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ABSTRACT

MOTOR DATA SCALING BY RESPIRATION FREQUENCIES IN REST

By

Amit Madhukar Kamble

Functional Magnetic Resonance Imaging (fMRI) is widely used as a tool to see activations in the different brain regions. Motor data acquired from fMRI scan is accompanied with signal due to hemodynamic changes taking place during the scan. This hemodynamic signal is dominated by parameter alteration in the large vessels of brain. Scaling of task induced BOLD signal with hypercapnic or breathold data is one of the effective methods to minimize the signal due to large vessels. Patient discomfort and compliance has been a major issue with these methods hence in this study we used respiration frequencies in rest data to scale task induced data and compared results with breathold scaling. The correlation between respiration frequencies and breathold signal was very good indicating presence of hemodynamic component in respiration. Scaling was done in both time and frequency domain. Standard deviation was used in time domain and frequency fluctuation amplitude was used in frequency. Results of scaling with respiration frequencies and with breathold signal; were comparable and active areas during performance of motor task reduced after scaling, minimizing the effect of large vessels. These outcomes showed that respiration frequencies can be efficiently used for scaling data.

MOTOR DATA SCALING BY RESPIRATION FREQUENCIES IN REST

by
Amit Madhukar Kamble

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MOTOR DATA SCALING BY RESPIRATION FREQUENCIES IN REST

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To my beloved family and all my friends who are the breath of my life and soul

TABLE OF CONTENTS

Chapter	Page
1 INTRODUCTION.....	1
1.1 Overview	1
1.2 Background Studies	4
2 FUNDAMENTALS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING.....	6
2.1 Nuclear Magnetic Resonance	6
2.1.1 Nuclear Spins.....	6
2.1.2 Application of External Magnetic Field.....	7
2.1.3 Magnetization of the Spin Systems.....	9
2.1.4 RF Pulse Excitation and Signal Reception.....	9
2.1.5 Relaxation of MR Signal.....	11
2.2 MR Image Formation	14
2.2.1 Slice Selection.....	15
2.2.2 Frequency Encoding.....	15
2.2.3 Phase Encoding.....	16
2.3 MR Contrast Mechanisms.....	17
2.3.1 Proton Density Contrast Images.....	17
2.3.2 T1 Weighted Images.....	18
2.3.3 T2 Weighted Images.....	18
2.4 Functional MRI	19
2.4.1 Generation of Functional MRI Signal.....	19
2.4.2 Variability in fMRI Signal.....	21

TABLE OF CONTENTS

Chapter	Page
3 METHODS.....	23
3.1 Theory.....	23
3.2 Data Acquisition	25
3.3 Data Analysis.....	27
3.3.1 Preprocessing.....	28
3.3.2 Post-Processing.....	28
4 RESULTS.....	30
4.1 Correlation.....	32
4.2 Motor Data Scaling.....	34
5 DISCUSSION AND CONCLUSION.....	37
5.1 Discussion.....	37
5.2 Conclusion.....	40
REFERENCES	41

LIST OF TABLES

Table		Page
4.1	Correlations of Standard Deviations of Different High and Low Frequency Datasets of Breathhold and Rest.....	33
4.2	Correlation of Sum of Frequency Fluctuation of High and Low Frequency of Breathhold and Rest.....	33

TABLE OF FIGURES

Figure	Page
1.1 fMRI signal output has neuronal activity signal added with signal due to hemodynamic activity when motor stimulus is given. fMRI signal represents just hemodynamic activity with negligible neuronal activity when there is hypercapnic stimulus.....	2
2.1 Precession of Parallel and Anti parallel spins on application of strong external magnetic field in the Z direction. m is the magnetic moment of individual spin.....	8
2.2 Excitation of Spins by RF pulse. Transition of spins from lower energy to higher energy state.....	10
2.3 Relaxation of Spin System after RF pulse excitation. Transition of spins from higher energy state to lower energy state	10
2.4 A) Transverse component (M_{xy}) decay after removal of RF pulse B) T2 exponential decay.....	12
2.5 A) Longitudinal Component (M_z) recovery after RF pulse removal B) T1 exponential recovery	14
2.6 Different gradients used in MRI.	14
2.7 Flowchart of the generation of BOLD contrast.....	20
3.1 Flowchart of different steps involved in the processing of data.....	27
4.1 Fourier spectrum of Breathhold data. Data was filtered in low and high frequency datasets. Low frequency BH data had range of 0.015 Hz to 0.06 Hz while high frequency was ranging between 0.06 Hz to 0.25 Hz. The frequency cutoff was decided looking frequency distribution of original unfiltered data.	30
4.2 Brain maps for standard deviation and sum of frequency fluctuations showing high values in the active areas. 65 th and 66 th slice of the brain showing left and right motor cortex areas.....	31

TABLE OF FIGURES

(Continued)

Figures	Page
4.3 Correlation of low and high frequency datasets of rest and breathhold.	34
A. SD correlation of rest and breathhold data. A1 has the correlation value of 0.83, A2 has correlation value of 0.88 and A3 has a correlation value of 0.77.....	
B. Sum of frequency fluctuations correlation of rest and breathhold data. B1 has the correlation value of 0.63, B2 has correlation value of 0.55 and B3 has a correlation value of 0.49.....	
4.4 Active areas in the motor region without and with scaling of low frequency Motor data with different parameters for a typical subject. Areas show spatial reduction after scaling.....	36

