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Investigation of the correlation between cerebral blood flow and bold

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INVESTIGATION OF THE CORRELATION BETWEEN CEREBRAL BLOOD FLOW AND BOLD

by

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Iowa City, Iowa

CERTIFICATE OF APPROVAL

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MASTER'S THESIS

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This is to certify that the Master's thesis of

Huijing Yang

has been approved by the Examining Committee
for the thesis requirement for the Master of Science
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ABSTRACT

There are lots of dynamic process exist co-currently and spontaneously when the neurons in the brain are activated by the external stimulation, like cerebral blood flow (CBF) change, oxygen extraction change. The study of the dynamic relationship among these physiological variables, which describe the brain activity through different aspects, can help people understand the brain function when it gets excited and researchers can interpret the physiological meaning of these parameters better. The most common functional magnetic resonance imaging techniques are BOLD and ASL fMRI, in this research, the correlation between these two methods has been studied through a simultaneous data acquisition strategy. Assessing such correlation between BOLD fMRI measures and CBF offers a link of these two to the underlying of the spontaneous brain activities.

In the study, an ASL pulse sequence PICORE has been used to perform the fMRI experiment on 7 health subjects. A rapid median nerve electrical stimulation paradigm has been used to detect the activation of the brain from seven normal health right-handed human subjects. Three ROIs (SMA, S1, M1) have been selected and the data were analyzed to investigate the correlation between CBF value and BOLD signal change during brain activities. We found the CBF value rises for 5 - 6 ml/min/100g for fixed ROI and 11 - 12 ml/min/100g for non-fixed ROI and the BOLD signal change was around 0.8% for both situations. Our results shows for a fixed size ROI of each individual subject, no significant difference has been found for CBF value difference and the BOLD signal change between different runs and neither did the ratio of these two parameters ($p > 0.05$). When studied the activation area size for each run, we found significant difference for both CBF value difference and BOLD signal change ($p < 0.05$) but no significant difference for the ratio of those two ($p > 0.05$). The dynamic relationship between CBF value difference and BOLD contrast signal change has been shown to be stable for a

fixed ROI study. The amount of neurons being activated (activation size) for these two approaches has a habituation and decreased between runs, but the relationship between them remains typically the same since the ratio has no significant difference.

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CHAPTER I
INTRODUCTION

The functional magnetic resonance imaging (fMRI) has been widely used both in the area of medicine and psychology since its discovery and development several decades ago. There are more and more researchers, physicians and psychologists eager to find out more effective approaches to detect how the human brains working and the mechanisms the brain obeys among different physiological variables (cerebral blood flow, oxygen metabolism, etc.). The two most popular used fMRI techniques are blood-oxygen level dependent (BOLD) and arterial spin labeling (ASL) fMRI, which are both helpful methods to study the coupling between neuronal activity and the regional cerebral hemodynamics. Although the BOLD fMRI develops the fastest and works with quite simple principle, it bears some limitations when researchers try to connect the measured data with physiological parameters because the data reflects a combination of three independent but related variables of the brain, cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood volume (CBV), while the ASL fMRI performances a more specific detection of the CBF changes during the brain activation. There might be some kind of correlation exists between these two approaches and it does benefit the understanding of the experimental data.

We are interested in the dynamic relationship between the CBF value change and the BOLD signal change during the brain activation brought by the electrical stimulation to the median nerve at the right wrist. The study focused on investigating the performance of the neurons' exciting strength (CBF value difference and BOLD signal percentage change) and the amount of neurons getting activated (the activation size) among different runs in a single simultaneously acquired ASL and BOLD fMRI

experiment. We would like to detect if there was a habituation or a potentiation through the process of the median nerve excitation and how the activation strength change. We emphasized on the comparison of the data between each two runs and would investigate the dynamic relationship between CBF value change and BOLD signal percentage change through calculating the ratio of these two variables.

CHAPTER II
BACKGROUND

Brain mapping techniques presently

For different kinds of needs to study the human brain on either clinical or research purpose, there are several common used brain mapping approaches developing in the past decades of years, like functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), positron emission tomography (PET), Near-infrared spectroscopy (NIRS) and other non-invasive scanning techniques.

Current fMRI brain mapping techniques

Blood Oxygen Level Dependent (BOLD) imaging

BOLD imaging is one of the earliest and most popular fMRI approaches which was developed in the 1990s. It is based on the change of the oxygenated hemoglobin (oxyHb) and the deoxygenated hemoglobin (deoxyHb) concentration at the activated brain region. When a specific area of the brain is excited due to the response to an external stimulation, the extraction fraction of oxygen from the local capillaries leads to an initial drop in oxyHb and an increase in local carbon dioxide (CO2) and deoxyHb. But after a lag for 2-6 seconds and the cerebral blood flow (CBF) increases which causes the oxyHb rises in abundance and washes away the deoxyHb. Since deoxyHb is paramagnetic, its reduction will lead to an increase of the T2-weighted MR signal. Hence, BOLD imaging actually detects a complex combination of several different physiological parameters.

Arterial Spin Labeling (ASL) imaging

Unlike the BOLD imaging, ASL techniques measure a more physiological specific correlate of the neuronal activity (cerebral blood flow-CBF) and own much better spatial

localization by targeting signal changes more closely related to neuronal activity (Yihong et al. 2004, Thomas et al. 2007). In ASL MRI, the non-invasive intrinsic tracer is the water molecules of the flowing blood that are labeled by external magnetic field. Typically, such labeling is produced by saturating or inverting the longitudinal (Z-axis) component of the MR signal using a specific pulse sequence. As the labeled water molecules pass through a tissue region, the local tissue longitudinal magnetization (M_z) will be changed, hence the T1-weighted MR signal will be reduced in the image slice with labeled blood flows in (labeled image) compared to the one that is fully relaxed, which is no labeling, control image.

The difference between these two images is quantifiable as a common physiological parameter, CBF. In general, the greater the blood flow into the imaging slice, the greater the signal changes in the labeled condition compared with the control condition. Thus, ASL MRI utilizes this property to measure CBF by simply subtracting the labeled image from the control image.

Different Types of Pulse Sequences for ASL fMRI

There are basically two types of approaches for ASL experiments: continuous ASL (CASL) and pulses ASL (PASL). Both work based on the same theory but there are some differences between them.

For continuous ASL, usually an additional hardware, like a labeling coil is required to conduct the labeling process. The coil can be set at the position of the carotid arteries of the neck and after the upstream blood gets labeling by the transmission coil, labeled blood travels to the brain and reaches the desired imaging slice, then the labeled image will be acquired. The labeling coil will then be turned off in order to let controlling blood enter the imaging slice and get the control image achieved. Also, a long (1-3 s) RF pulse is often used and the labeling plane is proximal to the region of interest, hence the continuous ASL owns high overall labeling efficiency. However, this technique has some limitation since the large amount of RF power needed is restricted by either the system

performance capabilities or the FDA guidelines governing the amount of RF energy as well as the absorption rate that can be taken by human (Alsop et al. 2005).

With the drawbacks of the continuous ASL, an alternative approach pulsed ASL is more popular among the researchers. The RF pulse used for labeling works shorter than that of CASL (5-20 ms) and followed by a delay the image will be acquired. The labeling process differs for locations and PASL has two main types, which are EPISTAR and FAIR. In EPISTAR, a slab selective inversion pulse is applied proximal to the imaging slice and another slab selective inversion pulse will be used distal to the imaging slice as a control image. In FAIR, the labeling process is achieved by a non-selective inversion pulse and the control condition is given by a selective inversion pulse applied just at the imaging region. Thus, for both methods, the control images' signals are registered as positive while the labeled signals are registered as negative in EPISTAR and positive in FAIR. But the subtraction images' signals will be positive at the end.

