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Early View

Original article

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

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Short title: Cerebrovascular reactivity in obstructive sleep apnea

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Take home message: This trial evaluated the effects of CPAP withdrawal and thus untreated OSA on cerebral vascular reactivity (CVR). The recurrence of OSA did not result in a significant reduction of CVR, despite clinically relevant increases in blood pressure.

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Abstract

Introduction: Impaired cerebral vascular reactivity (CVR) increases long-term stroke risk. Obstructive sleep apnoea (OSA) is associated with peripheral vascular dysfunction and vascular events. The aim of this trial was to evaluate the effect of continuous positive airway pressure (CPAP) withdrawal on CVR.

Methods: 41 OSA patients (88% male, mean age 57± 10 yrs.) were randomised to subtherapeutic, or continuation of therapeutic, CPAP. At baseline, and after two weeks, patients underwent a sleep study and magnetic resonance imaging (MRI). CVR was estimated by quantifying the blood oxygen level dependent (BOLD MRI) response to breathing stimuli.

Results: OSA did recur in the subtherapeutic-CPAP group (mean treatment effect apnoea-hypopnoea-index [95%CI] +38.0 [+24.2/+52.0] events/h, p<0.001) but remained controlled in the therapeutic group. Although there was a significant increase in blood pressure upon CPAP withdrawal (mean treatment effect [95%CI] +9.37 [+1.36 to 17.39] mmHg, p=0.023), there was no significant effect of CPAP withdrawal on CVR assessed via BOLD MRI under either, hyperoxic or hypercapnic conditions.

Conclusion: Short-term CPAP withdrawal did not result in statistically significant different changes of CVR assessed by functional MRI despite recurrence of OSA. We thus conclude that unlike peripheral endothelial function, CVR is not affected by short- term CPAP withdrawal.

Key words: Obstructive sleep apnea; continuous positive airway pressure; cerebral vascular reactivity, magnetic resonance imaging

Introduction

In population-based studies, the prevalence of moderate-to-severe sleep-disordered breathing in the middle-aged population is estimated to be between 9%-23% in women and 17% to 50% in men.[1, 2]Obstructive sleep apnoea (OSA), characterized by complete or partial obstruction of the upper airway, causes intermittent hypoxia, hypercapnia, increase of sympathetic nervous system activity, surges in blood pressure, as well as impairment of peripheral vascular function.[3, 4]An association between OSA and increased risk of stroke, cardiovascular events, heart failure, and impaired neurocognitive function has been shown.[5-7] However, the underlying pathophysiological mechanisms are poorly understood. Contrasting findings exist about cerebral vascular reactivity (CVR) and cerebral blood flow (CBF) deregulation in OSA patients and how these impairments contribute to the risk of stroke remains to be clarified. The usage of different imaging techniques, different statistical thresholds, and lack of standardized measurement methods makes it difficult to compare results of previous studies.[8-17]

Functional magnetic resonance imaging (MRI) during respiratory challenges allows estimation of CVR and CBF. [18] Blood-oxygenation-level-dependent MRI (BOLD MRI) is able to detect magnetic field variations induced by changes in oxyhemoglobin and deoxyhemoglobin concentrations. The BOLD signal responds to changes in the arterial gas concentration induced by the administration of gas mixtures or breath holding (BH). [18] While pure oxygen inhalation mostly induces a change in the deoxyhemoglobin concentration and, in turn, a BOLD-signal increase, the administration of gas mixtures

containing carbon dioxide results in an additional vascular modulation of the BOLD response.[19]

CPAP therapy is sometimes interrupted e.g. during upper airway infections or during vacations.These interruptions, and thus recurrence of OSA, might impair CVR and CBF by several possible mechanisms such as impaired endothelial function, augmented sympathetic activity, and an increase in oxidative stress due to intermittent hypoxia as well as reduced cerebral tissue oxygenation.[3, 20] During apnoeic episodes, increases in intracranial pressure, correlating with systemic blood pressure (BP) fluctuations, could result in an excess of flow in brain vessels following apnea termination, leading to capillary damage, as brain tissue is sensitive to rapid reperfusion.[21]. Information on CVR in OSA patients assessed via BOLD MRI is sparse and originates mainly from small and mostly case- control studies. [8, 11, 15, 17]

Thus, we conducted a two-week CPAP-withdrawal randomised controlled trial in patients with moderate-to-severe OSA to examine the link between OSA, CVR and brain perfusion, respectively. We hypothesized that CPAP-withdrawal would result in a reduction of daytime CVR and CBF.

Methods

Trial design

A randomised, double blind, placebo-controlled parallel-group trial (therapeutic vs subtherapeutic CPAP) including 41 patients with moderate -to -severe OSA. Patients had been treated with CPAP for at least one year. Dynamic MRI acquisitions were performed between 07.00 and 09.00 am in the morning during the inhalation of medical air (i.e. 21% O_2), oxygen (99.5% O_2) and carbogen (5% CO_2 +95% O_2). We refer to the situations induced by medical air (MA), oxygen and carbogen by the terms 'normoxia', 'hyperoxia', and 'hypercapnia', respectively. Gases were administered in blocks of 3 minutes each (MA-oxygen-MA-oxygen-MA-carbogen-MA). Participants wore a mask with a one-way valve and a 0.5-L reservoir bag, covering mouth and nose completely, tightly adjusted to the face. We requested the subjects to breathe normally; gas flow rates were set to 10 L/min each (e-Figure 5).

Subjects

Participants were eligible if they met the following inclusion criteria: 1) age between 20-75 years, 2) apnoea-hypopnoea-index (AHI) and/or oxygen desaturation index ($ODI_{4\%}$)≥20/h in their in-laboratory sleep study at the time of diagnosis, 3) treated with CPAP for at least one year with high compliance (device usage ≥4h/night on at least 80% of the past 365 days with

a current AHI≤10/h on treatment, measured from the CPAP machine download data), 4) an $ODI_{4\%}$≥15/h from current nocturnal pulse oximetry studies during a preliminary five-night period off CPAP treatment. The trial was approved by the local Ethics Committee (KEK-ZH-No.2014-0684), and all procedures in this trial involving human participants were performed in accordance to GCP guidelines. The trial was registered prior to commencement (ClinicalTrials.gov-Identifier: NCT02493673). See supplement for details.

Patient evaluation and follow-up

Recruitment started in June 2015 and the last follow-up was completed in December 2017. Once the persistence of relevant OSA was confirmed ($ODI_{4\%}$ ≥15/h) by home overnight pulse oximetry (Pulsox-300i, Konica Minolta Sensing Inc., Osaka, Japan) during the preliminary five-night period off CPAP, patients resumed CPAP-therapy for at least two weeks. An MS-DOS program (MINIM, London, UK) allocated participants by using two minimisation criteria: $ODI_{4\%}$ </> 30/h and body mass index </> 35 kg/m^2. Baseline in-laboratory assessments were performed on all subjects using therapeutic CPAP. Follow-up assessments were performed after two weeks on either therapeutic (control arm) or subtherapeutic CPAP (intervention arm) settings. Participants as well as outcome assessors remained blinded to the treatment assignment until completion of the data analysis.