CHAPTER 1

INTRODUCTION

1.1 Overview

Functional Magnetic Resonance Imaging (fMRI) has been very effective to observe and detect different brain regions corresponding to different stimulus. It has become reliable and successful modality. Difference in the magnetic properties of oxygenated and deoxygenated blood is used to detect signal changes in fMRI. Blood Oxygen Level Dependent (BOLD) principle provides contrast to fMRI images of various tasks like breathhold, finger tap (motor) or memory related tasks. Subjects are asked to perform these various tasks. This increases perfusion and creates a need of oxygen. As a result, blood flow increases hence, oxygenated blood increases in the blood stream while deoxygenated blood reduces. The oxyhemoglobin levels increase and deoxyhemoglobin levels decrease. Deoxyhemoglobin has the stronger paramagnetic properties compared to oxyhemoglobin. These changes in the magnetic properties of blood provide good contrast, required for functional Neuroimaging. In this way, active areas give higher signal than inactive areas. fMRI can be used for cognitive neuroscience as well as clinical applications.

Cognitive neuroscience studies focus more to find results that can be applicable to bigger populations, rather than single subject and, comparative studies between patients and healthy controls. Patients and healthy controls are motivated to go through such study. On the other hand, clinical studies deal with a single patient.

As mentioned earlier, BOLD image shows higher amplitude of signal in the active parts of brain but, neuronal activity is not the only source of the signal. Noise sources are always present in the acquired data. Non homogeneous magnetic field, pulse sequence, TR variations, motion artifacts etc. contribute to noise. There is one major source of noise present; hemodynamic activity taking place during the neuronal stimulation. Large vessels present in the brain contribute to the signal predominantly. While performing different tasks, there is not only change in the flow of the blood but also in the shape and diameter of the vessels. These changes in the large vessels produce a considerable amount BOLD signal even if these vessels are not really in close proximity of the exact active area. It leads to a very important issue about reliability of the signal.

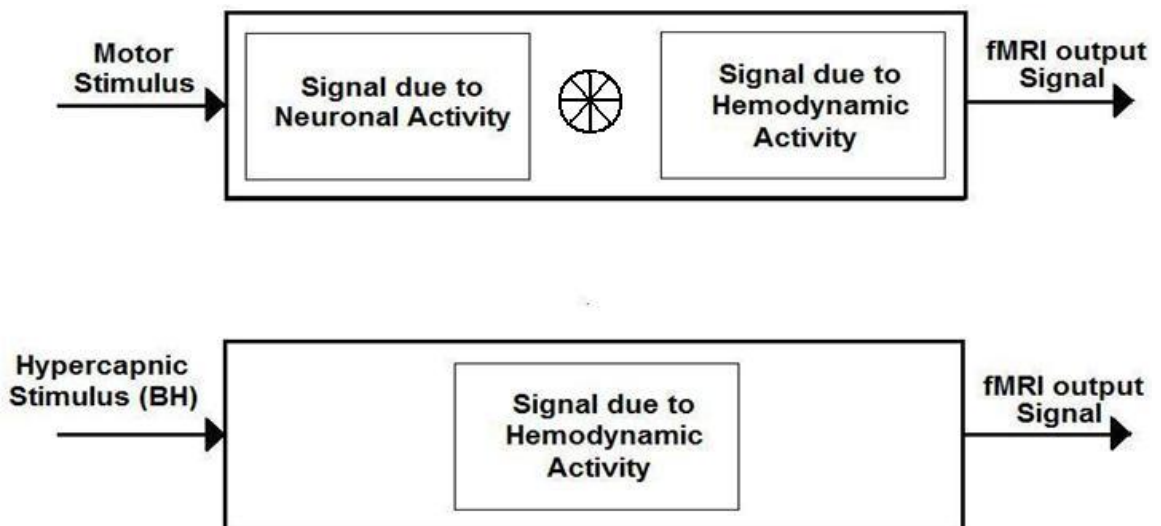


Figure 1.1 fMRI signal output has neuronal activity signal added with signal due to hemodynamic activity when motor stimulus is given. fMRI signal represents just hemodynamic activity with negligible neuronal activity when there is hypercapnic stimulus.

One method to reduce effect of hemodynamic activity is scaling of fMRI signal. Hypercapnia is been used several times to do the calibration of activity. As shown in Figure 1.1, hypercapnia induces signal that represents the hemodynamic activity in the brain. It causes concentration of CO₂ in the blood to increase. CO₂ acts as a vasodilator, increasing the diameter of vessel as well as the blood flow. It increases the signal in large vessels hence representing the hemodynamic activity without much neural activity. Similarly, breathold paradigm, which comprises of holding breath for long time and then releasing the breath followed by breathing it normally and this cycle, continues 3-4 times. It also leads to an increase in CO₂ concentration but, more rapidly than hypercapnia. It causes vasodilation of blood vessels and induces same effect as hypercapnia. Scaling motor task data with hypercapnic or breathold induced signal, is supposed to reduce effects of hemodynamic activity and, show the true neuronal activation which is independent of vessel parameters.

Calibration of neuronal activation by hypercapnia or breathold has been widely used and accepted method. But while performing hypercapnia subject compliance and discomfort is always an issue. Subject has to wear a mask and inhale CO₂/air gas mixture. Special populations like old age subjects or very young age kids are less cooperative to such paradigms. Due to these problems Breathold is preferred over hypercapnia. Breathold method is less complicated to perform with better subject cooperation. Even in the breathold, subject has to hold breath for long periods like 20 sec. Body's need for oxygen prompts a sensory stimulation, which leads to neuronal activity. This stimulation due to air hunger can get reflected in the BOLD data, making result less reliable and

efficient. Looking at problems associated with the hypercapnic or breathhold scaling, a necessity of an alternate method which will try to overcome these issues; arises.

