Effects of short-term CPAP withdrawal on cerebral vascular reactivity measured by BOLD MRI in OSA: a randomised controlled trial

Sira Thiel[1]*, Franziska Lettau[1]*, Protazy Rejmer[1], Cristina Rossi[2], Sarah R. Haile[3], Esther I. Schwarz[1], Anna S. Stöberl[1], Noriane A. Sievi[1], Andreas Boss[3], Anton Becker[3], Sebastian Winklhofer[5], John R. Stradling[4], Malcolm Kohler[1, 6]

[1] Sleep Disorders Centre and Pulmonary Division, University Hospital of Zurich, Zurich, Switzerland
[2] Department of Diagnostic and Interventional Radiology, University Hospital of Zurich, Zurich, Switzerland
[3] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland
[4] National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford United Kingdom
[5] Department of Neuroradiology, University Hospital of Zurich, Zurich, Switzerland
[6] Centre for Integrative Human Physiology, University of Zurich, Zurich, Switzerland
* Contributed equally.

Information: Consent for publication was obtained from all participants who are featured in the pictures.

Table of Contents

Supplementary methods

Subjects

Exclusion criteria were 1) previous cerebral stroke, 2) known cerebral vascular anomalies, 3) carotid artery stenosis ≥70%, 4) use of alpha-and beta-adrenergic blocking medication, 5) antianginal medications, triptans or selective cyclooxygenase (COX)-inhibitors, 6) unstable, or untreated, coronary or peripheral artery disease, 7) inadequately controlled arterial hyper- or hypotension (≥180/110 or ≤ 90/60 mmHg), 8) MRI-incompatible implants, pacemakers and internal cardiac defibrillators, coronary artery stents, 9) previous ventilatory failure (awake SpO_2 ≤93% and/ or $PaCO_2$ ≥ 6 kPa), 10) Cheyne-Stokes breathing, 11) professional driving, 12) previously reported sleep-related traffic accidents and 13) chronic obstructive pulmonary disease.

Primary outcome measures

BOLD-MRI acquisition and gas administration protocols

The MR data were acquired using a three-tesla (3T) whole-body scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany). The signals were recorded using a 64-channel head coil, while the built-in body transmit coil was used for spin excitation. A three-dimensional T1-weighted Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) sequence (TR = 7 ms, TE = 2.32 ms, flip angle = 8°, TI = 900 ms, parallel imaging using GRAPPA, acceleration factor 2) was acquired for anatomical orientation. Dynamic changes in the T2*-weighted MR signal due to respiratory challenges were monitored by acquiring fat-saturated Echo Planar Imaging (EPI) sequences (TR = 3000 ms; TE = 30 ms; echo spacing = 0.50 ms; bandwidth in EPI readout direction = 2440 Hz/px, GRAPPA acceleration factor = 2; voxel size = 3 x 3 x 3 mm^3; number of slices = 34).

BOLD MR-signal modeling

To correct for potential rigid head motion, T2*-weighted volumes were realigned to the first dynamic volume using the “coregister” toolbox of SPM 12 (Statistical Parametrical Mapping 12, Wellcome Trust Centre for Neuroimaging, London, UK). Three-dimensional T1-weighted anatomical images were segmented into grey matter (GM) and white matter (WM) using the automated segmentation tool of SPM12 and then co-registered to the first T2*-weighted volume.

For each subject and for each dynamic acquisition, we measured the mean BOLD signal over the segmented GM and WM, separately. For each tissue type, a compartment model was fitted to the

dynamic datasets using routines written with Matlab (MATLAB Release 2013b, The MathWorks, Inc., Natick, Massachusetts, United States). The compartment model proposed by Boss et al. was adapted to the breathing protocol of the trial, by assuming an exponential temporal dependence of the signal intensities; and a complete wash-out between two successive gas administrations. The model corrects for a linear signal drift.(3)

The logarithm of the T2*-weighted signal was fitted to the following curves:

$lineardrift: a - c \cdot t, t < 180s$ [1]

$firstoxygenadministration: a - c \cdot t + \frac{\gamma}{\beta}\left(1 - e^{-\beta(t-180)}\right) + Noise, 180s \leq t < 360s$ [2]

$secondoxygenadministration: a - c \cdot t + \frac{\gamma}{\beta}\left(1 - e^{-\beta(t-360)}\right) + Noise, 540s \leq t < 720s$ [3]

$firstcarbondioxideadministration: a - c \cdot t + \frac{\gamma}{\beta}\left(1 - e^{-\beta(t-900)}\right) + Noise, 900s \leq t < 1080s$ [4]

Fitting parameters were baseline signal intensity (a), signal drift slope (c), characteristic signal increase constant (β), and signal increase in saturation (γ/β). Before least square fitting of the signal pattern to the functions [1-4], a one-dimensional median linear filter was applied to the signal. For each of the three challenges the relative signal change in percentages between baseline (breathing medical air) and the hyperoxic and hypercapnic gas administration were computed.