Sleep studies and CPAP devices

In-hospital respiratory polygraphies (Alice 5 Diagnostics System; Respironics, PA, USA) were scored manually according to the American Academy of Sleep Medicine task force

criteria.[22] The severity of OSA was quantified using the AHI and oxygen desaturations ≥4% per hour ($ODI_{4\%}$). Patients in both groups received the same CPAP device (REMstar Auto A-Flex, Philips Respironics, PA, USA). In the therapeutic group, pressure and mode were set according to the previous individual's settings. In the withdrawal group, subtherapeutic pressure was generated by setting the CPAP device to the lowest pressure, insertion of a flow-restricting connector at the machine outlet, and insertion of six extra holes in the collar of the tube at the end of the mask to prevent rebreathing of CO_2 (e -Figure 4 and 5).

Primary outcome

The primary outcome was CVR in response to hyperoxia and hypercapnia of grey matter, white matter, and the whole brain assessed by functional MRI as measures of cerebral endothelial function. See supplement for details.

Secondary outcome measures

Before gas administration, CBF was assessed using Arterial Spin Labeling (ASL) MRI.

Participants measured their blood pressure (BP) and heart rate (HR) in triplicate every morning, the average of three measurements was used for further analysis.

Subjective sleepiness was assessed by using the Epworth Sleepiness Score (ESS). See supplement for details.

Statistical Methods / Data Analysis

Normally distributed data are expressed as mean (SD) unless stated otherwise. For all outcomes, we calculated an effect size and 95% confidence intervals (CIs) with a linear regression analysis adjusting for treatment group and baseline measurements of the outcome. A multivariable linear regression adjusting for several variables (e.g. sex, age, blood pressure at home and in hospital, AHI, OHI) was also performed to generate and adjust effect size; a two-sided significance level of <0.05 was used to determine statistical significance. The statistical analysis was performed in R (R Core Team, Vienna Austria 2013, R version 3.4.4. [2018.03.15]).See supplement for more information (e – Table 1 and 2).

Results

Trial profile and patient characteristics

The trial flow chart is presented in Figure 1. 49 patients were randomised and allocated to therapeutic (n=27) or subtherapeutic (n=22) CPAP for two weeks. The two trial arms were similar regarding baseline patient characteristics (Table 1).

Effects of CPAP-withdrawal on cerebral vascular reactivity

There was no significant effect of short-term CPAP withdrawal on CVR assessed via BOLD MRI in grey matter (GM), white matter (WM) and whole brain under either, hyperoxic or hypercapnic, conditions (Table 2, and e- Figure 1-3). As expected, the quantitative BOLD response analysis showed an effect on the signal pattern depending on the applied stimulus and tissue type (Figure 2 and 3).

Multivariable linear regression modelling to calculate the treatment effect size, adjusting for baseline measurements, as well as age, sex, SBP, DBP and HR, AHI and ODI, did not change the results significantly (e -Table 1 and 2).

Effects of CPAP-withdrawal on secondary outcomes

Cerebral blood flow (CBF)

A two week CPAP withdrawal was not associated with a significant change of CBF assessed via functional MRI over GM and WM (mean treatment effect GM [95%CI] +4.20 [-0.96 to +9.36] ml/100g/min, p=0.110), (mean treatment effect WM [95%CI] -0.62 [-3.90 to +2.66] ml/100g/min, p=0.700) [Table 3]).

Subjective sleepiness

CPAP withdrawal lead to a statistically significant increase in the ESS compared with continuing CPAP ((mean treatment effect [95%CI] +3.29 [+0.87 to +5.72] points, p=0.009) [Table 3]).

Ambulatory blood pressure and heart rate

Discontinuation of CPAP for two weeks compared with continuing CPAP lead to a statistically significant increase in systolic BP (mean treatment effect [95%CI] +9.37 [+1.36 to + 17.39] mmHg, p=0.023), and diastolic BP (mean treatment effect [95%CI] +7.61 [+1.40 to +13.83] mmHg, p=0.018). There was a trend towards an increase in HR in the subtherapeutic CPAP group (mean treatment effect [95%CI] +4.01 [-0.37 to +8.40] mmHg, p=0.071) [Table 3]).

Effects of CPAP-withdrawal on OSA

Withdrawal of CPAP was associated with return of OSA as demonstrated by a significant increase in AHI (mean treatment effect [95%CI] +38.0 [+24.2 to + 52.0] events/h, p<0.0001) and ODI (mean treatment effect [95%CI] +38.0 [+23.1 to +53.0] events/h, p<0.0001) [Table 3]) at two weeks.

Discussion

This randomised controlled trial investigated the possible changes of CVR and CBF induced by short-term withdrawal of CPAP in patients with moderate- to- severe OSA. The recurrence of OSA upon CPAP withdrawal was documented by a return of sleep-disordered

breathing as well as increased sleepiness and BP. Contrary to our hypothesis, there was no significant effect of short-term CPAP withdrawal on daytime CVR as a measure of cerebral endothelial function or on daytime CBF assessed by functional MRI.

A causal relationship between OSA, peripheral endothelial dysfunction and BP has been demonstrated; these measures of cardiovascular risk improve with CPAP treatment.[3, 4] Further evidence from a randomised controlled trial indicated a protective effect of CPAP from severe nocturnal cerebral hypoxia similar in magnitude and duration compared to values causing cerebral dysfunction during unilateral carotid artery clamping during neurosurgery, assessed via near-infrared spectroscopy.[20]. Observational studies have also described that the use of CPAP, especially among patients with high treatment adherence, is associated with lower incidence and relative risk reduction of stroke.[23, 24] However, a recent randomised controlled trial has not shown reduction in major cardiovascular endpoints in OSA patients with manifest cardiovascular disease allocated to CPAP.[25] Therefore, the beneficial effect of CPAP treatment on major cardiovascular outcomes has been subject to extensive discussion. [26, 27]

Several techniques have been used to asses CVR, such as transcranial Doppler ultrasonography (TCD) and positron emission tomography (PET) or single photon emission computed tomography (SPECT).[28-30] However, MRI provides the possibility to map the entire brain with high spatial resolution without the use of radiation and higher reliability compared to ultrasound methods.[31, 32] The utilization of BOLD and ASL MRI enables to investigate two separate, but complementary aspects of the vascular regulation. Baseline CBF is age- depended and higher in the GM compared to the WM due to the differences in

metabolic demands, neural activity, and vascular anatomy. Although hyperoxia is believed to be a mild vasoconstrictor, the absence of negative BOLD signal changes implies that oxygen-induced vasoconstriction plays a minor role in brain perfusion in contrast to CO_2, being a strong vasodilator.[33-35] In the literature, the average BOLD response to hyperoxia induced by breathing of 100% O_2 in healthy controls is in the order of 1% in the WM and of 3% in the GM. The overall signal change induced by hypercapnia in the brain, on the other hand, has a mean magnitude of 2-3%.[33, 36, 37] Our results are in line with the literature concerning the dependence of the response from the stimulus and from the tissue type (Table 2, Figure 2 - 3).

Assuming autonomic impairments could possibly contribute to cerebral injury, Macey et al. performed different tasks (handgrip, cold stimulus, Valsalva manoeuvre) in treatment naïve OSA patients based on previous reported time-lagged and weaker HR responses to blood pressure changes.[11, 38] Interestingly, they did not find a significant BOLD signal change during Valsalva manoeuvre in the OSA group compared to healthy controls. Although HR changes occurred during the challenge in the latter study, the BOLD signal response was not delayed, suggesting that cerebral auto regulatory mechanisms may adopt faster than peripheral autonomic regulatory pathways.[11] Thus, our finding of BOLD responses with a mean magnitude comparable with responses described in healthy controls, as a surrogate measure of CVR could reflect an underlying regulatory mechanism including the cerebral vasculature to ensure blood supply and CVR, hitherto not studied in OSA patients.

