# Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial.

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**SUPPLEMENTARY INFORMATION**

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# 1 Methods

## 1.1 Inclusion criteria

- Age above 18 years
- Reported post-COVID-19 cognitive deterioration that affects the quality of life and has persisted for at least three months after a confirmed infection. Confirmed infection was established by a positive PCR test for COVID-19 along with clinical signs and symptoms of acute infection (at least two of the following: fever, cough, sputum, sore throat, muscle pain, diarrhea, leukopenia (under 500 cells) or low oxygen saturation).
- Subject is willing and able to read, understand and sign an informed consent.

## 1.2 Exclusion criteria

- Inability to attend scheduled clinic visits and/or comply with the study protocol
- History of TBI or any other non-COVID brain pathology
- Active malignancy
- Substance use at baseline
- Severe or unstable physical disorders or major cognitive deficits at baseline
- HBOT for any reason prior to study enrolment
- Chest pathology incompatible with pressure changes (including moderate to severe asthma)
- Ear or sinus pathology incompatible with pressure changes
- An inability to perform an awake brain MRI

### 1.3 The NeuroTrax cognitive battery test

The primary endpoint of the study was a cognitive health assessment as evaluated by the NeuroTrax computerized cognitive testing battery (NeuroTrax Corporation, Bellaire, TX) [1,2]. This assessment comprises of several cognitive tests that evaluate various aspects of brain capabilities including: memory, executive function, attention, information processing speed, and motor skills. In the current study, the cognitive index was based on scores of six cognitive tests:

1. Verbal memory: Ten pairs of words are presented, followed by a recognition test in which the first word of a previously presented pair appears together with a list of four words from which the participant chooses the other member of the pair. There are four immediate repetitions and one delayed repetition after 10 minutes.
2. Non-verbal memory. Eight pictures of simple geometric objects are presented, followed by a recognition test in which four versions of each object are presented, each oriented in a different direction. There are four immediate repetitions and one delayed repetition after 10 minutes.
3. Go–no-go test. In this continuous performance test, a colored square (red, green, white or blue) appears randomly on the center of the screen. The participant is asked to respond quickly, only to red squares, by pressing the mouse button, and not to react to the presentation of any other colored square.
4. Stroop test. Timed test of response inhibition, modified from the Stroop paper-based test. In the first phase, participants choose a colored square matching the color of a general word (for example, the word "Cat" appears in red letters; the participant must choose the red square of two-colored squares in the following screen). In the next phase (termed the choice reaction time test), the task is to choose the colored square matching the name of the color presented in white letter–color. In the final (Stroop interference) phase, participants are asked to choose the colored square that matches the color and not the meaning of a former color-naming word, presented in an incongruent color (for example, the word "RED" appears in green letters, the patient is asked to choose the color green and not red, a task requiring the ability to inhibit an automatic response to the meaning of the word).
5. Staged information processing test. A timed test requiring a reaction based on solving simple arithmetic problems (pressing the right/left mouse button if the answer is higher/lower than 4, respectively), with three levels of information processing load (single-digit, two-digit addition/subtraction and three-digit addition/subtraction problems), each containing three speed levels (3, 2, and 1 second for the presentation of the stimuli).

6. Catch game. A test of motor planning that requires participants to "catch" a falling object on a computer screen by moving a paddle horizontally.

The cognitive domains are combined of several sub-tests, as detailed in the table below. The global score is the mean value of the cognitive domains.

**Cognitive Domains and Sub-Test Measures**

| Domain | Description |
|---|---|
| Memory | Verbal memory: Total accuracy<br>Delayed verbal memory: Accuracy<br>Non-verbal memory: Total accuracy<br>Delayed non-verbal memory: Accuracy |
| Executive function | Go-no-go: Composite score<br>Stroop: Composite score, level 3<br>Catch Game: Total score |
| Attention | Go-no-go: Response time<br>Go-no-go: Response time standard deviation<br>Stroop interference: Response time, level 2<br>Staged information processing speed: Response time, level 1.2<br>Staged information processing speed: Accuracy, level 2.3 |
| Information processing speed | Staged information processing speed: Composite scores, levels 1.1, 1.3, 2.1 and 2.2 |
| Motor skills | Finger tapping: Inter-tap interval<br>Finger tapping: Tap interval standard deviation<br>Catch game: Time to make first move |

The assigned scores are uploaded to the NeuroTrax central server. Outcome parameters are calculated using custom software blind to diagnosis or the testing site. To minimize differences related to age and education, each outcome parameter is normalized and fit to an IQ-like scale (mean=100, STD=15), according to the participants' age and education. We note that the scores are evaluated according to normative data from cognitively healthy individuals, collected in controlled research studies that were conducted at more than 10 clinical sites [2]. Additional information is also available on the NeuroTrax website (http://www.neurotrax.com/).

### 1.4 MRI protocol and analysis

MRI scans were performed on a MAGNETOM VIDA 3T scanner, configured with 64-channel receiver head coils (Siemens Healthcare, Erlangen, Germany). The MRI protocol included T2-weighted, 3D fluid attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI), pre- and post-contrast high-resolution MPRAGE 3D T1-weighted, dynamic susceptibility contrast (DSC), and diffusion tensor imaging (DTI).

#### *MRI scans sequences parameters*

***DSC-MRI:*** Fifty T2*-weighted gradient-echo echo planar imaging (EPI) volumes were acquired, two repetitions before a bolus injection of gadolinium-DTPA (Gd-DTPA, 0.2 ml/kg, administered at 5 ml/sec), 48 repetitions after injection of Gd-DTPA. Sequence parameters: TR: 2,500 ms, TE: 30 ms, flip angle: 30°, voxel size: 1.8 x1.8, Matrix: 128x128, number of slices: 35, and slice thickness = 3 mm.

***DTI:*** Whole brain diffusion weighted images were acquired with the following parameters: Sixty axial slices, slice thickness = 2 mm, voxel size = 2 x 2 mm, TR = 3400 ms, TE = 63 ms, and matrix = 248 x 128 mm, SMS factor = 3. Diffusion gradients were applied along 64 noncollinear directions (b = 1000 s/mm2) and seven volumes without diffusion weighting, including five volumes in read directions and two volumes in phase direction to compensate for EPI distortions.

***MPRAGE*** was acquired in sagittal orientation with 1 mm isotropic resolution. Sequence parameters: TR: 2,000 ms, TE: 1.9 ms, flip angle: 9°, TI: 920 ms, FOV: 256 x 256, and 256 contiguous slices.