Secondary outcome measures

ASL MRI

We performed Arterial Spin Labeling (ASL) MRI to estimate the CBF of each subject before gas administration. For ASL, a flow-sensitive alternating inversion recovery (FAIR) preparation scheme was applied with alternative slice-selective inversion and global inversion of the magnetization. (4)

The inversion time delay was set to 1 s. The imaging slice thickness was 5 mm and the inversion slab thickness for slice-selective inversion was 12.5 mm. After FAIR preparation, centric-reordered k-space sampling was performed using a true fast imaging in steady precession (TrueFISP) approach. For each subject, a single slice was acquired with TR = 4.04 ms, TE = 2.02 ms, and acquisition bandwidth of 650 Hz/pixel. The delay time between the end of TrueFISP acquisition and the next inversion pulse was set to 2800 ms. Twenty-five image pairs were acquired for off-line CBF quantification. (5)

Perfusion MR-signal modeling

Quantitative CBF values, in units of ml/100g/min, were computed using the equation:

$CBF = \frac{\lambda}{2TI} \cdot \frac{\Delta M}{M_0} \cdot exp\left(\frac{TI}{T1}\right)$, [5]

where λ = 0.90 ml/g is the brain-blood partition coefficient, T1 = 1.650 s is the T1 of the arterial blood at 3 Tesla, M0 is the signal intensity of a proton density weighted reference TrueFISP image, ΔM is the signal difference between the selective and the global inversion pixels. (5)

CBF values ranged between 0 and 200 ml/100g/min. Negative CBF values arising from noise fluctuations were set to zero before performing the statistical analysis. A threshold of 200 ml/100g/min was set for excluding areas of macroscopic blood flow contamination. For each subject, mean CBF values were computed over the WM and the GM, respectively, from ten Regions of Interest (RoIs) manually drawn over the tissue. The RoIs drawn over the proton-density weighted reference image were copied onto the CBF parametrical map. Computation of parametrical maps and RoI analysis were performed pixel-wise using in-house custom software written in Matlab. (6)

Ambulatory blood pressure and heart rate

We asked participants to measure their blood pressure and heart rate (HR) in triplicate every morning of the trial period with a standard digital automatic monitor (Omron Healthcare Company, Kyoto, Japan). Measurements were performed according to a standardised protocol: in a sitting position after a period of rest ≥5 minutes, immediately after getting up, before breakfast and before intake of antihypertensive drugs, one minute intervals between the three measurements. We used the average of three measurements for further analysis.

Sample size

We performed a sample size estimation based on previously reported expected values of cerebral vasodilator response to L-arginine in healthy subjects, and in OSA patients before and after six weeks of treatment measured by transcranial Doppler. Based on the assumption that a minimally important difference in cerebral vasoreactivity measured by transcranial Doppler between both groups is 20 %, power calculation indicated that we would need 20 individuals in each trial arm (power of 80%). According to our previous experience with the CPAP-withdrawal model, we took a dropout rate of 5-6% into account. Thus, the initial recruitment goal was adjusted to 49 individuals. (1, 2)

e Table 1. Multivariate models considered

Model name	formula
M0	follow- up ~ treatment
M1	follow- up ~ treatment + baseline
M2	follow- up ~ treatment + baseline + AHI (follow- up)
M3	follow- up ~ treatment + baseline + ODI (follow- up)
M4	follow- up ~ treatment + baseline + SBP (home)
M5	follow- up ~ treatment + baseline + DBP (home)
M6	follow- up ~ treatment + baseline + age + sex + SBP (home)+ DBP (home)+ HR (home)+ AHI (follow- up) + ODI (follow- up)
M7	follow- up ~ treatment + baseline + age + sex + SBP (home)+ DBP (home)+ HR (home)+ AHI (follow- up)
M8	follow- up ~ treatment + baseline + age + sex + SBP (hosp)+ DBP (hosp)+ HR (hosp)+ AHI (baseline) + ODI (baseline)
M9	follow- up ~ treatment + baseline + age + sex + SBP (hosp)+ HR (hosp)+ AHI (baseline)

Multivariate models considered (M0-M9). Follow-up indicates the given outcome at the follow-up visit, while baseline indicates the same outcome at the baseline visit. Treatment is the treatment variable, indicating whether the patient received subtherapeutic or therapeutic CPAP. Blood pressure and heart rate were observed either at the hospital or at home. In adjusting for AHI and ODI, either the follow- up values or the baseline values were considered.
AHI, apnoea-hypopnoea-index (events/h); ODI, oxygen-desaturation-index (events/h); SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

e Table 2. Summarized treatment effects overall

y	model	est	ci	pval
BOLD response whole brain hypercapnic stimulus	M0	0.031	[-0.518, 0.580]	0.91
BOLD response whole brain hypercapnic stimulus	M1	0.100	[-0.417, 0.616]	0.70
BOLD response whole brain hypercapnic stimulus	M2	0.132	[-0.654, 0.919]	0.74
BOLD response whole brain hypercapnic stimulus	M3	0.006	[-0.779, 0.790]	0.99
BOLD response whole brain hypercapnic stimulus	M4	0.084	[-0.497, 0.665]	0.77
BOLD response whole brain hypercapnic stimulus	M5	0.107	[-0.492, 0.705]	0.72
BOLD response whole brain hypercapnic stimulus	M6	0.313	[-0.537, 1.163]	0.45
BOLD response whole brain hypercapnic stimulus	M7	0.378	[-0.460, 1.216]	0.36
BOLD response whole brain hypercapnic stimulus	M8	-0.295	[-0.929, 0.339]	0.35
BOLD response whole brain hypercapnic stimulus	M9	-0.105	[-0.731, 0.520]	0.73
BOLD response whole brain 1st hyperoxic stimulus	M0	-0.203	[-0.664, 0.258]	0.38
BOLD response whole brain 1st hyperoxic stimulus	M1	-0.123	[-0.568, 0.322]	0.58
BOLD response whole brain 1st hyperoxic stimulus	M2	0.198	[-0.458, 0.853]	0.54
BOLD response whole brain 1st hyperoxic stimulus	M3	0.146	[-0.515, 0.807]	0.66
BOLD response whole brain 1st hyperoxic stimulus	M4	-0.169	[-0.737, 0.399]	0.55
BOLD response whole brain 1st hyperoxic stimulus	M5	-0.218	[-0.788, 0.352]	0.44
BOLD response whole brain 1st hyperoxic stimulus	M6	0.240	[-0.600, 1.080]	0.56
BOLD response whole brain 1st hyperoxic stimulus	M7	0.287	[-0.520, 1.095]	0.47
BOLD response whole brain 1st hyperoxic stimulus	M8	-0.286	[-0.808, 0.236]	0.27
BOLD response whole brain 1st hyperoxic stimulus	M9	-0.126	[-0.659, 0.406]	0.63
BOLD response whole brain 2nd hyperoxic stimulus	M0	-0.172	[-0.649, 0.304]	0.47
BOLD response whole brain 2nd hyperoxic stimulus	M1	-0.106	[-0.563, 0.350]	0.64
BOLD response whole brain 2nd hyperoxic stimulus	M2	-0.098	[-0.765, 0.569]	0.77
BOLD response whole brain 2nd hyperoxic stimulus	M3	-0.224	[-0.884, 0.437]	0.50
BOLD response whole brain 2nd hyperoxic stimulus	M4	-0.054	[-0.506, 0.398]	0.81
BOLD response whole brain 2nd hyperoxic stimulus	M5	-0.127	[-0.598, 0.344]	0.59

