. The 201
28 normative data used by NeuroTrax consist of test data from cognitively healthy 202
29 individuals in controlled research studies at more than 10 sites. (31) 203

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32 Specifically, the patients were given two different versions of the NeuroTrax test 204
33 battery before and after HBOT, to allow repeated administrations with minimal 205
34 learning effects. Test-retest reliability for these versions was evaluated and found to 206

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3 be high, with no significant learning effect.(32, 33) Regarding the current study 207
4 cohort, in a previous randomized controlled trial in patients suffering from TBI, the 208
5 NeuroTrax scores were found to be stable in the retest of the control group.(21) 209
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10 *Brain SPECT imaging* 210

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12 Brain activity was assessed using single photon emission computed tomography 211
13 (SPECT) 1-2 weeks prior to and after the HBOT period. The SPECT method was 212
14 selected for evaluation due to its known normal range and test/retest established 213
15 validity. The imaging was conducted using 925–1,110 MBq (25–30 mCi) of a 214
16 technetium-99-methyl-cysteinate-dimer (Tc-99m-ECD) at 40–60 min post injection, 215
17 using a dual detector gamma camera (ECAM or Symbia T, Siemens Medical 216
18 Systems) equipped with high resolution collimators. Data was acquired in 3-degree 217
19 steps and reconstructed iteratively using the Chang method of attenuation correction 218
20 ($\mu = 0.12/\text{cm}$). (34) 219
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33 Both pre- and post-treatment SPECT images were normalized to the median maximal 220
34 brain activity in the entire brain, and were then reoriented into Talairach space using 221
35 NeuroGam software (Segami Corporation) to identify Brodmann cortical areas and to 222
36 compute the mean perfusion in each Brodmann area (BA). In addition, volume- 223
37 rendered brain perfusion images were reconstructed and normalized to the entire brain 224
38 median maximal activity. All SPECT analyses were done by study team members 225
39 who were blinded to the laboratory and clinical data. SPECT scans were performed 226
40 late morning to midday. On the day of the SPECT scan, patients were treated with 227
41 only their chronic medications and were instructed not to smoke. Changes in 228
42 perfusion in all Brodmann areas for each subject were determined by calculating the 229
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3 percentage of the difference of the normalized activity values between post-treatment 230
4 and pre-treatment divided by the pre-treatment value. 231
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8 *Statistical Analysis* 232
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10 Continuous data were expressed as means \pm standard deviations. The normal 233
11 distribution for all variables was tested using the Kolmogorov-Smirnov test. The 234
12 mean differences between cognitive index scores before and after HBOT were 235
13 analyzed using one-way ANOVA with post-hoc Bonferroni tests. Multiple linear 236
14 regression models and multivariate logistic regression models were performed to 237
15 control for potential confounders and to determine independent predictors for clinical 238
16 outcome. The alpha level was set to 0.05. Data were statistically analyzed using SPSS 239
17 software (version 22.0). 240
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Results

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Patient profiles

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Of the 242 patients suffering from neurocognitive impairment due to TBI treated by HBOT between January 2008 and January 2017, 25 patients had potential additional brain insults and 63 did not have repeat computerized neurocognitive evaluations. Therefore, 154 patients were included in the final analysis, of whom 100 patients completed pre- and post-HBOT SPECT imaging (Figure-1).

The patients' baseline characteristics are summarized in Table 1. The average age was 42.7±14.6 years and 58.4% were males. All patients had documented traumatic brain injury 3 months to 33 years (mean 4.6±5.8, median 2.75 years) prior to HBOT. Sixty-nine (44.8%) had neurocognitive impairments due to mild TBI, 24 (15.6%) moderate TBI and 61 (39.6%) severe TBI. Most of the patients (86.2%) complained of cognitive impairment as their main symptom (Table 1).

Patients were treated with 40-70 (mean 52.0±9.9) sessions of hyperbaric oxygen at 1.5-2 ATA. 18 (12%) patients reported adverse events, which included mild barotrauma of the ears and palpitations/dyspnea, while in the chamber.

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3 *Severity of TBI* 273
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5
6 In our cohort, patients who suffered severe TBI were found to be younger with higher 274
7 proportion of males than in the mild and moderate TBI groups ($P<0.0001$, $P=0.002$ 275
8 respectively, Table 1). As expected, the severe TBI group had significantly higher 276
9 proportions of cognitive impairment and motor deficits ($p=0.004$ and $p<0.0001$ 277
10 respectively, Table 1). The mild and moderate TBI groups had higher percentages of 278
11 tinnitus and/or dizziness ($p<0.0001$, $p=0.002$ respectively, Table 1). 279

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18 *Severe TBI* 280
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21 Sixty-one patients had severe TBI. The main imaging findings at their admission are 281
22 summarized in Figure-2. Of those 61 patients, 36 (59%) had surgical intervention 282
23 during the acute event. 283
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30 *Neurocognitive evaluation* 285
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33 The effect of HBOT on the patients' cognitive functions, as assessed by the eight 286
34 cognitive summary scores, is summarized in Table 2 and Figure-3. As can be seen, 287
35 HBOT induced significant improvements in all of the cognitive domains with a mean 288
36 change of 4.6 ± 8.5 ($p<0.00001$). The most prominent improvement was in the memory 289
37 index, with 8.1 ± 16.9 ($p<0.00001$), and in attention, with 6.8 ± 16.5 ($p<0.0001$) (Table 290
38 2, Figure-3). 291
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46 The mild TBI group had the largest improvement in attention (8.8 ± 2.1), followed by 292
47 memory (7.9 ± 2.3). Patients in the moderate TBI group had noticeable improvements 293
48 in memory (11.1 ± 3.1), followed by information processing speed (6.6 ± 3.5). Lastly, 294
49 the severe TBI group had the largest improvement in memory (7.0 ± 2.0), followed by 295
50 attention (6.3 ± 1.9) (Figure-4). Using ANOVA analysis for repeated measures, there 296
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3 were no significant differences in all cognitive domains improvements between the 297
4 different TBI severity groups. 298
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8 The magnitude of the change in a cognitive score has different implications for 299
9 patients at low or high baseline levels. Therefore, we further inspected the effect of 300
10 HBOT on the relative changes, i.e., the changes relative to the baseline value, in each 301
11 of the cognitive measured indexes. Marked improvements defined as >10% increase 302
12 compared to baseline cognitive index were found, with different percentages, in all 303
13 three study groups as summarized in Table 3. 304
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23 *Confounders* 306

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25 Relative change higher than 10% from baseline was considered a significant clinical 307
26 improvement. Age, gender, education level, TBI severity, the time from injury to 308
27 HBOT, HBOT protocol and number of sessions had no significant effect on the 309
30 clinical improvement in the general, memory, attention, information processing speed 310
31 and executive functions domains ($p>0.05$). 311
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38 *Metabolic imaging of the brain using SPECT* 313

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40
41 One hundred patients had brain SPECT evaluations before and after HBOT. When 314
42 calculating the mean relative change in each cortical Brodmann area for the entire 315
43 cohort, the largest changes were in the anterior temporal tip areas (BA 38, BA 28, BA 316
44 20) and in the prefrontal cortex (BA 10) (Figure-5). However, these changes were 317
45 minor, in the range of 3-4% relative change. Further analysis per TBI severity group 318
46 revealed several differences in Brodmann areas with involvement of the perirhinal 319
47 cortex (BA 36) and the primary visual cortex (BA 18), as seen in Figure-6. 320
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3 To correlate SPECT imaging and cognitive changes, analysis was performed on the 321
4 top twenty patients who had the largest cognitive improvement (>10% relative 322
5 increase from baseline). There was a significantly larger magnitude of metabolism 323
6 increase (5-8%), compared to the entire cohort average increase (2-4%) ($p<0.05$). The 324
7 most striking changes were found in the anterior cingulate (BA 24, ($p=0.01$)) and the 325
8 post-central cortex (BA 5, ($p=0.04$)), in the prefrontal areas (BA 10 ($p=0.04$), BA 11 326
9 ($p=0.07$), BA 46 ($p=0.07$) and in the temporal areas (BA 20 ($p=0.02$), BA 38 327
10 ($p=0.07$), BA 36 ($p=0.1$)). 328

27 ***Discussion*** 332

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30 The present study demonstrates the neurotherapeutic effects of HBOT for chronic TBI 333
31 of all severities. Even though treatment started during late chronic stages (mean 334
32 4.6±5.8 years, median 2.75 years) after the acute insult, HBOT was still found to be 335
33 effective regardless of the TBI severity. The clinical improvements seen in all 336
34 cognitive domains were well documented by objective computerized neurocognitive 337
35 tests. The most significant measurable improvements were in memory, attention and 338
36 executive function. We found the clinical improvement to be well correlated with 339
37 increased brain activity in relevant brain areas, with significantly higher increases in 340
38 patients with better cognitive improvements. 341