#### *DSC-MRI analysis*

Whole-brain quantitative perfusion analysis was performed as described in previous studies [3,4]. MR signal intensity was converted to Gd concentrations, AIF was determined automatically, fitted to the gamma variate function and deconvolved on a voxel-by-voxel basis to calculate the CBF, CBV, and MTT maps according to the following steps:

1. Conversion of signal intensity to concentration of Gd-DTPA with respect to time:

$$C_m(t) = -K * \ln(\frac{S(t)}{S_0})$$

where $C_m(t)$ is the measured concentration of Gd-DTPA with respect to time, K is a proportionality constant that is inversely proportional to the TE and depends on the MR scanner, S(t) is the MRI signal intensity with respect to time, and $S_o$ is the baseline MRI

signal before the presence of Gd-DTPA and after a steady-state magnetization has been achieved [5].

2. Arterial input function (AIF): the AIF was measured automatically, using the following algorithm:
    a. The volume with maximum $C_m(t)$ intensity was identified ($10^{th}$-$13^{th}$ volume). Only voxels with maximum intensity in this volume were identified as AIF candidates.
    b. Only voxels with maximum intensity higher than the $96^{th}$ percentile and lower than the $99.9^{th}$ percentile were included.
    c. Only voxels with a shape of sharp increase and sharp decrease were included.
    d. The AIF voxel candidates were fitted to the gamma variate function using the following equation[5]. Goodness of fit was evaluated and only voxels with $R^2 > 0.96$ were included.

$$AIF_{fit}(t) \; or \; C_{fit}(t) = \; -K(x-\Delta)^{\alpha} * e^{-\frac{x-\Delta}{B}} * F_{step}(x-\Delta)$$

    e. The final AIF was an average of the $C_m(t)$ signal in the voxels passing the above criteria.
    f. Normalization of AIF: To allow a uniform time of injection in all subjects and DSC scans, the $C_m(t)$ was shifted in case of early/late injection to allow a uniform AIF peak at the $10^{th}$ volume.
3. Gamma fitting of AIF and Cm: The AIF and $C_m(t)$ were fitted to the gamma variate function using the gamma fit equation (see above) [5], where $AIF_{fit}(t)$ and $C_{fit}(t)$ are the fitted AIF(t) and $C_m(t)$ curves, respectively, K is a constant, x is the image number, $\Delta$ is the delay between image 0 and the arrival of the bolus (a

positive number), a and B are gamma variate parameters, and $F_{step}$ is a step function defined by:

$$F_{step} = \begin{cases} 1 \ for \ (x - \Delta) \geq 0 \\ 0 \ for \ (x - \Delta) < 0 \end{cases}$$

4. SVD deconvolution: The fitted AIF was used to calculate C(t) (the tissue response to an instantaneous arterial bolus) using SVD deconvolutionas[6]. In short, the values for the AIF and $C_m(t)$ curves can be written in vector notation as C = AIF−1 • Cm, where C represents the matrix of the deconvolved C(t) curve. This equation can be solved using the SVD technique, whereby the matrix AIF is decomposed into three matrices AIF = U • W • VT. The inverse of AIF can be calculated as $AIF^{-1}$ = V • [diag(1/wj)] • UT, where [diag(1/wj)] represents the reciprocals of the diagonal elements of W. When calculating $AIF^{-1}$, problems arise when W contains singular values (i.e., wj = 0 or is close to 0) and will cause the curve C(t) to oscillate. Therefore, we used a cutoff threshold of 10% [7].

5. Calculation of CBV was performed based on the fitted $C_m(t)$ and AIF:

$$CBV = \frac{k}{\rho} * \frac{\int C_m(t)\, dt}{\int AIF(t)\, dt}$$

where κ = (1 − HCTLV)/(1 − HCTSV) corrects for the fact that the hematocrit in large vessels (HCTLV was set to 0.45) is larger than the hematocrit of small vessels (HCTSV was set to 0.25) and ρ is the density of brain tissue (1.04 g/ml) [5].

6. Calculation of CBF was performed using the following equation:

$$\frac{CBV}{CBF} = \frac{\int C(t)\, dt}{C_{max}}$$

where C(t) is the concentration of Gd-DTPA in a tissue region and $C_{max}$ is the maximum of this curve [5].

7. MTT was calculated as:

$$MTT = \frac{CBV}{CBF}$$

8. Normalization of the CBF: Since the amount of injection was not uniform between scans, the CBF was normalized using a factor of 1.6 divided by the AIF peak value.

Perfusion maps were performed using an in-house software written in Matlab R2021b (Mathworks, Natick, MA).

### 1.5 References


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# 2 Supplementary Tables

**Table 1: Baseline symptoms***

| Symptom | HBOT | Control | P-value |
|---|---|---|---|
| N | 37 | 36 | |
| Fatigue | 26 (70.3) | 30 (83.3) | 0.269 |
| Concentrating | 28 (75.7) | 25 (69.4) | 0.607 |
| Sleep | 27 (73.0) | 24 (66.7) | 0.616 |
| Forgetfulness | 24 (64.9) | 26 (72.2) | 0.616 |
| Finding words | 19 (51.4) | 23 (63.9) | 0.346 |
| Quality of sleep | 27 (73.0) | 28 (77.8) | 0.787 |
| Muscle aches | 20 (54.1) | 21 (58.3) | 0.815 |
| Joint aches | 15 (40.5) | 19 (52.8) | 0.352 |
| Anxiety | 7 (18.9) | 10 (27.8) | 0.417 |
| Sadness | 6 (16.2) | 12 (33.3) | 0.109 |
| Swallowing | 3 (8.1) | 3 (8.3) | 1.000 |
| Taste | 9 (24.3) | 6 (16.7) | 0.564 |
| Smell | 9 (24.3) | 8 (22.2) | 1.000 |
| Loss of appetite | 7 (18.9) | 3 (8.3) | 0.308 |
| Everyday activities | 13 (35.1) | 14 (38.9) | 0.811 |
| Strained activities | 22 (59.5) | 26 (72.2) | 0.326 |
| Confusion | 11 (29.7) | 10 (27.8) | 1.000 |

* Self-reported

**Table 2: Covid-19 infection symptoms**

| Symptom | HBOT | Control | P-value |
|---|---|---|---|
| N | 37 | 36 | |
| Abdominal pain | 1 (2.7) | 0 (0.0) | 1.000 |
| Chills | 1 (2.7) | 0 (0.0) | 1.000 |
| Dry cough | 10 (27.0) | 16 (44.4) | 0.147 |
| Diarrhea | 8 (21.6) | 3 (8.3) | 0.190 |
| Dyspnea | 10 (27.0) | 12 (33.3) | 0.616 |
| Fever ≥ 38˚c | 22 (59.5) | 24 (66.7) | 0.630 |
| Headache | 12 (32.4) | 11 (30.6) | 1.000 |
| Joint ache | 1 (2.7) | 0 (0.0) | 1.000 |
| Problem in taste sensation | 16 (43.2) | 7 (19.4) | 0.043 |
| Problem in smell sensation | 12 (32.4) | 5 (13.9) | 0.096 |
| Low saturation | 4 (10.8) | 7 (19.4) | 0.345 |
| Muscle aches | 23 (62.2) | 21 (58.3) | 0.813 |
| Myalgia | 1 (2.7) | 1 (2.8) | 1.000 |
| Sore throat | 4 (10.8) | 5 (13.9) | 0.736 |
| Sputum | 0 (0.0) | 2 (5.6) | 0.240 |
| Fatigue | 4 (10.8) | 3 (8.3) | 1.000 |