BOLD response whole brain 2nd hyperoxic stimulus	M6	0.092	[-0.600, 0.785]	0.78
BOLD response whole brain 2nd hyperoxic stimulus	M7	0.147	[-0.530, 0.824]	0.66
BOLD response whole brain 2nd hyperoxic stimulus	M8	-0.153	[-0.736, 0.430]	0.60
BOLD response whole brain 2nd hyperoxic stimulus	M9	-0.083	[-0.609, 0.444]	0.75
Cerebral blood flow mean grey matter	M0	4.207	[-0.894, 9.309]	0.10
Cerebral blood flow mean grey matter	M1	4.203	[-0.955, 9.361]	0.11
Cerebral blood flow mean grey matter	M2	5.279	[-2.482, 13.040]	0.18
Cerebral blood flow mean grey matter	M3	5.786	[-1.933, 13.506]	0.14
Cerebral blood flow mean grey matter	M4	3.511	[-2.286, 9.308]	0.22
Cerebral blood flow mean grey matter	M5	3.439	[-2.411, 9.290]	0.24
Cerebral blood flow mean grey matter	M6	2.393	[-4.938, 9.724]	0.50
Cerebral blood flow mean grey matter	M7	2.279	[-4.728, 9.286]	0.51
Cerebral blood flow mean grey matter	M8	7.704	[1.798, 13.610]	0.012
Cerebral blood flow mean grey matter at follow up visit	M9	6.785	[1.252, 12.318]	0.018
BOLD response grey matter hypercapnic stimulus	M0	-0.047	[-0.782, 0.688]	0.90
BOLD response grey matter hypercapnic stimulus	M1	0.069	[-0.610, 0.749]	0.84
BOLD response grey matter hypercapnic stimulus	M2	0.446	[-0.531, 1.423]	0.36
BOLD response grey matter hypercapnic stimulus	M3	0.314	[-0.672, 1.300]	0.52
BOLD response grey matter hypercapnic stimulus	M4	-0.045	[-0.788, 0.697]	0.90
BOLD response grey matter hypercapnic stimulus	M5	-0.059	[-0.782, 0.665]	0.87
BOLD response grey matter hypercapnic stimulus	M6	0.438	[-0.576, 1.452]	0.38
BOLD response grey matter hypercapnic stimulus	M7	0.533	[-0.443, 1.510]	0.27
BOLD response grey matter hypercapnic stimulus	M8	-0.034	[-0.894, 0.826]	0.94
BOLD response grey matter hypercapnic stimulus	M9	0.066	[-0.725, 0.857]	0.87
BOLD response grey matter 1st hyperoxic stimulus	M0	-0.540	[-1.137, 0.057]	0.075
BOLD response grey matter 1st hyperoxic stimulus	M1	-0.544	[-1.104, 0.015]	0.056
BOLD response grey matter 1st hyperoxic stimulus	M2	-0.256	[-1.117, 0.605]	0.55

