Effects of hyperbaric oxygen therapy on functional and structural connectivity in post-COVID-19 condition patients: a prospective randomized, sham-controlled trial

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SUPPLEMENTARY MATERIALS

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1 Materials and methods

1.1 Mathematical definitions of structural connectivity measures

Measure	Description	Equation	Ref
MD	Mean Diffusivity	$MD = \langle\lambda\rangle = \frac{1}{3}\sum_{i=1}^{3}\lambda_i\,;\quad i = 1..3$	[1]
FA	Fractional Anisotropy	$FA = \sqrt{\frac{3}{2}}\frac{\sqrt{\sum_{i=1}^{3}(\lambda_i - \langle\lambda\rangle)^2}}{\sqrt{\sum_{i=1}^{3}\lambda_i^2}};\quad i = 1..3$	[1]
RD	Radial Diffusivity	$RD = \frac{1}{2}(\lambda_2 + \lambda_3)$	[1]
AD	Axial diffusivity	λ_1	[1]
Cl	Linear anisotropy index	$Cl = \frac{\lambda_1 - \lambda_2}{3\langle\lambda\rangle}$	[1]
Cp	Planar anisotropy index	$Cp = \frac{2(\lambda_2 - \lambda_3)}{3\langle\lambda\rangle}$	[1]
Cs	Spherical anisotropy index	$Cs = \frac{\lambda_3}{3\langle\lambda\rangle}$	[1]
DW_{ROI}	Density weight	$DW_{ROI} = \frac{NT_{ROI}}{A_{ROI}}$	[2]
E	Global efficacy	$E = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}^{-1}}{n-1}$	[3, 4]

where,
λi, i=1..3, are the eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3 > 0$) of the diffusion tensor matrix.
NT_{ROI} is the number of tracts passing through an ROI, A_{ROI} is the area of the ROI
N is the set of all nodes in the network, n is the number of nodes, and d is the distance between nodes i and j.

