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Simultaneous-multi-slice (SMS) acquisition enhances the sensitivity of hemodynamic mapping using gas challenges

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Abstract

Hemodynamic mapping using gas inhalation has received increasing interests in recent years. Cerebrovascular reactivity (CVR), which reflects the ability of the brain vasculature to dilate in response to a vasoactive stimulus, can be measured with CO₂ inhalation while continuously acquiring BOLD MRI images. Cerebral blood volume (CBV) can be measured with O₂ inhalation. These hemodynamic mapping methods are appealing because of their absence of gadolinium contrast agent, ability to assess both baseline perfusion and vascular reserve, and utility in calibrating fMRI signal. However, like other functional and physiological indices, a major drawback of these measurements is their poor sensitivity and reliability. Simultaneous multi-slice (SMS) EPI is a fast-imaging technology that allows the excitation and acquisition of multiple 2D slices simultaneously, and has been shown to enhance the sensitivity of several MRI applications. To our knowledge, the benefit of SMS in gas inhalation imaging has not been investigated. In this work, we compare the sensitivity of CO₂ and O₂ inhalation data collected using SMS factor 2 (SMS 2) and SMS factor 3 (SMS 3) with those using conventional EPI (SMS 1). We showed that the sensitivity of SMS scans was significantly ($p=0.01$) higher than that of conventional EPI, although no difference was found between SMS 2 and SMS 3 ($p=0.3$). On a voxel-wise level, approximately 20-30% of voxels in the brain showed a significant enhancement in sensitivity when using SMS compared to conventional EPI, with other voxels showing an increase but not reaching statistical significance. When using SMS, the scan duration can be reduced by half while maintaining the sensitivity of a conventional EPI. The availability of a sensitive acquisition technique can further enhance the potential of gas inhalation MRI in clinical applications.

Graphical abstract

In this work, we investigated the benefit of simultaneous-multi-slice (SMS) acquisition for gas inhalation imaging. We showed that sensitivity of CO₂ and O₂ inhalation data collected using SMS (SMS2 & SMS3) acquisition is higher when compared with the convention EPI acquisition

(SMS1). The sensitivity improvement of SMS acquisition was present throughout the brain. Furthermore, we found that using SMS, the scan duration can be reduced by half while maintaining the sensitivity of a conventional EPI.

Keywords

Cerebrovascular reactivity; CO₂; MRI; Gas inhalation; Brain; SMS

Introduction

Assessment of brain hemodynamic function is of significant value in pathological conditions such as steno-occlusive condition (1-3), stroke (4, 5), brain tumor (6) and dementia (7, 8) and in proper interpretation of functional MRI signal (9-11). Hemodynamic mapping using gas challenges has received increasing attention in recent years (12-15), due to several advancements including increasing availability of breathing apparatus (16-18), development of more comfortable breathing paradigm (19), and more sophisticated analysis tools (20). Compared to the current clinical standard of gadolinium-based perfusion imaging which measures baseline perfusion parameters only, gas-based hemodynamic imaging has the capacity of providing both baseline and reactivity evaluations of cerebral vessels. Furthermore, gas challenge does not require the consideration of glomerular filtration rate and thus may become an important alternative for patients who cannot receive gadolinium-based contrast agent.

Gas challenge studies typically use the inhalation of carbon dioxide (CO₂) and oxygen (O₂), interleaved with room air breathing, while collecting BOLD MR images continuously. BOLD response to O₂ reflects a baseline parameter, cerebral blood volume (CBV), while BOLD response to CO₂ represents the dilatory capacity of the arterial vasculature to a vasoactive stimulus, commonly referred to as cerebrovascular reactivity (CVR). Importantly, the CO₂ and O₂ challenges can be applied concomitantly using newer breathing paradigms (21).

BOLD signal change to CO₂ and O₂ inhalation is on the order of 2-3%. Although it is greater than typical fMRI signal (0.5-1%), this magnitude of signal is still considerably lower than that observed in contrast agent experiments (10-30%) (22). Therefore, improving sensitivity of this technique is an imminent issue, in order for it to become a complementary technique to the conventional perfusion methods. Over the past few years, fMRI studies have

increasingly adopted a fast image acquisition technique known as simultaneous-multi-slice (SMS) EPI. SMS EPI allows the excitation and acquisition of multiple 2D slices simultaneously (23). Although each image in SMS has a lower signal-to-noise (SNR) (10% lower) compared to non-SMS acquisition, the higher temporal resolution associated with SMS is thought to be able to overcome the SNR loss and enhance the overall fMRI detection power.