BOLD response grey matter 1st hyperoxic stimulus	M3	-0.154	[-1.002, 0.694]	0.72
BOLD response grey matter 1st hyperoxic stimulus	M4	-0.496	[-1.148, 0.156]	0.13
BOLD response grey matter 1st hyperoxic stimulus	M5	-0.488	[-1.114, 0.139]	0.12
BOLD response grey matter 1st hyperoxic stimulus	M6	-0.247	[-1.248, 0.754]	0.61
BOLD response grey matter 1st hyperoxic stimulus	M7	-0.231	[-1.197, 0.735]	0.63
BOLD response grey matter 1st hyperoxic stimulus	M8	-0.577	[-1.252, 0.098]	0.091
BOLD response grey matter 1st hyperoxic stimulus	M9	-0.587	[-1.229, 0.056]	0.072
BOLD response grey matter 2nd hyperoxic stimulus	M0	-0.285	[-0.954, 0.384]	0.39
BOLD response grey matter 2nd hyperoxic stimulus	M1	-0.287	[-0.940, 0.367]	0.38
BOLD response grey matter 2nd hyperoxic stimulus	M2	0.084	[-0.898, 1.067]	0.86
BOLD response grey matter 2nd hyperoxic stimulus	M3	0.003	[-0.979, 0.985]	0.99
BOLD response grey matter 2nd hyperoxic stimulus	M4	-0.274	[-1.014, 0.467]	0.46
BOLD response grey matter 2nd hyperoxic stimulus	M5	-0.254	[-0.974, 0.466]	0.48
BOLD response grey matter 2nd hyperoxic stimulus	M6	0.277	[-0.861, 1.416]	0.62
BOLD response grey matter 2nd hyperoxic stimulus	M7	0.243	[-0.850, 1.336]	0.65
BOLD response grey matter 2nd hyperoxic stimulus	M8	-0.413	[-1.270, 0.444]	0.33
BOLD response grey matter 2nd hyperoxic stimulus	M9	-0.280	[-1.070, 0.510]	0.48
BOLD response white matter hypercapnic stimulus	M0	0.214	[-0.381, 0.808]	0.47
BOLD response white matter hypercapnic stimulus	M1	0.210	[-0.389, 0.809]	0.48
BOLD response white matter hypercapnic stimulus	M2	0.503	[-0.368, 1.374]	0.25
BOLD response white matter hypercapnic stimulus	M3	0.404	[-0.469, 1.277]	0.35
BOLD response white matter hypercapnic stimulus	M4	0.100	[-0.594, 0.795]	0.77
BOLD response white matter hypercapnic stimulus	M5	0.152	[-0.535, 0.840]	0.65
BOLD response white matter hypercapnic stimulus	M6	0.398	[-0.614, 1.410]	0.42
BOLD response white matter hypercapnic stimulus	M7	0.454	[-0.518, 1.427]	0.34
BOLD response white matter hypercapnic stimulus	M8	0.147	[-0.610, 0.904]	0.69
BOLD response white matter hypercapnic stimulus	M9	0.363	[-0.347, 1.074]	0.31

BOLD response white matter 1st hyperoxic stimulus	M0	-0.058	[-0.616, 0.501]	0.84
BOLD response white matter 1st hyperoxic stimulus	M1	-0.109	[-0.652, 0.434]	0.69
BOLD response white matter 1st hyperoxic stimulus	M2	0.372	[-0.438, 1.181]	0.36
BOLD response white matter 1st hyperoxic stimulus	M3	0.516	[-0.277, 1.308]	0.20
BOLD response white matter 1st hyperoxic stimulus	M4	-0.265	[-0.965, 0.435]	0.44
BOLD response white matter 1st hyperoxic stimulus	M5	-0.324	[-1.015, 0.366]	0.34
BOLD response white matter 1st hyperoxic stimulus	M6	0.402	[-0.575, 1.379]	0.40
BOLD response white matter 1st hyperoxic stimulus	M7	0.199	[-0.839, 1.236]	0.70
BOLD response white matter 1st hyperoxic stimulus	M8	0.095	[-0.640, 0.831]	0.79
BOLD response white matter 1st hyperoxic stimulus	M9	-0.063	[-0.738, 0.611]	0.85
BOLD response white matter 2nd hyperoxic stimulus	M0	0.318	[-0.198, 0.833]	0.22
BOLD response white matter 2nd hyperoxic stimulus	M1	0.245	[-0.256, 0.745]	0.33
BOLD response white matter 2nd hyperoxic stimulus	M2	0.577	[-0.183, 1.338]	0.13
BOLD response white matter 2nd hyperoxic stimulus	M3	0.644	[-0.104, 1.391]	0.089
BOLD response white matter 2nd hyperoxic stimulus	M4	0.511	[-0.131, 1.152]	0.11
BOLD response white matter 2nd hyperoxic stimulus	M5	0.468	[-0.158, 1.094]	0.14
BOLD response white matter 2nd hyperoxic stimulus	M6	0.813	[-0.190, 1.815]	0.11
BOLD response white matter 2nd hyperoxic stimulus	M7	0.744	[-0.259, 1.747]	0.14
BOLD response white matter 2nd hyperoxic stimulus	M8	0.336	[-0.364, 1.036]	0.33
BOLD response white matter 2nd hyperoxic stimulus	M9	0.383	[-0.237, 1.003]	0.22
Cerebral blood flow mean white matter	M0	-1.518	[-5.086, 2.051]	0.39
Cerebral blood flow mean white matter	M1	-0.620	[-3.901, 2.660]	0.70
Cerebral blood flow mean white matter	M2	-2.601	[-7.458, 2.256]	0.28
Cerebral blood flow mean white matter	M3	-2.153	[-6.965, 2.660]	0.37
Cerebral blood flow mean white matter	M4	-1.394	[-5.160, 2.372]	0.45
Cerebral blood flow mean white matter	M5	-1.375	[-5.002, 2.252]	0.44
Cerebral blood flow mean white matter	M6	-4.260	[-9.889, 1.369]	0.13

Cerebral blood flow mean white matter	M7	-4.189	[-9.597, 1.218]	0.12
Cerebral blood flow mean white matter	M8	1.309	[-2.547, 5.165]	0.49
Cerebral blood flow mean white matter	M9	-0.142	[-4.049, 3.765]	0.94

M0-M9, Multivariable models considered, see e Figure 1. Estimate is the estimated treatment effect for the subtherapeutic CPAP group compared to the therapeutic CPAP group, adjusted for the other variables in the model. For the simplest model (M0), this is equivalent to the mean outcome in the subtherapeutic CPAP group minus the mean outcome in the therapeutic CPAP group. 95% confidence intervals and p- values are given. BOLD, blood- oxygen- level dependent.