In contrast to these results, others have described reductions of CVR in the brainstem during swallowing in OSA patients.[8] This finding was interpreted as a potential contributor to the pathogenesis of OSA as altered brainstem CVR may be involved in the control of upper

airway muscles. Prilipko et al. described significantly higher CVR in several brain regions in healthy subjects compared to age-matched OSA patients. Furthermore, they described that CPAP treatment in the OSA group led to an improvement in CVR but was not associated with a change of CBF after two months. However, the observed changes were neither homogeneous nor did they follow major vascular territories.[13]

GM CBF values reported in two prior studies were comparable with our results.[10, 16] In addition, decreased, as well as increased, CBF values in various brain areas of awake, untreated OSA patients assessed by ASL MRI have been described.[9, 10, 12-14, 16].We choose to perform ALS measurements assessing cerebral blood flow in absence of evoked responses or challenges. Measuring CBF in this setup is comparable with those of previous studies. [9, 10, 12, 13, 16] To further refine detection of brain blood flow changes, measurements using ALS also during respiratory challenges could potentially provide additional information.[17]

When interpreting the BOLD signal response, several important considerations need to be taken into account. Carbon dioxide is an important modulator of vascular tone and has an influence on systemic BP, via the activation of the sympathetic nervous system, which may in turn affect CVR. [39, 40] To address this issue in TCD studies, the cerebrovascular conductance index (CCI) has been introduced. The CCI takes the BP into account by dividing the cerebral artery velocity trough the mean arterial BP (MAP).[41] Ryan et al. described normal hypercapnic cerebrovascular conductance in OSA patients, and in particular no overnight decline in conductance CVR. Moreover, they did not find any difference between the OSA and healthy control group regarding the MAP response. [40] Others have described that interpretation of the CVR results after correction for BP changes is more accurate in TCD

measurements, therefore continuous monitoring of BP during the scan would be desirable.[42] However, it is important to mention, that TCD studies themselves have the limitation to measure blood flow velocity, rather than volumetric flow itself, which is only representative of blood flow if the diameter of the insonated vessel remains constant. [43, 44] Up to date all studies assessing OSA and CVR via BOLD MRI lacked continuous BP recording during the scan.[8, 11, 13, 15, 17]

Furthermore, the relaxation of vascular smooth vessels and increasement of CBF is not always characterized by a linear, but by a sigmoidal relationship, with attenuated responses at the extremes, presuming that BP is constant.[18] Under circumstances when vessels are maximally dilated in response to low systemic BP (e.g. hypovolaemia) the vascular response to hypercapnia is subdued and once the vasodilation mediated through CO_2 has reached its limit, increases in perfusion pressure could lead to passive CBF increases. [18, 41]

However, TCD measurements in OSA subjects using the Duffin rebreathing method showed that the maximum P_{ETCO2} achieved did not differ between OSA and healthy controls. [40] Although rises of the P_{ETCO2} up to 57 mmHg were achieved, most of the responses were not suitable for a sigmoidal fitting. [40]

Furthermore, preliminary results on BOLD signal modeling and vascular resistance, described the possibility of differentiating multiple CBF response patterns based on CO_2 stimuli.[45] While this is an interesting research approach, these models assume MAP, neural activation and metabolism to be constant, which is not the case in a clinical setting.[46]

However, there are several more factors potentially contributing to the complexity of this topic, e.g. viscosity and composition of the blood, the role of cardiac output or rate of cerebral local oxygen consumption. [47] Indeed, direct assessment of CBF, arterial BP and

other parameters, using invasive methods such as thermal diffusion are only employed in critical ill patients.

We did not measure and adjust for gas concentrations delivered to, or expired by, the subjects. Poinsang et al. measured end-tidal gas concentration during breathing of 5%CO_2 enriched air and BH- BOLD MRI. They found no difference between OSA patients and controls in the BOLD response to hypercapnia. Even when adjusted for the change in O_2/CO_2 levels of the hypercapnia BOLD CVR response, the result was still not significant. [17] However, for any future studies on this topic, we suggest that measurement of gases delivered to and expired by the subject should be monitored by using computerized gas control systems, which provide precise and repeatable sequences of P_{ETCO2} and P_{ETO2}.[17] As MRI measurements were performed in the morning, we cannot exclude that there is an impairment of CBF or CVR during nocturnal apnoeic episodes. Another possible limitation is the withdrawal period of two weeks, which might not be sufficient to show the full extent of OSA recurrence and its consequences on CVR and CBF. Furthermore, the current trial population only consisted of a selected group of patients with vascular risk factors (i.e. hypertension, dyslipidaemia, diabetes) and optimal therapy compliance, but without any known major cerebral vascular pathologies or a history of stroke. Thus, there might be a different response to CPAP withdrawal in patients with previous cerebrovascular events.

In conclusion, despite the recurrence of OSA and its immediate effects on blood pressure we found no effect of CPAP withdrawal on CVR or CBF assessed by functional MRI.

In particular, daytime CVR did not show any significant reduction after two weeks of CPAP withdrawal, assuming that CVR regulation seems to outlast other pathophysiological effects

of OSA in the short term. We suggest that also other mechanisms besides changes in CVR must be considered to attribute to the increased risk of stroke.

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Conflicts of Interest

ST, FL, PR, CR, SRH, EIS, ASS, NAS, ASB, SW and AB have nothing to disclose.

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Tables

Table 1. Baseline characteristics of the trial population.

	Subtherapeutic CPAP (n=21)	**Therapeutic CPAP (n=20)**
Age, years (mean±SD)	56.2 ± 9.2	57.6 ± 11.1
Male gender, n (%)	20 (95%)	16 (80%)
BMI, kg/m^2 (mean±SD)	35.1 ± 5.6	32.8 ± 7.2
Comorbidities		

Hypertension, n (%)	10 (48%)	10 (50%)
Diabetes mellitus, n (%)	6 (29%)	4 (20%)
Dyslipidaemia, n (%)	2 (10%)	2 (10%)
Obesity, n (%)	17 (81%)	14 (70%)
Medications		
ACE Inhibitor, n (%)	3 (14%)	6 (30%)
AT 2 Antagonist, n (%)	5 (24%)	2 (10%)
Calcium Channel Blocker, n (%)	5 (24%)	5 (25%)
Diuretics, n (%)	4 (19%)	6 (30%)
AD, n (%)	6 (29%)	4 (20%)
Statins, n (%)	4 (19%)	5 (25%)
Other medication, n (%)	10 (48%)	15 (75%)
OSA Severity and CPAP usage		
ODI 5 nights off CPAP, events per hour	42.3 ± 23.6	37.0 ± 16.2
AHI under CPAP, events per hour	2.9 ± 2.0	2.1 ± 2.2
CPAP usage, % days in one year	94.8 ± 6.9	96.0 ± 5.0
CPAP usage, hours	6.1 ± 1.3	6.4 ± 1.3

ACE, angiotensin converting enzyme; AD, antidiabetic drugs; AHI apnoea/hypopnea index; AT 2, angiotensin II blocker; BMI, body mass index; CPAP, continuous positive airway pressure; ODI, oxygen desaturation index. Data are presented as mean±SD unless stated otherwise.