To our knowledge, the value of SMS acquisition in gas challenge studies has not yet been investigated. Gas challenge studies differ from fMRI in that the “stimulus” is slower due to the time it takes for blood gas content to change (on the order of seconds), compared to neural activation (on the order of milliseconds). Therefore, one may argue that the higher temporal resolution afforded by SMS may not translate to better sensitivity. In this work, we examined the benefit of SMS acquisition in gas challenge experiments, by comparing data collected using SMS factor 2 (SMS 2) and SMS factor 3 (SMS 3) with those using conventional EPI (SMS 1). Furthermore, we investigated the potential of SMS in shortening scan time.

Methods

The study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. All subjects gave informed written consent before participation. All experiments were performed on a 3T MRI system (Philips Healthcare, Best, The Netherlands) using a 32 channel head coil. Five healthy volunteers (Age 30±4 years, 2 males, 3 females) were scanned for this study.

Experimental Procedure

Each participant received three gas challenge scans using SMS1 (conventional single-shot EPI), SMS 2 (i.e. 2 slices excited and acquired at a time), and SMS 3 (3 slices excited and acquired at a time) acquisitions, respectively. The SMS sequence followed the implementation of Setsompop et al. (23) and used the blipped-CAIPI scheme to control for aliasing between simultaneously excited slices. The duration of the three scans are identical. However, since TR decreases with the increase of SMS factor, the number of image volumes acquired increases with SMS factor. The complete scan parameters are listed in Table 1. Note that the TE used is shorter than typical values used in fMRI, in order to minimize artifactual negative signal related to CSF partial voluming (see Discussion for more explanations) (24). The order of the scans was counter-balanced across participants.

The gas challenge protocol was the same for the three scans and used a recently developed paradigm that allows concomitant hypercapnia and hyperoxia challenge in a single experiment, providing an estimation of both cerebral blood volume (CBV) and cerebrovascular reactivity (CVR) (21). The in-scanner gas delivery and monitor system has been described previously (17, 19). Briefly, the subject was fitted with a nose clip and a mouthpiece to allow breathing through the mouth. The end of the mouthpiece is connected to a five-way valve which is connected to three Douglas bags containing different gas mixtures. The composition of the gas mixtures is: hypercapnia (5% CO₂, 21% O₂, and 74% N₂), hyperoxia (95% O₂ and 5% N₂) and carbogen (95% O₂ and 5% CO₂). The gas

inhalation timing paradigm used in this study is shown in Figure 1. Briefly, the CO₂ and O₂ challenges are applied concomitantly during the scan, but their timing were carefully designed so that they are orthogonal to each other in the time domain and have different modulation frequencies. With this design, the post-processing algorithm can extract separate responses due to CO₂ and O₂. The duration of the scan is 9.3 minutes. During this period, BOLD weighted images are collected continuously using the above described sequences. Throughout the experiment, end tidal CO₂ (EtCO₂) was recorded using a capnograph device (Capnogard, Model 1265, Novamatrix Medical Systems, Wallingford, CT, USA) and end tidal O₂ (EtO₂) was recorded using an O₂ monitoring device (Biopac system, Goleta, CA, USA).

Data analysis

The Statistical Parametric Mapping (SPM) software (University College London, UK) and in-house MATLAB (MathWorks, Natick, MA) scripts were used for the processing of the data. Pre-processing included realignment of BOLD images, normalization to Montreal-Neurological-Institute (MNI) template space with a resolution of 2×2×2 mm³, and finally smoothing using a 6mm full width half maximum (FWHM) Gaussian kernel.

For post-processing, a General Linear Model (GLM) analysis was used as described previously (19, 21), in which BOLD time course is the dependent variable and EtCO₂ and EtO₂ time courses are the independent variables. For each voxel, we obtained a CVR index, a CBV index, and their associated Z scores, which represent the statistical significance of the indices. The CVR index is calculated as the % BOLD signal change per mmHg CO₂. The CBV index is calculated as %BOLD signal change per 100mmHg O₂. Voxel-wise maps and whole brain averaged values of CVR and CBV were obtained.