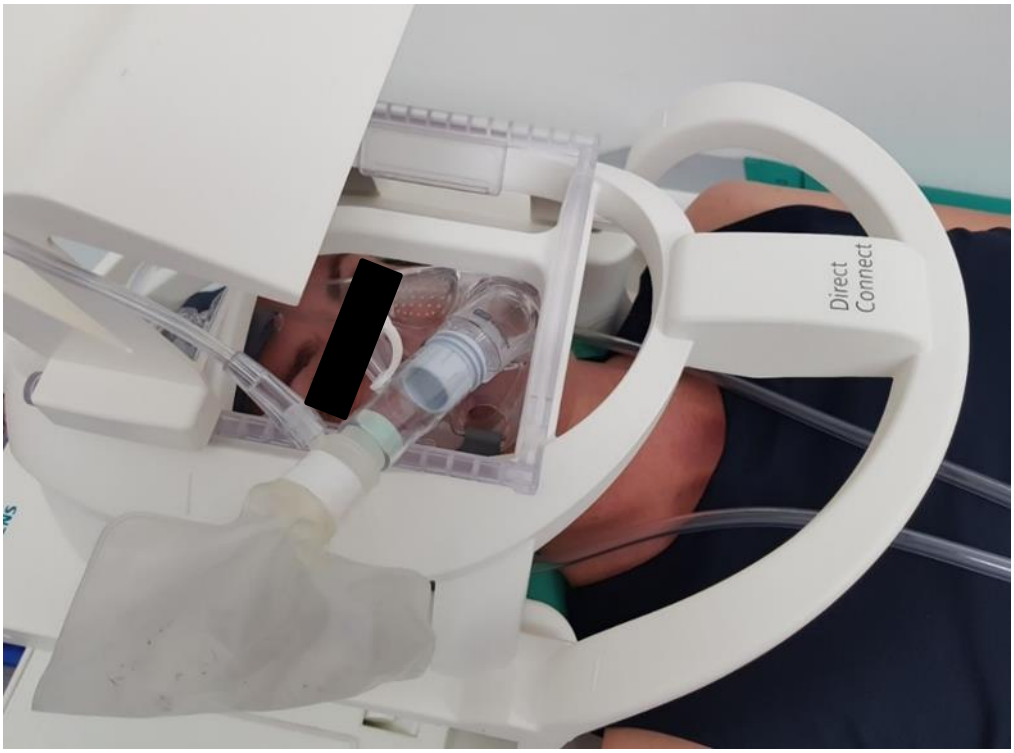
e Table 3. Follow- up characteristics by study arm

	Subtherapeutic CPAP (n=21)	**Therapeutic CPAP (n=20)**	**p-value**
Apnoea to hypopnea index, events per h	46.73(28.28)	4.34(3.85)	<0.001
CPAP usage, hours (IQR)	01:41(0 to 2:37)	06:48(06:25 to 07:24)	<0.001
Epworth Sleepiness Scale, points (max. 24)	11.9(5.5)	7.65(3.86)	0.007

CPAP, continuous positive airway pressure. Data are presented as mean±SD unless stated otherwise.

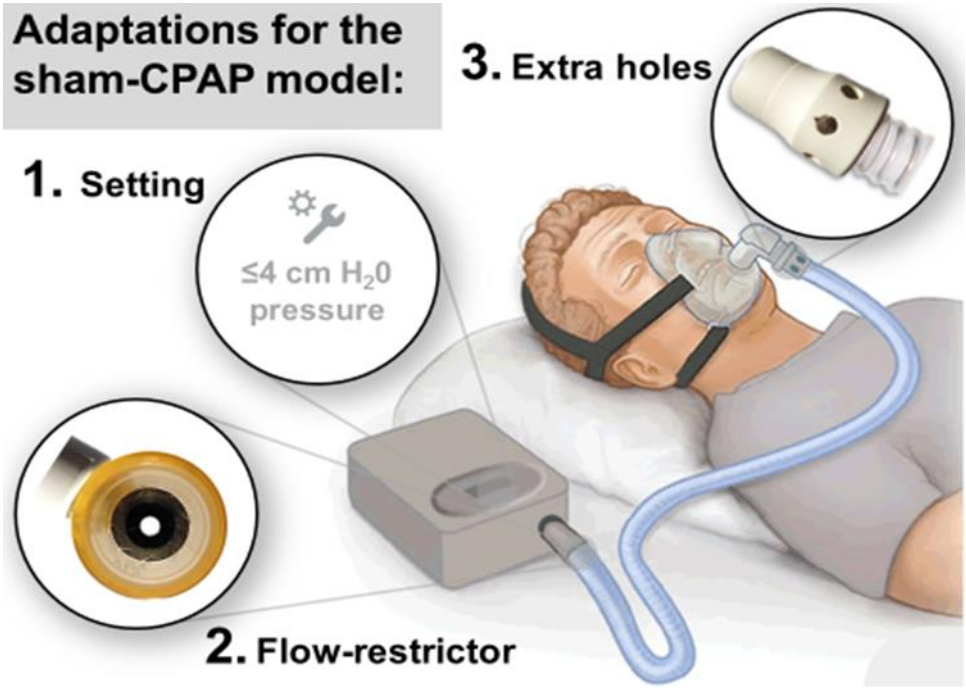
e Figure 1. Study mask setup

Shown is the breathing mask (0.5L reservoir bag) and the birdcage head coil.