Table 2. BOLD MRI signal changes during hyperoxic and hypercapnic challenges.

		Subtherapeutic CPAP group N=21			Therapeutic CPAP group N=20				
		Baseline	**Follow-up**	**Change**	**Baseline**	**Follow-up**	**Change**	**Treatment effect***	**p-value***
BOLD signal change in %, grey matter	O_2 1st	2.61 ± 1.13	2.57 ± 0.87	-0.04 ± 1.14	2.59 ± 0.86	3.11 ± 1.01	0.52 ± 1.02	-0.54 (-1.10 to 0.02)	0.056
	O_2 2nd	2.57 ± 0.97	2.57 ± 1.00	0.00 ± 1.24	2.56 ± 1.09	2.85 ± 1.12	0.30 ± 1.28	-0.29 (-0.94 to 0.37)	0.38
	CO_2	3.49 ± 1.37	3.47 ± 1.21	-0.02 ± 1.18	3.89 ± 2.00	3.52 ± 1.12	-0.37 ± 2.00	0.07 (-0.61 to 0.75)	0.84
BOLD signal change in %, overall brain	O_2 1st	2.36 ± 0.81	2.52 ± 0.89	0.16 ± 0.66	2.75 ± 1.53	2.72 ± 0.50	-0.03 ±1.56	-0.12 (-0.57 to 0.32)	0.58
	O_2 2nd	2.24 ± 0.82	2.30 ± 0.79	0.06 ± 0.81	2.47 ± 1.03	2.47 ± 0.72	0.00 ± 1.11	-0.11 (-0.56 to 0.35)	0.64
	CO_2	2.96 ± 0.99	3.19 ± 1.00	0.22 ± 0.93	3.18 ± 1.14	3.15 ± 0.70	-0.03 ± 1.23	0.10 (-0.42 to 0.62)	0.70
BOLD signal change in %, white matter	O_2 1st	1.56 ± 0.55	1.58 ± 0.98	0.02 ± 0.86	1.45 ± 0.66	1.64 ± 0.76	0.19 ± 0.97	-0.11 (-0.65 to 0.43)	0.69
	O_2 2nd	1.65 ± 0.86	1.68 ± 0.97	0.03 ± 1.05	1.41 ± 0.84	1.36 ± 0.61	-0.05 ± 0.88	0.24 (-0.26 to 0.75)	0.33
	CO_2	1.90 ± 0.71	2.02 ± 0.96	0.12 ± 1.09	1.87 ± 1.07	1.81 ± 0.92	-0.07 ± 1.36	0.21 (-0.39 to 0.81)	0.48

BOLD, Blood-oxygen-level dependent, CPAP, continuous positive airway pressure. Values are presented as mean ± SD for the individual outcomes, or mean (95%CI) for the treatment effects.

* treatment effect (mean follow-up measurement in the subtherapeutic CPAP arm minus mean follow-up measurement in the therapeutic CPAP arm), adjusted for baseline of subtherapeutic CPAP

Table 3. Secondary outcomes.

	Treatment effect after two weeks CPAP withdrawal (95% CI)	**Adjusted p-value***
CBF grey matter, ml/100g/min	4.20 (-0.96 to 9.36)	0.110
CBF white matter, ml/100g/min	-0.62 (-3.90 to 2.66)	0.700
systolic morning blood pressure, mmHg	9.37 (1.36 to 17.39)	0.023
diastolic morning blood pressure, mmHg	7.61 (1.40 to 13.83)	0.018
heart rate, bpm	4.01 (-0.37 to 8.40)	0.071
Apnoea to hypopnea index, events per h	38.0 (24.2 to 52.0)	<0.001
Oxygen desaturation index, events per h	38.0 (23.1 to 53.0)	<0.001
Epworth Sleepiness Scale, points (max. 24)	3.29 (0.87 to 5.72)	0.009

* adjusted for baseline; bpm, beats per minute; CBF, cerebral blood flow; CI, confidence interval; CPAP, continuous positive airway pressure. Blood pressure data from 14 days home measurements