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41 In addition to tissue oxygenation, numerous mechanisms of cellular and vascular 342
42 repair by HBOT have been suggested in addition to tissue oxygenation.(5) These 343
43 include improved mitochondrial function and cellular metabolism, improved blood- 344
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3 brain barrier and inflammatory reactions, reduced apoptosis, alleviation of oxidative 345
4 stress, increased levels of neurotrophins and nitric oxide, and upregulation of axonal 346
5 guidance agents.(5, 13, 35) Moreover, the effects of HBOT on neurons can be 347
6 mediated indirectly by glial cells. HBOT may also promote neurogenesis of 348
7 endogenous neural stem cells.(13, 35) The common denominator underlying all these 349
8 mechanisms is that they are oxygen-dependent. HBOT may enable the metabolic 350
9 change simply by supplying the missing energy/oxygen needed for these regeneration 351
10 processes. (35) The induction of angiogenesis and improved brain metabolism, as 352
11 demonstrated in this study, may serve as the infrastructure that enables the 353
12 regenerative process and the preservation of newly generated neuronal functioning. 354
13 (14, 36) 355

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29 The correlation between specific cognitive function improvements with the metabolic 357
30 brain imaging changes gives further strength to the study results and serves as an 358
31 excellent tool for gaining better understanding of brain functionality (Figure-6): 359

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37 • The perirhinal cortex activation after HBOT was most prominent in 360
38 patients who had significant memory improvement. The perirhinal 361
39 cortex has a critical role in object recognition memory while 362
40 interacting with the hippocampus.(37) Since the memory assessments 363
41 in the cognitive tests were indeed recognition tasks, this area is 364
42 expected to be involved. 365
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50 • The pre-frontal cortex (BA 10, BA 11) and more specifically, the 366
51 inferior frontal gyrus (BA 46, BA 47) activations after HBOT were 367
52 prominent in all patients with significant executive function 368
53 improvements. The right frontal gyrus is known to mediate a go/no go 369

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3 task, (38) which was among the executive function tests used in the 370
4
5 present study. The prefrontal gyrus is presumed to act as a filtering 371
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7 system that enhances goal directed activities and inhibits irrelevant 372
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9 activations. This filtering mechanism enables executive control.(39) 373
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11 • The anterior cingulate gyrus (BA 24) activation after HBOT was seen 374
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13 in the subjects with attention improvement. The anterior cingulate 375
14
15 gyrus is presumed to be involved in error detection, especially in a 376
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17 Stroop task,(40) which was used in the attention tests. Lesions in this 377
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19 area can cause inattention to akinetic mutism.(40) 378
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25 This study has several limitations. The major one relates to its retrospective 380
26
27 methodology. This limitation is diminished when considering that this large cohort of 381
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29 patients was treated at late chronic stages. The findings presented here are in 382
30
31 agreement and reinforce the findings from previous prospective controlled trials in 383
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33 which the neuroplasticity effects of HBOT were demonstrated in chronic stages of 384
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35 different types of brain injuries.(15, 21, 41, 42) Moreover, the correlation between the 385
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37 changes in cognitive function and the metabolic brain imaging gives further strength 386
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39 to the results. 387
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42 Another important limitation relates to the HBOT protocol which was inconsistent 388
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44 across the cohort. Although significant neurotherapeutic effects were seen with 60 389
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46 minutes of 1.5 ATA, the optimal protocol needed to induce maximal neuroplasticity 390
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48 for the specific individual, with minimal side effects has not been investigated. 391
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53 The strengths of the study are worth mentioning. First, objective cognitive 393
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55 assessments using computerized tests were performed on each patient both pre- and 394
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3 post-treatment. Objective measures are significantly superior to PCS questionnaires 395
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5 which are inaccurate, variable and contain various confounders rather than reflect the 396
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7 true PCS state.(43) Second, most of the patients in the study underwent an objective 397
8
9 ancillary brain SPECT to confirm PCS diagnosis prior to HBOT. This practice is 398
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11 crucial when considering the differential diagnosis following TBI (PTSD, depression, 399
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13 etc.). 400
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16 Moreover, post-treatment brain SPECTs revealed an anatomical-functional 401
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18 correlation in regards to HBOT's effect in brain neuroplasticity. Third, the study 402
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20 cohort consisted of a civilian population that does not have any potential secondary 403
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22 gain (such as financial compensation) by reporting sick. 404
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26 Previous studies included post-concussion syndrome patients who suffered mild TBI 406
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28 injury. Considering its strengths and limitations, the current study implies that the 407
29
30 cognitive function of patients post TBI, can be improved significantly, irrespectively 408
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32 of whether the primary brain injury was classified as mild, moderate or severe. 409
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35 Although long term data is still lacking, considering the high safety profile of the 410
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37 treatment, these results are promising and should encourage rehabilitation centers to 411
38
39 consider HBOT for patients with chronic neurocognitive deficits following TBI. 412
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42 Future studies should monitor these patients in the long term (6 months, 12 months) 413
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44 as well as their return to activities of daily living. 414
45

46 **Conclusions** 415
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48 HBOT induced significant cognitive improvements in patients who suffer from 416
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50 chronic neurocognitive deficits due to mild, moderate and severe TBI. Improvement 417
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52 in memory correlated with activation of the perirhinal cortex, improvement of 418
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3 executive functions correlated with activation of the inferior frontal gyrus, and 419
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5 improvement in attention correlated with activation of the anterior cingulate gyrus. 420
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Table 1: Baseline patient characteristics.

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Number of patients	154 (100%)	69 (44.8%)	24 (15.6%)	61 (39.6%)	
Age (years)	42.7±14.6	48.8±12.0	41.7±12.7	36.2±15.3	P<0.0001
Sex					
Males	90 (58.4%)	31 (44.9%)	13 (54.2%)	46 (75.4%)	P=0.002
Females	64 (41.6%)	38 (55.1%)	11 (45.8%)	15 (24.6%)	
Education (years)	14.8±3.3	14.9±3.6	14.9±3.3	14.6±3.1	P=0.895
Traumatic event					

Motor Vehicle					
Accident	116 (75.3%)	56 (81.2%)	17 (70.8%)	43 (70.5%)	P=0.048
Fall	21 (13.6%)	8 (11.6%)	1 (4.2%)	12 (57.1%)	
Blow	12 (7.8%)	5 (7.2%)	5 (20.8%)	2 (3.3%)	
Blast	4 (2.6%)	0	1 (4.2%)	3 (4.9%)	
Penetrating	1 (0.6%)	0	0	1 (0.6%)	
Time from trauma (years)	4.6±5.8	4.4±5.9	5.0±5.8	4.6±5.7	P=0.923

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Table 1: Baseline patient characteristics (continued).

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Symptoms					
Cognitive	100 (86.2%)	38 (74.5%)	19 (90.5%)	43 (97.7%)	P=0.004
Motor	22 (19.0%)	1 (4.8%)	1 (4.8%)	20 (45.5%)	P<0.0001
Sensory	32 (27.6%)	12 (23.5%)	7 (33.3%)	13 (29.5%)	P=0.653
Dizziness/Vertigo	17 (14.7%)	14 (27.5%)	2 (9.5%)	1 (2.3%)	P=0.002
Tinnitus	30 (25.9%)	26 (51.0%)	2 (9.5%)	2 (4.5%)	P<0.0001
Headaches	20 (17.2%)	12 (23.5%)	3 (14.3%)	5 (11.4%)	P=0.272
HBO sessions	52.0±9.9	49.4±10.1	49.0±10.3	56.1±8.2	P=0.0001

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HBO protocol (ATA)	1.5	106 (69.3%)	46 (67.6%)	18 (75.0%)	42 (68.9%)	P=0.795
	2	47 (30.7%)	22 (32.4%)	6 (25.0%)	19 (31.1%)	
Adverse Events		18 (12.0%)	10 (15.2%)	3 (12.5%)	5 (8.3%)	P=0.499

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Table 2: Cognitive indices pre- and post-HBOT of the entire study cohort

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	Baseline	Post HBOT	Mean Change	P-Value
General	88.3±15.2	92.9±14.2	4.6±8.5	P<0.0001
Memory	81.7±23.2	89.9±21.9	8.1±16.9	P<0.0001
Executive Functions	88.3±16.6	94.2±15.1	5.9±12.0	P<0.0001
Attention	84.3±20.5	91.1±18.4	6.8±16.5	P<0.0001
IPS	87.5±17.0	92.4±15.7	4.9±13.1	P<0.0001

VSP	95.0±18.0	98.5±18.0	3.4±14.6	P=0.005
Motor skills	92.3±17.3	96.2±14.5	3.9±11.7	P<0.0001

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IPS=information processing speed, VSP=visual spatial processing

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Table 3: Large significant increases (>10% change) in cognitive indices proportions across TBI groups.