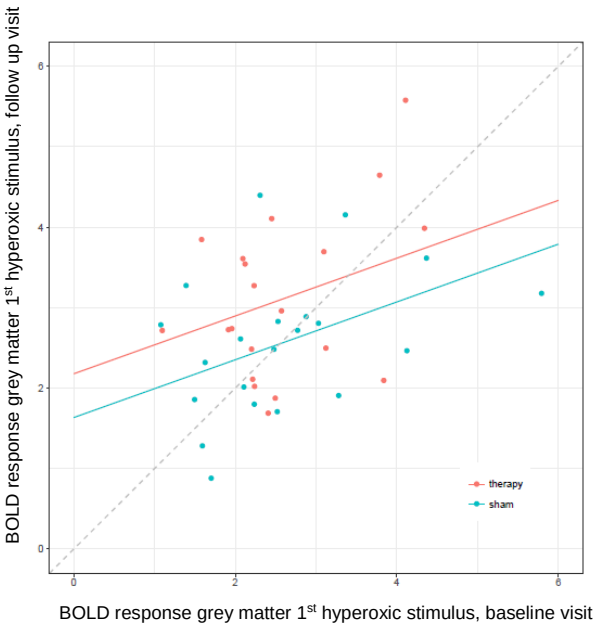
e Figure 2. Subtherapeutic CPAP setup

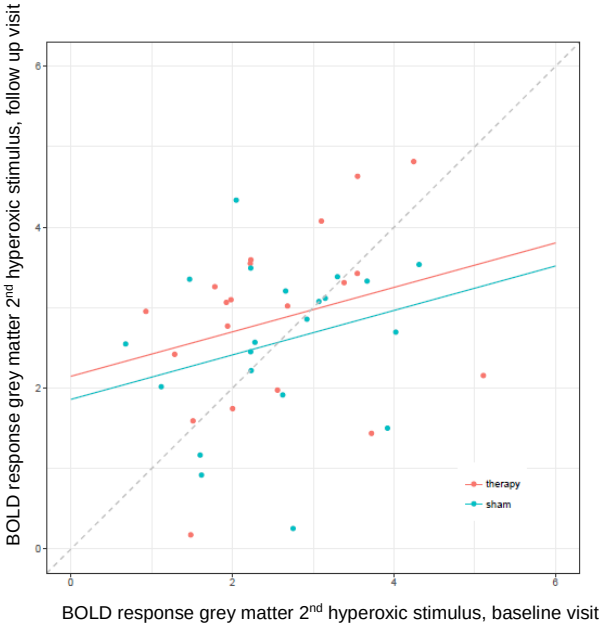
Shown are the different adaptations of the subtherapeutic CPAP device.

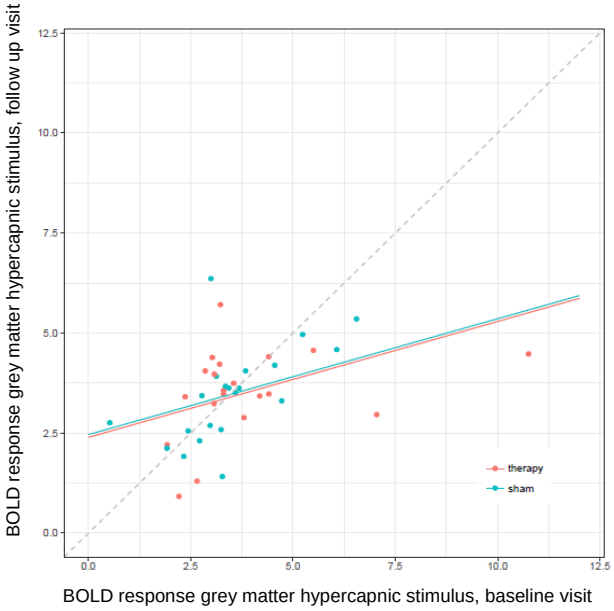


e Figure 3. Adjusted analysis BOLD signal grey matter

Shown is the adjusted comparisons of the BOLD signal change grey matter by treatment arm, adjusted for the same measurement at the previous visit.