Figure Legends

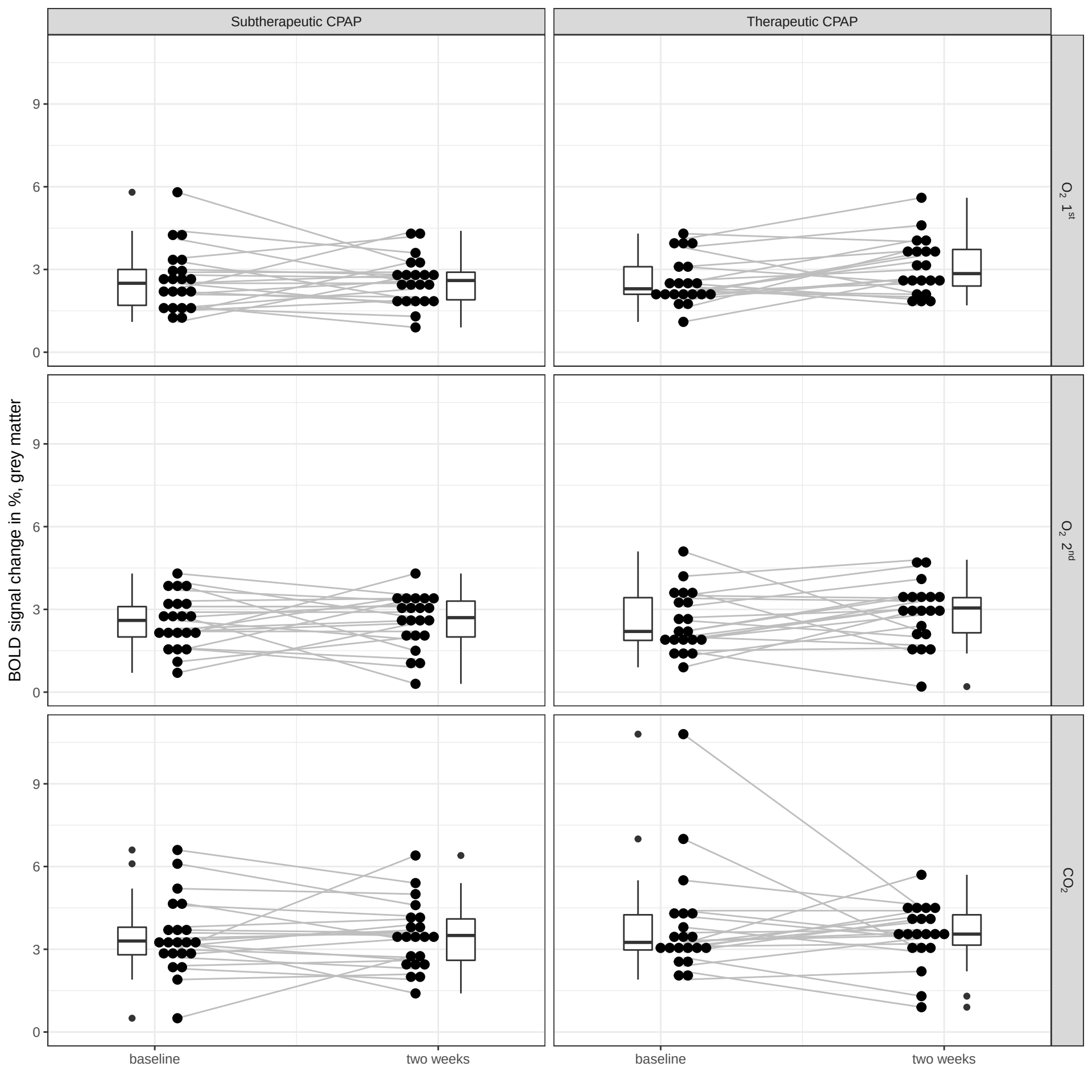
Figure 1. CONSORT Flow Diagram

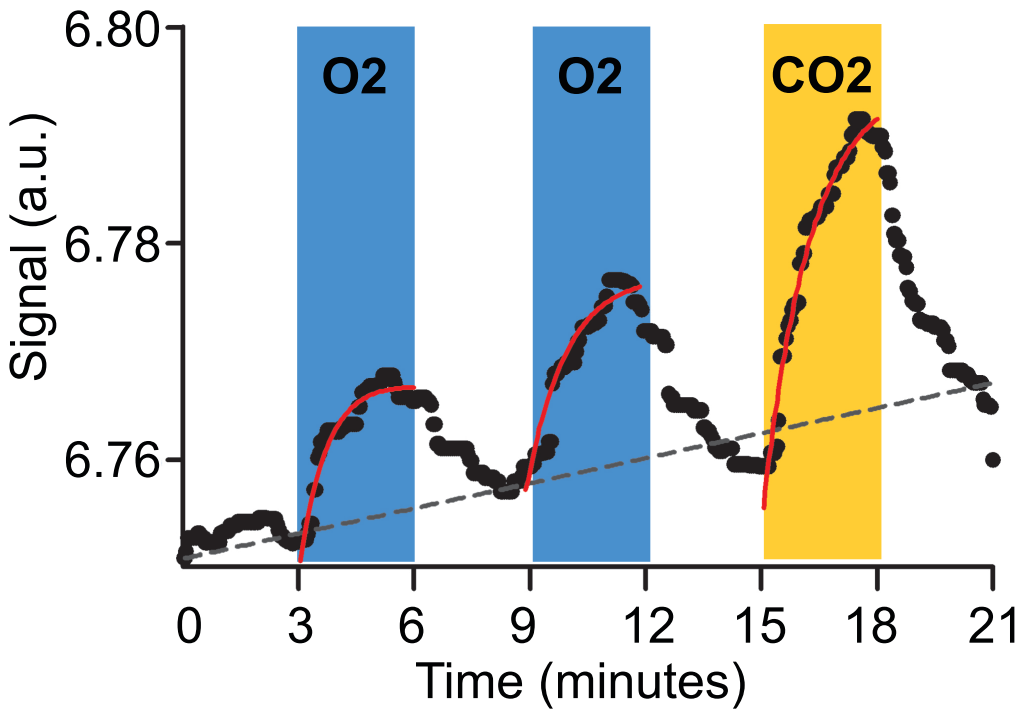
Figure 2. BOLD signal change grey matter in %. Shown is the subtherapeutic CPAP group on the left and the therapeutic CPAP group on the right. The boxplots are shown for the first and second hyperoxic stimulus (O_2 1^{st} and O_2 2^{nd}) as well as the hypercapnic stimulus (CO_2) at baseline and follow- up after two weeks.

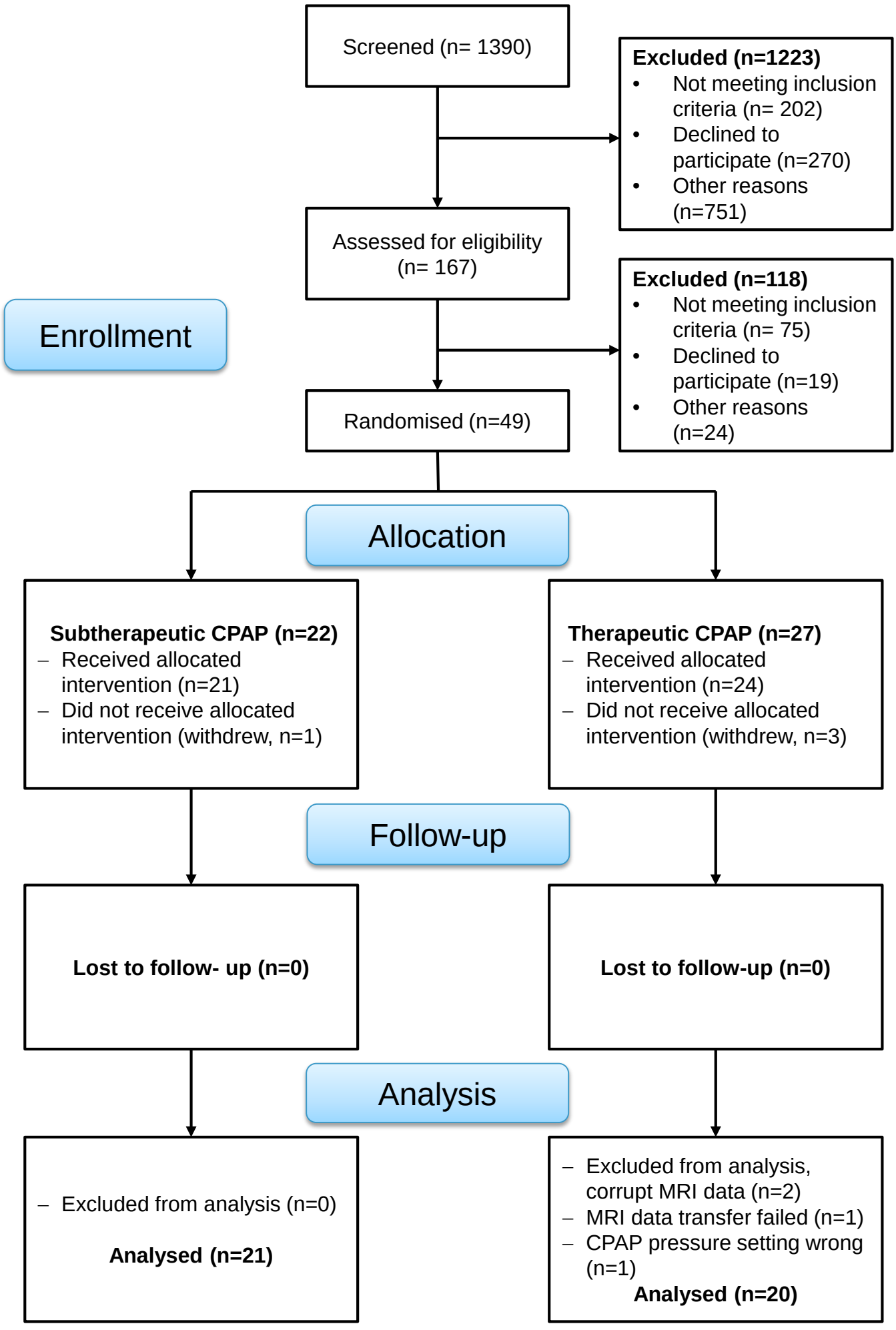
Figure 3. Example of a BOLD-signal curve of a random participant. The grey line indicates shift correction of the scanner. The hyperoxic stimuli are presented in blue colour and the hypercapnic stimulus in yellow colour. The red lines are the mathematically fitted curves. The black dots represent the BOLD signal acquisition. On the y- axis, the signal change is shown in arbitrary units (a.u.).