In this study, the hypothesis was tested that, the resting state fMRI can be used in lieu of commonly used hypercapnic stimulus including 5% CO₂ and breath holding. We focused on relation between high frequency rest data and breathhold data to check if they have similarities and then assess ability of high frequency data of rest i.e. respiration itself to calibrate task data; followed by comparison of the results with established method of scaling by Breathhold.

As rest paradigm doesn't need any kind of patient activity or attention to any task, subject compliance issues can be taken care.

1.2 Background Research

Parameters of blood vessels in the brain change during the activation due to any neural stimulation. The hemodynamic response varies from one subject to another (D' Esposito et al., 1999). It also depends on the regional basis (Huettel and McCarthy, 2001). These differences can be dependent on the vascular sensitivity changes across the different age groups (Riecker et al., 2003). Inducing a stimulus which will increase signal due to hemodynamic activity but without changing much of neural activity was done by many groups like Kastrup et al. (1999), Li et al. (1999).

Hypercapnic stimulus is one of the stimuli used to replicate hemodynamic changes taking place in the body and its effect on cerebral metabolic rate for oxygen. Bandettini et al. (1997), Davis et al. (1998), Cohen et al. (2004) used scaling of fMRI data with hypercapnic signal to compensate for vascular differences. One more method

used to replicate the hemodynamic changes is breathhold technique. Handwerker et al. (2006), Thomson et al. (2007) performed calibration of BOLD data using breathhold data. Kannurpatti, Biswal (2007) used partial inspirational breath hold signal to scale the data. These studies showed reduction in variability of fMRI signal after scaling done by hemodynamic stimulus produced either by hypercapnia or breathhold.

Hypercapnic method has a major problem of patient discomfort. The mixture of CO₂/air is inhaled through the mask. It becomes very uncomfortable to very old or young populations. Though breathhold scaling ensures more cooperation of the subjects, it includes holding breath for around 20 seconds which becomes an issue with old or very young populations (Thomson et al 2005).

Kannurpatti, Biswal (2008) showed that task induced data can be scaled by rest signal. Rest signal can be used as representative of hemodynamic response and motor data can be scaled as comparable as hypercapnic scaling. Rest paradigm is very simple and it increases the patient cooperation.

CHAPTER 2

THE FUNDAMENTALS OF MAGNETIC RESONANCE IMAGING (MRI)

Magnetic Resonance Imaging is very useful modality to visualize detailed internal structure of the body. It is used in neurological, musculoskeletal, cardiovascular and oncological imaging. It is based upon the Nuclear Magnetic Resonance (NMR) phenomenon and there are imaging techniques developed like Magnetic Resonance Spectroscopy (MRS), Diffusion MRI, Magnetization transfer MRI, Fluid Attenuated Inversion Recovery (FLAIR), MR angiography, functional MRI (fMRI) based on the same principle with some modifications. In MRI, hydrogen atoms are most commonly used. Strong magnetic fields are used to align the hydrogen atoms or protons in the body and their reaction to RF pulse excitation is recorded to get the image.

2.1 Nuclear Magnetic Resonance

2.1.1 Nuclear Spins

Protons spin about their axis due to thermal energy. Rotation motion of the proton gives rise to angular momentum j . It also has an ability to work as a magnet with a magnetic moment μ when put in the magnetic field. Angular momentum (J) and Magnetic moment (μ) are in the direction defined by right hand thumb rule. If the nuclei has even number of protons, then J or μ tends to get cancel hence to nuclei should have odd no of protons to be used in MRI. Hydrogen has just one proton in the nucleus and it is abundantly present in human body hence it is very suitable to be used as a nuclei or proton in MRI.

Angular momentum and magnetic moment are interrelated to each other. The relation between them is given as:

$$\mu = (q/2m). J \quad (2.1)$$

Where q is the charge of a proton and m is the mass of proton. The constant $q/2m$ is called a Gyromagnetic Ratio (γ) and it is dependant only on charge and mass of a particular nuclei.

Protons having both angular momentum and magnetic moment are individually called spin and collection of them forms a spin system. In absence of any external magnetic field these spins are randomly oriented and they to cancel out each other. Net magnetization at normal conditions is very insignificant or zero.

2.1.2 Application of External Magnetic Field (B)

On the application magnetic field, a suspended iron rod aligns itself to direction of the applied magnetic field. Similarly when protons are placed in very strong magnetic field they also change their orientation but instead of aligning themselves completely to the field spins initiate a gyroscopic motion. This gyroscopic motion is termed as Precession and it can compared to spinning top which has its axis of rotation changing around the axis of applied force i.e., Gravity. Protons precess with axis of rotation which is rotating or changing the direction around the axis of applied magnetic field B . Frequency of precession depends on a type of nucleus. Same nuclei will precess with same frequency under the same applied magnetic field. Frequency of precession is called Larmor Frequency.