**Table 3: Neurocognitive performance changes ANOVA (group x time)**

| | **Main effect of group** | | **Main effect of time** | | **Interaction effect** | |
|---|---|---|---|---|---|---|
| | F | P-value | F | P-value | F | P-value |
| Score | 0.33 | 0.566 | 26.88 | 0.000 | 4.47 | 0.038 |
| Memory | 0.07 | 0.793 | 43.79 | 0.000 | 0.23 | 0.636 |
| Executive function | 1.82 | 0.182 | 10.85 | 0.002 | 4.16 | 0.045 |
| Attention | 0.00 | 0.978 | 3.12 | 0.082 | 3.91 | 0.052 |
| Information processing speed | 0.47 | 0.495 | 16.52 | 0.000 | 1.67 | 0.200 |
| Motor skills | 0.22 | 0.637 | 2.23 | 0.140 | 2.08 | 0.154 |

**Table 4: Questionnaire scores analysis - ANOVA (group x time)**

| | Main effect of group | | Main effect of time | | Interaction effect | |
|---|---|---|---|---|---|---|
| | **F** | **P-value** | **F** | **P-value** | **F** | **P-value** |
| **SF-36** | | | | | | |
| Physical functioning | 1.422 | 0.237 | 5.482 | 0.022 | 1.322 | 0.254 |
| Physical limitations | 0.001 | 0.970 | 17.754 | 0.000 | 5.430 | 0.023 |
| Emotional limitations | 0.570 | 0.453 | 18.927 | 0.000 | 0.846 | 0.361 |
| Energy | 1.707 | 0.196 | 19.378 | 0.000 | 4.976 | 0.029 |
| Emotional wellbeing | 0.760 | 0.386 | 12.819 | 0.001 | 3.841 | 0.054 |
| Social function | 0.047 | 0.830 | 25.863 | 0.000 | 2.795 | 0.099 |
| Pain domain | 0.074 | 0.787 | 25.913 | 0.000 | 1.179 | 0.281 |
| General health domain | 5.241 | 0.025 | 7.472 | 0.008 | 2.088 | 0.153 |
| **PSQI** | | | | | | |
| Global | 0.190 | 0.664 | 23.453 | 0.000 | 4.302 | 0.042 |
| Sleep quality | 0.625 | 0.432 | 19.472 | 0.000 | 1.753 | 0.190 |
| Sleep latency | 0.462 | 0.499 | 25.595 | 0.000 | 1.730 | 0.193 |
| Sleep duration | 0.006 | 0.939 | 0.282 | 0.597 | 2.364 | 0.129 |
| Sleep efficiency | 0.021 | 0.884 | 3.767 | 0.056 | 0.041 | 0.840 |
| Sleep disturbances | 0.038 | 0.845 | 12.138 | 0.001 | 3.940 | 0.051 |
| Sleep medication | 0.019 | 0.892 | 1.737 | 0.192 | 1.150 | 0.287 |
| Daytime dysfunction | 0.232 | 0.631 | 13.821 | 0.000 | 0.891 | 0.348 |
| **BSI-18** | | | | | | |
| Total | 0.056 | 0.813 | 16.799 | 0.000 | 7.372 | 0.008 |
| Somatization | 0.037 | 0.849 | 12.457 | 0.001 | 6.312 | 0.014 |
| Depression | 0.029 | 0.866 | 11.792 | 0.001 | 4.395 | 0.040 |
| Anxiety | 0.065 | 0.800 | 7.036 | 0.010 | 3.169 | 0.079 |
| **BPI** | | | | | | |
| Pain severity score | 0.117 | 0.734 | 0.465 | 0.498 | 0.011 | 0.917 |
| Pain interference score | 0.021 | 0.884 | 13.103 | 0.001 | 11.204 | 0.001 |

**Table 5: Brain regions with significant perfusion (CBF) increases in gray matter**

| | | MNI Coordinates | | | | | |
|---|---|---|---|---|---|---|---|
| **Anatomical location** | **BA** | **X** | **Y** | **Z** | **t-value** | **Cluster size** | **P value** |
| Supramarginal Gyrus R (Parietal) | 40 | 61 | -36 | 47 | 4.47 | 306 | 0.000008* |
| Superior Parietal Lobule R (Parietal) | 7 | 42 | -62 | 52 | 4.46 | 138 | 0.000008* |
| Parahippocampal Gyrus L | | -24 | -14 | -9 | 4.29 | 396 | 0.000009* |
| Insula R | 13 | 42 | 17 | 0 | 4.22 | 247 | 0.000012* |
| Supplementary Motor Area L (Frontal) | 6 | -6 | 20 | 66 | 4.21 | 197 | 0.000013* |
| Supramarginal Gyrus L (Parietal) | 40 | -46 | -53 | 54 | 4.33 | 193 | 0.000015* |
| Supramarginal Gyrus L (Parietal) | 40 | -63 | -22 | 27 | 4.32 | 177 | 0.000015* |
| Anterior Cingulate Gyrus\ Medial Superior Frontal Gyrus L | 10/32 | -4 | 50 | 9 | 4.32 | 188 | 0.000026* |
| Anterior Cingulate Gyrus\ Dorsal Prefrontal R | 32 \9 | 4 | 35 | 24 | 3.96 | 413 | 0.000037 |
| Putamen R | | 29 | -6 | -3 | 3.95 | 229 | 0.000039 |
| Frontal Operculum \ Insula R | 13 | 35 | -24 | 21 | 3.93 | 287 | 0.000042 |
| Inferior Frontal Gyrus \ Lateral orbitofrontal Cortex L | 47 | -40 | 31 | -13 | 3.92 | 89 | 0.000044 |
| Temporal pole \ Middle Temporal Gyrus L | 38 | -38 | 11 | 37 | 3.86 | 219 | 0.000056 |
| Postcentral Gyrus L (Parietal) | 3 | -46 | -17 | 40 | 3.76 | 162 | 0.000086 |
| Superior Temporal Gyrus L | 42 | -62 | -29 | 6 | 3.73 | 81 | 0.000097 |
| Hippocampus L | | -17 | -8 | -11 | 3.75 | 52 | 0.000130 |
| Insula L | 13 | -44 | 6 | 6 | 3.73 | 53 | 0.000137 |
| Fusiform Gyrus R | 37 | -62 | -52 | 2 | 3.72 | 73 | 0.000143 |
| Anterior Insula L | 13 | -40 | 16 | -8 | 3.7 | 157 | 0.000153 |
| Inferior Frontal Gyrus \ Posterior Orbitofrontal Cortex R | 47 | 26 | 26 | -20 | 3.63 | 68 | 0.000197 |
| Putamen L | | -20 | 4 | -6 | 3.62 | 69 | 0.000207 |
| Inferior Frontal Gyrus L | 45 | -44 | 18 | 3 | 3.58 | 57 | 0.000239 |