Simultaneous BOLD and ASL fMRI Experiments

Simultaneous detection of BOLD and ASL perfusion data has been recognized having many advantages like minimizing the temporal variations compared to the detection made by separate experiments due to potential head motion and changes of physiologic status between scans. Secondly, since these two methods studies the brain function depends on different physiologic parameters, a combination of them would provide a better understanding of the transduction mechanisms among neuronal activity, hemodynamics and fMRI signals.

Yihong et al. (2004) reported a design of an inversion recovery pulse sequence that performs the concurrent measurement of three hemodynamic parameters (VASO, ASL and BOLD) within a single scan. Specifically, a dual gradient-echo EPI acquisition is used at a later time of TI_2 to obtain the ASL and BOLD data, which second TE is longer enough for a BOLD signal acquisition. On the other hand, because the ASL perfusion signals are obtained by pair-wise subtraction between adjacently acquired control and

labeled images, motion artifact and baseline drift are effectively reduced in ASL fMRI (Wong et al. 1999), and Yihong et al. (2004) does mentioned in the report that a single arterial spin labeling (ASL) perfusion fMRI can simultaneously capture BOLD and cerebral blood flow (CBF) signals. The perfusion and BOLD signals' measurements can be achieved from a series of ASL images simply by subtracting or adding the control and labeled images, respectively.

Also it is widely accepted that simultaneously measurements of BOLD and ASL contrast can allow the estimation of both CBF and $CMRO_2$, providing key information on neuronal activity as well as vascular coupling. Ai-Ling et al. (2008) reported an evaluation of two MRI models both aiming at the measurements of local cerebral metabolic rate of oxygen ($CMRO_2$) through the co-currently acquired ASL and BOLD fMRI data using three different methods, which are the single-compartment model (SCM) and the multi-compartment model (MCM). The report also included the result compared to the positron emission tomography (PET) technique. Negative results are reported for the first method, using SCM and identical parameters as prior study, however the second method (using SCM as well but with parameters directly measured) and the third method (the MCM model) are evaluated to have aligned result with PET from the literature.

Quantification analysis for cerebral blood flow

Cerebral blood flow is a physiological variable which reflects the volume of blood passing through a point in the brain circulation per unit time (Guyton, 1977). The standard unit for CBF is (milliliters of blood) / (100 grams of tissue) / (minute). The measurement of CBF value typically based on several methods as single photon emission computed tomography (SPECT), positron emission tomography (PET), MRI with contrast agents such as gadolinium, and ASL MRI (Thomas et al. 2007). The mechanism behind them are all depended on the tracer's concentration that is delivered to and cleared from the tissue by the blood flow.

In ASL MRI, taking the difference between the control and labeled images yields an

image $\Delta M=M_{control}-M_{label}$ which is proportional to CBF value. The amount of magnetization difference occur at a specific time rely on the delivery of magnetization by arterial flow as well as the clearance of the magnetization by venous outflow and longitudinal relaxation (Buxton et al. 1998). Yihong et al. (2004) did the quantitative analysis of the perfusion data via the perfusion model of Detre et al. (1992) and reported that CBF values of gray and white matter in the brain ware 66.4 ± 8.2 and 25.2 ± 4.3 (cc/100g/min), respectively from ASL data that acquired simultaneously with BOLD.

CHAPTER III
METHOD

Subjects' selection

Seven physically and neurologically healthy, right-handed subjects were recruited through the Iowa City (four females and three males, age averaged at 24). All subjects provided informed consent in accordance with the regulations of the Institutional Review Board of the University of Iowa.

Stimulation paradigm

The passive electric stimulus, a square wave pulse with duration of 0.2 msec, was delivered by a Grass S8 stimulator (Grass Technologies, West Warwick, Rhode Island, USA) to subjects' median nerve at the right wrist. The stimulation voltage used during the fMRI scan was 15 volts above the motor threshold, which is individually defined as the minimum voltage required in order to obtain a thumb twitch.

A block design paradigm was used with four off/on cycles (48 time points off, 48 time points on). The subjects were required to perform nothing but lie in the scanner and keep still and awake, thus the variances in response time due to subjects' motivation and attention would be eliminated.

Protocol and parameters

The MRI data was acquired on a Siemens 3T Trio scanner (Siemens Medical Solutions, Erlangen, Germany). T1-weighted anatomical images were acquired with parameters of TR=2530 ms, TE=3.71 ms, flip angle=10 degrees.

For functional images, pulse sequence PICORE (proximal inversion with a control for off-resonance effects) was used, which belongs to the Pulsed ASL (PASL) spin labeling method and is a derivative of EPISTAR. The "label" is applied using a slab selective inversion proximal to the imaging slice and the "control" is an off resonance

inversion pulse that is applied at the same frequency offset relative to the imaging slice as the tag, but in the absence of a slab selective gradient (Wong et al. 1997). The parameters for functional ASL images are TR=2453 ms, TE=23 ms, TI_1=600 ms, TI_2=1600 ms, flip angle=90 degrees, number of slices=9, slice thickness=5 mm with a 1 cm gap.

CBF quantification model

The CBF quantification model used is listed below:

$$CBF = \frac{\Delta M \times \lambda}{2 \times \alpha \times M_{0b} \times TI_1 \times q \times e^{(-TI_2/T_{1blood})}}$$

where λ is the blood-brain partition coefficient. This coefficient is defined by the ratio between blood volume and brain tissue masses that contain equal amounts of water, its typical value is about 0.9mL/g. α is the label efficiency and for PASL, it equals to 0.95. q is a factor to correct for the difference between blood and tissue T1 and venous outflow, which is set to be 0.93 (Wong et al. 1997).

M_{0b} is defined as the signal of a voxel containing 100% blood in thermal equilibrium and can be estimated from measured signal of white matter, indicated as M_{0wm}, in a region of interest as the following equation (Warmuth et al. 2003, Wong et al. 1998).

$$M_{0b} = R_{wm} \times M_{0wm} \times e^{((\frac{1}{T_{2wm}} - \frac{1}{T_{2b}}) \times TE)}$$

where R_{wm} is the proton density ratio between blood and white matter which equals to 1.06 (Wong et al. 1997). T_{2wm} and T_{2b} at 3T are 44.7ms and 43.6ms, respectively.

Data analysis

In general, 225 anatomical T1 images were acquired and formatted in AFNI for each

subject. 385 functional images were generated by ASL sequence for each run. There were three runs for each subject in total.

The data was processed in part by using Analysis of Functional NeuroImages (AFNI) and custom written MatLab scripts. AFNI was used to do despiking, volume registration as well as the skull removing and MR signal detrending. The first 3 images of each run were discarded before the data was loaded in MatLab for further processing.

A Gaussian filter with full width half maximum of 5mm was used to smooth the images. The pairs of control and labeled images were calculated through the method of surround subtraction to get the ASL perfusion image, which is shown as following,

$$Perfusion\ image = image\ \#2 - (image\ \#1 + image\ \#3)/2$$

where image #2 is a control image, image #1 and image #3 are labeled images.

BOLD data were acquired by calculating the average image between each adjacent control/label image pair.

$$BOLD\ image = (image\ \#1 + image\ \#2)/2$$

The CBF value of each point in the ASL data time series was calculated using the previous mentioned quantification model. A mean value was created for each off/on cycle in each run for both CBF difference value and BOLD signal percentage change, which generated 4 pair (ΔCBF and ΔBOLD%) of data per subject.

Two approaches, fixed ROI with CBF difference value and BOLD signal percentage change analysis, activation size change analysis, were used in order to perform the statistical analysis. A fixed ROI was chosen respectively in three potential activated areas (SMA, S1, M1) of each individual subject for all 3 runs and a paired t-test ($\alpha = 0.05$) was conducted between 2 runs with an ANOVA test among the 3 runs held in advance. For

the second method, the size of the activated area was calculated and recorded as an indicator of how many neurons were activated in different runs. Also, an ANOVA test and a paired t-test ($\alpha = 0.05$) were conducted in order to examine the difference between each two runs.