Larmor Frequency is given by the equation

$$\omega_0 = \gamma B_0 \quad \text{or} \quad f_0 = \gamma B_0 / 2 \pi \quad (2.2)$$

Where, γ = Gyromagnetic ratio, ω = precession frequency

f = Linear frequency in MHz ($= \omega / 2 \pi$) and B = Magnetic strength in T (tesla)

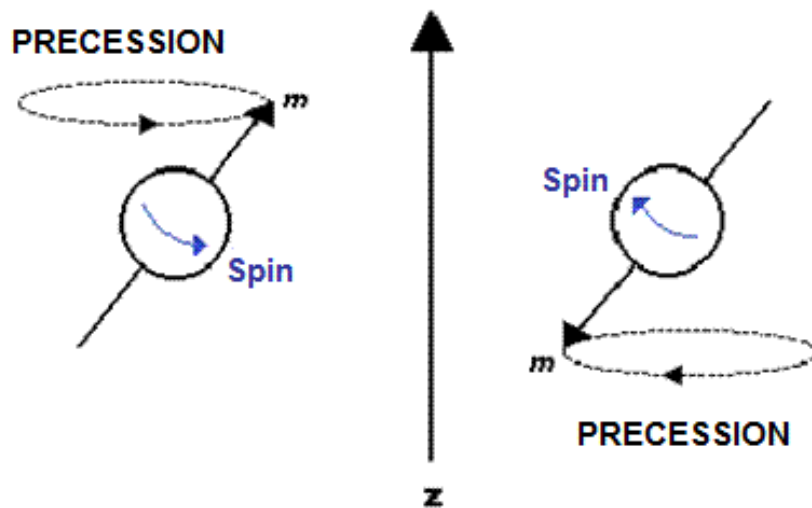


Figure 2.1 Precession of Parallel and Anti parallel spins on application of strong external magnetic field in the Z direction. m is the magnetic moment of individual spin.

As seen in the Figure 2.1, protons can precess in one of the two directions. Either parallel to magnetic field or anti parallel to the magnetic field. Protons in anti parallel state have more energy than parallel state but parallel state protons are more stable. Due to the factor of stability, protons in the parallel state are more in number. If the temperature increases, then some of the protons will gain energy to go from parallel state to anti parallel state.

2.1.3 Magnetization of Spin System

A strong magnetic field is applied on spin system. All individual spins sum up to form a magnetization vector (M). Magnetization vector can have two components, a transverse component (M_{xy}) and a longitudinal component (M_z). Transverse component (M_{xy}) is perpendicular to the applied magnetic field and it cancels out hence we do not have net magnetization in the transverse plane.

Parallel state spins are more in number than anti parallel spins hence longitudinal component (M_z) is parallel to applied magnetic field. According to Zeeman's effect, net magnetization is increased by increase in applied magnetic field (B). MR signal in 3T scanner is 4 times larger than in 1.5 T scanner.

One problem with net magnetization is that it can't be measured directly hence we have to disturb equilibrium of protons and measure their reaction or recovery from the disturbance to equilibrium.

2.1.4 RF Pulse Excitation and Signal Reception

Change in equilibrium of protons is realized by application of Radio Frequency (RF) pulse on them. Radio frequency pulses are electromagnetic waves. Due to excitation by RF pulse, transition between two energy levels of the precessing proton is triggered. RF signal is adjusted to resonant frequency of an atom. Hydrogen atom has the resonant frequency of 42MHz per Tesla.



Figure 2.2 Excitation of Spins by RF pulse. Transition of spins from lower energy to higher energy state.

As seen in Figure 2.2, excitation provides energy to spins in the low energy level i.e., parallel state spins to make a transition to high energy level or anti parallel spin state. Number of spins in the anti parallel state starts to increase. It means that magnetization vector is shifted from longitudinal direction to transverse plane. The RF pulse excitation pulse for this particular procedure is called '90 degree excitation pulse'. If the RF excitation pulse is applied furthermore, then comes a point when the net magnetization becomes completely reverse. This excitation pulse is called '180 degree excitation pulse'. If the excitation is continued further then magnetization starts to reduce and behavior becomes reverse.



Figure 2.3 Relaxation of Spin System after RF pulse excitation. Transition of spins from higher energy state to lower energy state

Once the RF excitation is stopped, excited spins start to come to their stable energy state. As seen in Figure 2.3, transition is now from high energy anti parallel state

to the low energy parallel spin state. In this transition high energy spins lose their energy to emit a photon and come to parallel state. Energy of the photon emitted is equal to energy difference between the two states.

The changes in transverse magnetization during transition can be detected by a radiofrequency coil tuned at Larmor frequency. Hence most of the time same coil is used for excitation as well as reception. Changing current in this detector coil constitutes the MR signal.

2.1.5 Relaxation of MR Signal

Excitation given by RF pulse has changes in two components of net magnetization. After 90 degree pulse, M_{xy} increases from 0 to a magnitude same as longitudinal magnetization before excitation and M_z decreases from its value to zero. Once the excitation is removed, M_{xy} decreases to zero and M_z recovers back to its original value but both things do not happen simultaneously. All the spins are in coherence when in transverse magnetization but they lose coherence very quickly after the RF pulse is removed and on the other hand longitudinal component recovery is very slow. These changes in MR signal are called as relaxation.

2.1.5.1 Transverse Decay. After RF excitation, the net magnetization is completely in transverse (xy) plane. Magnetization is composed of vector sum of many individual spins. It has largest value when all the spins are in coherence i.e., in same phase and same frequency.

Once the excitation is removed, spins start to go in their original state but they lose their coherence and some start precessing with higher frequency and some with low frequency. These difference leads to an exponential decay of transverse component with time constant of T2. The M_{xy} can be given by the equation in terms of T2 by the equation:

$$M_{xy} = M_0(e^{-t/T_2}) \quad (2.3)$$

Where, M_0 is the Original Magnetization. t = time following excitation at which M_{xy} is measured.