2 Supplementary Figures

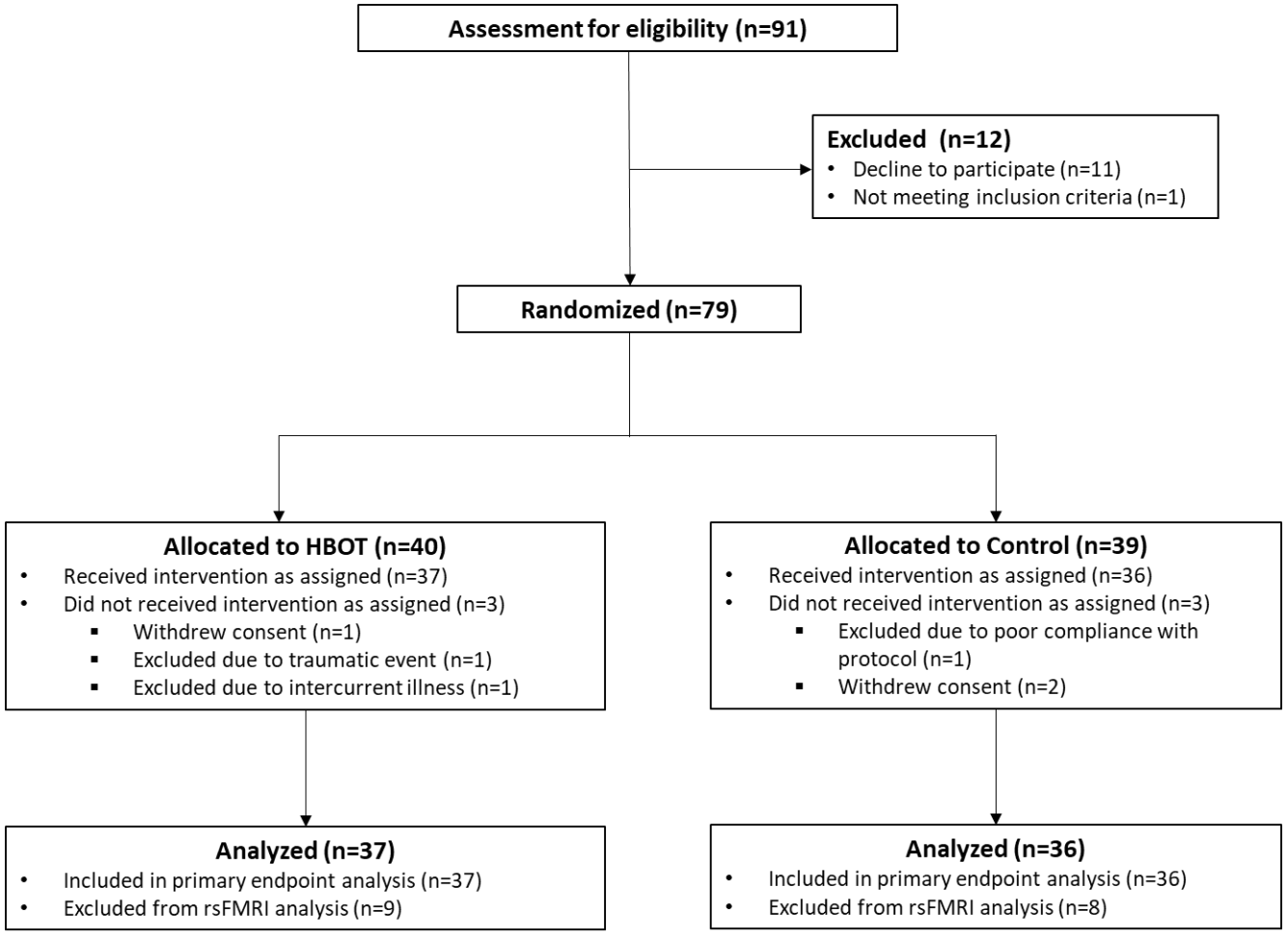

Fig. S1. Study flowchart

3 Supplementary Tables

Table S1: Functional connectivity networks with regions of interest and center of mass coordinates

Resting-state networks	ROI	MNI coordinates*		
		X	Y	Z
Default Mode Network	Medial Prefrontal Cortex (MPFC)	1	55	-3
	Left Lateral Parietal (LP)	-39	-77	33
	Right Lateral Parietal (LP)	47	-67	29
	Posterior Cingulate Cortex (PCC)	1	-61	38
Sensorimotor Network	Right Lateral area	-55	-12	29
	Left Lateral area	56	-10	29
	Superior area	0	-31	67
Salience Network	Left Anterior Insular Cortex (AInsula)	-44	13	1
	Right Anterior Insular Cortex (AInsula)	47	14	0
	Left Rostral Prefrontal Cortex (RPFC)	-32	45	27
	Right Rostral Prefrontal Cortex (RPFC)	32	46	27
	Left Supramarginal Gyrus (SMG)	-60	-39	31
	Right Supramarginal Gyrus (SMG)	62	-35	32
Dorsal Attention Network	Left Frontal Eye Fields (FEF)	-27	-9	64
	Right Frontal Eye Fields (FEF)	30	-6	64
	Left Intraparietal Sulcus (IPS)	-39	-43	52
	Right Intraparietal Sulcus (IPS)	39	-42	54
Fronto Parietal Network	Left Lateral Prefrontal Cortex (LPFC)	-43	33	28
	Left Posterior Parietal Cortex (PPC)	-46	-58	49
	Right Lateral Prefrontal Cortex (LPFC)	41	38	30
	Pight Posterior Parietal Cortex (PPC)	52	-52	45
Language Network	Left Inferior Frontal Gyrus (IFG)	-51	26	2
	Right Inferior Frontal Gyrus (IFG)	54	28	1
	Left posterior Superior Temporal Gyrus (pSTG)	-57	-47	15
	Right posterior Superior Temporal Gyrus (pSTG)	59	-42	13
	Right Insular Cortex (IC)	37	3	0
	Left Insular Cortex (IC)	-36	1	0
	Right Hippocampus	26	-21	-14
	Left Hippocampus	-25	-23	-14
	Right Amygdala	23	-4	-18
	Left Amygdala	-23	-5	-18

* MNI coordinates correspond to network nodes provided by the CONN toolbox (v.18b) and obtained from the Human Connectome Project [5].

Table S2: Fazekas score for WM hyperintensities

Grade	HBOT	Control	P-VALUE
N	37	36	
PVWM			
Grade 0	23	24	0.687
Grade 1	12	11	0.863
Grade 2	2	1	0.571
DWM			
Grade 0	17	20	0.412
Grade 1	20	15	0.289
Grade 2	0	1	1.000

PVWM, periventricular white matter; DWM, deep white matter

Table S3: Group differences in structural connectivity measures: Group-by-time ANOVA model