CHAPTER IV
RESULTS

CBF value difference and BOLD percentage change in fixed ROI

Basically, for ASL data, the area of S1 has a better consistency and the activation size is bigger than that of both SMA and M1, but for BOLD data, we found significant activation in SMA and the consistency is good among all subjects.

Fixed ROI in SMA

According to the CBF value calculated through the model presented above, the CBF value has been raised by 6.81 ml/min/100g averagely among all seven subjects when the ROI is activated. The BOLD signal change is around 0.76% for the same condition. As shown in Table 2, there is no significant difference found for the CBF value difference between runs, $t_{12} = -0.61$, $t_{23} = 0.62$, $t_{13} = 0.36$, for Run1 – Run2, Run2 – Run3, Run1 – Run3, respectively ($t_{0.05/df=6} = 1.94$, $p > 0.05$). Same as the situation of CBF value, the BOLD signal change has no significant difference neither, $t_{12} = -0.68$, $t_{23} = 1.75$, $t_{13} = 1.08$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$). Then the ratio between BOLD signal change and CBF value difference has been compared, $t_{12} = -1.02$, $t_{23} = 1.35$, $t_{13} = -0.78$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$), no significant difference was evident as well.

Fixed ROI in S1

Similar as the result found for SMA, the average increased CBF amount for the activation area among all subjects is approximately 7.27 ml/min/100g, slightly higher than that in SMA and the BOLD signal changes for about 0.77%. Table 4 indicates no significant difference for CBF value difference between runs, $t_{12} = -1.35$, $t_{23} = 1.43$, $t_{13} = 0.23$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$). Same results are shown for BOLD signal change, $t_{12} = -1.99$, $t_{23} = 0.20$, $t_{13} = -0.76$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$) and the ratio between these two

variables, $t_{12} = 1.61$, $t_{23} = -2.38$, $t_{13} = 0.46$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$).

Fixed ROI in M1

The smallest amount of CBF augment has been found for the area of M1 during activation, which is 4.41 ml/min/100g and the BOLD signal change remains typically the same (0.76%). T-test result comparing two runs could be found in Table 6 and no evidence showing any significant difference, neither. For CBF value difference the test results are $t_{12} = 1.06$, $t_{23} = -0.31$, $t_{13} = 1.78$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$) and $t_{12} = 0.32$, $t_{23} = -1.90$, $t_{13} = -0.52$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$) for BOLD signal change. The ΔBOLD% /ΔCBF is also very stable between runs, $t_{12} = 0.17$, $t_{23} = -0.09$, $t_{13} = 0.31$ ($t_{0.05/df=6} = 1.94$, $p > 0.05$).

Activation size comparison

Table 7 recorded the activation size for both ASL and BOLD data during the co-current data acquisition. According to Figure 7 and Figure 8, typically, the largest activation area size could be detected in Run1 for both ASL and BOLD and when it came to Run3, most subjects showed no activation.

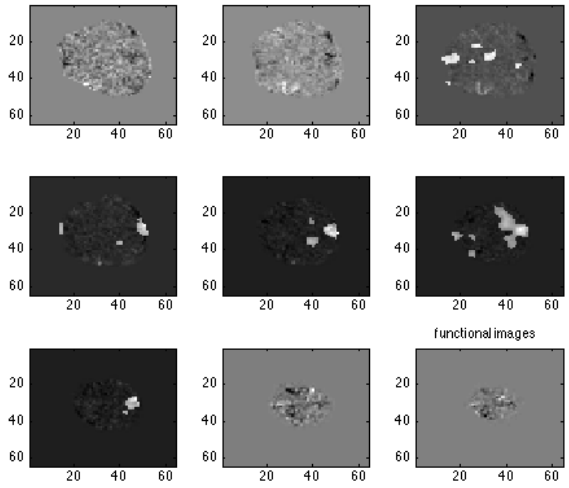
As shown in Table 8, the activation size for ASL data has a mean value of 25.71, 10.57 and 4 for Run1, Run2 and Run3, respectively. And we had 38.71, 16.71 and 4.71 for those of the BOLD data.

Then the ANOVA tests (Table 8 and Table 9) were performed for ASL and BOLD experiments' data separately, the results are $F = 10.98$, p-level = 0.00076, $F_{0.05/df} = 3.55$ and $F = 3.81$, p-level = 0.04, $F_{0.05/df} = 3.55$ for ASL and BOLD respectively, which indicated that the data for three runs differed significantly.

Follow-up t-tests examined the difference between each of two groups and as revealed by Table 10, the activation size performs a big difference between runs for ASL data, $t_{12} = 2.32$, $t_{23} = 2.53$, $t_{13} = 3.83$ ($t_{0.05/df=6} = 1.94$, $p < 0.05$). The difference is not that significant for that of BOLD data between Run1 and 2 and Run2 and 3 ($t_{12} = 1.46$, $t_{23} = 1.05$, $p > 0.05$) but got much more obvious when comparing Run1 and 3, $t_{13} = 3.84$

($t_{0.05/df=6} = 1.94$, $p < 0.05$).

For the comparison of the ratio, the data contains zero as denominator were recorded as "N/A" and were excluded from the t-test. We can tell from Table 10 that there is no significant difference between Run1 and 2 as well as Run2 and 3 for the ratio of ASL and BOLD activation size ($t_{12} = -0.85$, $t_{0.05/df=6} = 1.94$ and $t_{23} = 0.77$, $t_{0.05/df=3} = 2.35$), however the result between Run1 and Run3 suggested the difference is a little more remarkable, $t_{13} = 2.79$ ($t_{0.05/df=3} = 2.35$, $p < 0.05$).



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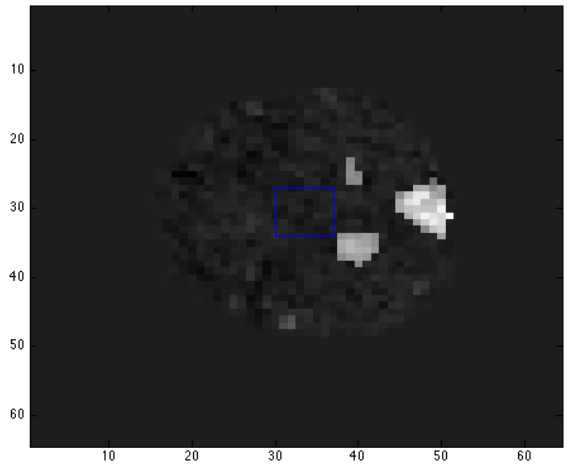
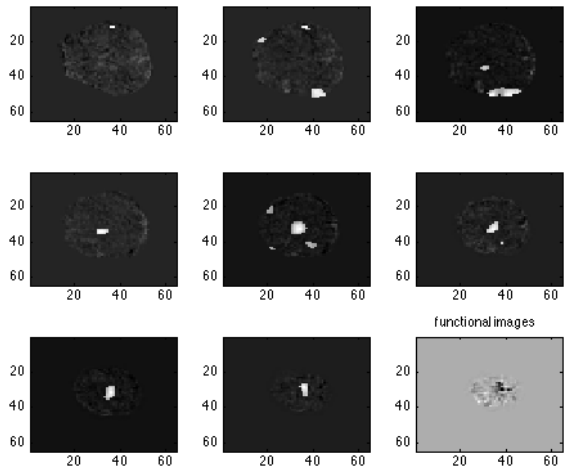


(b)

Figure 1. Activation maps and fixed ROI selection (ASL data in SMA)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of SMA