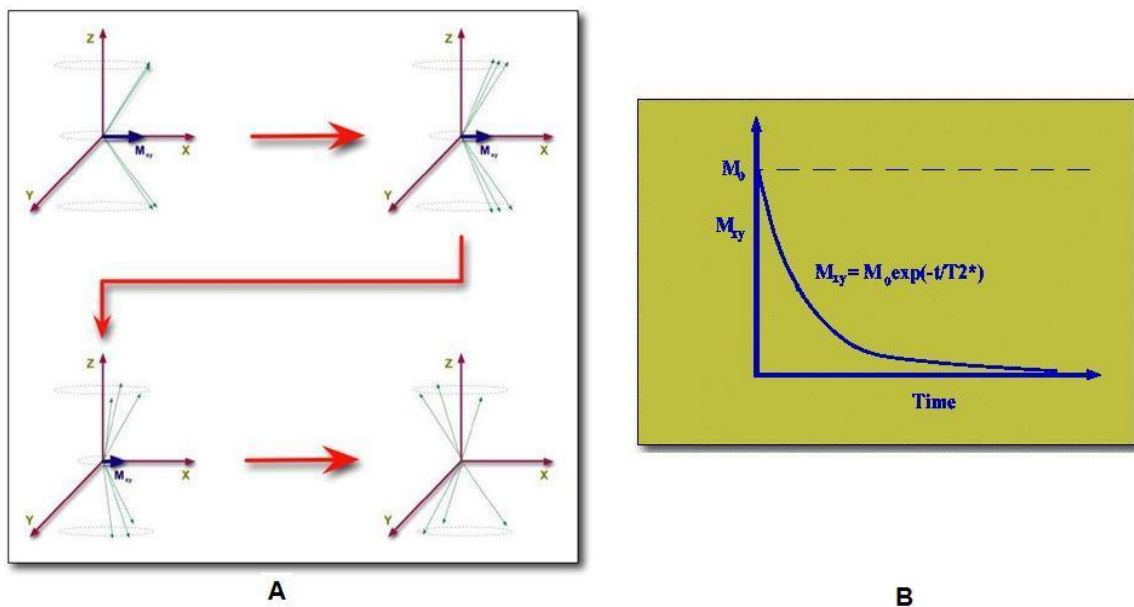


Figure 2.4 A) Transverse component (M_{xy}) decay after removal of RF pulse B) T2 exponential decay.

The magnetic field doesn't perfectly homogeneous throughout the space. There are some inhomogeneities present spatially which adds up to the speed of the decay.

This combined effect gives the time constant called T2*. Hence this decay is called T2* decay. Transverse decay has duration of few tens of milliseconds.

2.1.5.2 Longitudinal Recovery. The longitudinal component (M_z) becomes zero after RF excitation. Spin system start coming to original position once the excitation stops. The system loses energy and the emitted electromagnetic waves are detected by receiver coil as MR signal. Finally, net magnetization come parallel applied external magnetic field. This recovery is relatively slow than transverse decay. It takes few hundreds of milliseconds to sometimes few seconds. The recovery of T1 is also exponential with time constant called T1. M_z is given by the equation in terms of T1 and M_0 as:

$$M_z = M_0 (1 - e^{-t/T1}) \quad (2.4)$$

Where, M_0 = original magnetization and t =time following excitation at which M_z is measured

T1 and T2 constants are different for different tissues and hence they give different signals for different tissues. In this way we can identify and image different tissue and organs in the body with MRI. A combination of T1 and T2 will determine the amplitude of the MRI signal and intensity of the image. Hence they should be properly chosen.

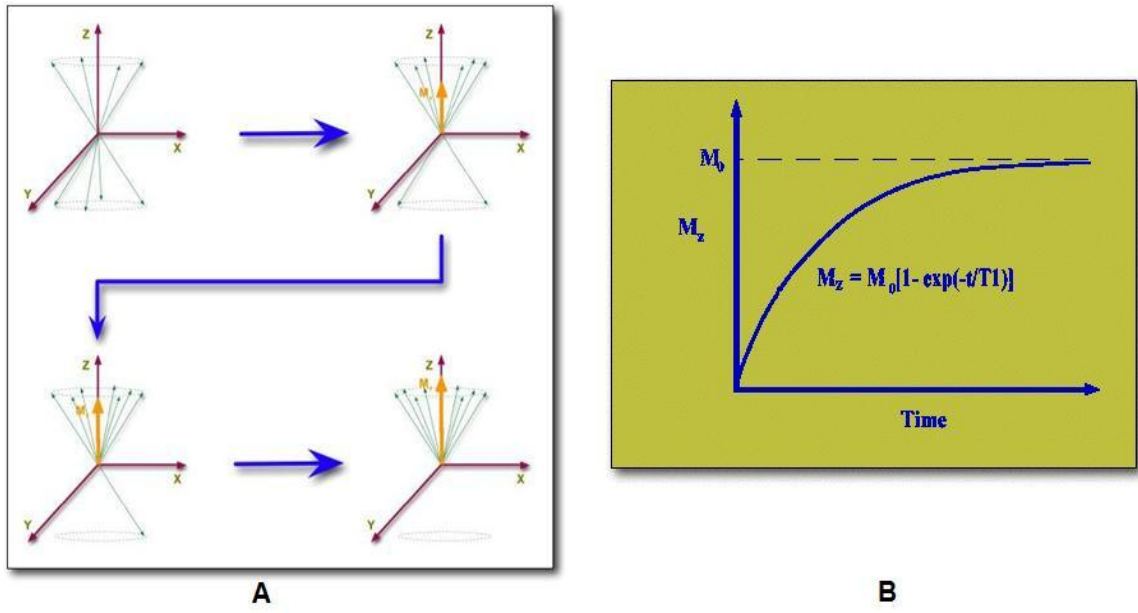


Figure 2.5 A) Longitudinal Component (M_z) recovery after RF pulse removal B) T1 exponential recovery

2.2 MR Image Formation

A sequence of gradient field changes, along with radiofrequency pulses, is used to create an MR image formation. MR image formation is based on 3 steps. First a slice selection is done to select a two dimensional slice of the object to be imaged, then frequency encoding and phase encoding is done to get the final MR image data.