	Baseline	Group Main effect of		Time Main effect of		effect Interaction	
	P-value	F	P-value	F	P-value	F	P-value
FA							
Amygdala (L)	0.692	0.010	0.919	0.846	0.361	7.805	**0.007**
Amygdala (R)	0.031	5.084	0.028	0.107	0.745	0.257	0.614
Hippocampus (L)	0.309	3.050	0.085	1.243	0.269	0.637	0.428
Hippocampus (R)	0.832	0.147	0.702	1.937	0.169	0.072	0.789
Insula (L)	0.720	0.013	0.909	0.961	0.330	0.676	0.414
Insula (R)	0.488	0.551	0.460	1.001	0.321	0.038	0.847
MD							
Amygdala (L)	0.855	0.272	0.604	2.736	0.103	1.204	0.277
Amygdala (R)	0.844	0.025	0.875	0.114	0.737	0.953	0.333
Hippocampus (L)	0.113	1.919	0.170	0.087	0.769	1.244	0.268
Hippocampus (R)	0.062	1.614	0.208	0.106	0.746	3.549	0.064
Insula (L)	0.970	0.429	0.514	4.052	0.048	1.722	0.194
Insula (R)	0.162	1.256	0.266	0.158	0.692	0.824	0.367
RD							
Amygdala (L)	0.758	0.132	0.717	1.456	0.232	4.815	0.032
Amygdala (R)	0.300	1.018	0.317	0.006	0.939	1.150	0.288
Hippocampus (L)	0.085	3.083	0.084	0.674	0.414	0.513	0.476
Hippocampus (R)	0.082	1.667	0.201	0.020	0.888	2.669	0.107
Insula (L)	0.892	0.347	0.558	2.867	0.095	2.676	0.106
Insula (R)	0.182	1.353	0.249	0.010	0.922	0.757	0.387
RA							
Amygdala (L)	0.933	0.291	0.592	3.253	0.076	0.251	0.618
Amygdala (R)	0.435	0.545	0.463	0.525	0.471	0.300	0.586
Hippocampus (L)	0.197	0.652	0.422	0.095	0.758	2.068	0.155
Hippocampus (R)	0.056	1.292	0.260	0.680	0.412	4.328	0.041
Insula (L)	0.826	0.475	0.493	4.112	0.046	0.646	0.424
Insula (R)	0.224	0.796	0.376	0.801	0.374	0.569	0.453
CI							
Amygdala (L)	0.758	0.104	0.748	0.076	0.784	8.452	**0.005**
Amygdala (R)	0.300	3.257	0.076	0.472	0.494	0.390	0.535
Hippocampus (L)	0.085	2.484	0.120	3.274	0.075	1.327	0.253
Hippocampus (R)	0.082	0.122	0.728	6.614	0.012	1.406	0.240
Insula (L)	0.892	0.002	0.961	0.607	0.438	0.785	0.379
Insula (R)	0.182	0.006	0.939	0.720	0.399	0.053	0.818
Cs							
Amygdala (L)	0.482	0.100	0.752	1.852	0.178	5.707	0.020
Amygdala (R)	0.026	5.871	0.018	0.009	0.926	0.077	0.782
Hippocampus (L)	0.255	2.625	0.110	0.044	0.834	0.171	0.681
Hippocampus (R)	0.391	0.367	0.546	0.252	0.617	0.768	0.384
Insula (L)	0.902	0.234	0.630	1.644	0.204	0.266	0.608
Insula (R)	0.200	1.862	0.177	0.858	0.357	0.262	0.611
Cp							
Amygdala (L)	0.407	0.850	0.360	3.390	0.070	0.383	0.538
Amygdala (R)	0.251	2.947	0.091	1.049	0.310	0.073	0.788
Hippocampus (L)	0.520	0.135	0.714	4.396	0.040	0.744	0.391
Hippocampus (R)	0.171	0.187	0.667	13.292	0.001	6.502	0.013
Insula (L)	0.437	0.425	0.517	1.184	0.280	0.337	0.564
Insula (R)	0.013	5.401	0.023	0.265	0.608	1.639	0.205
Average tract length							
Amygdala (L)	0.631	0.324	0.571	0.063	0.803	7.642	**0.007**
Amygdala (R)	0.128	1.381	0.244	2.148	0.148	0.501	0.482
Hippocampus (L)	0.647	0.894	0.348	7.667	0.007	0.388	0.535
Hippocampus (R)	0.430	0.201	0.655	2.591	0.112	0.930	0.338
Insula (L)	0.810	0.184	0.669	0.116	0.735	0.026	0.873
Insula (R)	0.341	1.075	0.303	2.012	0.161	0.004	0.950

Density weight							
Amygdala (L)	0.735	0.093	0.761	0.496	0.484	5.366	0.024
Amygdala (R)	0.053	3.809	0.056	0.145	0.705	0.029	0.866
Hippocampus (L)	0.456	1.562	0.216	2.666	0.107	0.192	0.662
Hippocampus (R)	0.467	0.100	0.753	0.521	0.473	2.252	0.138
Insula (L)	0.552	0.320	0.573	0.549	0.461	0.066	0.797
Insula (R)	0.378	0.649	0.423	0.162	0.688	0.120	0.730
Efficacy							
Amygdala (L)	0.343	0.149	0.701	1.324	0.254	5.980	0.017
Amygdala (R)	0.605	0.266	0.608	0.530	0.469	0.019	0.892
Hippocampus (L)	0.756	1.487	0.227	0.536	0.467	1.644	0.204
Hippocampus (R)	0.357	1.315	0.255	6.470	0.013	0.061	0.805
Insula (L)	0.255	0.707	0.403	0.023	0.879	0.513	0.476
Insula (R)	0.446	0.935	0.337	0.022	0.883	0.057	0.812
Whole brain density	0.214	0.006	0.94	2.036	0.158	2.702	0.105
Whole brain efficacy	0.484	0.33	0.567	0.52	0.472	0.24	0.628

Fractional anisotropy (FA), mean diffusion (MD), radial diffusion (RD), axial diffusivity (AD), linear anisotropy (Cl), planar anisotropy (Cp), and spherical anisotropy (Cs)

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