Abbreviations

3T	Three tesla
AHI	Apnoea-hypopnoea-index
ASL	Arterial spin labelling
BMI	Body mass index
BOLD	Blood oxygen level dependant
BP	Blood pressure
CBF	Cerebral blood flow
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CVR	Cerebral vascular reactivity
ESS	Epworth Sleepiness Scale
HR	Heart rate
MRI	Magnetic resonance imaging
O_2	Oxygen
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
RCT	Randomised controlled trial


Subtherapeutic CPAP
Therapeutic CPAP
O_2 1st
O_2 2nd
CO_2
BOLD signal change in %, grey matter
0
3
6
9
baseline
two weeks


6.80
6.78
6.76
Signal (a.u.)
O2
O2
CO2
0
3
6
9
12
15
18
21
Time (minutes)


Screened (n= 1390)
Excluded (n=1223)
• Not meeting inclusion criteria (n= 202)
• Declined to participate (n=270)
• Other reasons (n=751)
Assessed for eligibility (n= 167)
Enrollment
Excluded (n=118)
• Not meeting inclusion criteria (n= 75)
• Declined to participate (n=19)
• Other reasons (n=24)
Randomised (n=49)
Allocation
Subtherapeutic CPAP (n=22)
– Received allocated intervention (n=21)
– Did not receive allocated intervention (withdrew, n=1)
Therapeutic CPAP (n=27)
– Received allocated intervention (n=24)
– Did not receive allocated intervention (withdrew, n=3)
Follow-up
Lost to follow- up (n=0)
Lost to follow-up (n=0)
Analysis
– Excluded from analysis (n=0)
Analysed (n=21)
– Excluded from analysis, corrupt MRI data (n=2)
– MRI data transfer failed (n=1)
– CPAP pressure setting wrong (n=1)
Analysed (n=20)

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 SpO2 ≤93% and/ or PaCO2 ≥ 6 kPa), 10) Cheyne-Stokes breathing, 11) professional driving, 12) previously reported sleep-related traffic accidents and 13) chronic obstructive pulmonary disease.

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)

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:

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

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

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

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

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.

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.

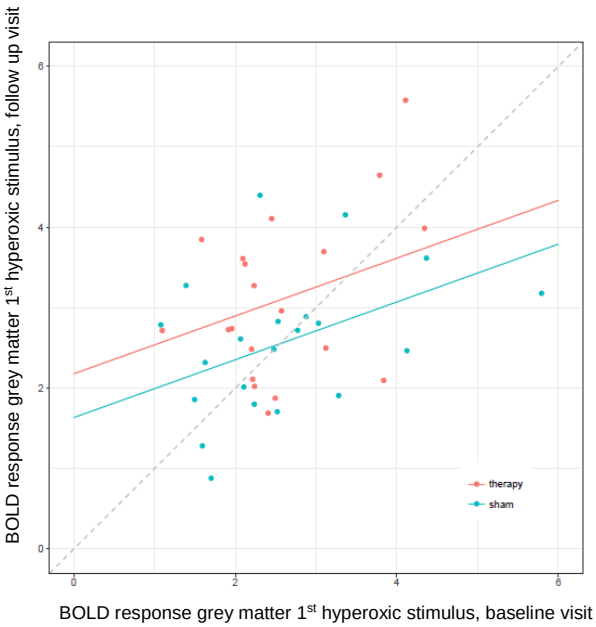
e Table 3. Follow- up characteristics by study arm

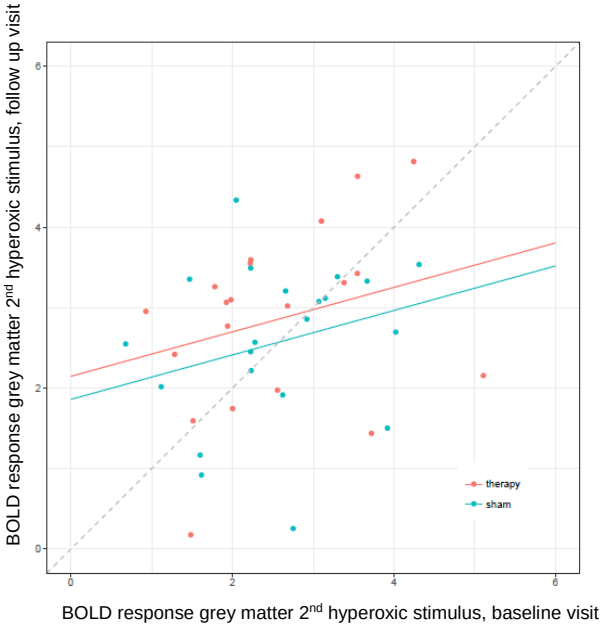
	Subtherapeutic CPAP (n=21)	**Therapeutic CPAP (n=20)**	**p-value**
Apnoea to hypopnea index, events per h	46.73(28.28)	4.34(3.85)	<0.001
CPAP usage, hours (IQR)	01:41(0 to 2:37)	06:48(06:25 to 07:24)	<0.001
Epworth Sleepiness Scale, points (max. 24)	11.9(5.5)	7.65(3.86)	0.007

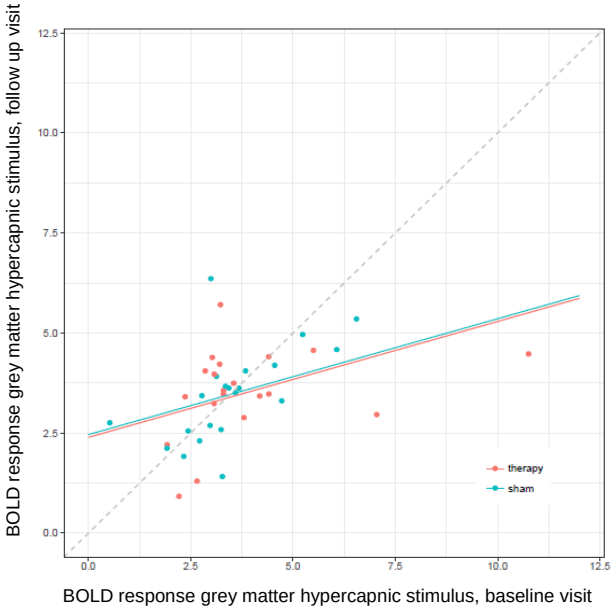
CPAP, continuous positive airway pressure. Data are presented as mean±SD unless stated otherwise.

e Figure 1. 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.