The table reports each brain region which was found significant in a time-by-group repeated measures ANOVA comparing the two groups. The results are shown in specific Montreal Neurological Institute (MNI) coordinates; X, sagittal, Y, coronal, Z, axial, refers to Montreal Neurological Institute. BA, Brodmann area. *significant after correction to multiple comparisons, $p<0.05$; All coordinates emerged at a threshold of $P < 0.0005$, uncorrected. R, right; L, left; CBF, cerebral blood flow.

**Table 6: Brain regions with significant DTI-MD increases in gray-matter**

| | | MNI Coordinates | | | | | |
|---|---|---|---|---|---|---|---|
| **Anatomical location** | **BA** | **X** | **Y** | **Z** | **t-value** | **Cluster size** | **P value** |
| Frontal Precentral Gyrus L | 6 | -33 | -8 | 62 | 4.58 | 454 | 0.000005* |
| Middle Frontal Gyrus R | 10 | 38 | 50 | 28 | 4.35 | 233 | 0.000013* |
| Middle Frontal Gyrus R | 8 | 38 | 16 | 57 | 3.99 | 325 | 0.000052* |
| Superior Frontal Gyrus L | 10 | -12 | 65 | 3 | 3.94 | 119 | 0.000064 |
| Superior Frontal Gyrus L | 6 | -16 | 2 | 72 | 3.9 | 366 | 0.000075 |
| Medial Superior Frontal Gyrus R | 8 | 7 | 32 | 48 | 3.61 | 282 | 0.000215 |
| Inferior Parietal Lobule L | 40 | 51 | -40 | 57 | 3.47 | 33 | 0.000350 |
| Middle Frontal Gyrus \Middle Orbital Gyrus L | 10 | 9 | 65 | -1 | 3.34 | 76 | 0.000536 |
| Post Central Gyrus R (S1) | 1 | 67 | -11 | 14 | 3.19 | 26 | 0.000863 |

The table reports each brain region which was found significant in a time-by-group repeated measures ANOVA comparing the two groups. The results are shown in specific Montreal Neurological Institute (MNI) coordinates; X, sagittal, Y, coronal, Z, axial, refers to Montreal Neurological Institute. BA, Brodmann area. *significant after correction to multiple comparisons, $p<0.05$; All coordinates emerged at a threshold of $P < 0.002$, uncorrected. R, right; L, left; MD, mean diffusivity

**Table 7: Brain regions with significant DTI-FA increases in white-matter**

| | MNI Coordinates | | | | | |
|---|---|---|---|---|---|---|
| **Anatomical location** | **X** | **Y** | **Z** | **t-value** | **Cluster size** | **P value** |
| Superior Corona Radiata R (Frontal) | 20 | -8 | 51 | 4.34 | 602* | 0.00006* |
| Superior Corona Radiata L (Frontal) | -26 | -16 | 51 | 3.96 | 345* | 0.00006* |
| Superior Longitudinal Fasciculus L (Parietal) | -29 | -53 | 35 | 3.83 | 74 | 0.00010 |
| U fibers to SMA\ WM Superior Corona Radiata L (Frontal) | -16 | 1 | 54 | 3.78 | 233 | 0.00014 |
| Pontine Crossing Tract- BS R | 6 | -28 | -37 | 3.73 | 173 | 0.00014 |
| Cingulum R | 19 | 5 | 48 | 3.51 | 79 | 0.00030 |
| Sagittal Stratum L (Temporal) | -44 | -25 | 3 | 3.43 | 110 | 0.00039 |
| External Capsule L (near Insula L) | -32 | -17 | 6 | 3.29 | 36 | 0.00070 |
| External Capsule R (near Putamen R) | 34 | -13 | 2 | 3.2 | 74 | 0.00070 |
| Superior Corona Radiata R (Frontal) | -21 | -12 | 23 | 3.26 | 187 | 0.00075 |
| External Capsule R (near Insula R) | 35 | 12 | -6 | 3.24 | 81 | 0.00075 |

The table reports each brain region which was found significant in a time-by-group repeated measures ANOVA comparing the two groups. The results are shown in specific Montreal Neurological Institute (MNI) coordinates; X, sagittal, Y, coronal, Z, axial, refers to Montreal Neurological Institute. BA, Brodmann area. *significant after correction to multiple comparisons, $p<0.05$; All coordinates emerged at a threshold of $P < 0.002$, uncorrected. R, right; L, left; FA, fractional anisotropy