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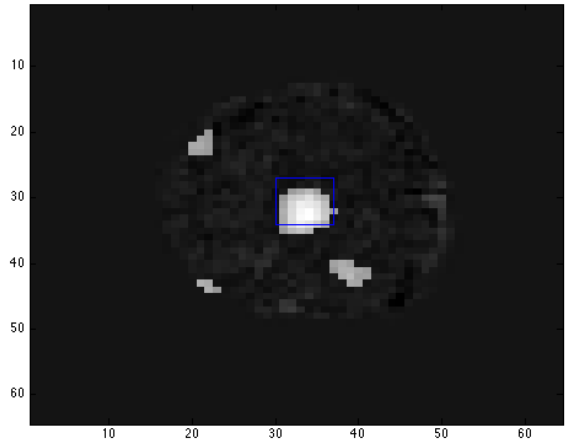
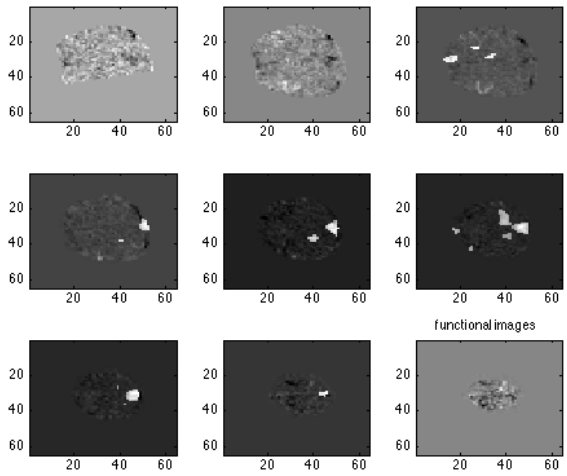


(b)

Figure 2. Activation maps and fixed ROI selection (BOLD data in SMA)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of SMA



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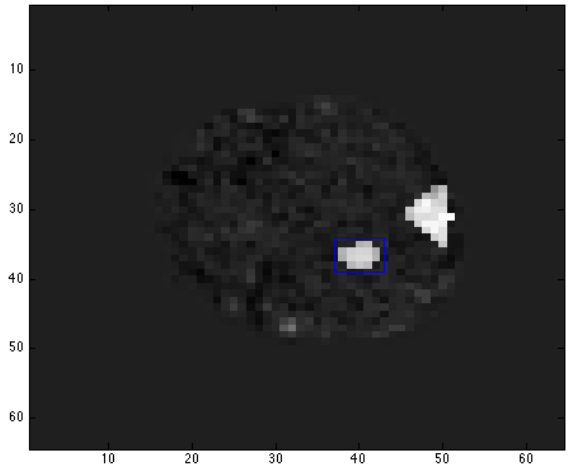
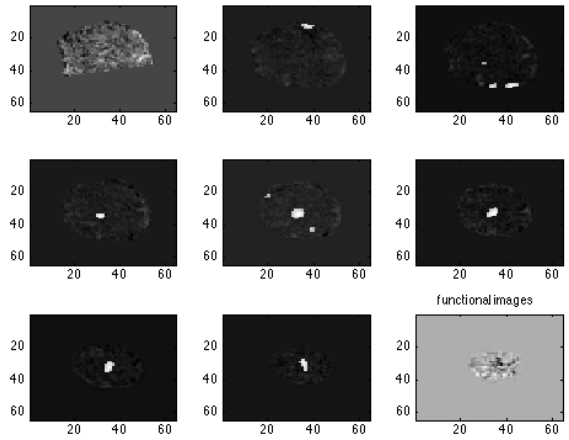


(b)

Figure 3. Activation maps and fixed ROI selection (ASL data in S1)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of S1



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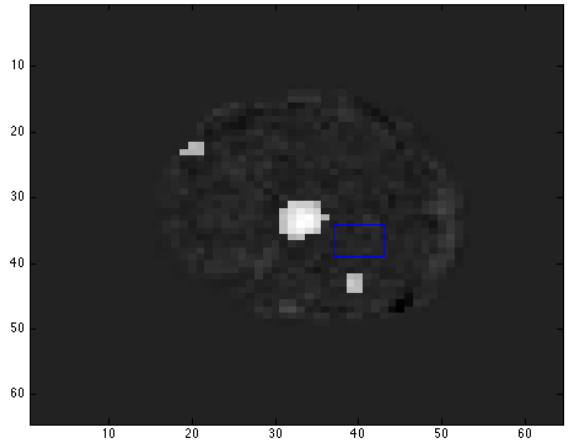
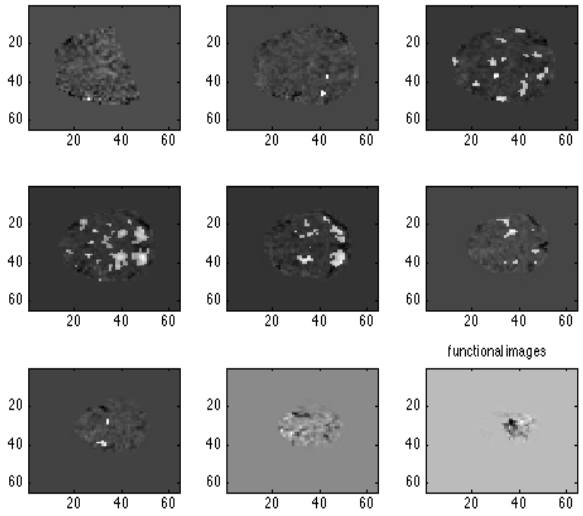


(b)

Figure 4. Activation maps and fixed ROI selection (BOLD data in S1)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of S1



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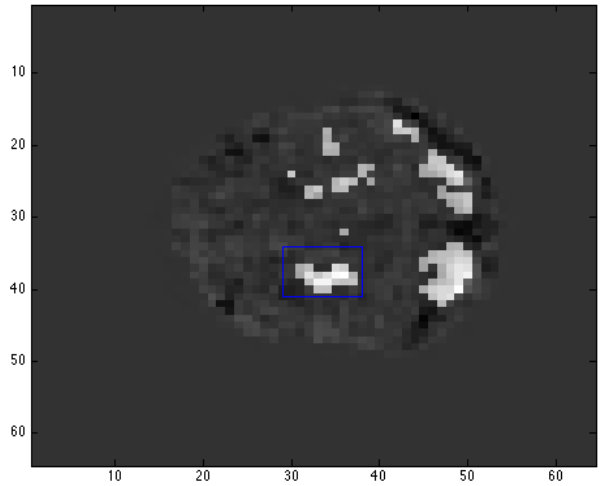
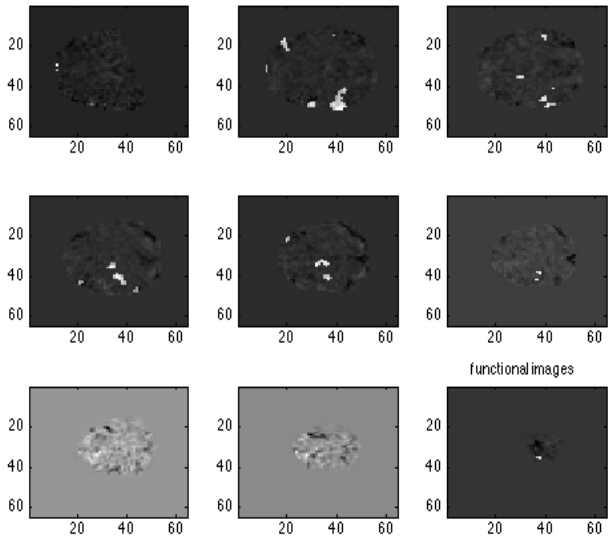


(b)

Figure 5. Activation maps and fixed ROI selection (ASL data in M1)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of M1



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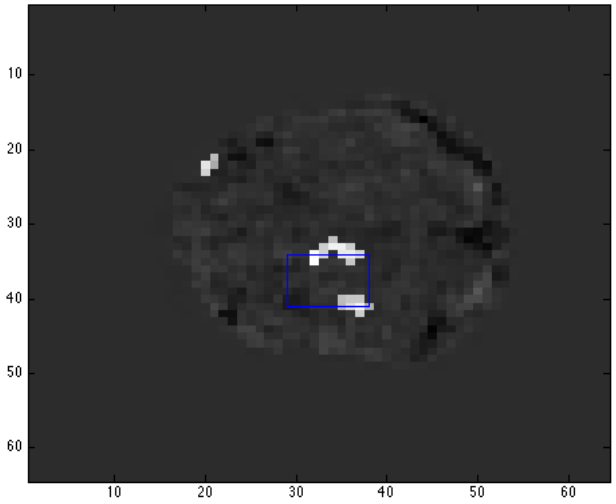