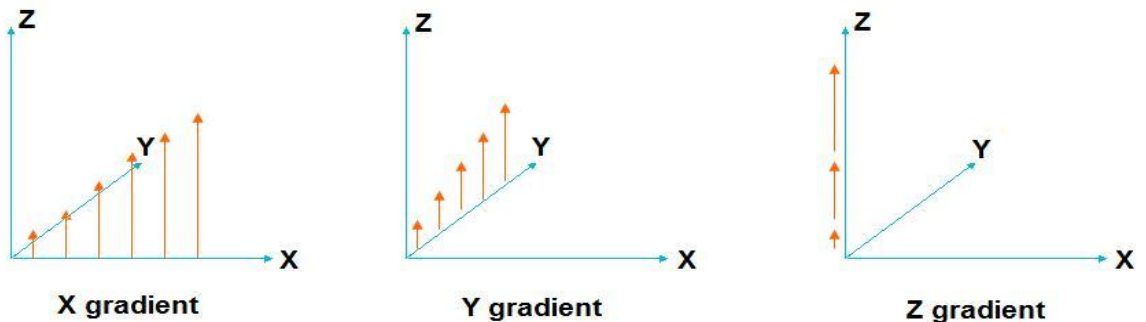


Figure 2.6 Different gradients used in MRI.

2.2.1 Slice Selection

In slice selection, a two dimensional slice selected at a time and then frequency and phase encoding is done on the particular slice.

Selection of any slice means that on the application of the RF pulse, spins from the particular slice only should get excited and rest other sample should not react. This can happen only when frequency of RF pulse matches only with the spins in the slice.

To achieve aim of excitation of spins in a particular slice, a spatial gradient (G) is applied along the direction of the magnetic field. (Assuming it is Z direction). It will cause a continuous change in the field strength of the magnetic field strength and hence the precession frequency of the spins along the length of the sample.

Now to get a particular slice, we need to excite particular range of frequency with RF pulse of same frequency range. If the characteristic of static magnetic field, gradient (G_z) and slice location is known then the centre frequency for excitation pulse can be determined. By calculating the frequency range for RF pulse, a slice is selected. It is done very rapidly like in few milliseconds since it is just application of one gradient and RF pulse.

2.2.2 Frequency Encoding

If only the slice selection is done and no other gradient is applied then all the spins in the slice will precess with the same frequency and they will not be able to give any individual different information. A difference in location of the protons would become impossible. Taking this problem into consideration a frequency and phase gradients are applied.

Frequency gradient makes spins within slice having different locations, to precess with different rates. A gradient is applied along length of the slice (Assuming it is X direction= G_x). At the one end of the slice the spins will precess faster while gradually the rate of spins will reduce towards the next end. The resulting MRI will still have high-frequency oscillations and transverse relaxation, but now there are slower oscillations superimposed on the faster oscillations at the resonant frequency that provide information about the width and spacing of two different organs in the slice. This gives the one dimensional map of the MR data.

2.2.3 Phase Encoding

Transforming a one dimensional map of data to complex two-dimensional image is done by applying sequential application of a second gradient within the slice that alters the spin precession frequencies in a spatially controlled manner. A gradient is applied in one direction (Assuming it is Y direction= G_y) then A gradient is applied in another (G_x). The intention behind applying G_y is to create a phase difference between spins not the considerable change in frequencies hence G_y is weak gradient so that by the time G_x is applied, the spins are out of phase but not much change in the frequency of spins. Now, spins have frequency as well as phase differences. MR signal will now have different individual information in each voxel or with every spin.

2.3 MR Contrast Mechanisms

Repetition Time (TR)

It is the time interval between two successive excitation pulses.

Echo Time (TE)

It is the time interval between excitation and data acquisition.

The transverse magnetization which translates to detectable MR signal is described in terms of TR and TE is as follows:

$$M_{xy}(t) = M_0 (1 - e^{-TR/T1}) e^{-TE/T2} \quad (2.5)$$

Contrast is just the difference between two MRI data coming from two different tissues at the same time.

2.3.1 Proton Density Contrast Images

Each voxel contains certain number of spins. Every voxel has different number of spins in it. As the name suggests, contrast depends on the density of spins in a voxel. This density is different in different type of tissue. To enhance proton density contrast, T1 and T2 contrast effects should be minimized. For T1 contrast reduction TR should either be very short or very long. For T2 contrast reduction TE should be either very short or very long. In practice, very long TR and very short TE values are used to get proton density weighted images. Very short TE gives minimal decay of transverse component and long TR gives full recovery of longitudinal component.

