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Supplementary Material

Article Title: Hyperbaric Oxygen Therapy for Veterans Suffering from Combat-Associated Posttraumatic Stress Disorder: A Randomized, Sham-Controlled Clinical Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

BOLD Preprocessing

Functional and anatomical data were preprocessed using a flexible preprocessing pipeline[4] including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI-space normalization and smoothing. Functional data were realigned using SPM realign & unwarp procedure[5], where all scans were coregistered to a reference image using the least squares approach and a 6 parameter (rigid body) transformation[6], and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions.

Temporal misalignment between different slices of the functional data (acquired in ascending order) was corrected following SPM slice-timing correction (STC) procedure[7,8], using sinc temporal interpolation to resample each BOLD slice timeseries to a common mid-acquisition time. Potential outlier slices were identified using ART[9] as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations[10,11], and a reference BOLD image was computed for each subject by averaging the slices excluding outliers.

Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and cerebrospinal fluid (CSF) tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure[11,12] using SPM unified segmentation and normalization algorithm[13,14] with the default IXI-549 tissue probability map template.

Functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM).

Functional data were then denoised using a standard denoising pipeline[15] including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), outlier scans (below 85 factors)[10], motion parameters and their first order derivatives (12 factors)[16], session and task effects and their first order derivatives (4 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries[17] between 0.008 Hz and 0.09 Hz. CompCor[18,19] noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of

freedom of the BOLD signal after denoising were estimated to range from 101.6 to 133.8 (average 131.1) across all subjects[11].

BOLD analysis

First-level analysis (individual maps)

Seed-based connectivity maps (SBC) and region of interest (ROI)-to-ROI connectivity matrices (RRC) were estimated characterizing the patterns of functional connectivity with 23 HPC-ICA networks[2] and Harvard-Oxford atlas ROIs[20]. The ROIs examined included PTSD commonly reported large-scale brain networks: default mode (DMN), salience (SN), fronto-parietal (FPN), thalami, amygdala and hippocampi . Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficient from a weighted general linear model (weighted-GLM[21]), defined separately for each pair of seed and target area. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

Second-level analysis (group-level analyses)

Second-level were performed using a General Linear Model (GLM)[22]. For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements.

Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory[23,24].

Results were thresholded using a combination of a cluster-forming $p < 0.001$-0.005 voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold[25].

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Supplementary Figure 1: Confusion Matrix

Confusion matrix showing treatment perception in the two groups. Accuracy was calculated as the true perceived HBOT or sham divided by the total participants. Recall was calculated as the number of true HBOT perceptions divided by the total actual HBOT perceptions. Precision was calculated as the number of true HBOT perceptions divided by the sum of true HBOT perceptions and false sham perceptions.

		Predicted condition	
		HBOT 36	SHAM 20
Actual condition	HBOT 28	True HBOT 18	False SHAM 10
	SHAM 28	False HBOT 18	True SHAM 10

Accuracy	0.5
Recall	0.642857
Precision	0.5

Supplementary Table 1:

Significant seed to voxel functional connectivity group-by-time interactions

Seed	**Regions**	**MNI coordinate**	**Cluster-size (voxels)**

Thalamus - Left	Right inferior parietal lobe-Supramarginal Gyrus(r) Angular gyrus(r) Supramarginal Gyrus(l)	54,-40,50 48,-52,50 -56,-36,44	242 227 204
Thalamus -Right	Middle Frontal Gyrus (l)	-38,26,38	351
DMN -mPFC (1,55,-3)	Lingual Gyrus(r) Intracalcarine Cortex (l)	8,-82,-8 -10,-84,6	208 125
FPN DLPFC -left (-43,38,28)	Thalamus (r) Thalamus (l)	10,-8,8 -14,-16,10	175 94
FPN DLPFC -right (41,38,30)	Supramarginal gyrus(r) Supramarginal gyrus(l) Angular gyrus(r) Angular gyrus(l) Putamen(r) Putamen(l) Insular cortex Precuneus Frontal pole(r)	52 -40 40 -56 -48 42 56 -50 38 -48 -54 48 28 0 4 -26 -4 4 36 -4 8 6 -66 50 34 46 18	412 222 141 127 326 299 176 220 350
Salience RPFC - left (-32,45,27)	Frontal Pole(r)	40,52,4	765

Salience **RPFC-** right (32,45, 27)	Frontal Pole(r) Superior frontal gyrus (r)	38,54,12 18,14,64	228 179