Statistical analysis

Analysis of variance (ANOVA) with repeated measure was performed to compare whole-brain-averaged Z scores across scans, to examine the sensitivity of different sequences. When a significant main effect is observed, post-hoc t tests were used to compare each pair. A Bonferroni-corrected p value less than 0.05 was considered statistically significant. Histograms of the voxel-wise Z maps were also plotted to examine the distribution of voxel-wise Z scores in these scans. Furthermore, a voxel-by-voxel paired t test was also performed on Z score maps to examine which voxels in the brain have significantly greater Z scores in SMS than in conventional EPI.

To evaluate whether the benefit of SMS can be used to shorten scan duration, the image time series of each scan were divided into 2 halves and were labeled first half and second half. The half data sets were again used to generate CVR and CBV measures. Intraclass correlation (ICC) coefficient (25) was calculated to test the consistency between the results obtained from the two halves. Z scores obtained from the half datasets were compared to those from the full dataset.

Results

Figure 2 shows representative BOLD images acquired with SMS1 (i.e. conventional EPI), SMS2, and SMS3 sequences. For SMS2 and SMS3 data, both aliased (top) and unfolded (bottom) images are displayed. It can be seen that the SMS sequence used can effectively unfold the images up to a factor of 3 with minimal residual aliasing effects.

Figures 3a and b show CVR and CBV maps of a representative subject, respectively. Visual inspection suggests that the image contrast of these maps is similar across different SMS scans, with the gray matter manifesting a greater value compared to the white matter. Table 2 lists quantitative values of whole-brain-averaged CVR and CBV, as well as end-tidal CO₂ and O₂ values during the gas-challenge experiment. As we can see, physiological parameters of CO₂ and O₂ are comparable across the scans. The CVR values are in good agreement with values reported in the literature (12, 19, 24), with a slightly higher value observed with higher SMS factors due to longer TE used in those protocols (24). It is known that longer TE results in a greater percent BOLD change for a given R²* change (26). The percent signal changes (Table 2) due to gas inhalation are also similar across SMS factors.

Sensitivity comparison across the scan protocols was performed using the Z scores from the GLM analysis, with higher Z score suggesting greater statistical significance. For CVR results, whole-brain-averaged Z scores were 13.5±1.0 (mean±SEM), 17.3±1.3, and 17.3±1.3 for SMS 1, SMS 2, and SMS 3 scans, respectively. For CBV, the scores were 20.0±0.6, 25.3±0.6, and 26.3±1.1 respectively. ANOVA test suggested that there was a significant effect of scan protocol on the Z score (p<0.001). Post-hoc tests revealed that the sequences using SMS yielded a higher Z score than the conventional EPI (corrected p=0.01), but there was no significant difference between SMS 2 and SMS 3 (p=0.3). Comparing the Z scores between CVR and CBV indices, it was found that the Z scores associated with CBV were significantly higher (p<0.005) than that of CVR, regardless the SMS factor. This suggests that O₂ inhalation (at 95% content) has a greater BOLD effect than CO₂ inhalation (at 5% content).

Figure 4 shows histograms of the Z score across different SMS factors, with CVR results shown on the left panel and CBV on the right panel. Consistent with the quantitative results described above, the histogram using the SMS 2 protocol is clearly shifted toward the higher values when compared to the conventional EPI, i.e. SMS 1. SMS 3 tends to shift the histogram further toward right, but the improvement is relatively minor. Figure 5 shows spatial distribution of voxel-wise Z scores, stratified by the range of the value for easier visualization. It can be seen that SMS-related enhancement in Z score is most pronounced in gray matter voxels, whereas in white matter (e.g. those with Z score < 10) the SMS effect is relatively small. This is consistent with the shapes of Z score histograms (Figure 4), in which the lower value range manifests a considerable overlap between the three SMS factors. When performing a voxel-by-voxel comparison of Z scores between the SMS and conventional EPI scans, it was found that 28% of the voxels in the CVR map showed a statistically greater Z score when using SMS 2 relative to conventional EPI. When comparing SMS 3 to conventional EPI, this fraction was 20%. Similar observations were made for the CBV data.