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	Total	Mild TBI	Moderate TBI	Severe TBI	
General	36 (23.4%)	15 (21.7%)	7(29.2%)	14 (23.0%)	P=0.756
Memory	64 (41.6%)	28 (40.6%)	9 (37.5%)	27 (44.3%)	P=0.830
Executive functions	51 (33.1%)	23 (33.3%)	7 (29.2%)	21 (34.9%)	P=0.897
Attention	62 (40.3%)	27 (39.1%)	8 (33.3%)	27 (44.3%)	P=0.631
Information processing speed	48 (31.2%)	23 (33.3%)	12 (50%)	13 (21.3%)	P=0.032

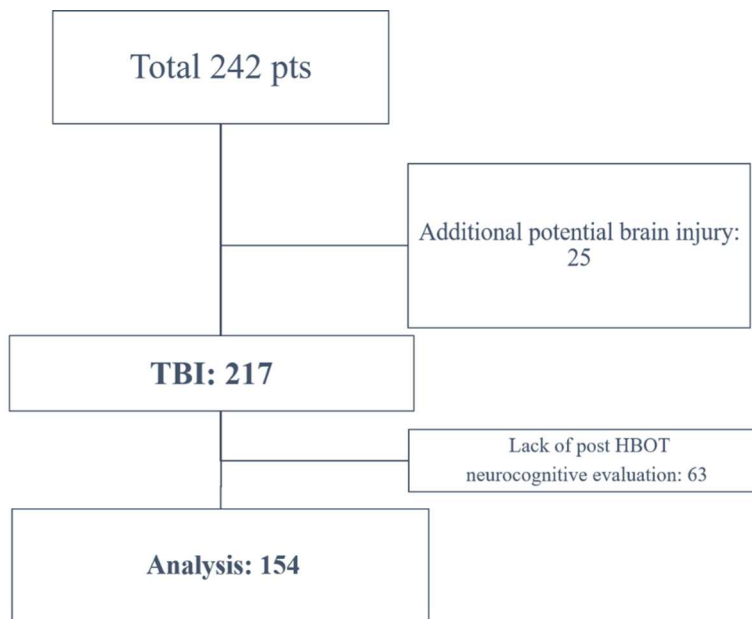
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3	Figures legends	620
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5	Figure-1: Patients flowchart.	621
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7	Figure-2: Imaging findings in the severe TBI group	622
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9	Figure-3: Mean changes of post- compared to pre-HBOT for the entire cohort.	623
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12	After HBOT, all cognitive domains improved significantly, with the most striking	624
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14	changes seen in memory and attention.	625
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17	*p<0.0001, **p=0.005, IPS=information processing speed	626
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20	Figure-4: Mean changes of post- compared to pre-HBOT across the different TBI	627
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22	severities.	628
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25	Both patients who suffered mild and severe TBI groups had improvements in general,	629
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27	memory, attention, information processing speed and motor skills scores, whereas	630
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29	patients who suffered moderate TBI had significant improvement in memory.	631
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32	*p<0.05, IPS =information processing speed	632
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35	Figure-5: The mean relative change in Brodmann areas post HBOT for the entire	633
36		
37	study cohort.	634
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40	Figure-6: Cognitive functions correlated with Brodmann areas.	635
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43	Each of the TBI groups(mild, moderate and severe) had perfusion/metabolism	636
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45	increase in specific Brodmann areas correlated with improved cognitive function.	637
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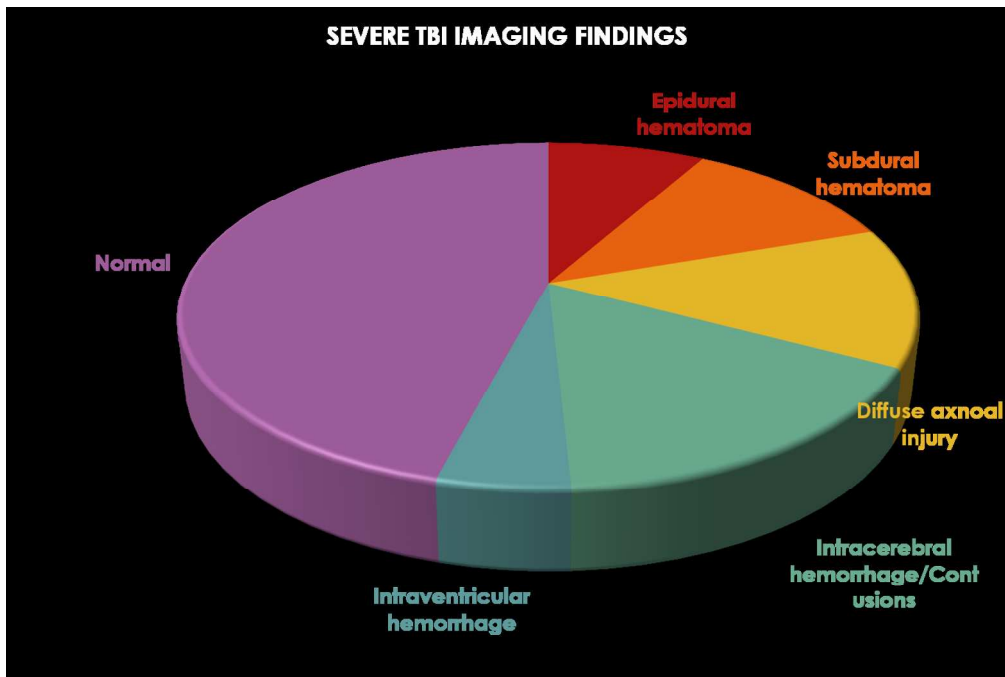


Patients flowchart

334x232mm (300 x 300 DPI)

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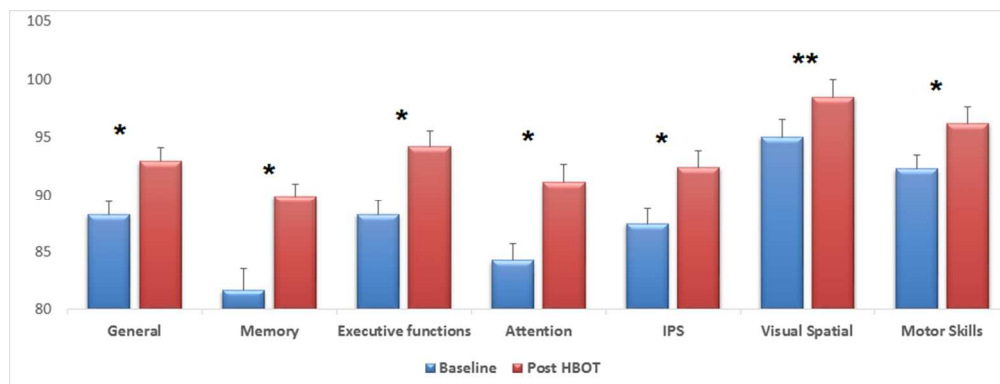
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Imaging findings in the severe TBI subgroup

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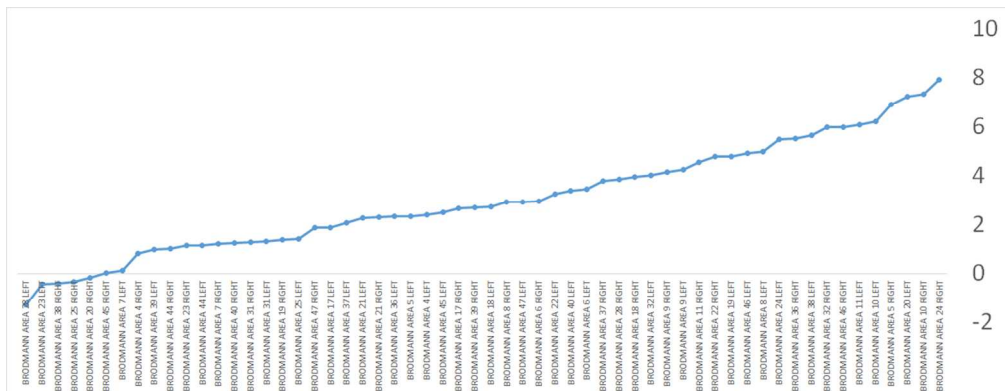


Mean changes of post- compared to pre-HBOT for the entire cohort. After HBOT, all cognitive domains improved significantly, where the most striking changes were seen in memory and attention.