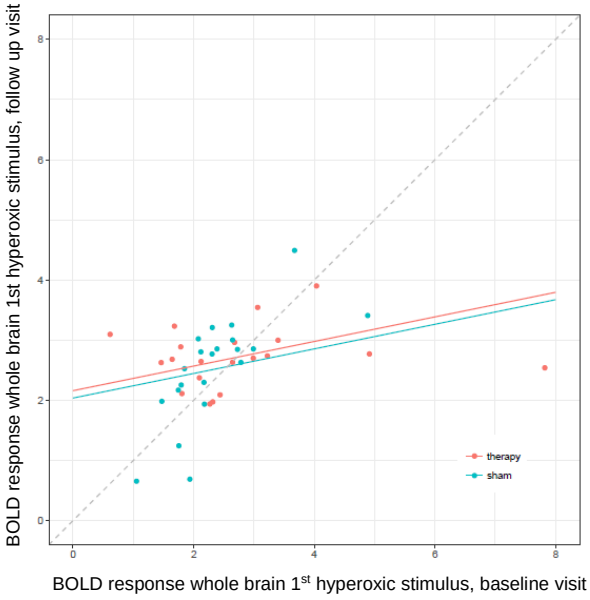


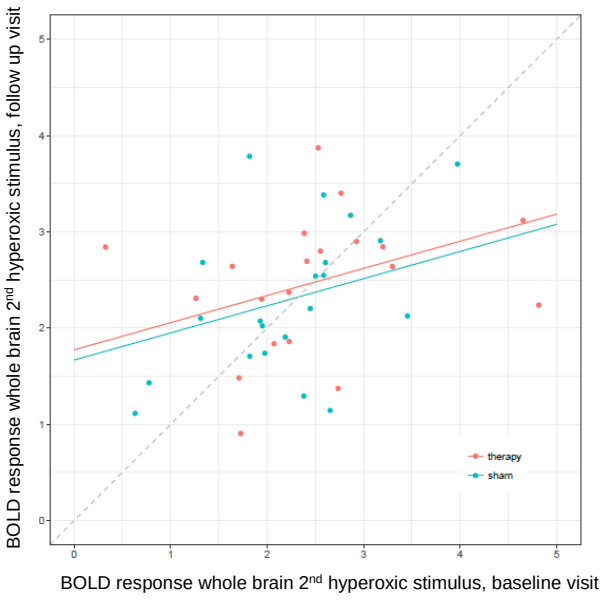


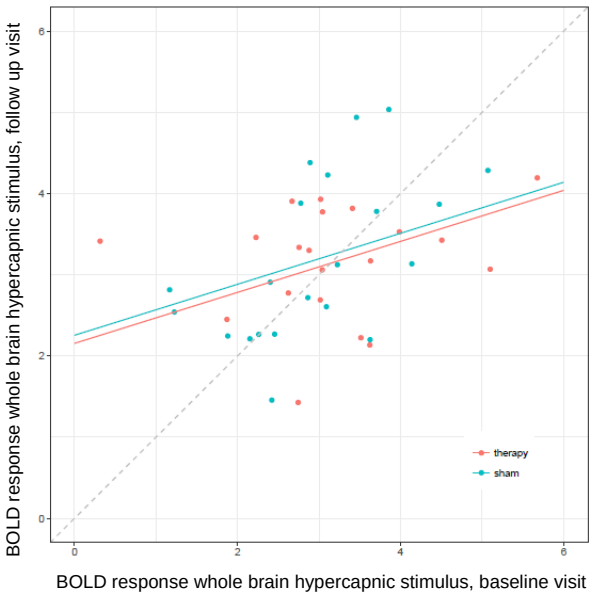


e Figure 2. Adjusted analysis BOLD signal whole brain

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

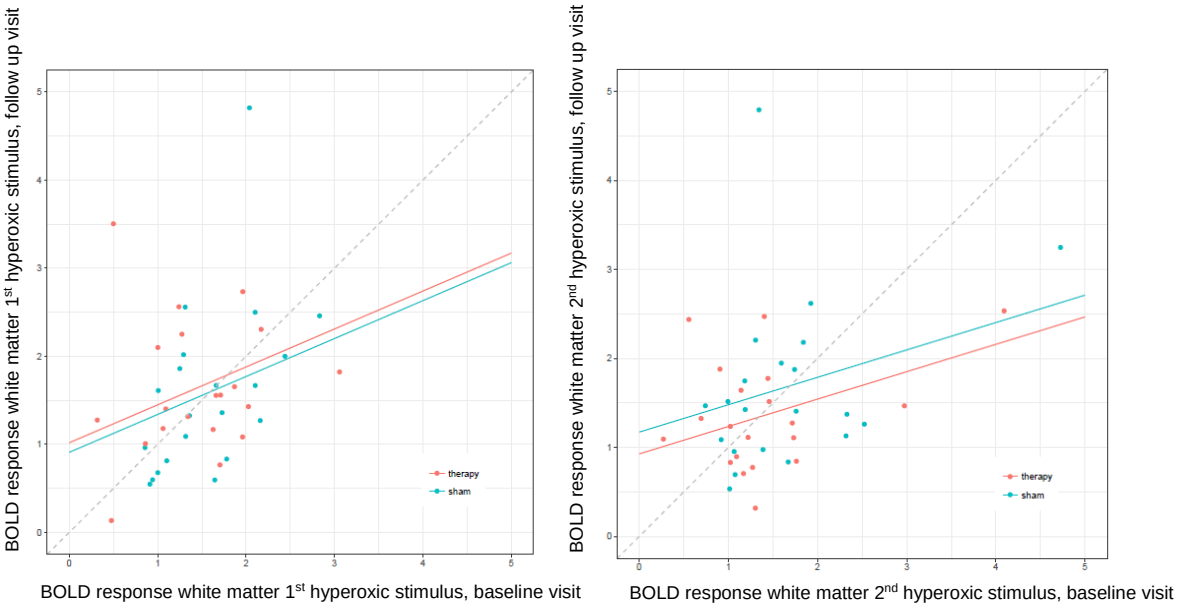


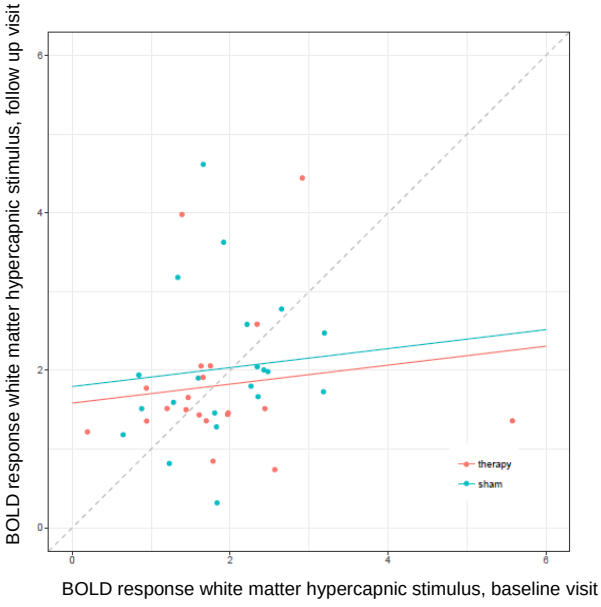




e Figure 3. Adjusted analysis BOLD signal white matter

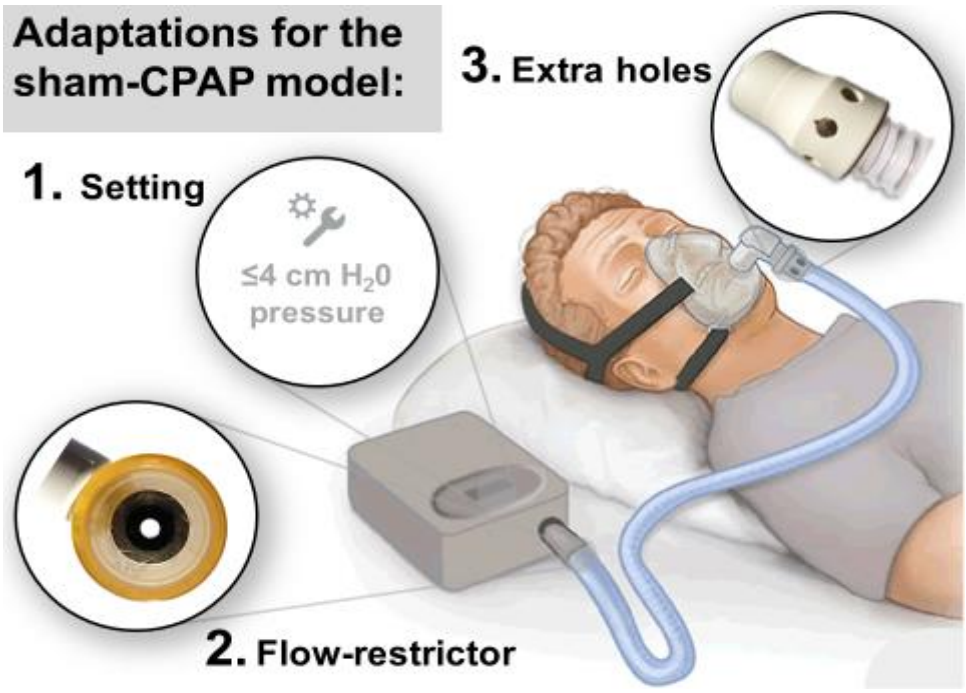