CVR and CBV maps generated using half datasets are shown in Figure 3c and 3d, respectively. Visual inspection of the results reveals that the maps obtained with reduced scan time are still of good quality. Comparing quantitative values between the results from the two halves, no significant difference was observed. ICC of CVR maps between the two halves was 0.93 ± 0.04 , 0.95 ± 0.03 , and 0.95 ± 0.02 for conventional EPI, SMS 2, and SMS 3 scans, respectively. Whole-brain-averaged Z scores using the half and full dataset are plotted in Figure 6. It can be observed that Z scores from the half dataset are consistently lower than those from the full dataset ($p<0.01$, paired t test). Interestingly, for both CVR and CBV results, whole-brain-averaged Z scores obtained with half SMS dataset are comparable to those obtained with full conventional EPI dataset (Figure 6). Similar results were found when examining the number of significant voxels. Specifically, compared to full conventional CVR dataset, half SMS2 dataset yielded $0.8\pm0.3\%$ fewer significant voxels while half SMS3 dataset yielded $0.6\pm0.3\%$ more significant voxels. These data suggest that the sensitivity of a SMS scan is similar to that of a conventional EPI scan of twice the scan time.

Discussion

BOLD based hemodynamic mapping is the most commonly used technique for CVR mapping, due to its higher signal reliability than ASL based method. However, this measurement still suffers from low sensitivity due to inherently small signal changes in BOLD signals. In this article, we showed the feasibility and superiority (in sensitivity) of SMS acquisition for hemodynamic mapping. To our knowledge, this is the first report to investigate the advantage of SMS acquisition in hemodynamic mapping. Furthermore, we found that SMS acquisition can provide a sensitivity similar to that of a conventional EPI scan of twice the scan duration.

Cerebrovascular reactivity is increasingly used in research settings due to its high specificity to cerebrovascular function (6, 15, 27, 28). The reason is that, unlike baseline perfusion or cerebral blood flow which is modulated by many factors such as neural activity and systemic vascular parameters, CVR is expected to be less susceptible to these confounding factors, therefore may be more sensitive to disease related vascular dysfunction. There is substantial evidence that cerebrovascular reactivity is one of the most sensitive markers for early detection of ischemia (1, 2, 4, 5, 29-32). In a study of 152 subjects, it has previously been shown that, even with normal aging, the rate of CVR decline is much more rapid than that of CBF (33). Comparing 80 years old to 20 years old, CVR diminishes by 54%, whereas CBF only drops by 18%. In clinical settings, measurement of CVR requires the injection of Diamox (acetazolamide) as a vasoactive agent, while acquiring perfusion images with SPECT (single photon emission computer tomography) or CT (computed tomography) (34-37). More recently, Diamox injection has been combined with ASL MRI (38-40) to reduce exposure to ionizing radiation. However, these procedures are still cumbersome and sometimes require two separate imaging sessions or patient visits. Moreover, the input function of the vasoactive stimulus is difficult to assess, thus quantitative evaluation of the results across participants is often not feasible. Therefore, recent efforts by several groups have been focused on altering the arterial CO_2 (a potent vasodilator) level via gas inhalation or breath-hold, while simultaneously collecting MRI images (9, 41-45). However, in order

for CO₂-based CVR to advance from the research arena to routine clinical applications, one of most important barriers is the sensitivity of the technique. The present work addresses this question and is therefore a timely study, given the recent interests in CVR in the community.

In our study, the assessment of sensitivity was primarily based on Z scores from the statistical parametric mapping. Comparing histogram of Z scores of SMS with conventional EPI, it was observed that the distribution of the Z scores was shifted toward higher values when SMS was used. Moreover, voxel-by-voxel comparison of Z scores also revealed that the SMS scan showed a greater sensitivity across the whole brain. Approximately 20-30% of the voxels in the brain showed a statistically significant improvement in sensitivity when SMS is used. Other voxels showed a similar trend although not reaching statistical significance. We further showed that the enhanced sensitivity can be used to reduce the scan time to half while maintaining overall data reliability.