*p<0.0001, **p=0.005, IPS=information processing speed

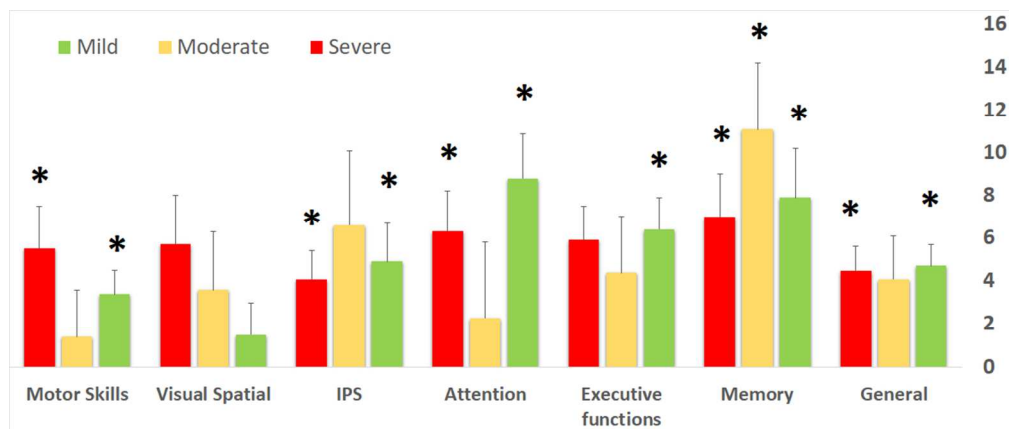
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The mean relative change in broadmann areas post HBOT for the entire study cohort
 261x101mm (300 x 300 DPI)

Peer review only



Mean changes of post- compared to pre-HBOT across the different TBI severities.

Both patients who suffered mild and severe TBI groups had improvements in general, memory, attention, information processing speed and motor skills scores, whereas patients who suffered moderate TBI had significant improvement in memory.

* $p < 0.05$, IPS = information processing speed

247x104mm (120 x 120 DPI)

STROBE (Strengthening The Reporting of OBServational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

BMJ Open

The effect of hyperbaric oxygen therapy on chronic neurocognitive function of deficits post traumatic brain injury patients – retrospective analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023387.R2
Article Type:	Research
Date Submitted by the Author:	27-Jun-2018
Complete List of Authors:	Hadanny, Amir; Galilee Medical Center, Neuosurgery; Assaf Harofeh Medical Center, Sagol Center for Hyperbaric Medicine and Research Abbott, Stefanie; Asaf Harofeh Medical Center, Sagol Center for Hyperbaric Medicine and Research Suzin, Gil; Asaf Harfoeh Medical Center, Sagol Center for Hyperbaric Medicine and Research Bechor, Yair; Asaf Harofeh Medical Center, Sagol Center for Hyperbaric Medicine and Research Efrati, Shai; Assaf Harofeh Medical Center, Sagol Center for Hyperbaric Medicine and Research; Tel Aviv University, Sackler School of Medicine
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	tbi, hbot, traumatic brain injury, hyperbaric oxygen, cognitive

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Manuscripts

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3 **The effect of hyperbaric oxygen therapy on chronic neurocognitive function of** 1
4
5 **deficits post traumatic brain injury patients – retrospective analysis** 2

6
7 Amir Hadanny MD^{1,2,3,5}, Stefanie Abbott BA², Gil Suzin MA², Yair Bechor BA², 3

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55 *Author Disclosure Statement* 22

1		
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3	No competing financial interests exist.	23
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6	No funding received for this work.	24
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9	No conflict of interests exists.	25
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17	SA: data collection, data analysis	28
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20	GS: data collection, manuscript review	29
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23	YB: data collection, manuscript review	30
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26	SE: concept, data analysis, manuscript draft, manuscript review	31
27		
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29	<i>Data sharing statement</i>	32
30		
31		
32	Extra data is available by emailing amir.had@gmail.com	33
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47	Figures: 6	39
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53		
54	Abstract	42
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56	<i>Objectives</i>	43
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3 The aim of the study is to evaluate the effect of hyperbaric oxygen therapy (HBOT) in 44
4 participants suffering from chronic neurological deficits due to traumatic brain injury 45
5 (TBI) of all severities in the largest cohort evaluated so far with objective cognitive 46
6 function tests and metabolic brain imaging. 47
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9

10 11 *Methods* 48 12

13 A retrospective analysis was conducted of 154 patients suffering from chronic 49
14 neurocognitive damage due to TBI, who had undergone computerized cognitive 50
15 evaluations pre- and post-HBOT treatment. 51
16
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19

20 21 *Results* 52 22

23 The average age was 42.7±14.6 years and 58.4% were males. All patients had 53
24 documented traumatic brain injury 0.3-33 years (mean 4.6±5.8, median 2.75 years) 54
25 prior to HBOT. HBOT was associated with significant improvement in all of the 55
26 cognitive domains, with mean change in global cognitive scores of 4.6±8.5 56
27 (p<0.00001). The most prominent improvements were in memory index and attention, 57
28 with mean changes of 8.1±16.9 (p<0.00001) and 6.8±16.5 (p<0.0001), respectively. 58
29
30 The most striking changes observed in brain single photon emission computed 59
31 tomography (SPECT) images were in the anterior cingulate and the post-central 60
32 cortex, in the prefrontal areas and in the temporal areas. 61
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43 44 *Conclusions* 62 45

46 In the largest published cohort of patients suffering from chronic deficits post TBI of 63
47 all severities, HBOT was associated with significant cognitive improvements. The 64
48 clinical improvements were well correlated with increased activity in the relevant 65
49 brain areas. 66
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1
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3 Keywords: hyperbaric oxygen, HBOT, post-concussion, PCS, TBI, traumatic brain 68
4
5 injury 69
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7 **Article Summary** 70
8

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10 *Strengths and limitations of the study* 71
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- 12
13 • The major limitation relates to its retrospective methodology, however this 72
14 limitation is diminished by the fact that all patients of the study large cohort 73
15 were treated at late chronic stages. 74
16
17 • In regards to strengths, objective cognitive assessments using computerized 75
18 tests (which are superior to any clinical questionnaire), were performed on 76
19 each patient both pre- and post-treatment. 77
20
21 • The study cohort consisted of a civilian population that does not have any 78
22 potential secondary gain (such as financial compensation by reporting sick). 79
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3	<i>Introduction</i>	81
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5		
6	Traumatic brain injury (TBI) is one of the leading causes of death and disability in the	82
7	general population.(1) Following TBI, patients may experience a set of symptoms	83
8	known as post-concussion syndrome (PCS). PCS symptoms include headaches,	84
9	dizziness, neuropsychiatric symptoms, and cognitive impairments.(2) PCS can	85
10	continue for weeks or months, and up to 25% of all patients experience prolonged	86
11	PCS (PPCS) in which the symptoms last for over six months.(3)	87
12		
13		
14	In the past years there is growing clinical evidence regarding the effect of hyperbaric	88
15	oxygen therapy (HBOT) on PCS.(4-6) Unfortunately, the clinical data gathered from	89
16	those studies can be conflicting due to several inherent procedural issues, such as the	90
17	use of non-objective end points, the lack of appropriate brain imaging as part of the	91
18	inclusion criteria, the inappropriate placebo of a hyperbaric environment, and the	92
19	inclusion of patients that may gain secondary benefits from reporting sick.(4, 5) The	93
20	current study represents the largest cohort evaluated until now of civilian participants	94
21	suffering from PCS treated by HBOT, who had undergone objective metabolic brain	95
22	imaging and a computerized neurocognitive test battery before and after the treatment.	96
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40	<i>Pathophysiology of PCS and HBOT</i>	97
41		
42	The most common pathological mechanism in TBI is diffuse shearing of axonal	98
43	pathways and small blood vessels, also known as diffuse axonal injury.(7) Secondary	99
44	pathological mechanisms of TBI include ischemia, mild edema, and other	100
45	biochemical and inflammatory processes culminating in impaired regenerative and/or	101
46	healing processes resulting from increasing tissue hypoxia.(8) Due to the diffuse	102
47	nature of injury, affecting multiple brain areas,(9, 10) cognitive impairments are	103
48	usually the predominant symptoms.	104
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3 Global brain hypoperfusion, and its related tissue ischemia, detected in patients 105
4 suffering from TBI, serves as a rate-limiting factor for any regenerative process.(11- 106
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6
7 13) By increasing the oxygen level in blood and body tissues, HBOT can augment the 107
8
9 repair mechanisms.(14) Various models have strongly suggested that HBOT can 108
10 induce angiogenesis, improve brain plasticity, enhance neurogenesis and 109
11 synaptogenesis and foster functional recovery.(15, 16) 110
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16 *Conflicting clinical HBOT data and objective measurements in PCS* 111