Shown is the adjusted comparisons of the BOLD signal change white matter by treatment arm, adjusted for the same measurement at the previous visit.





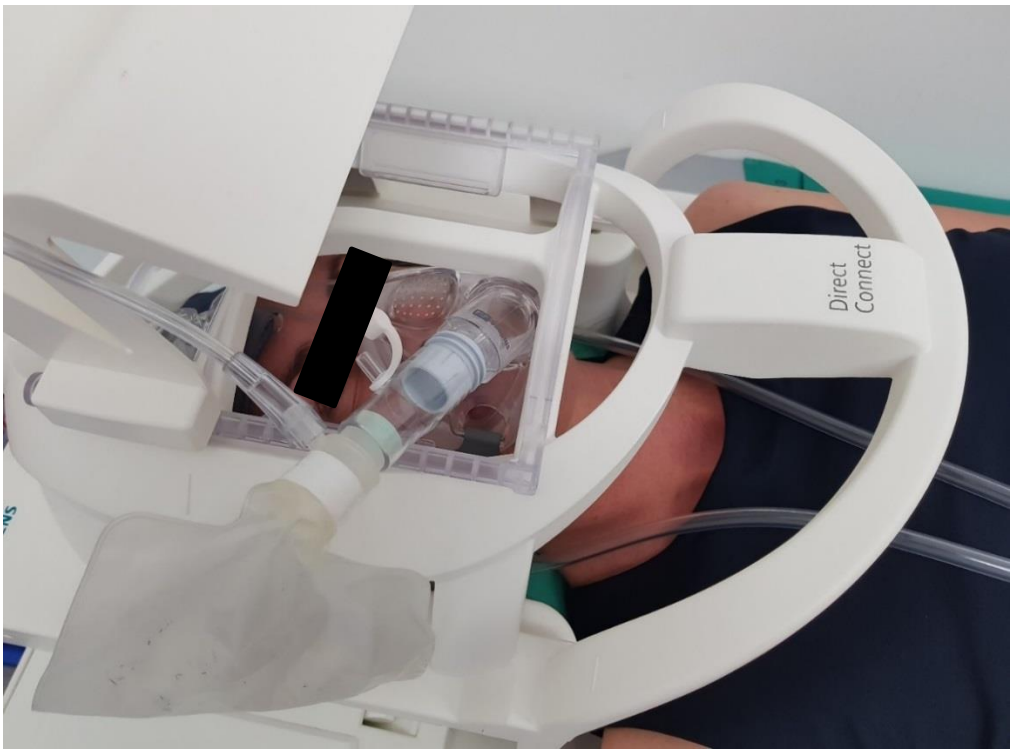
e Figure 4. Subtherapeutic CPAP setup

Shown are the different adaptations of the subtherapeutic CPAP device.



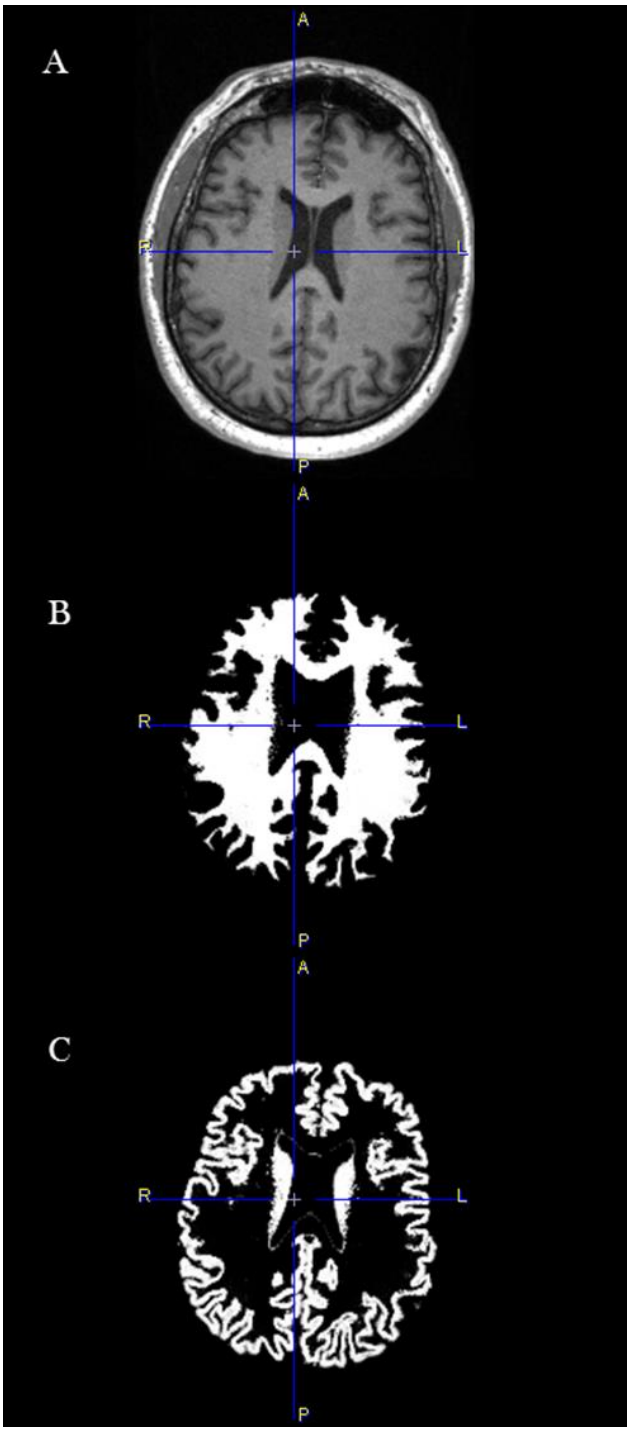
e Figure 5. Study mask setup

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



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.



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