(b)

Figure 6. Activation maps and fixed ROI selection (BOLD data in M1)
(a) Activation maps for all 9 slices of one single subject
(b) Fixed ROI chosen for slice #5 in the area of M1

Table 1. CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of SMA for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
S1	27.04	11.47	20.47	0.85	0.82	0.72	0.03	0.07	0.04
	-2.95	17.49	3.51	0.78	0.79	0.62	-0.27	0.05	0.18
	0.81	-3.29	-7.06	0.69	0.78	1.04	0.84	-0.24	-0.15
	1.00	-9.14	-10.57	0.77	0.75	0.52	0.77	-0.08	-0.05
S2	24.05	22.84	20.58	0.88	0.79	0.84	0.04	0.03	0.04
	6.73	7.75	18.58	0.74	0.79	0.78	0.11	0.10	0.04
	-2.15	1.02	24.29	0.72	0.79	0.78	-0.33	0.77	0.03
	-10.19	-12.56	-4.63	0.88	0.79	0.77	-0.09	-0.06	-0.17
S3	13.35	30.00	10.67	0.66	0.82	0.72	0.05	0.03	0.07
	15.08	8.12	28.94	0.74	0.89	0.74	0.05	0.11	0.03
	-1.53	7.80	-8.05	0.89	0.68	0.87	-0.58	0.09	-0.11
	-0.19	-17.14	-2.42	0.57	0.87	0.72	-3.00	-0.05	-0.30
S4	28.34	16.91	1.91	0.81	0.66	0.78	0.03	0.04	0.41
	1.98	10.62	5.64	0.66	0.81	0.79	0.33	0.08	0.14
	9.42	2.66	13.32	0.93	0.77	0.79	0.10	0.29	0.06

Table 1-Continued

	-4.53	7.40	-6.76	0.77	0.78	0.79	-0.17	0.11	-0.12
S5	31.70	8.50	19.89	0.83	0.79	0.93	0.03	0.09	0.05
	16.83	7.23	28.05	0.72	0.79	0.42	0.04	0.11	0.01
	-13.47	-12.43	-10.16	0.80	0.79	0.98	-0.06	-0.06	-0.10
	-6.53	-2.46	-5.00	0.78	0.79	0.59	-0.12	-0.32	-0.12
S6	5.79	15.72	7.93	0.79	0.79	0.64	0.14	0.05	0.08
	17.52	40.79	29.56	0.70	0.72	0.74	0.04	0.02	0.03
	-6.14	4.57	5.61	0.71	0.85	0.94	-0.12	0.19	0.17
	-1.26	-5.93	-18.71	0.82	0.68	0.71	-0.65	-0.11	-0.04
S7	29.36	22.70	11.27	0.76	0.66	0.81	0.03	0.03	0.07
	3.99	25.20	-7.13	0.70	0.64	0.76	0.18	0.03	-0.11
	5.42	5.21	-10.67	0.77	1.05	1.06	0.14	0.20	-0.10
	-2.79	12.47	2.84	0.71	0.60	0.21	-0.25	0.05	0.07

Table 2. T-test Results for CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of SMA for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	R12	R23	R13	R12	R23	R13	R12	R23	R13
S1	2.35	2.55	4.89	-0.01	0.06	0.05	0.40	-0.05	0.34
S2	-0.15	-9.94	-10.09	0.01	0.00	0.01	-0.28	0.22	-0.06
S3	-0.52	-0.09	-0.61	-0.10	0.06	-0.04	-0.91	0.12	-0.79
S4	-0.60	5.87	5.28	0.04	-0.03	0.00	-0.05	0.00	-0.05
S5	6.92	-7.98	-1.06	-0.01	0.06	0.05	0.02	-0.01	0.01
S6	-9.81	7.69	-2.12	0.00	0.00	0.00	-0.18	-0.02	-0.21
S7	-7.40	17.32	9.92	0.00	0.03	0.03	-0.05	0.09	0.04
Mean	-1.31	2.20	0.89	-0.01	0.02	0.01	-0.15	0.05	-0.10
SE	2.14	3.55	2.45	0.02	0.01	0.01	0.15	0.04	0.13
t	-0.61	0.62	0.36	-0.68	1.75	1.08	-1.02	1.35	-0.78
$t_{0.05/df}$	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94

Note: All difference values are calculated from the average value for each subject and R12 means subtracting the Run2's value from those of Run1.

Table 3. CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of S1 for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
S1	19.83	25.53	12.90	0.76	0.78	0.69	0.04	0.03	0.05
	-2.61	14.21	6.79	0.71	0.74	0.70	-0.27	0.05	0.10
	-3.92	-4.16	-9.03	0.79	0.80	0.95	-0.20	-0.19	-0.11
	-5.78	-3.54	-11.34	0.74	0.72	0.63	-0.13	-0.20	-0.06
S2	24.95	14.42	15.28	0.81	0.76	0.80	0.03	0.05	0.05
	0.87	11.30	19.45	0.73	0.82	0.80	0.84	0.07	0.04
	-5.93	-4.29	3.77	0.71	0.66	0.63	-0.12	-0.15	0.17
	-4.81	-8.38	-10.21	0.84	0.77	0.84	-0.17	-0.09	-0.08
S3	16.97	31.91	24.62	0.75	0.79	0.79	0.04	0.02	0.03
	10.11	15.30	11.71	0.78	0.79	0.79	0.08	0.05	0.07
	-7.18	-6.16	-12.62	0.81	0.79	0.79	-0.11	-0.13	-0.06
	-5.37	-13.85	-6.80	0.74	0.79	0.79	-0.14	-0.06	-0.12
S4	26.93	24.75	2.59	0.71	0.79	0.72	0.03	0.03	0.28
	2.25	9.39	16.24	0.55	0.68	1.07	0.24	0.07	0.07
	20.50	-6.68	12.39	1.08	0.88	0.70	0.05	-0.13	0.06

Table 3-Continued

	5.07	4.80	9.67	0.67	0.72	0.89	0.13	0.15	0.09
S5	24.90	12.06	17.10	0.78	0.74	0.88	0.03	0.06	0.05
	3.94	14.70	10.75	0.72	0.74	0.57	0.18	0.05	0.05
	-4.27	-5.49	-6.91	0.76	0.75	0.86	-0.18	-0.14	-0.12
	-9.56	-7.40	-4.54	0.75	0.79	0.65	-0.08	-0.11	-0.14
S6	10.55	38.61	12.80	0.85	0.88	0.79	0.08	0.02	0.06
	19.53	32.73	27.36	0.75	0.70	0.79	0.04	0.02	0.03
	13.95	29.13	18.30	0.69	1.11	0.81	0.05	0.04	0.04
	2.09	-5.64	-10.30	0.88	0.64	0.78	0.42	-0.11	-0.08
S7	27.75	35.77	26.69	0.83	0.73	0.91	0.03	0.02	0.03
	21.43	32.45	11.02	0.67	0.90	0.75	0.03	0.03	0.07
	-15.72	-7.84	-4.47	0.74	0.62	0.59	-0.05	-0.08	-0.13
	-8.33	-13.97	-10.27	0.71	0.82	0.66	-0.08	-0.06	-0.06

Table 4. T-test Results for CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of S1 for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	R12	R23	R13	R12	R23	R13	R12	R23	R13
S1	-6.13	8.18	2.05	-0.01	0.02	0.01	-0.06	-0.08	-0.14
S2	0.51	-3.81	-3.30	0.02	-0.02	0.00	0.18	-0.07	0.10
S3	-3.17	2.57	-0.60	-0.02	0.00	-0.02	0.00	-0.01	-0.01
S4	5.62	-2.16	3.46	-0.02	-0.08	-0.09	0.08	-0.09	-0.01
S5	0.28	-0.63	-0.35	0.00	0.02	0.01	0.02	0.01	0.03
S6	-12.18	11.67	-0.51	-0.04	0.04	0.00	0.16	-0.02	0.13
S7	-5.32	5.86	0.54	-0.03	0.04	0.01	0.00	0.00	0.01
Mean	-2.91	3.10	0.19	-0.01	0.00	-0.01	0.05	-0.04	0.02
SE	2.16	2.16	0.81	0.01	0.02	0.01	0.03	0.02	0.03
t	-1.35	1.43	0.23	-1.99	0.20	-0.76	1.61	-2.38	0.46
$t_{0.05/df}$	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94

Note: All difference values are calculated from the average value for each subject and R12 means subtracting the Run2's value from those of Run1.