17
18
19 Some of the previous studies which evaluated the effect of HBOT on chronic 112
20 neurological and cognitive impairments due to TBI, mainly used self-assessment 113
21 questionnaires as their primary endpoints.(17-19) Such endpoints have several 114
22 inherent disadvantages. First, they lack an objective evaluation that is not biased by 115
23 the patients' perspectives. Second, self-administrated questionnaires are exposed to 116
24 various confounding variables such as litigation and compensation.(20). Unlike the 117
25 questionnaires, standardized cognitive tests with high test-retest reliability can and 118
26 should be used as objective evaluations of neurocognitive impairments.(21) In 119
27 addition, novel brain imaging techniques such as single photon emission computed 120
28 tomography (SPECT) and perfusion sequences in magnetic resonance imaging (MRI), 121
29 which evaluate cerebral blood flow and brain metabolism, can shed new light in PCS 122
30 diagnosis and in evaluating therapeutic interventions.(21) In clinical studies which 123
31 utilized objective cognitive assessments, HBOT was found to induce significant 124
32 improvements in patients suffering from PCS due to mild TBI. (6, 14, 16, 22) 125
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34
35 However, to the best of our knowledge, the objective effect of HBOT on chronic 126
36 neurocognitive impairments stemming from moderate to severe TBI (in addition to 127
37 mild) has not been investigated. 128
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3 In addition to objective evaluations, there are inherent ethical and logistic difficulties 129
4 in handling the sham control in HBOT trials.(4, 5, 21, 23) HBOT includes two active 130
5 ingredients: pressure and oxygen. Pressure is needed to increase plasma oxygen, but 131
6 the pressure change alone may also have significant cellular effects.(5) Additionally, 132
7 the greatest effect of pressure is in human tissues that are under tight autoregulation 133
8 pressure control, such as the brain, where the intracranial pressure is normally 0.0092- 134
9 0.0197atm.(24, 25) To generate a pressure sensation, the chamber pressure must be 135
10 1.2ATA or higher. However, such a change in environmental pressure (from 1ATA 136
11 to 1.2 ATA) and subsequent tissue oxygenation (with an increase of tissue 137
12 oxygenation by at least 50%) has a significant biologic effect (26, 27) Thus, sham 138
13 therapy in previous studies using 1.2 ATA on 21% inhaled oxygen (i.e., air) cannot be 139
14 regarded as an inert or sham control but rather as a lower dose of the active 140
15 ingredient.(4, 21) In regards to a possible effect of vasoconstriction of the large blood 141
16 vessels induced by hyperbaric oxygen - it has been well established that the tissues 142
17 are saturated by hyperoxia and do not suffer from hypoxia, as the vasoconstriction 143
18 effect is compensated by increased plasma oxygen content and microvascular blood 144
19 flow. (28) 145

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21
22 Any increase in pressure, even with reduced oxygen percentage, cannot serve as a true 146
23 placebo, but rather as a low dosage of the active ingredient, further supporting the 147
24 need for objective data gathered from large cohorts of patients suffering from PCS 148
25 and treated by HBOT. 149

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27
28 The aim of the current study was to evaluate the objective effects of HBOT on TBI 150
29 patients suffering from chronic neurological deficits stemming from mild, moderate, 151
30 and severe TBI, in the largest cohort evaluated until now. Since all the patients had 152
31 metabolic brain imaging and a computerized neurocognitive test battery before and 153

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3 after HBOT, correlations between specific cognitive indexes and their related brain 154
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5 regions activity were also evaluated. 155
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2		
3	<i>Materials and Methods</i>	157
4		
5		
6	<i>Participants</i>	158
7		
8	A retrospective analysis was conducted on patients suffering from TBI-related chronic	159
9	neurocognitive damage (more than 3 months from injury), treated by HBOT between	160
10	January 2008 and January 2017 at the Sagol Center for Hyperbaric Medicine and	161
11	Research, Assaf Harofeh Medical Center, Israel. Patients were included if they had	162
12	pre- and post-HBOT computerized cognitive evaluations. Patients with a history of	163
13	potential additional brain insults, such as spontaneous subarachnoid hemorrhage,	164
14	anoxic brain injury, or history of prior cognitive impairment, were excluded (Figure-	165
15	1).	166
16		
17	The study was approved by the Institutional Review Board of Asaf Harfoeh Medical	167
18	Center.	168
19		
20	<i>Patients and public involvement</i>	169
21		
22	Patients and public weren't involved in the study due to its retrospective nature.	170
23		
24	<i>TBI severity</i>	171
25		
26	TBI severities were rated according to the TBI admission documents. Mild TBI was	172
27	defined as loss of consciousness (LOC) with duration of 0–30 minutes, post traumatic	173
28	amnesia (PTA) with duration of less than a day and a Glasgow coma scale (GCS)	174
29	grade of 13–15. (29) Moderate TBI was defined as LOC with duration of more than	175
30	30 minutes and up to 24 hours, PTA with duration of 1-7 days and GCS grade of 9-	176
31	12. Severe TBI was defined as LOC with duration of more than 24 hours, PTA with	177
32	duration of more than seven days, and GCS less than 9. In addition, if there was	178
33	imaging evidence of an injury such as a hematoma, contusion or hemorrhage, then the	179
34	TBI was classified as moderate to severe. (29)	180
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36	<i>Hyperbaric oxygen treatment</i>	181
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3 Patients were treated with 40-70 daily hyperbaric sessions, 5 days a week. Each 182
4 session consisted of 60 minutes of exposure to 100% oxygen at 1.5-2 ATA. 183
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6
7 *Cognitive assessment* 184
8

9
10 The patients' cognitive functions were assessed by NeuroTrax computerized cognitive 185
11 tests (NeuroTrax Corp., NY).(30) The NeuroTrax tests evaluate various aspects of 186
12 brain functions and include verbal memory (immediate and delayed recognition), non- 187
13 verbal memory (immediate and delayed recognition), go/no go response inhibition, 188
14 problem solving, Stroop interference, finger tapping, catch game, staged information 189
15 processing speed (single digit, two-digit and three-digit arithmetic), verbal function 190
16 and visual spatial processing. Cognitive index scores were computed from the 191
17 normalized outcome parameters for memory, executive function, attention, 192
18 information processing speed, visual spatial, verbal function and motor skills 193
19 domains.(31) A global cognitive score was computed as the average of all index 194
20 scores for each individual. 195
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34 After administration, the NeuroTrax data were uploaded to the NeuroTrax central 196
35 server, and outcome parameters were automatically calculated using software blind to 197
36 diagnosis or testing site. To account for the well-known effects of age and education 198
37 on cognitive performance, each outcome parameter was normalized and fit to an IQ- 199
38 like scale (mean=100, S.D.=15) according to the patient's age and education. The 200
39 normative data used by NeuroTrax consist of test data from cognitively healthy 201
40 individuals in controlled research studies at more than 10 sites. (32) 202
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50 Specifically, the patients were given two different versions of the NeuroTrax test 203
51 battery before and after HBOT, to allow repeated administrations with minimal 204
52 learning effects. Test-retest reliability for these versions was evaluated and found to 205
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3 be high, with no significant learning effect.(33, 34) Regarding the current study 206
4 cohort, in a previous randomized controlled trial in patients suffering from TBI, the 207
5 NeuroTrax scores were found to be stable in the retest of the control group.(22) 208
6
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10 *Brain SPECT imaging* 209

11
12 Brain activity was assessed using single photon emission computed tomography 210
13 (SPECT) 1-2 weeks prior to and after the HBOT period. The SPECT method was 211
14 selected for evaluation due to its known normal range and test/retest established 212
15 validity. The imaging was conducted using 925–1,110 MBq (25–30 mCi) of a 213
16 technetium-99-methyl-cysteinate-dimer (Tc-99m-ECD) at 40–60 min post injection, 214
17 using a dual detector gamma camera (ECAM or Symbia T, Siemens Medical 215
18 Systems) equipped with high resolution collimators. Data was acquired in 3-degree 216
19 steps and reconstructed iteratively using the Chang method of attenuation correction 217
20 ($\mu = 0.12/\text{cm}$). (35) 218
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33 Both pre- and post-treatment SPECT images were normalized to the median maximal 219
34 brain activity in the entire brain, and were then reoriented into Talairach space using 220
35 NeuroGam software (Segami Corporation) to identify Brodmann cortical areas and to 221
36 compute the mean perfusion in each Brodmann area (BA). In addition, volume- 222
37 rendered brain perfusion images were reconstructed and normalized to the entire brain 223
38 median maximal activity. All SPECT analyses were done by study team members 224
39 who were blinded to the laboratory and clinical data. SPECT scans were performed 225
40 late morning to midday. On the day of the SPECT scan, patients were treated with 226
41 only their chronic medications and were instructed not to smoke. Changes in 227
42 perfusion in all Brodmann areas for each subject were determined by calculating the 228
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3 percentage of the difference of the normalized activity values between post-treatment 229
4 and pre-treatment divided by the pre-treatment value. 230
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8 *Statistical Analysis* 231
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10 Continuous data were expressed as means \pm standard deviations. The normal 232
11 distribution for all variables was tested using the Kolmogorov-Smirnov test. The 233
12 mean differences between cognitive index scores before and after HBOT were 234
13 analyzed using one-way ANOVA with post-hoc Bonferroni tests. Multiple linear 235
14 regression models and multivariate logistic regression models were performed to 236
15 control for potential confounders and to determine independent predictors for clinical 237
16 outcome. The alpha level was set to 0.05. Data were statistically analyzed using SPSS 238
17 software (version 22.0). 239
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Results

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Patient profiles

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Of the 242 patients suffering from neurocognitive impairment due to TBI treated by HBOT between January 2008 and January 2017, 25 patients had potential additional brain insults and 63 did not have repeat computerized neurocognitive evaluations. Therefore, 154 patients were included in the final analysis, of whom 100 patients completed pre- and post-HBOT SPECT imaging (Figure-1).