2.3.2 T1 Weighted Images

The most commonly used structural contrast for anatomical images of brain is T1 weighting. The effect of T2 to get good T1 weighted contrast should be minimized. If the TR is very small, the recovery is very small or almost nothing and if TR is very long then all the longitudinal components from different tissues will recover hence we don't get much contrast signal but at intermediate values of TR there are some tissues which will recover faster than others so having more longitudinal component amplitude than others so contrast is established. TE is kept very low hence signal from transverse component is also very high in all the tissues hence T2 weighting is minimized.

For more effective T1 contrast, 180 degree inversion pulse is used. By introducing inversion pulse range over which tissues have to recover becomes twice and with intermediate TR times, contrast between two tissues enhances.

2.3.3 T2 Weighted Images

Fluid filled regions such as tumors, malformations are imaged using T2 weighting. T1 weighting effect should be reduced to get good T2 weighting. If TE is very small then transverse component will be high in all tissues similarly if TE is long then transverse component is going to get reduced to zero in all the tissues hence in both cases no T2 contrast will be apparent. If TE values are intermediate then in some tissues transverse component will decay more than other tissues and that fact gives the T2 weighted contrast. TR values are kept very long so that recovery of longitudinal component is done in all the tissues and effect of T1 weighting is reduced.

2.4 Functional MRI

2.4.1 Generation of Functional MRI Signal

Any neural activity increases the blood flow in brain by changing its volume and velocity. Blood Pressure, blood vessel parameter, density of the red blood cell, age, health, activity level of particular subject and many other factors make blood volume and velocity different for different subjects. Blood flow is proportional to the 4th power of radius of vessel. Any minor changes in the vessels radius can cause a major change in blood flow. It is been observed that smaller arteries and arterioles or venules have bigger resistance to blood flow than there bigger counterparts. Velocity is considerably more in the arteries compared to veins.

A study conducted by Iadecola et al. (1997), suggests that neuronal activity causes changes in the blood flow but, alteration in the blood flow velocity and volume is also observed in few millimeters away where there is no motor activity hence, it leads to the fact that, local micro-vascular blood supply would be a crucial determinant of the signal in the functional Neuroimaging techniques.

Vessels size modification is observed more in arterioles than venules. Physiological perturbations like hypocapnia (low levels of CO₂ in blood) or hypercapnia (high levels of CO₂ in blood) shows that dilation of venules is much less than arterioles. Due to change in flow capillaries distend themselves and, it leads to increase in surface area. Surface area expansion facilitates more transfer of oxygen and glucose to active neurons.

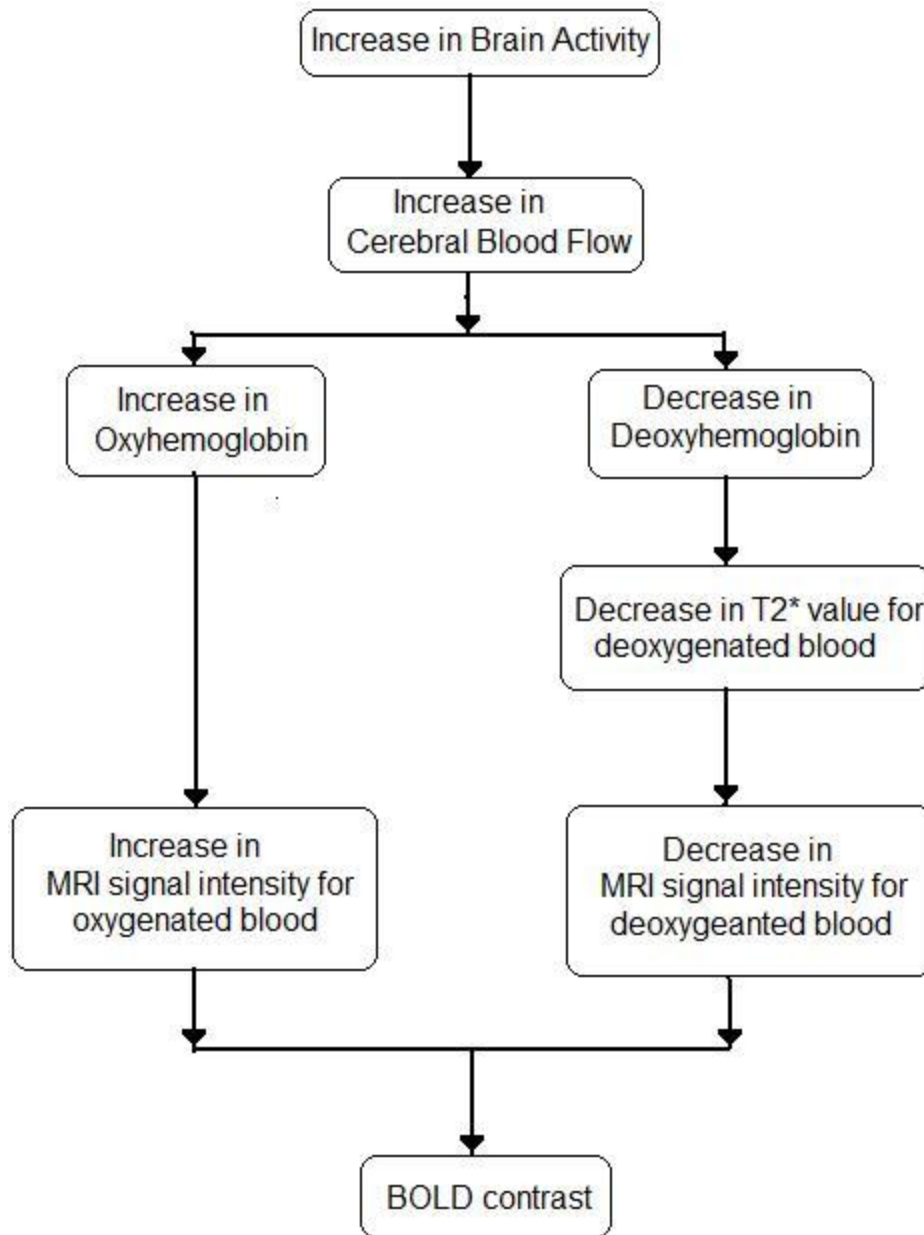


Figure 2.7 Flowchart of the generation of BOLD contrast.