**Table 8: Smell and taste changes**

| | HBOT | | | | | Control | | | | | ANOVA (group-by-time) Interaction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Pre** | **Post** | **Change** | **Two months P-value** | **N** | **Pre** | **Post** | **Change** | **Two months P-value** | **P-value Baseline** | **Net effect size*** | **F** | **P-value** |
| Smell | | | | | | | | | | | | | | |
| All | 37 | 9.1±1.9 | 10.1±2.1 | 0.9±2.0 | 0.006 | 36 | 9.3±2.3 | 9.6±2.2 | 0.4±1.6 | 0.156 | 0.780 | 0.311 | 1.76 | 0.189 |
| Abnormal at baseline | 27 | 8.3±1.6 | 9.6±2.2 | 1.3±2.2 | 0.005 | 25 | 8.3±2.2 | 9.2±2.4 | 0.9±1.7 | 0.0143 | 0.9653 | 0.215 | 0.597 | 0.443 |
| Taste | | | | | | | | | | | | | | |
| All | 37 | 8.3±3.2 | 9.1±2.9 | 0.8±2.4 | 0.068 | 36 | 9.2±2.5 | 9.0±2.5 | -0.2±2.3 | 0.6679 | 0.212 | 0.388 | 2.749 | 0.102 |
| Sweet | 37 | 2.0±1.0 | 2.7±1.3 | 0.7±1.2 | 0.001 | 37 | 2.2±1.0 | 2.6±1.1 | 0.4±1.0 | 0.0199 | 0.346 | 0.259 | 1.226 | 0.272 |
| Sour | 37 | 1.9±0.7 | 2.0±0.8 | 0.1±1.0 | 0.737 | 37 | 2.1±0.7 | 1.8±0.8 | -0.3±1.1 | 0.1426 | 0.429 | 0.318 | 1.850 | 0.178 |
| Salty | 37 | 2.0±1.1 | 1.8±0.9 | -0.1±1.3 | 0.523 | 37 | 2.1±1.1 | 1.8±1.1 | -0.3±1.2 | 0.177 | 0.611 | 0.115 | 0.241 | 0.625 |
| Bitter | 37 | 2.4±1.4 | 2.5±1.3 | 0.1±1.0 | 0.431 | 37 | 2.8±1.1 | 2.8±1.2 | -0.0±1.3 | 0.8968 | 0.216 | 0.141 | 0.361 | 0.550 |
| Abnormal at baseline | | | | | | | | | | | | | | |
| Total | 18 | 5.6±2.2 | 7.6±2.9 | 2.0±2.4 | 0.003 | 12 | 6.3±1.5 | 6.8±1.8 | 0.4±2.7 | 0.6007 | 0.347 | 0.626 | 2.825 | 0.104 |
| Sweet | 18 | 1.3±0.7 | 2.2±1.4 | 0.9±1.2 | 0.007 | 12 | 1.4±0.6 | 2.3±1.1 | 0.8±1.2 | 0.0341 | 0.744 | 0.046 | 0.015 | 0.903 |
| Sour | 18 | 1.6±0.7 | 1.8±0.8 | 0.2±1.1 | 0.528 | 12 | 1.8±0.7 | 1.4±0.9 | -0.4±1.4 | 0.3177 | 0.405 | 0.480 | 1.656 | 0.209 |
| Salty | 18 | 1.3±0.7 | 1.6±1.0 | 0.3±1.2 | 0.350 | 12 | 1.3±0.9 | 1.3±0.9 | 0.0±1.0 | 1.0000 | 0.930 | 0.240 | 0.414 | 0.525 |
| Bitter | 18 | 1.4±1.1 | 2.1±1.4 | 0.7±1.0 | 0.014 | 12 | 1.8±0.9 | 1.8±1.1 | 0.0±1.1 | 1.0000 | 0.274 | 0.624 | 2.800 | 0.105 |

Data are presented as mean ± SD; Bold, significant after Bonferroni correction; * Cohen's d net effect size

**Table 9: Spirometry test changes**

| | HBOT | | | | Control | | | | ANOVA (group-by-time) Interaction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Two months P-value** | **Change** | **Pre** | **Post** | **Two months P-value** | **Change** | **P-value Baseline** | **Net effect size*** | **F** | **P-value** |
| N | | 37 | | | | 36 | | | | | | |
| IC | 3.0±1.0 | 3.2±1.1 | 0.0788 | 0.2±0.6 | 2.9±0.8 | 3.2±0.7 | 0.1150 | 0.2±0.9 | 0.857 | -0.074 | 0.094 | 0.760 |
| %pred | 107.4±21.3 | 114.1±23.0 | 0.1257 | 5.1±18.9 | 113.1±33.7 | 121.8±23.3 | 0.1450 | 8.7±34.9 | 0.408 | -0.127 | 0.28 | 0.598 |
| VC | 3.6±1.1 | 3.7±1.1 | 0.1225 | 0.1±0.2 | 3.5±0.7 | 3.6±0.7 | 0.0225 | 0.1±0.3 | 0.586 | -0.159 | 0.444 | 0.508 |
| %pred | 86.6±13.7 | 88.0±12.6 | 0.1258 | 1.4±5.3 | 88.5±13.1 | 91.0±12.4 | 0.0284 | 2.6±6.7 | 0.576 | -0.183 | 0.586 | 0.447 |
| IRV | 2.0±1.0 | 2.3±0.9 | 0.1002 | 0.2±0.7 | 2.1±0.8 | 2.3±0.7 | 0.1972 | 0.2±0.9 | 0.585 | -0.008 | 0.001 | 0.972 |
| VT | 1.0±0.6 | 1.0±0.6 | 0.7592 | -0.0±0.6 | 0.8±0.4 | 0.8±0.5 | 0.7385 | 0.0±0.5 | 0.159 | -0.110 | 0.208 | 0.650 |
| FVC | 3.5±1.1 | 3.6±1.0 | 0.5803 | 0.0±0.3 | 3.5±0.7 | 3.5±0.7 | 0.1923 | 0.0±0.2 | 0.701 | -0.103 | 0.187 | 0.667 |
| %pred | 85.7±14.3 | 86.6±13.0 | 0.4272 | 0.8±6.1 | 88.6±12.3 | 90.0±13.0 | 0.1238 | 1.4±5.5 | 0.380 | -0.106 | 0.2 | 0.656 |
| FEV1 | 2.8±0.9 | 2.8±0.9 | 0.9657 | -0.0±0.2 | 2.9±0.6 | 2.9±0.6 | 0.3062 | 0.0±0.2 | 0.802 | -0.181 | 0.573 | 0.452 |
| %pred | 85.2±14.8 | 85.5±14.2 | 0.7763 | 0.3±6.5 | 91.9±13.5 | 93.3±13.8 | 0.1547 | 1.4±5.8 | 0.055 | -0.181 | 0.573 | 0.452 |
| FEV1/FVC | 79.8±6.5 | 79.2±6.5 | 0.313 | -0.6±3.5 | 83.1±5.3 | 82.6±5.0 | 0.6625 | -0.3±4.0 | 0.025 | -0.081 | 0.115 | 0.736 |
| %pred | 99.3±7.7 | 98.5±7.4 | 0.2858 | -0.8±4.4 | 103.3±6.7 | 102.6±6.1 | 0.6946 | -0.3±5.1 | 0.025 | -0.096 | 0.162 | 0.689 |
| PEF | 6.8±2.2 | 6.9±2.1 | 0.5362 | 0.1±1.0 | 6.6±1.9 | 7.0±1.9 | 0.0433 | 0.4±1.3 | 0.641 | -0.287 | 1.466 | 0.230 |
| fef25-75 | 2.8±1.2 | 2.8±1.1 | 0.6918 | -0.0±0.4 | 3.3±1.0 | 3.2±1.0 | 0.6588 | -0.0±0.5 | 0.091 | 0.025 | 0.011 | 0.917 |
| %pred | 88.1±25.6 | 88.2±26.8 | 0.952 | 0.1±13.9 | 107.0±27.6 | 107.3±30.6 | 0.9105 | 0.3±16.2 | 0.004 | -0.011 | 0.0020 | 0.964 |
| fev1/vcmax | 77.8±6.3 | 76.9±7.9 | 0.331 | -0.9±5.7 | 81.5±6.0 | 79.1±8.7 | 0.1723 | -2.1±8.9 | 0.016 | 0.155 | 0.422 | 0.518 |
| %pred | 96.8±7.3 | 95.6±9.3 | 0.3201 | -1.2±7.2 | 101.2±7.1 | 99.8±6.2 | 0.3224 | -1.0±5.9 | 0.014 | -0.035 | 0.021 | 0.885 |