The patients' baseline characteristics are summarized in Table 1. The average age was 42.7±14.6 years and 58.4% were males. All patients had documented traumatic brain injury 3 months to 33 years (mean 4.6±5.8, median 2.75 years) prior to HBOT. Sixty-nine (44.8%) had neurocognitive impairments due to mild TBI, 24 (15.6%) moderate TBI and 61 (39.6%) severe TBI. Most of the patients (86.2%) complained of cognitive impairment as their main symptom (Table 1).

Patients were treated with 40-70 (mean 52.0±9.9) sessions of hyperbaric oxygen at 1.5-2 ATA. 18 (12%) patients reported adverse events, which included mild barotrauma of the ears and palpitations/dyspnea, while in the chamber.

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3 *Severity of TBI* 272
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6 In our cohort, patients who suffered severe TBI were found to be younger with higher 273
7
8 proportion of males than in the mild and moderate TBI groups ($P<0.0001$, $P=0.002$ 274
9
10 respectively, Table 1). As expected, the severe TBI group had significantly higher 275
11
12 proportions of cognitive impairment and motor deficits ($p=0.004$ and $p<0.0001$ 276
13
14 respectively, Table 1). The mild and moderate TBI groups had higher percentages of 277
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16 tinnitus and/or dizziness ($p<0.0001$, $p=0.002$ respectively, Table 1). 278

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19 *Severe TBI* 279

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21 Sixty-one patients had severe TBI. The main imaging findings at their admission are 280
22
23 summarized in Figure-2. Of those 61 patients, 36 (59%) had surgical intervention 281
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25 during the acute event. 282

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30 *Neurocognitive evaluation* 284

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32 The effect of HBOT on the patients' cognitive functions, as assessed by the eight 285
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34 cognitive summary scores, is summarized in Table 2 and Figure-3. As can be seen, 286
35
36 HBOT induced significant improvements in all of the cognitive domains with a mean 287
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38 change of 4.6 ± 8.5 ($p<0.00001$). The most prominent improvement was in the memory 288
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40 index, with 8.1 ± 16.9 ($p<0.00001$), and in attention, with 6.8 ± 16.5 ($p<0.0001$) (Table 289
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42 2, Figure-3). 290

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46 The mild TBI group had the largest improvement in attention (8.8 ± 2.1), followed by 291
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48 memory (7.9 ± 2.3). Patients in the moderate TBI group had noticeable improvements 292
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50 in memory (11.1 ± 3.1), followed by information processing speed (6.6 ± 3.5). Lastly, 293
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52 the severe TBI group had the largest improvement in memory (7.0 ± 2.0), followed by 294
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54 attention (6.3 ± 1.9) (Figure-4). Using ANOVA analysis for repeated measures, there 295

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3 were no significant differences in all cognitive domains improvements between the 296
4 different TBI severity groups. 297
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8 The magnitude of the change in a cognitive score has different implications for 298
9 patients at low or high baseline levels. Therefore, we further inspected the effect of 299
10 HBOT on the relative changes, i.e., the changes relative to the baseline value, in each 300
11 of the cognitive measured indexes. Marked improvements defined as >10% increase 301
12 compared to baseline cognitive index were found, with different percentages, in all 302
13 three study groups as summarized in Table 3. 303
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23 *Confounders* 305

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25 Relative change higher than 10% from baseline was considered a significant clinical 306
26 improvement. Age, gender, education level, TBI severity, the time from injury to 307
27 HBOT, HBOT protocol and number of sessions had no significant effect on the 308
28 clinical improvement in the general, memory, attention, information processing speed 309
29 and executive functions domains ($p>0.05$). 310
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38 *Metabolic imaging of the brain using SPECT* 312

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41 One hundred patients had brain SPECT evaluations before and after HBOT. When 313
42 calculating the mean relative change in each cortical Brodmann area for the entire 314
43 cohort, the largest changes were in the anterior temporal tip areas (BA 38, BA 28, BA 315
44 20) and in the prefrontal cortex (BA 10) (Figure-5). However, these changes were 316
45 minor, in the range of 3-4% relative change. Further analysis per TBI severity group 317
46 revealed several differences in Brodmann areas with involvement of the perirhinal 318
47 cortex (BA 36) and the primary visual cortex (BA 18), as seen in Figure-6. 319
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3 To correlate SPECT imaging and cognitive changes, analysis was performed on the 320
4 top twenty patients who had the largest cognitive improvement (>10% relative 321
5 increase from baseline). There was a significantly larger magnitude of metabolism 322
6 increase (5-8%), compared to the entire cohort average increase (2-4%) ($p<0.05$). The 323
7 most striking changes were found in the anterior cingulate (BA 24, ($p=0.01$)) and the 324
8 post-central cortex (BA 5, ($p=0.04$)), in the prefrontal areas (BA 10 ($p=0.04$), BA 11 325
9 ($p=0.07$), BA 46 ($p=0.07$) and in the temporal areas (BA 20 ($p=0.02$), BA 38 326
10 ($p=0.07$), BA 36 ($p=0.1$)). 327

28 ***Discussion*** 331

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30 The present study demonstrates the neurotherapeutic effects of HBOT for chronic TBI 332
31 of all severities. Even though treatment started during late chronic stages (mean 333
32 4.6±5.8 years, median 2.75 years) after the acute insult, HBOT was still found to be 334
33 effective regardless of the TBI severity. The clinical improvements seen in all 335
34 cognitive domains were well documented by objective computerized neurocognitive 336
35 tests. The most significant measurable improvements were in memory, attention and 337
36 executive function. We found the clinical improvement to be well correlated with 338
37 increased brain activity in relevant brain areas, with significantly higher increases in 339
38 patients with better cognitive improvements. 340

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41 In addition to tissue oxygenation, numerous mechanisms of cellular and vascular 341
42 repair by HBOT have been suggested in addition to tissue oxygenation.(5, 36) These 342
43 include improved mitochondrial function and cellular metabolism, improved blood- 343

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3 brain barrier and inflammatory reactions, reduced apoptosis, alleviation of oxidative 344
4 stress, increased levels of neurotrophins and nitric oxide, and upregulation of axonal 345
5 guidance agents.(5, 14, 37) Moreover, the effects of HBOT on neurons can be 346
6 mediated indirectly by glial cells. HBOT may also promote neurogenesis of 347
7 endogenous neural stem cells.(14, 37) The common denominator underlying all these 348
8 mechanisms is that they are oxygen-dependent. HBOT may enable the metabolic 349
9 change simply by supplying the missing energy/oxygen needed for these regeneration 350
10 processes. (37) The induction of angiogenesis and improved brain metabolism, as 351
11 demonstrated in this study, may serve as the infrastructure that enables the 352
12 regenerative process and the preservation of newly generated neuronal functioning. 353
13 (15, 36, 38) 354

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29 The correlation between specific cognitive function improvements with the metabolic 356
30 brain imaging changes gives further strength to the study results and serves as an 357
31 excellent tool for gaining better understanding of brain functionality (Figure-6): 358

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- The perirhinal cortex activation after HBOT was most prominent in 359
patients who had significant memory improvement. The perirhinal 360
cortex has a critical role in object recognition memory while 361
interacting with the hippocampus.(39) Since the memory assessments 362
in the cognitive tests were indeed recognition tasks, this area is 363
expected to be involved. 364
 - The pre-frontal cortex (BA 10, BA 11) and more specifically, the 365
inferior frontal gyrus (BA 46, BA 47) activations after HBOT were 366
prominent in all patients with significant executive function 367
improvements. The right frontal gyrus is known to mediate a go/no go 368