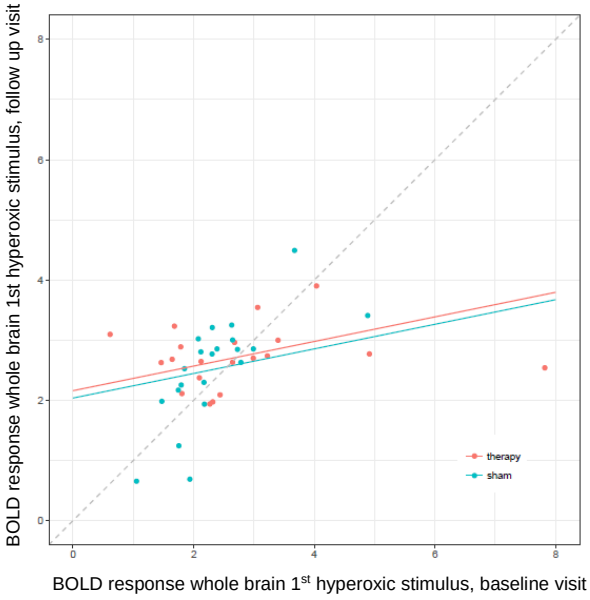


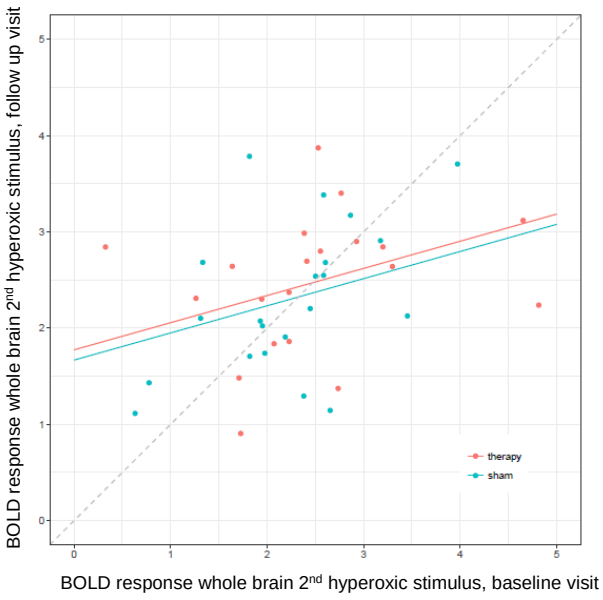


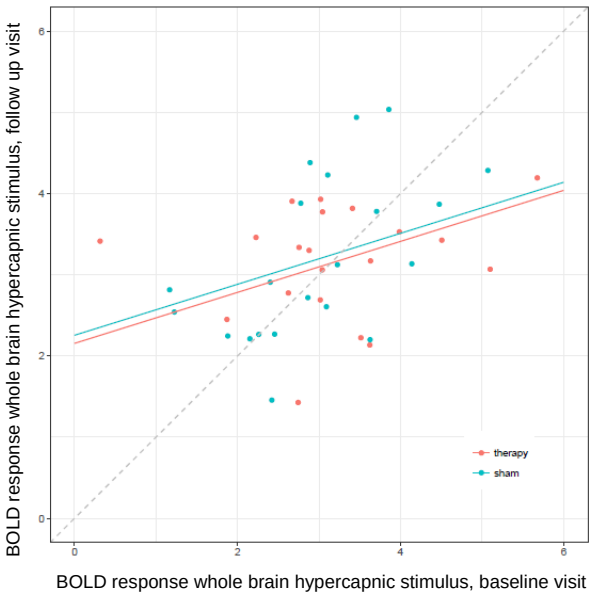


e Figure 4. Adjusted analysis BOLD signal whole brain

Shown is the adjusted comparisons of the BOLD signal change whole brain by treatment arm, adjusted for the same measurement at the previous visit.