Table 5. CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of M1 for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
S1	22.38	16.33	13.85	0.73	0.77	0.73	0.03	0.05	0.05
	4.01	8.54	9.10	0.73	0.77	0.72	0.18	0.09	0.08
	0.29	-8.28	-9.25	0.79	0.74	0.91	2.73	-0.09	-0.10
	-2.22	-8.86	0.38	0.74	0.75	0.65	-0.33	-0.08	1.70
S2	29.77	17.25	10.41	0.81	0.76	0.83	0.03	0.04	0.08
	1.33	14.14	22.34	0.73	0.78	0.80	0.55	0.06	0.04
	-6.98	-7.09	3.98	0.71	0.70	0.64	-0.10	-0.10	0.16
	-2.63	-12.94	-9.94	0.85	0.75	0.85	-0.32	-0.06	-0.09
S3	16.07	21.28	18.74	0.71	0.75	0.79	0.04	0.04	0.04
	19.29	6.82	8.96	0.76	0.82	0.79	0.04	0.12	0.09
	-9.34	4.66	-8.91	0.81	0.75	0.79	-0.09	0.16	-0.09
	-1.65	-2.81	-5.30	0.69	0.80	0.79	-0.42	-0.28	-0.15
S4	18.23	17.71	13.21	0.75	0.77	0.72	0.04	0.04	0.05
	-4.15	-5.01	2.63	0.69	0.74	0.83	-0.17	-0.15	0.32
	1.77	3.29	10.42	0.86	0.84	0.69	0.49	0.25	0.07

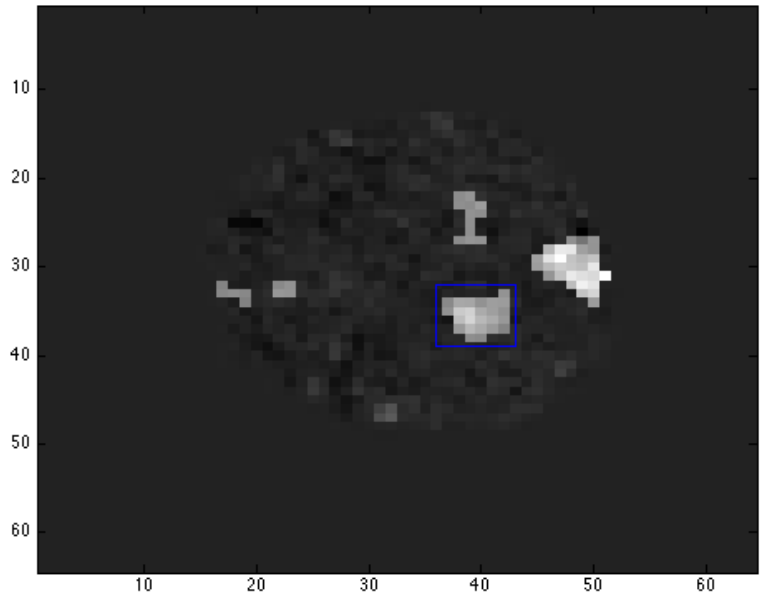
Table 5-Continued

	5.16	0.32	-10.08	0.72	0.71	0.80	0.14	2.25	-0.08
S5	15.66	2.69	11.73	0.82	0.78	1.01	0.05	0.29	0.09
	9.79	8.39	3.72	0.81	0.74	0.45	0.08	0.09	0.12
	-10.40	-22.01	-8.78	0.73	0.51	0.92	-0.07	-0.02	-0.11
	-5.03	-13.29	-4.53	0.80	0.90	0.61	-0.16	-0.07	-0.13
S6	5.12	16.57	12.32	0.72	0.63	0.67	0.14	0.04	0.05
	21.84	33.14	15.44	0.71	0.83	0.66	0.03	0.02	0.04
	1.64	-6.67	6.09	0.75	0.82	0.92	0.46	-0.12	0.15
	1.09	2.96	0.74	0.81	0.67	0.68	0.74	0.22	0.92
S7	29.68	19.71	14.08	0.83	0.68	1.11	0.03	0.03	0.08
	8.24	10.07	2.96	0.63	1.62	0.75	0.08	0.16	0.25
	-1.21	-7.32	-7.02	0.87	-0.68	1.07	-0.73	0.09	-0.15
	-18.29	-5.42	-0.55	0.70	1.47	0.22	-0.04	-0.27	-0.39

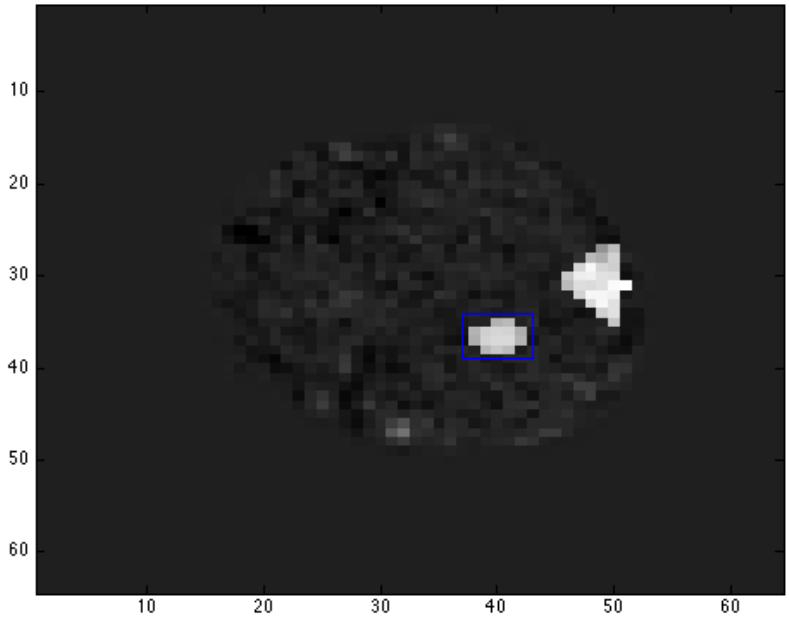
Table 6. T-test Results for CBF Value Difference, BOLD Signal Changes and the Ratio Between Them of the Fixed ROI of M1 for All Subjects

	ΔCBF (ml/min/100g)			ΔBOLD%			ΔBOLD% /ΔCBF		
	R12	R23	R13	R12	R23	R13	R12	R23	R13
S1	4.18	-1.59	2.59	-0.01	0.00	-0.01	0.66	-0.44	0.22
S2	2.54	-3.86	-1.32	0.03	-0.03	-0.01	0.05	-0.06	-0.01
S3	-1.39	4.11	2.72	-0.04	-0.01	-0.05	-0.11	0.03	-0.08
S4	1.18	0.03	1.21	-0.01	0.00	-0.01	-0.48	0.51	0.04
S5	8.56	-6.59	1.97	0.06	-0.02	0.04	-0.10	0.08	-0.02
S6	-4.08	2.85	-1.23	0.01	0.00	0.01	0.30	-0.25	0.05
S7	0.35	1.89	2.24	-0.02	-0.01	-0.03	-0.17	0.06	-0.11
Mean	1.62	-0.45	1.17	0.00	-0.01	-0.01	0.02	-0.01	0.01
SE	1.53	1.45	0.66	0.01	0.00	0.01	0.14	0.11	0.04
t	1.06	-0.31	1.78	0.32	-1.90	-0.52	0.17	-0.09	0.31
$t_{0.05/df}$	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94	1.94

Note: All difference values are calculated from the average value for each subject and R12 means subtracting the Run2's value from those of Run1.