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3 task, (40) which was among the executive function tests used in the 369
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5 present study. The prefrontal gyrus is presumed to act as a filtering 370
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7 system that enhances goal directed activities and inhibits irrelevant 371
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9 activations. This filtering mechanism enables executive control.(41) 372
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11 • The anterior cingulate gyrus (BA 24) activation after HBOT was seen 373
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13 in the subjects with attention improvement. The anterior cingulate 374
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15 gyrus is presumed to be involved in error detection, especially in a 375
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17 Stroop task,(42) which was used in the attention tests. Lesions in this 376
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19 area can cause inattention to akinetic mutism.(42) 377
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25 This study has several limitations. The major one relates to its retrospective 379
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27 methodology. This limitation is diminished when considering that this large cohort of 380
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29 patients was treated at late chronic stages. The findings presented here are in 381
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31 agreement and reinforce the findings from previous prospective controlled trials in 382
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33 which the neuroplasticity effects of HBOT were demonstrated in chronic stages of 383
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35 different types of brain injuries.(16, 22, 43, 44) Moreover, the correlation between the 384
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37 changes in cognitive function and the metabolic brain imaging gives further strength 385
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39 to the results. 386
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42 Another important limitation relates to the HBOT protocol which was inconsistent 387
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44 across the cohort. Although significant neurotherapeutic effects were seen with 60 388
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46 minutes of 1.5 ATA, the optimal protocol needed to induce maximal neuroplasticity 389
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48 for the specific individual, with minimal side effects has not been investigated. 390
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53 The strengths of the study are worth mentioning. First, objective cognitive 392
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55 assessments using computerized tests were performed on each patient both pre- and 393
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3 post-treatment. Objective measures are significantly superior to PCS questionnaires 394
4 which are inaccurate, variable and contain various confounders rather than reflect the 395
5 true PCS state.(45) Second, most of the patients in the study underwent an objective 396
6 ancillary brain SPECT to confirm PCS diagnosis prior to HBOT. This practice is 397
7 crucial when considering the differential diagnosis following TBI (PTSD, depression, 398
8 etc.). 399

15 Moreover, post-treatment brain SPECTs revealed an anatomical-functional 400
16 correlation in regards to HBOT's effect in brain neuroplasticity. Third, the study 401
17 cohort consisted of a civilian population that does not have any potential secondary 402
18 gain (such as financial compensation) by reporting sick. 403
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26 Previous studies included post-concussion syndrome patients who suffered mild TBI 405
27 injury. Considering its strengths and limitations, the current study implies that the 406
28 cognitive function of patients post TBI, can be improved significantly, irrespectively 407
29 of whether the primary brain injury was classified as mild, moderate or severe. 408

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31 Although long term data is still lacking, considering the high safety profile of the 409
32 treatment, these results are promising and should encourage rehabilitation centers to 410
33 consider HBOT for patients with chronic neurocognitive deficits following TBI. 411

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35 Future studies should monitor these patients in the long term (6 months, 12 months) 412
36 as well as their return to activities of daily living. 413
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40 **Conclusions** 414

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42 HBOT was associated with significant cognitive improvements in patients who suffer 415
43 from chronic neurocognitive deficits due to mild, moderate and severe TBI. 416
44 Improvement in memory correlated with activation of the perirhinal cortex, 417
45 improvement of executive functions correlated with activation of the inferior frontal 418
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3 gyrus, and improvement in attention correlated with activation of the anterior 419
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Table 1: Baseline patient characteristics.

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Number of patients	154 (100%)	69 (44.8%)	24 (15.6%)	61 (39.6%)	
Age (years)	42.7±14.6	48.8±12.0	41.7±12.7	36.2±15.3	P<0.0001
Sex					
Males	90 (58.4%)	31 (44.9%)	13 (54.2%)	46 (75.4%)	P=0.002
Females	64 (41.6%)	38 (55.1%)	11 (45.8%)	15 (24.6%)	
Education (years)	14.8±3.3	14.9±3.6	14.9±3.3	14.6±3.1	P=0.895
Traumatic event					

	Motor Vehicle					
	Accident	116 (75.3%)	56 (81.2%)	17 (70.8%)	43 (70.5%)	P=0.048
	Fall	21 (13.6%)	8 (11.6%)	1 (4.2%)	12 (57.1%)	
	Blow	12 (7.8%)	5 (7.2%)	5 (20.8%)	2 (3.3%)	
	Blast	4 (2.6%)	0	1 (4.2%)	3 (4.9%)	
	Penetrating	1 (0.6%)	0	0	1 (0.6%)	
	Time from trauma (years)	4.6±5.8	4.4±5.9	5.0±5.8	4.6±5.7	P=0.923

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Table 1: Baseline patient characteristics (continued).

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Characteristics	Total	Mild TBI	Moderate TBI	Severe TBI	Significance
Symptoms					
Cognitive	100 (86.2%)	38 (74.5%)	19 (90.5%)	43 (97.7%)	P=0.004
Motor	22 (19.0%)	1 (4.8%)	1 (4.8%)	20 (45.5%)	P<0.0001
Sensory	32 (27.6%)	12 (23.5%)	7 (33.3%)	13 (29.5%)	P=0.653
Dizziness/Vertigo	17 (14.7%)	14 (27.5%)	2 (9.5%)	1 (2.3%)	P=0.002
Tinnitus	30 (25.9%)	26 (51.0%)	2 (9.5%)	2 (4.5%)	P<0.0001
Headaches	20 (17.2%)	12 (23.5%)	3 (14.3%)	5 (11.4%)	P=0.272
HBO sessions	52.0±9.9	49.4±10.1	49.0±10.3	56.1±8.2	P=0.0001

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HBO protocol (ATA)	1.5	106 (69.3%)	46 (67.6%)	18 (75.0%)	42 (68.9%)	P=0.795
	2	47 (30.7%)	22 (32.4%)	6 (25.0%)	19 (31.1%)	
Adverse Events		18 (12.0%)	10 (15.2%)	3 (12.5%)	5 (8.3%)	P=0.499

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Table 2: Cognitive indices pre- and post-HBOT of the entire study cohort

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	Baseline	Post HBOT	Mean Change	P-Value
General	88.3±15.2	92.9±14.2	4.6±8.5	P<0.0001
Memory	81.7±23.2	89.9±21.9	8.1±16.9	P<0.0001
Executive Functions	88.3±16.6	94.2±15.1	5.9±12.0	P<0.0001
Attention	84.3±20.5	91.1±18.4	6.8±16.5	P<0.0001
IPS	87.5±17.0	92.4±15.7	4.9±13.1	P<0.0001

VSP	95.0±18.0	98.5±18.0	3.4±14.6	P=0.005
Motor skills	92.3±17.3	96.2±14.5	3.9±11.7	P<0.0001

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IPS=information processing speed, VSP=visual spatial processing

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Table 3: Large significant increases (>10% change) in cognitive indices proportions across TBI groups.

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	Total	Mild TBI	Moderate TBI	Severe TBI	
General	36 (23.4%)	15 (21.7%)	7(29.2%)	14 (23.0%)	P=0.756
Memory	64 (41.6%)	28 (40.6%)	9 (37.5%)	27 (44.3%)	P=0.830
Executive functions	51 (33.1%)	23 (33.3%)	7 (29.2%)	21 (34.9%)	P=0.897
Attention	62 (40.3%)	27 (39.1%)	8 (33.3%)	27 (44.3%)	P=0.631
Information processing speed	48 (31.2%)	23 (33.3%)	12 (50%)	13 (21.3%)	P=0.032