Our experimental observation of an improved data sensitivity with SMS can be explained by the following theoretical considerations of the signal mechanism. Statistical significance of the BOLD signal change associated with gas-inhalation is determined by a combined effect of several factors, including EtCO₂ (or EtO₂) change due to challenge, CVR value, baseline signal magnitude, thermal noise, number of averages (image volumes), and physiological noise level. As demonstrated in our results, EtCO₂ or EtO₂ changes are similar across scans. For CVR values, SMS scans had a larger CVR value compared to the conventional EPI scan due to the longer TE used. On the other hand, baseline signal magnitude is lower in SMS scans due to longer TE resulting in more T2* signal decay and shorter TR resulting in less T1 signal recovery. Thermal noise level in SMS is expected to be higher, although with the blipped implementation of SMS such g-factor penalty has been reported to be relatively minor (23). SMS acquires more image volumes for given scan time, thus provides more averages (46). The above-described factors will roughly cancel out according to our previous estimation (24). What was not considered in our previous calculation and could be an underlying reason for the observed sensitivity enhancement is that, by sampling data at higher temporal frequency using SMS, physiological noise associated with breathing (around 0.3 Hz) and cardiac pulsation (around 0.8 Hz) is no longer aliased to the low frequency range corresponding to the gas challenge paradigm (around 0.1 Hz). Similar to the case of fMRI (47), the reduction of physiological noise in the data represents a major advantage of SMS in gas-inhalation experiments.

In this study, our main goal was to evaluate whether fast imaging using SMS can improve the sensitivity of CVR mapping. Thus, the primary experimental parameter that was varied systematically was the TR. However, we note that TE of the sequence was also varied across the three scans. This is because each TR has a designated TE that we have previously shown to be optimal for CVR mapping (24). It is now reasonably well accepted that BOLD sequence parameters used for CVR mapping should be slightly different from those for functional MRI. It has been demonstrated by a number of studies that, when directly applying functional MRI sequence parameters for CVR mapping, artifactually negative CVR values will be observed (1, 20). We have recently shown that this is due to a blood volume effect in CSF-rich regions (12) and have proposed a TR-specific TE scheme for CVR mapping, in order to minimize such artifacts (24). Therefore, although seemingly

inconsistent, our choice of using different TE for different TR is most relevant for our goal of optimizing CVR acquisition schemes for practical purposes. From the signal model point-of-view, a higher TE will result in a larger percent signal change in BOLD. In the meanwhile, higher TE also results in a lower baseline signal intensity. Thus, the overall sensitivity of the data is dependent on the combined effect of these signal mechanisms. Our experimental outcomes using Z-statistic are expected to reflect the results of all these factors.

The present study also employed O₂ inhalation to provide an estimate of venous CBV (45, 48). CBV can be measured with Gadolinium contrast agent. The O₂ method provides an alternative approach that may be useful for patients who cannot undergo the traditional Gadolinium scan due to potential allergic reaction, nephrogenic systemic fibrosis, or concerns of long-term deposition of the contrast agent (49). Our data suggested that SMS can also benefit CBV mapping with O₂ inhalation.

Analysis of CVR data has not been standardized in the field. In this study, we calculated CVR maps in the MNI space and the data were smoothed with a 6 mm FWHM Gaussian kernel, following the analysis steps used in our previous studies (8, 19, 33). However, we have also examined CVR results using unsmoothed data, and found similar results.

A limitation of this study is a small sample size. Nonetheless, the major findings of the study have all reached statistical significance. In fact, the Z score in SMS was greater than the conventional EPI in all participants studied. Another caveat of this study is that we have primarily focused on physiological aspects of the data but did not perform a systematic technical investigation of the SMS sequence itself. This was because sequence aspects of SMS have been extensively studied previously (50-52). Additionally, we should point out that the SMS sequence we used in this study (on a Philips 3T Achieva) was not implemented by our group, thus we had limited access to sequence optimization or parameter adjustments. On our system, we were only able to perform SMS up to an accelerating factor of 3. Beyond SMS3, aliasing artifacts became apparent. However, we are aware that, on other platforms, higher SMS factors such as SMS4 and SMS8 have been used in fMRI and DTI studies (23, 53). Therefore, while the present study reveals that SMS can improve the sensitivity of CVR mapping, the exact value of optimal SMS factor is likely dependent on the particular SMS sequence implementation and overall quality of the data.

In conclusion, we have shown that physiological mapping of cerebrovascular reactivity and cerebral blood volume using gas inhalation can be enhanced by the use of SMS acquisition. With SMS, one can reduce the scan duration to half while maintaining sensitivity in terms of Z scores.