Data are presented as mean ± SD; Bold, significant after Bonferroni correction; * Cohen's d net effect size

**Table 10: Chemistry blood tests**

| | HBOT | | | | Control | | | | ANOVA (group-by-time) Interaction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Pre** | **Post** | **Two months P-value** | **Change** | **Pre** | **Post** | **Two months P-value** | **Change** | **P-value Baseline** | **Net effect size*** | **F** | **P-value** |
| URAC-B | 4.9±1.4 | 5.0±1.3 | 0.376 | 0.1±0.8 | 4.8±1.4 | 4.9±1.5 | 0.237 | 0.1±0.6 | 0.843 | -0.011 | 0.002 | 0.964 |
| OSMOLcal | 289.4±3.6 | 288.5±5.0 | 0.404 | -0.8±5.8 | 288.1±5.2 | 289.3±3.8 | 0.212 | 1.3±5.7 | 0.229 | -0.369 | 2.243 | 0.139 |
| Globulin-B | 25.8±3.6 | 25.8±3.9 | 1.000 | 0.0±2.7 | 26.5±3.0 | 27.2±4.1 | 0.125 | 0.8±2.8 | 0.430 | -0.279 | 1.266 | 0.265 |
| ALB-B | 45.6±2.6 | 45.7±3.0 | 0.942 | 0.0±2.4 | 44.8±2.9 | 44.8±2.5 | 1.000 | 0.0±2.9 | 0.266 | 0.012 | 0.002 | 0.962 |
| BILT-B | 0.5±0.2 | 0.5±0.3 | 0.780 | 0.0±0.2 | 0.5±0.4 | 0.5±0.4 | 0.828 | 0.0±0.2 | 0.571 | 0.006 | 0.001 | 0.982 |
| Ca-B | 9.4±0.4 | 9.4±0.4 | 0.702 | 0.0±0.4 | 9.4±0.4 | 9.4±0.4 | 0.704 | 0.0±0.4 | 0.800 | -0.006 | 0.001 | 0.981 |
| CR-B | 0.8±0.1 | 0.8±0.2 | 0.119 | 0.0±0.1 | 0.8±0.2 | 0.8±0.2 | 0.526 | 0.0±0.1 | 0.938 | 0.152 | 0.381 | 0.539 |
| GLU-B | 93.2±9.4 | 95.4±13.3 | 0.303 | 1.8±10.2 | 89.9±9.2 | 89.7±10.3 | 0.899 | -0.2±9.5 | 0.155 | 0.210 | 0.726 | 0.397 |
| LDH-B | 348.8±55.2 | 361.7±66.9 | 0.069 | 14.1±42.2 | 320.4±59.8 | 329.5±48.6 | 0.213 | 9.1±41.1 | 0.051 | 0.119 | 0.232 | 0.632 |
| ALP-B | 74.1±23.4 | 76.4±25.1 | 0.256 | 2.3±11.2 | 67.1±21.4 | 67.6±23.5 | 0.758 | 0.5±9.5 | 0.214 | 0.170 | 0.473 | 0.494 |
| K-B | 4.3±0.3 | 4.3±0.3 | 0.326 | -0.1±0.3 | 4.3±0.3 | 4.3±0.4 | 0.597 | -0.0±0.3 | 0.805 | -0.111 | 0.206 | 0.652 |
| PROT-T-B | 71.3±3.4 | 71.3±4.5 | 0.956 | 0.0±3.2 | 71.2±4.1 | 71.9±5.0 | 0.372 | 0.7±4.4 | 0.906 | -0.174 | 0.486 | 0.488 |
| Na-B | 139.7±1.7 | 139.2±2.2 | 0.323 | -0.5±2.6 | 139.2±2.1 | 139.7±1.8 | 0.265 | 0.5±2.8 | 0.277 | -0.373 | 2.294 | 0.135 |
| AST-B | 22.3±11.2 | 22.6±9.7 | 0.871 | -0.3±10.8 | 17.6±4.3 | 19.1±8.4 | 0.212 | 1.4±6.4 | 0.030 | -0.195 | 0.628 | 0.431 |
| ALT-B | 27.3±27.5 | 27.2±24.5 | 0.843 | -0.8±23.1 | 17.0±7.4 | 19.3±14.5 | 0.199 | 2.4±10.4 | 0.044 | -0.177 | 0.518 | 0.474 |
| UREA-B | 28.8±6.0 | 29.1±6.8 | 0.621 | 0.5±5.4 | 28.7±8.6 | 29.9±6.8 | 0.338 | 1.2±7.1 | 0.936 | -0.115 | 0.216 | 0.643 |
| CRP-B | 3.4±4.1 | 4.5±6.0 | 0.012 | 1.1±2.4 | 2.5±3.5 | 2.9±3.6 | 0.352 | 0.4±2.3 | 0.376 | 0.298 | 1.467 | 0.23 |
| Ferritin | 154.0±101.1 | 140.8±90.3 | 0.345 | -7.6±44.8 | 113.4±167.5 | 104.8±163.8 | 0.433 | -8.6±58.4 | 0.254 | 0.020 | 0.006 | 0.938 |
| URAC-B | 4.9±1.4 | 5.0±1.3 | 0.376 | 0.1±0.8 | 4.8±1.4 | 4.9±1.5 | 0.237 | 0.1±0.6 | 0.843 | -0.011 | 0.002 | 0.964 |

Data are presented as mean ± SD; Bold, significant after Bonferroni correction; * Cohen's d net effect size

**Table 11: Adverse events during treatment period**

| AE | HBOT | Control |
|---|---|---|
| Barotrauma | 4 | 3 |
| Ear pain without barotrauma | 1 | 0 |
| Palpitation | 3 | 1 |
| Allergic rash | 0 | 1 |
| Headache | 1 | 0 |
| Emergency referral secondary to chest pain / epigastric pain | 1 | 2 |
| Fever | 1 | 1 |
| Urinary tract infection | 0 | 2 |
| Hospitalization due to herpes zoster infection | 1 | 0 |
| Cellulitis requiring antibiotic treatment | 0 | 1 |
| Pre-syncope | 0 | 1 |
| Hypertension | 1 | 0 |
| Pregnancy | 0 | 1 |
| Emotional distress with psychological intervention | 0 | 1 |
| **Total*** | **13** | **14** |