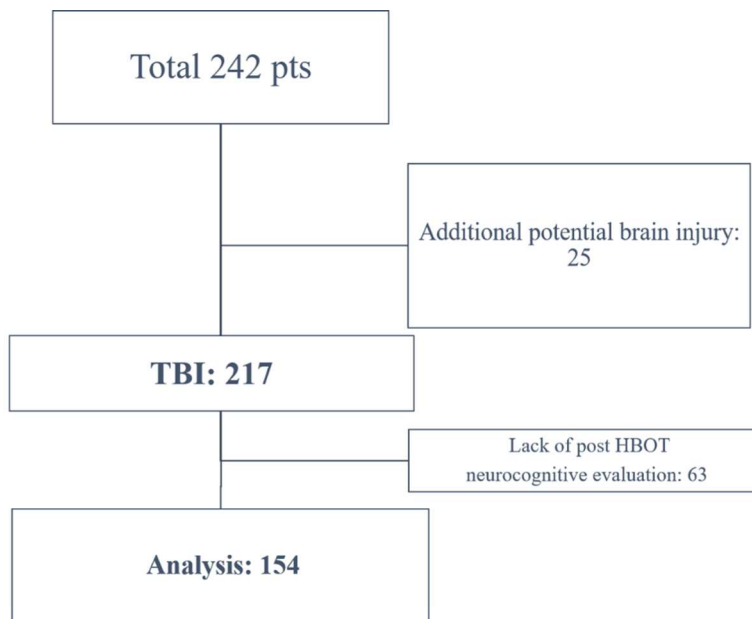
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3	Figures legends	628
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5	Figure-1: Patients flowchart.	629
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7	Figure-2: Imaging findings in the severe TBI group	630
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9	Figure-3: Mean changes of post- compared to pre-HBOT for the entire cohort.	631
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12	After HBOT, all cognitive domains improved significantly, with the most striking	632
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14	changes seen in memory and attention.	633
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17	*p<0.0001, **p=0.005, IPS=information processing speed	634
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20	Figure-4: Mean changes of post- compared to pre-HBOT across the different TBI	635
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22	severities.	636
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25	Both patients who suffered mild and severe TBI groups had improvements in general,	637
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27	memory, attention, information processing speed and motor skills scores, whereas	638
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29	patients who suffered moderate TBI had significant improvement in memory.	639
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32	*p<0.05, IPS =information processing speed	640
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35	Figure-5: The mean relative change in Brodmann areas post HBOT for the entire	641
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37	study cohort.	642
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40	Figure-6: Cognitive functions correlated with Brodmann areas.	643
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44	Each of the TBI groups(mild, moderate and severe) had perfusion/metabolism	644
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46	increase in specific Brodmann areas correlated with improved cognitive function.	645
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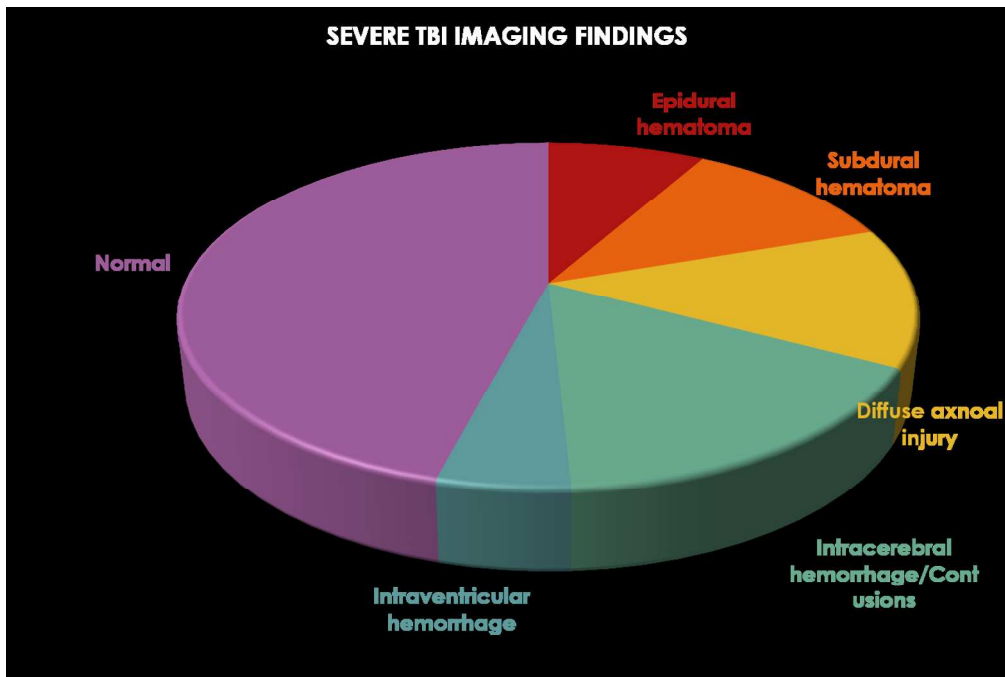


Patients flowchart

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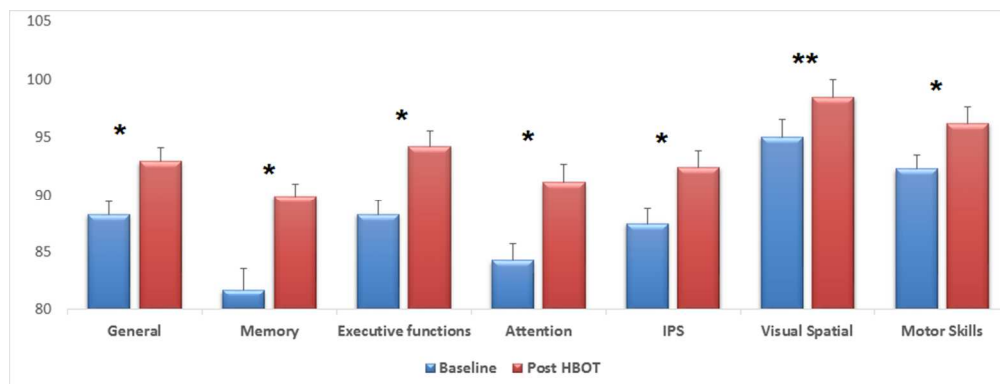
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Imaging findings in the severe TBI subgroup

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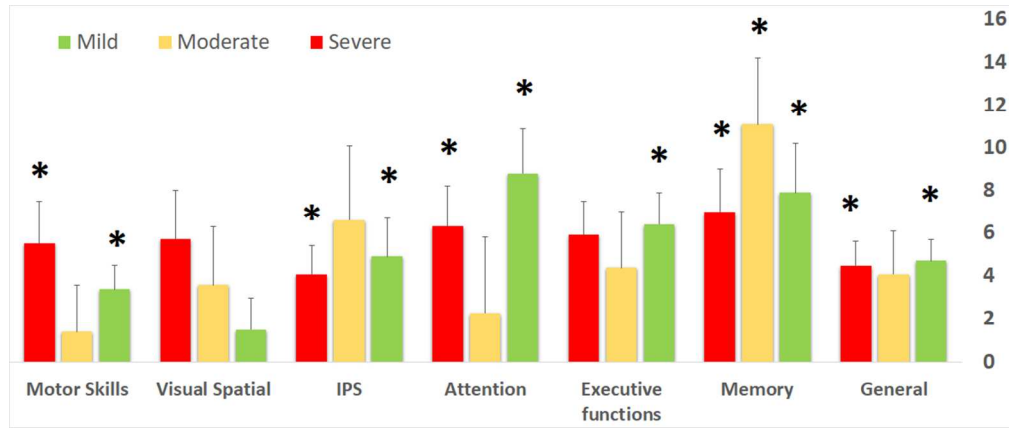
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Mean changes of post- compared to pre-HBOT for the entire cohort. After HBOT, all cognitive domains improved significantly, where the most striking changes were seen in memory and attention.

*p<0.0001, **p=0.005, IPS=information processing speed

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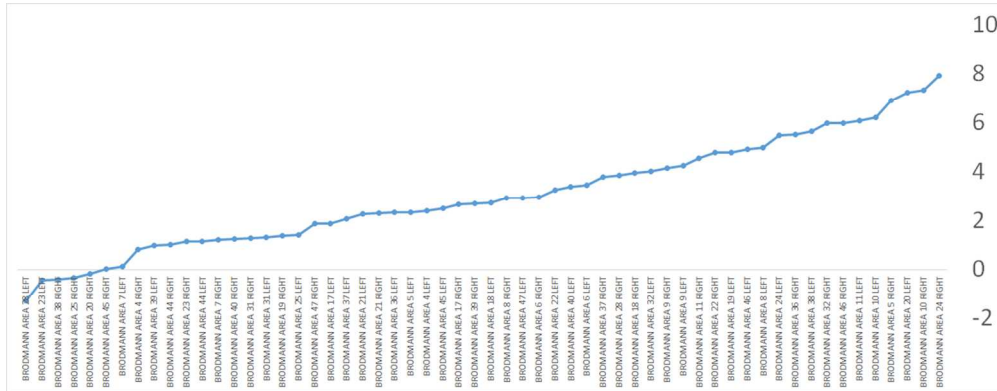
Mean changes of post- compared to pre-HBOT across the different TBI severities.

Both patients who suffered mild and severe TBI groups had improvements in general, memory, attention, information processing speed and motor skills scores, whereas patients who suffered moderate TBI had significant improvement in memory.

* $p < 0.05$, IPS = information processing speed

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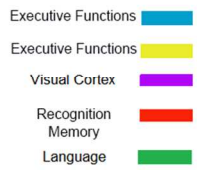
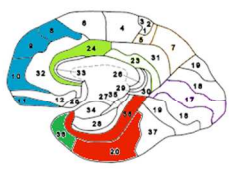
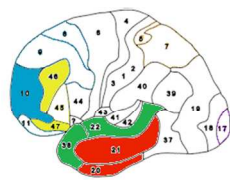
The mean relative change in broadmann areas post HBOT for the entire study cohort

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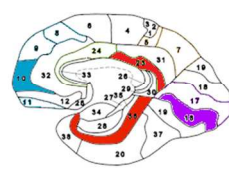
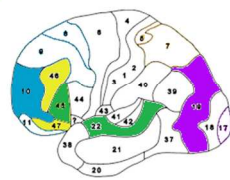
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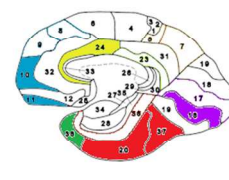
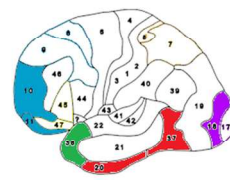
Mild TBI



Moderate TBI



Severe TBI



Cognitive functions correlated with Brodmann areas.
Each of the TBI severities (mild, moderate and severe) had perfusion/metabolism increase in specific Brodmann areas correlated with improved cognitive function

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STROBE (Strengthening The Reporting of OBServational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.