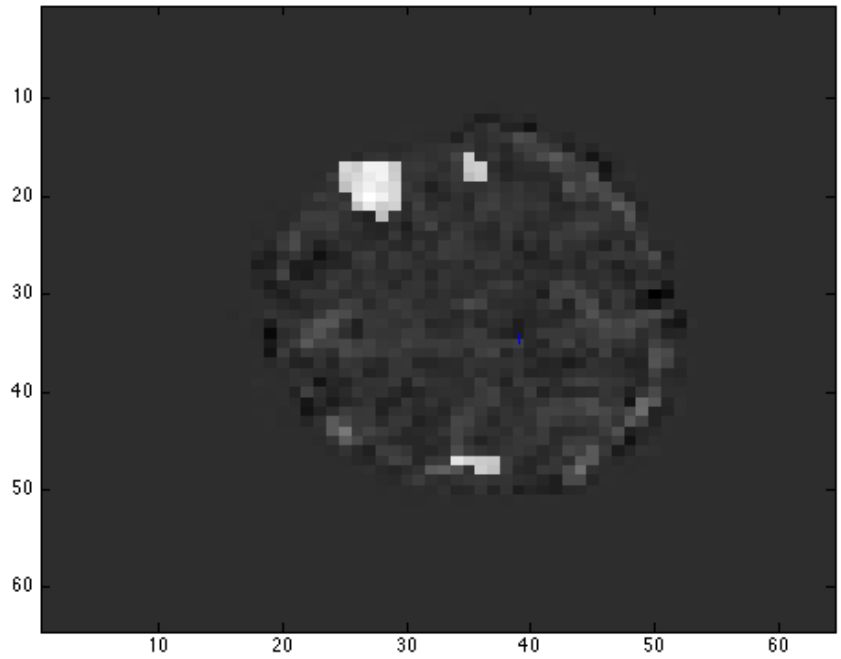


(a)



(b)

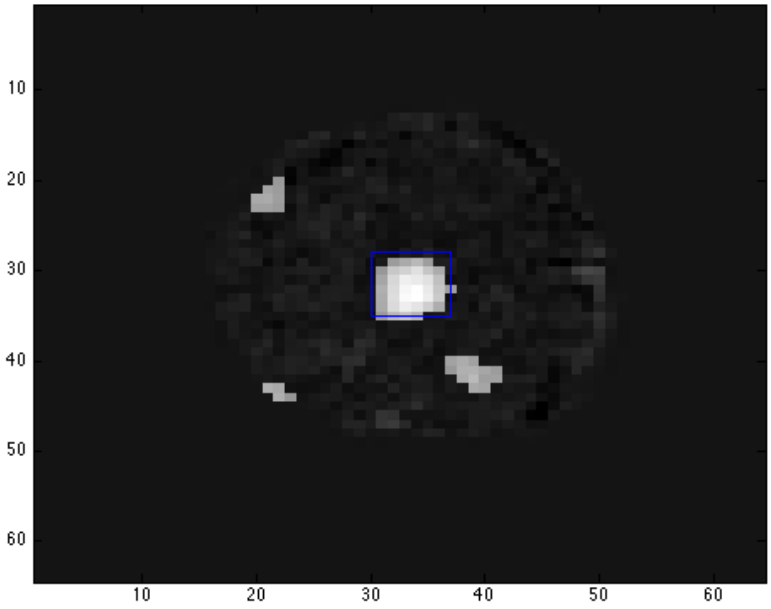
Figure 7. Activation map for ASL Images, Single Subject
(a) Activation Map for Subject 3, Run1
(b) Activation Map for Subject 3, Run2



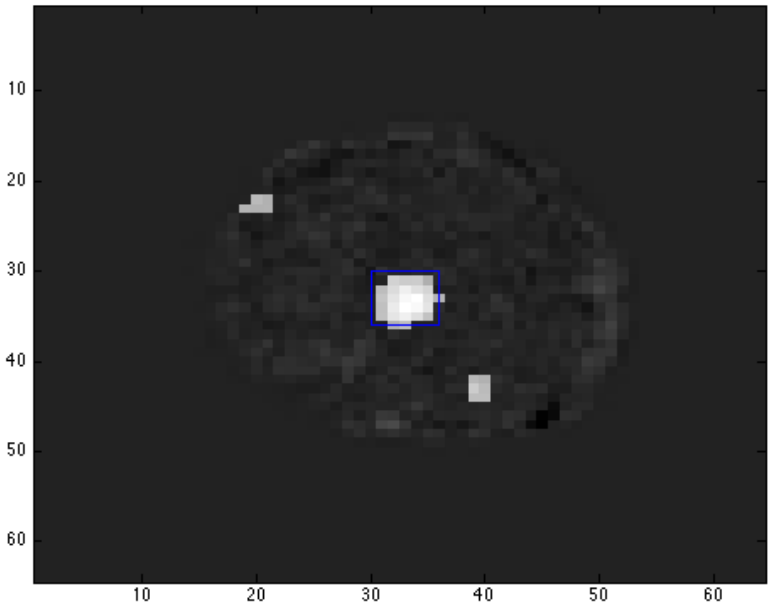
(c)

Figure 7. Continued

(c) Activation Map for Subject 3, Run3

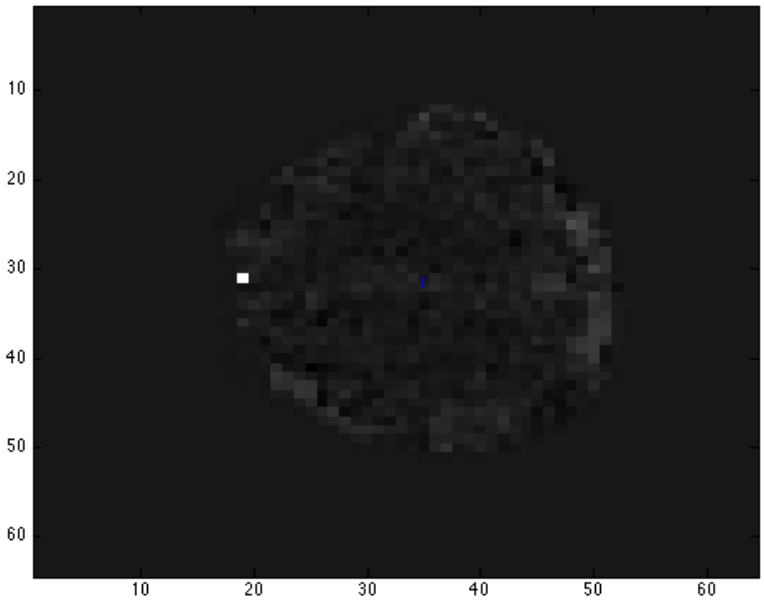


(a)



(b)

Figure 8. Activation map for BOLD Images, Single Subject
(a) Activation Map for Subject 3, Run1
(b) Activation Map for Subject 3, Run2



(c)

Figure 8. Continued
(c) Activation Map for Subject 3, Run3

Table 7. Activation Size for ASL, BOLD Experiments and the Ratio Between Them for All Subjects