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Abbreviations used

BOLD	Blood oxygen level dependent
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CO₂	Carbon dioxide
CSF	Cerebrospinal fluid
CT	Computer tomography
CVR	Cerebrovascular reactivity
DF	Degrees of freedom
EPI	Echo planar imaging
EtCO₂	End-tidal CO ₂
EtO₂	End-tidal O ₂
FOV	Field-of-view
FWHM	Full width half maximum
GLM	General linear model
ICC	Intraclass correlation coefficient
MNI	Montreal-Neurological-Institute
ROI	Region of interest
SMS	Simultaneous-multi-slice
SPECT	Single photon emission computer tomography
SPM	Statistical Parametric Mapping
SNR	Signal to noise ratio

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Figure 1.

A graphical illustration of the concomitant hypercapnia and hyperoxia experimental design. The breathing paradigm used in this study includes both hypercapnia and hyperoxia challenges. The timing of these challenges is selected such that they are orthogonal to each other in time domain and have different frequency in the frequency domain. This paradigm allows the mapping of both cerebrovascular reactivity and cerebral blood volume in a single scan.

Figure 2. BOLD images acquired with SMS1, SMS2, and SMS3 sequences. Slice number 23 (out of 36) is shown in SMS1. Slice number 5 and 23 are shown in SMS2. Slice number 11, 23, and 35 are shown in SMS3. The top row shows aliased images. The bottom row shows unfolded images.

Figure 3. CVR and CBV maps from a representative subject. a) CVR maps using different SMS acceleration factors. b) CBV maps using different SMS acceleration factors. c) CVR maps obtained with half of the experimental data. d) CBV maps obtained with half of the experimental data.

Figure 4.

Histograms of voxel-wise Z scores associated with the hemodynamic parameters. (a) Z scores associated with CVR and averaged across all participants. (b) Z scores associated with CBV and averaged across all participants. For both panels, the histograms are found to shift toward the right-hand side when SMS acceleration is used.

Figure 5. Spatial distributions of voxel-wise Z scores, stratified by ranges. The Z scores were based on the average of all five participants.

Figure 6.

Average Z scores when using the half data set compared to the full data set. (a) Average Z scores of CVR. (b) Average Z scores of CBV. The dashed line indicates the level of Z scores when the full data set of conventional EPI is used, which serves as a bench mark for comparisons. Note that the Z scores using half data set in the SMS scans showed similar Z score values when compared to Z score values of conventional EPI scans using full data set.

Table 1

Summary of the imaging parameters used in this study.

Common parameters	SMS1	SMS2	SMS3
Vox=3.2×3.2×3.5 mm ³ , Matrix size=64×64×36, SENSE=2, FOV=205×205 mm ² , Slice number=36 SMS shifting factor 1/2	TR=1550 ms	TR=900 ms	TR=650 ms
	TE=21 ms	TE=25 ms	TE=27 ms
	Dynamics=362	Dynamics=624	Dynamics=862

Table 2

Summary of physiological and MRI signal changes due to gas inhalation (mean $\pm$ SEM).

	SMS1	SMS2	SMS3
End-tidal CO ₂ change due to CO ₂ inhalation	7.3 $\pm$ 0.5 mmHg	6.6 $\pm$ 0.4 mmHg	6.4 $\pm$ 0.4 mmHg
CVR	0.19 $\pm$ 0.01 %/mmHg	0.21 $\pm$ 0.02 %/mmHg	0.22 $\pm$ 0.01 %/mmHg
BOLD signal change due to CO ₂ inhalation	1.35 $\pm$ 0.09 %	1.35 $\pm$ 0.10 %	1.42 $\pm$ 0.12 %
End-tidal O ₂ change due to O ₂ inhalation	512.7 $\pm$ 11.8 mmHg	507.6 $\pm$ 11.3 mmHg	503.1 $\pm$ 21.1 mmHg
CBV	0.48 $\pm$ 0.01 %/100mmHg	0.49 $\pm$ 0.02 %/100mmHg	0.52 $\pm$ 0.03 %/100mmHg
BOLD signal change due to O ₂ inhalation	2.45 $\pm$ 0.06 %	2.46 $\pm$ 0.10 %	2.62 $\pm$ 0.13 %