* P-value = 0.739

# 3 Supplementary Figures

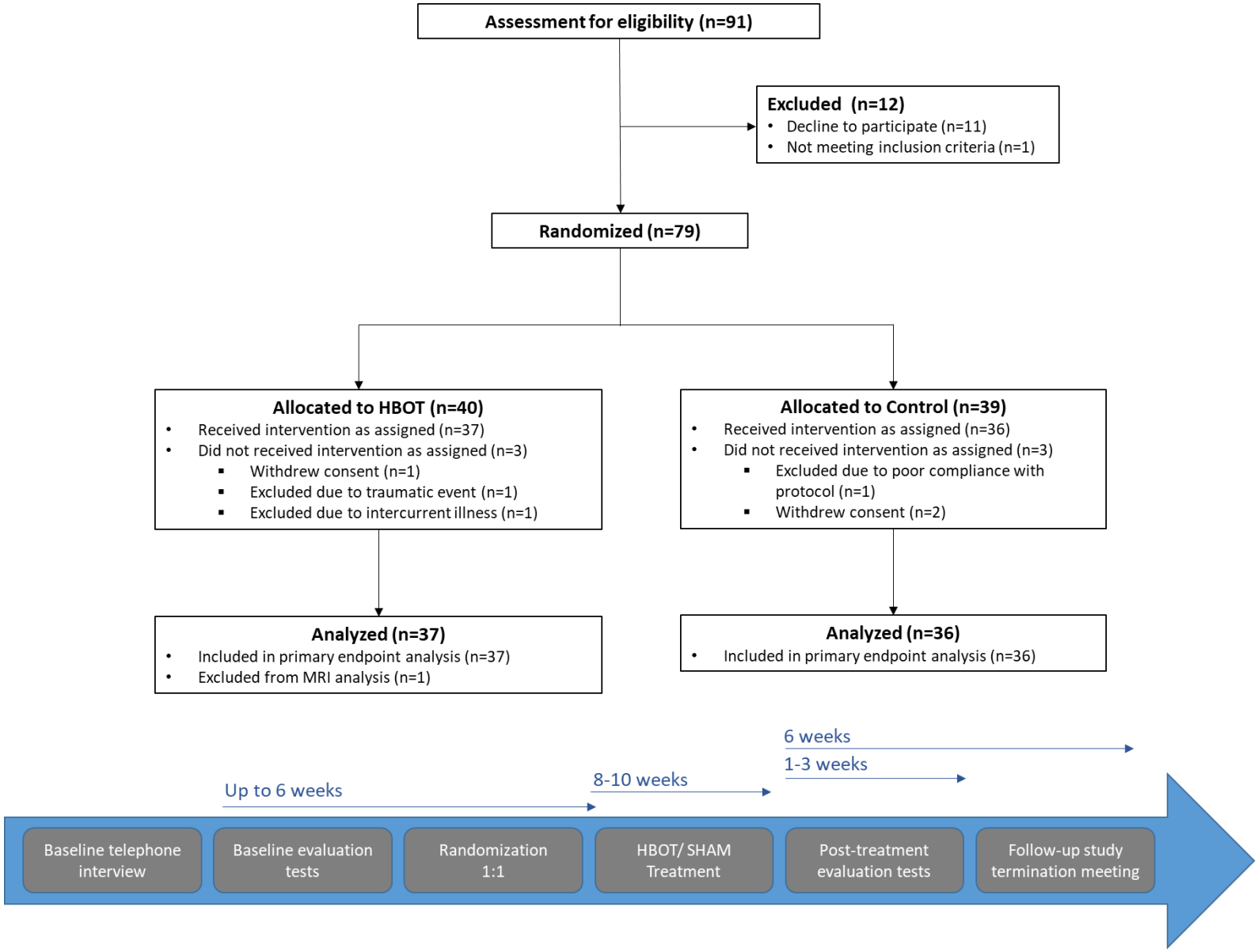


**Figure 1. Study flowchart and timeline**

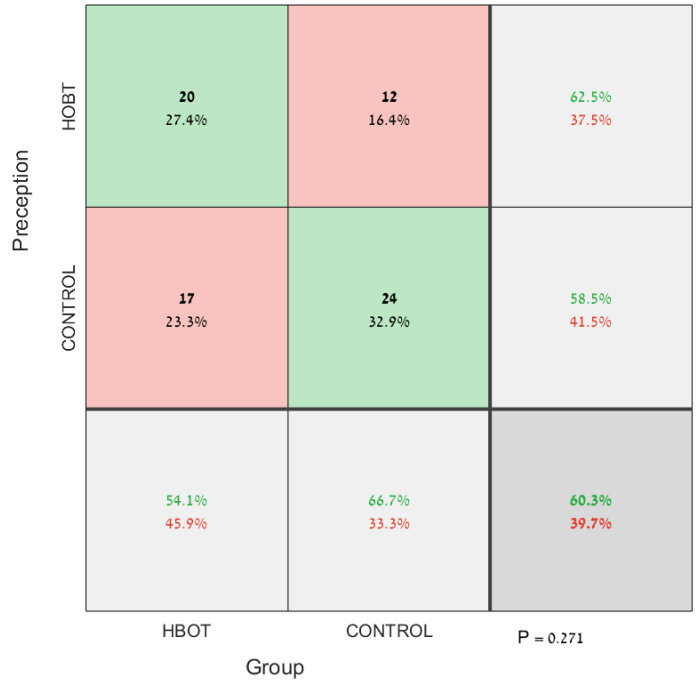


**Figure 2. SHAM test results matrix**. The green squares correspond to true perception, and the red squares represent false perception. The right column of the plot shows the percentages of the precision of the correct perception in each group separately. The overall correct perception rate is 60.3% (54.1% and 66.7% in the HBOT and CONTROL groups respectively).