	ASL			BOLD			BOLD / ASL		
	Run1	Run2	Run3	Run1	Run2	Run3	Run1	Run2	Run3
S1	54	1	0	40	72	1	0.74	72.00	N/A
S2	20	8	12	72	1	12	3.60	0.13	1.00
S3	30	20	6	25	24	0	0.83	1.20	0.00
S4	16	12	0	77	0	20	4.81	0.00	N/A
S5	20	16	4	48	20	0	2.40	1.25	0.00
S6	24	8	6	9	0	0	0.38	0.00	0.00
S7	16	9	0	0	0	0	0.00	0.00	N/A

Table 8. Analysis of Variance for ASL (One-Way)

Summary						
Groups	Sample Size	Sum	Mean	Variance		
Run1	7	180	25.71	179.24		
Run2	7	74	10.57	37.95		
Run3	7	28	4	20		
ANOVA						
Source of variance	SS	df	MS	F	p-level	F_{crit}
Between runs	1736	2	868	10.98	0.00076	3.55
Within runs	1423.14	18	79.06			
Total	3159.14	20				

Table 9. Analysis of Variance for BOLD (One-Way)

Summary				
Groups	Sample Size	Sum	Mean	Variance
Run1	7	271	38.71	871.9
Run2	7	117	16.71	700.9
Run3	7	33	4.71	64.9

ANOVA						
Source of variance	SS	df	MS	F	p-level	F_{crit}
Between runs	4162.67	2	2081.33	3.81	0.04	3.55
Within runs	9826.29	18	545.9			
Total	13988.95	20				

Table 10. T-test Results for Activation Size for ASL, BOLD Experiments and the Ratio Between Them for All Subjects

	ASL			BOLD			BOLD / ASL		
	R12	R23	R13	R12	R23	R13	R12	R23	R13
S1	53	1	54	-32	71	39	-71.26	N/A	N/A
S2	12	-4	8	71	-11	60	3.48	-0.88	2.60
S3	10	14	24	1	24	25	-0.37	1.20	0.83
S4	4	12	16	77	-20	57	4.81	N/A	N/A
S5	4	12	16	28	20	48	1.15	1.25	2.40
S6	16	2	18	9	0	9	0.38	0.00	0.38
S7	7	9	16	0	0	0	0.00	N/A	N/A
Mean	15.14	6.57	21.71	22	12	34	-8.83	0.39	1.55
SE	6.52	2.60	5.66	15.02	11.47	8.85	10.43	0.51	0.56
t	2.32	2.53	3.83	1.46	1.05	3.84	-0.85	0.77	2.79
$t_{0.05/df}$	1.94	1.94	1.94	1.94	1.94	1.94	1.94	2.35	2.35

CHAPTER V
DISCUSSION AND SUMMARY

Significance of the study

Most normal simultaneous perfusion and BOLD fMRI experiments focused on the activation region or the signal plot comparison, which is static. In our study, the correlation between CBF value change and BOLD signal percentage change was measured and evaluated dynamically through three different runs, which offers an assessment of the actional change of the experimental CBF and BOLD signal data as well as the relationship between these two physiological parameters. Since the relationship of perfusion and BOLD is not always constant, the dynamic comparison gives a more complete and reasonable understanding of the quantifying regional brain function.

Systematic errors in the quantification of CBF

The systematic errors exist during CBF quantification are related to two vascular effects. One is the transit delay between the initial labeling and the delivery of the labeled blood to the imaging region. The other one is the inclusion of intravascular signal from labeled blood in the perfusion measurement from vessels just passing through, but not perfusing, the imaging slice (Wong et al. 1997). Also, venous blood tagged either by the labeling pulse or the control pulse and subsequently moves into the voxel might result in either an underestimation or an overestimation of the signal depending on whether the blood comes from the bottom or the top of the slice. Since the time the blood needed to travel from the labeling region to the imaging region is just near the T1 recovery time of the blood, the images were usually acquired with many different dynamic processes like delivery, exchange and clearance either by T1 recovery or simply by the blood flow. Hence, if the images are acquired too early after the labeling process, the CBF value might be underestimated due to the transit delay or might be overestimated because of the

unwanted inclusion of intravascular signal that passing through the imaging slice. If we wait too long after the labeling to acquire the images, T1 decay effects will wash out most the signal and it will be much more difficult to quantify the CBF value.

BOLD contamination

When doing simultaneously perfusion and BOLD imaging, it is always the fact that the time series of the difference images between control and labeled contains BOLD weighting. If the difference images were achieved just using simple paired subtraction, they would contain signals that are unrelated to perfusion since during the transitions between off/on conditions, the overall signal is usually either rising or falling. Hence, we used the surround subtraction to get the difference image in order to avoid the signal sensitivity to the linear trends in the overall signal.

Also, we've tried to minimize the TE time aiming at eliminating the BOLD contamination in perfusion signal. Other researchers have used a dual echo spiral sequence to manually control the BOLD contamination, the perfusion estimates can be obtained from the first echo with a very small TE and BOLD estimates can be gained from the second echo with a optimized TE value for BOLD contrast (Thomas et al. 2005). Non-subtractive methods using background suppression were also reported, however the quantification of CBF value based on these methods will be more difficult.

Perfusion weighting of BOLD time series

Wong et al. (1997) used a pulse with an in-plane pre-saturation to separate the perfusion signal from the BOLD signal. The pre-saturation makes the labeling inflowing blood's longitudinal magnetization M_z is just smaller by the amount of M_{0b} than that of the blood it is replacing immediately after inversion. So for the control state, the M_z of the inflowing blood is M_{ob} larger, which causes the difference signal between control and labeled images is directly proportional to $2*M_{ob}$, while the average of control and labeled signals is approximately independent of flow and that can be used as a BOLD contrast time series.

The parameter q in the quantification model

The CBF quantification model used is based on Warmuth et al. (2003)'s report and is under the assumption that a fast and compete exchange of blood and tissue spins has occurred. The correction factor q is close to unity under most conditions, such correction is needed because there is always a shift for the decay of rate of the label condition from that of blood to that of tissue after the labeled blood reaches the imaging slice and starts to exchanges into the tissue. Practically, it is difficult to determine the value of q accurately since it relates to the details of the water exchange between blood and tissue. We set it to be 0.93 since the sequence parameters are similar to those of Wong et al. (1997)'s report (TR = 2s, TI_1 = 600-700ms, TI_2 = 1200-1400ms).

Summary

During the median nerve excitation brought by the electrical stimulation to the right wrist, three possible activation areas (SMA, S1 and M1) were found and were studied separately. In general, the S1 area owns better reproducibility when the origin data is processed by the perfusion weighted image method (surround subtraction) and on the other hand, the SMA has a more consistency if the images were paired added and averaged in order to get the BOLD-weighted data. However, the BOLD signal percentage change has a quite stable mean value for all three regions, which is around 0.76%, while S1 owns the strongest response for CBF value change during the activation which is near 7.71 ml/min/100g, for SMA and M1 area, the results are 6.81 ml/min/100g and 4.41 ml/min/100g, respectively.

There is no statistical significant difference for CBF increment and BOLD signal percentage change for a fixed ROI in all three activation areas, thus, no habituation or potentiation for the neuron response strength exists during the median nerve stimulation. The t-scores were pretty small compared to the t critical value, this might because the subject sample size is too small, only seven, so the data used in t-test is not statistically powerful enough to reject the null hypothesis.

For the activation size comparison section, significant difference has been found for activation size among different runs in ASL data and as shown in Table 10, the t-score gets larger for R23 and R13 indicating there is a habituation for number of neurons got activated in the area.

We found significant difference for the ratio of BOLD/ASL between Run1 and Run3, which does not exist for R12 and R23. This might because the difference between Run1 and Run2 for the BOLD data is not that obvious than those for the ASL data. Also, since there are more zero activations in Run3 for BOLD, the amount of ratio values related to Run3 is limited, which would cause a variance for the ratio.

But in general, we can tell from the second method, the amount of neurons getting activated by the stimulation is decreasing through three runs for both perfusion and BOLD data, and since the ratio of these two is basically the stable, there is a dynamic relationship exists between CBF value and BOLD contrast signal.

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