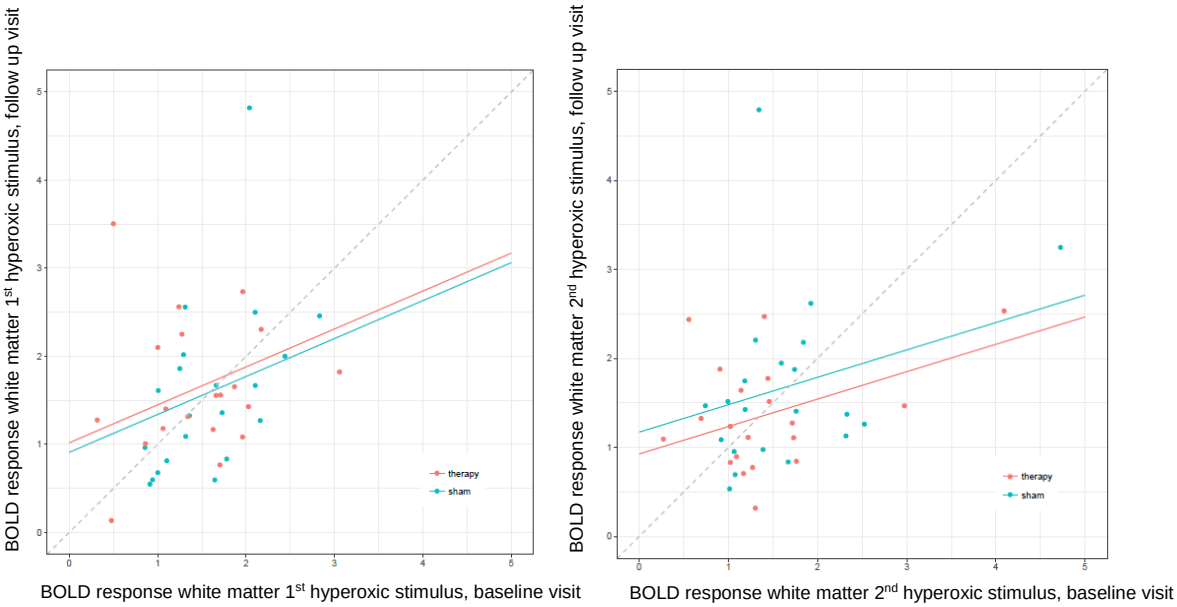


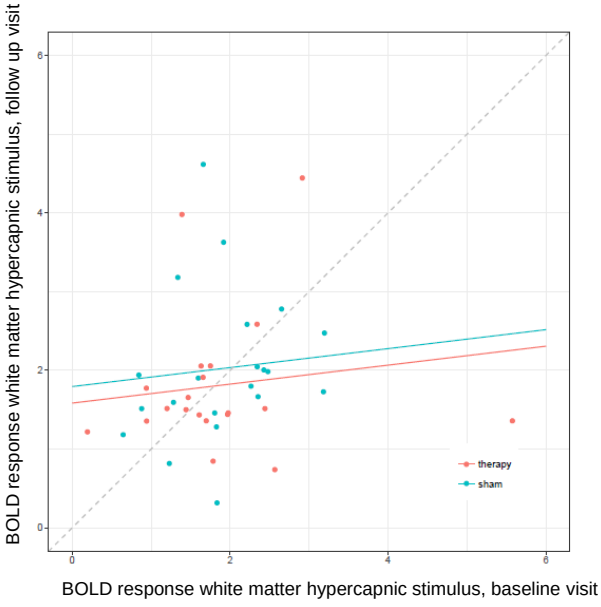




e Figure 5. Adjusted analysis BOLD signal white matter

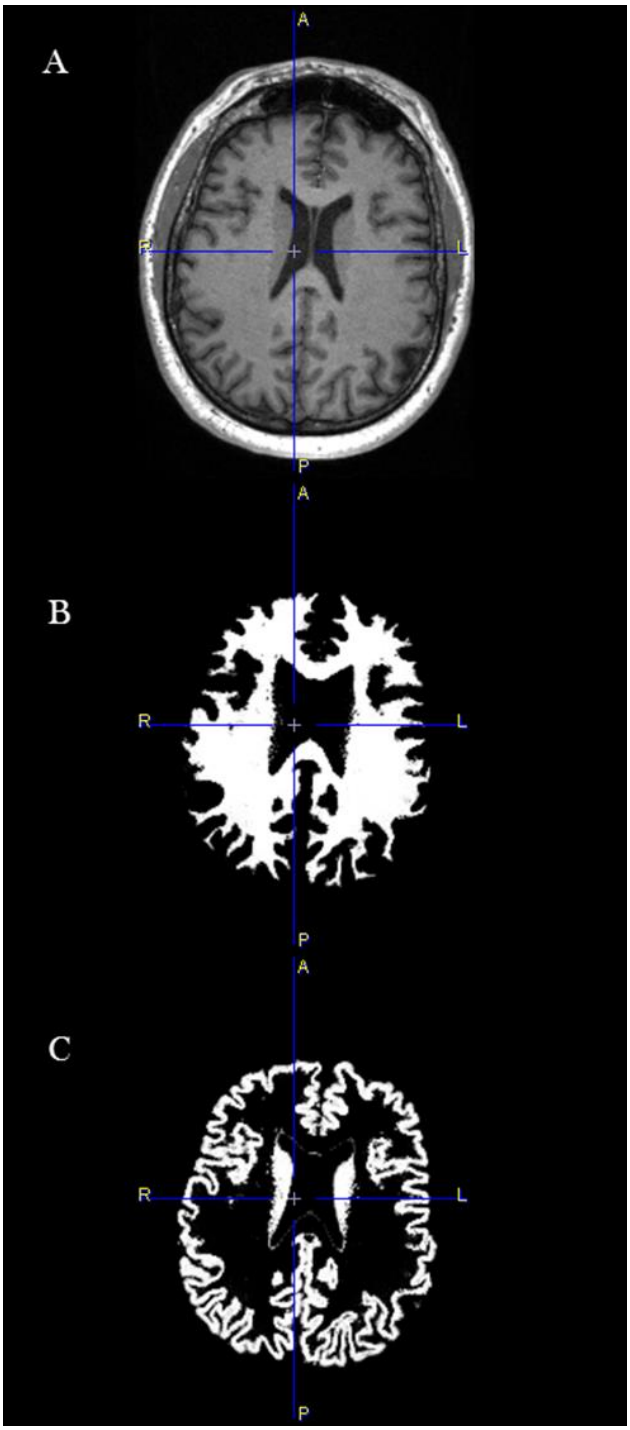
Shown is the adjusted comparisons of the BOLD signal change white matter by treatment arm, adjusted for the same measurement at the previous visit.





e Figure 6. Example of exemplarily cerebral MRI image.

Shown is the T1- weighted anatomical image (A), as well as the segmented white matter (B) and grey matter (C). For segmentation, the automated tool of SPM12 was used.



References

1. Reichmuth KJ, Dopp JM, Barczi SR, Skatrud JB, Wojdyla P, Hayes D, Jr., Morgan BJ. Impaired vascular regulation in patients with obstructive sleep apnea: effects of continuous positive airway pressure treatment. *American journal of respiratory and critical care medicine* 2009; 180: 1143-1150.
2. Micieli G, Bosone D, Costa A, Cavallini A, Marcheselli S, Pompeo F, Nappi G. Opposite effects of L-arginine and nitroglycerin on cerebral blood velocity: nitric oxide precursors and cerebral blood velocity. *Journal of the neurological sciences* 1997; 150: 71-75.
3. Boss A, Martirosian P, Jehs MC, Dietz K, Alber M, Rossi C, Claussen CD, Schick F. Influence of oxygen and carbogen breathing on renal oxygenation measured by T2*-weighted imaging at 3.0 T. *NMR in biomedicine* 2009; 22: 638-645.
4. Martirosian P, Klose U, Mader I, Schick F. FAIR true-FISP perfusion imaging of the kidneys. *Magnetic resonance in medicine* 2004; 51: 353-361.
5. Boss A, Martirosian P, Klose U, Nagele T, Claussen CD, Schick F. FAIR-TrueFISP imaging of cerebral perfusion in areas of high magnetic susceptibility differences at 1.5 and 3 Tesla. *Journal of magnetic resonance imaging : JMRI* 2007; 25: 924-931.
6. Aslan S, Xu F, Wang PL, Uh J, Yezhuvath US, van Osch M, Lu H. Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. *Magnetic resonance in medicine* 2010; 63: 765-771.