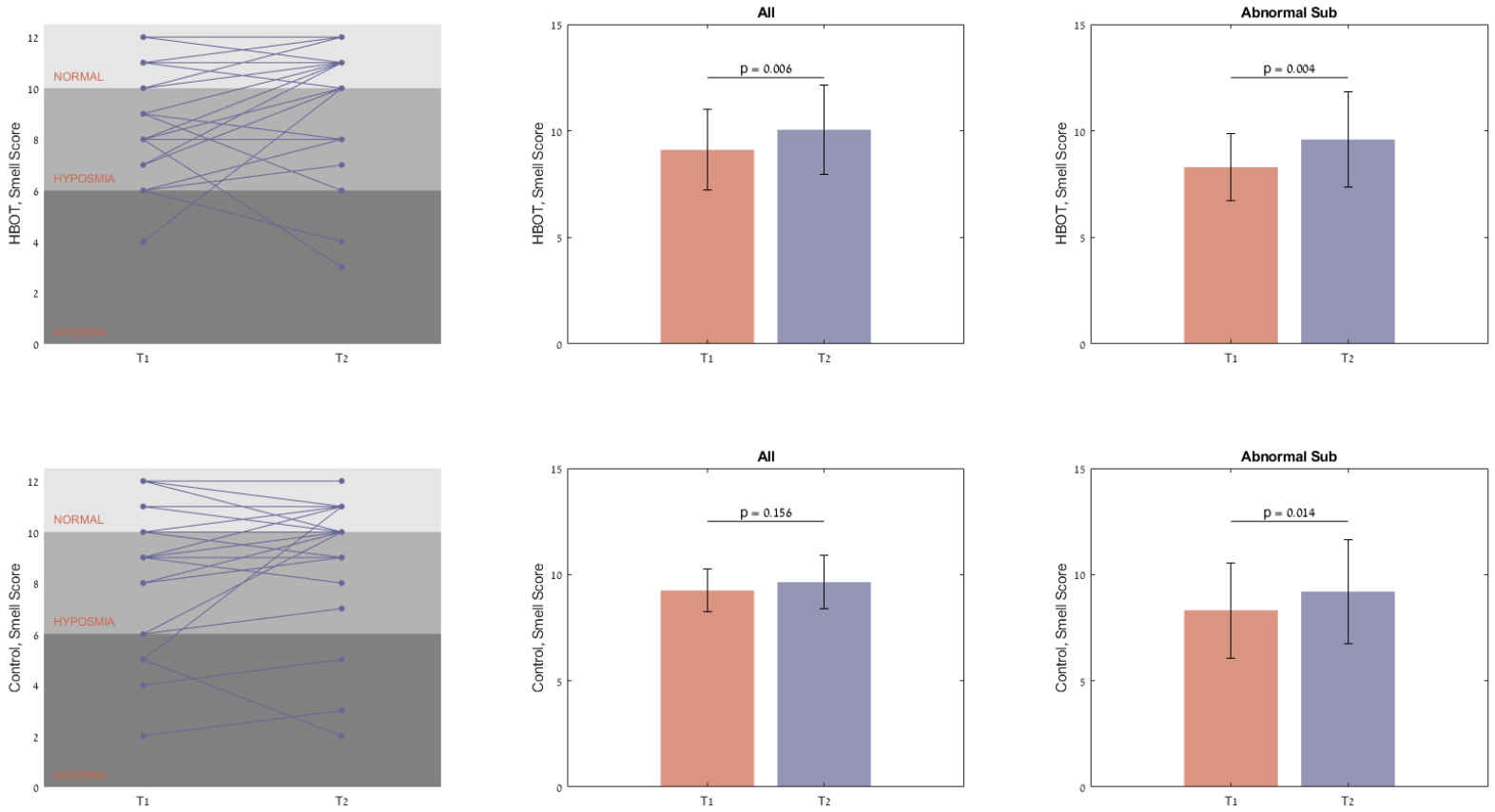


**Figure 3. Smell total score changes in HBOT and control arms.** Left plots, each line represents a patient's flow from baseline (T1) to post-intervention HBOT/Control (T2). Values are mean ± SD.

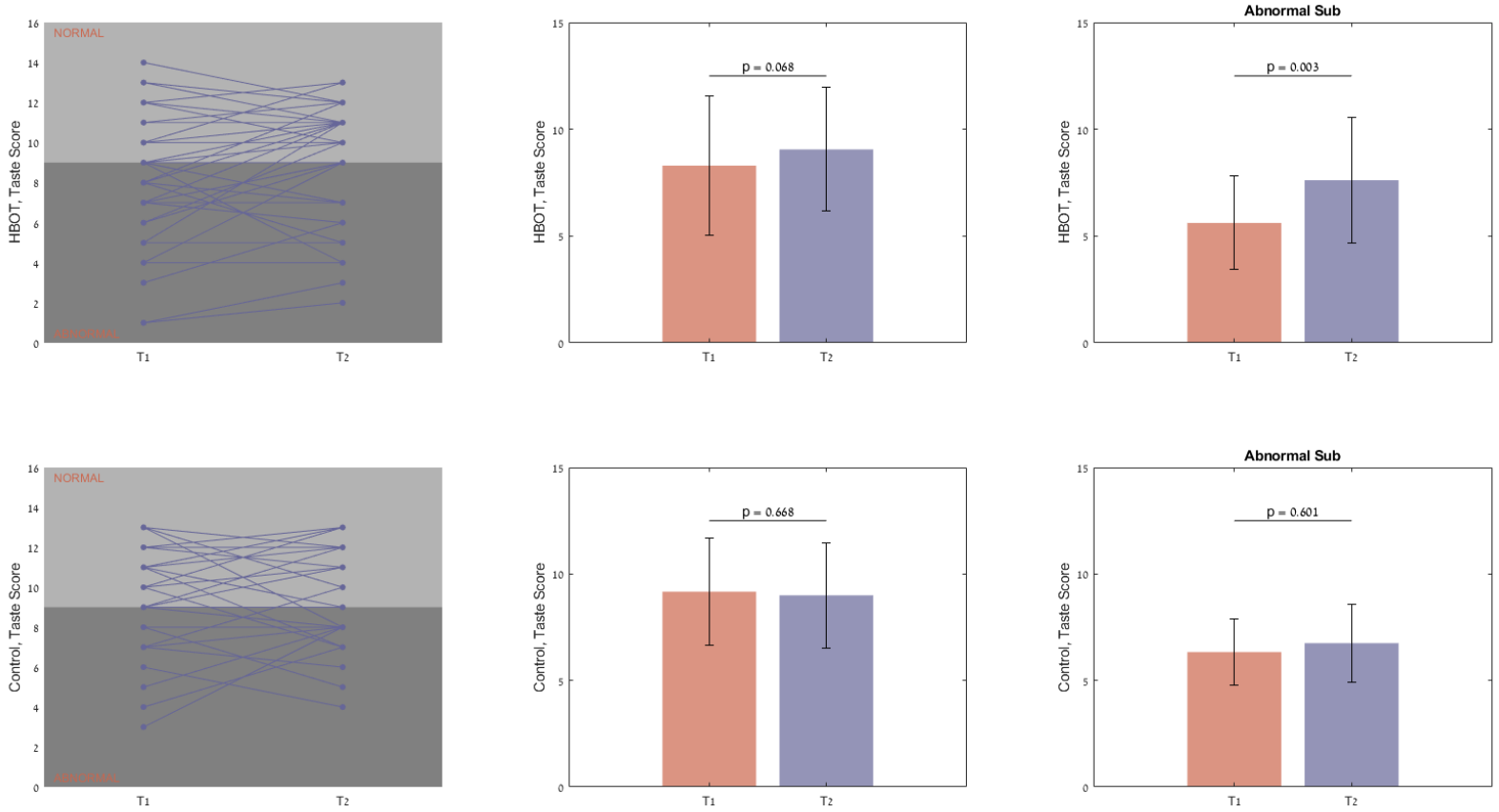


**Figure 4. Taste total score changes in HBOT and control arms**. Left plots, each line represents a patient's flow from baseline (T1) to post-intervention HBOT/Control (T2). Values are mean ± SD.