In 1936, Linus Pauling and his student Charles Coryell discovered that hemoglobin molecule has a magnetic properties that differ depending on whether hemoglobin is bound to oxygen or not. As shown in Figure 2.7, Oxyhemoglobin is diamagnetic and has less magnetic susceptibility while deoxyhemoglobin has

paramagnetic properties and has 20 % more susceptibility. Paramagnetic substances distort the surrounding magnetic field strength increasing the inhomogeneity of the field. It contributes more rapid T_2^* decay. Hence a signal from deoxygenated blood will decay faster than oxygenated blood. Hence oxygenated blood gives more MR signal than deoxygenated blood.

S Ogawa et al, (1980) speculated that blood oxygen level dependant contrast could identify areas of the brain activity. Their experiments showed that BOLD contrast depends on the amount of deoxygenated hemoglobin present in the brain. It is dependent on amount of oxygen consumption and supply balance.

With increase in neuronal activity, oxygen consumption increases so as the increase in oxygenated blood in brain, due to its requirement. Hence neuronal activity actually increases the signal of T_2^* images.

Studies by Fox and Raichle (1986) suggest that whenever, brain is stimulated by any task there is increase in Cerebral Blood Flow (CBF). This increase, however, is more than what brain needs. This extra increase in blood also flow increases the oxyhemoglobin levels of the brain while deoxygenated hemoglobin concentration decreases and, it leads to enhancement of the contrast of fMRI image.

2.4.2 Variability in the fMRI Signal

Harrison et al., (2002) observed that fMRI signal also changes according to the density of blood vessels and capillaries in the brain region. Areas with large vascular density showed prominent signal. High signal due to neuronal activity and, due to vascular

density matches pretty well spatially but sometimes stimulated regions and high contrast regions do not match because of the variability in vascular density. It leads to the fact that areas which are not actually active can give high signal while, areas which are stimulated by task activity can have low signal. This observation also reduces the reliability of the neuronal activation.

Another factor associated with blood vessels having effect on fMRI signal is vascular compliance. It is the tendency of vessels to dilate when there is increase in blood flow. Deoxygenated blood contains CO_2 which acts as a vasodilator and it changes blood flow. Vascular compliance varies from one region to another in the brain and, it leads to variability in the fMRI signal.

Age and physical condition of the subject also adds up to the variability in the signal because, compliance and density are different for different subjects as well as it changes with the age. Old age subjects show differences in various factors like global volume, micro-vascular organization, oxygen uptake etc. It leads to alteration in fMRI signal obtained from older subjects compared to younger subjects.

CHAPTER 3

METHODS

3.1 Theory

Davis et al (1998) proposed a model to establish relation between induced BOLD signal, CMR_{O_2} and CBF where CMR_{O_2} is cerebral metabolic rate for oxygen and CBF is cerebral blood flow. Transverse relaxation rate ΔR_2^* is linearly proportional to blood volume fraction fv and magnetic susceptibility difference $\Delta\chi^\beta$ where imaging parameter β is a constant. And it can vary between 1 and 2 depending on field strength. $\Delta\chi$ is has a proportional relation with deoxygenated hemoglobin dHb. Deoxygenated hemoglobin can be expressed as ratio of CMR_{O_2} and CBF. Hence ΔR_2^* between time 0 and t can be expressed in terms of CMR_{O_2} and CBF as:

$$\Delta R_2^*(t) \propto fv(t) (CMR_{O_2}(t) / CBF(t))^\beta - fv(0) (CMR_{O_2}(0) / CBF(0))^\beta \quad (3.1)$$

$CMR_{O_2}(0)$ and $CBF(0)$ represent the baseline activity. For a small change in relaxivity the bold signal is $B_t \approx (1 - TE \Delta R_2^*(t))$. We substitute this relation in equation (3.1) and then to normalize the activity at time t we can divide it with the baseline activity to get the expression as:

$$B_t - 1 \propto fv(0) (CMR_{O_2}(0) / CBF(0))^\beta (1 - Vt (rCMR_{O_2} / Ft)^\beta) \quad (3.2)$$

Where Vt is ratio of $fv(t)$ and $fv(0)$, Ft is a ratio of $CBF(t)$ and $CBF(0)$ and $rCMR_{O_2}$ is $CMR_{O_2}(t)$ relative to $CMR_{O_2}(0)$

According to Grubb et al. (1974) $V_t = Ft^\alpha$ where α is constant with the value 0.38.

Equation (3.2) can be modified as:

$$B_t - 1 \propto f\nu(0) \left(\frac{\text{CMRO}_2(0)}{\text{CBF}(0)} \right)^\beta (1 - r\text{CMRO}_2)^\beta \cdot (Ft)^{\alpha-\beta} \quad (3.3)$$

The proportionality constant that relates BOLD signal change to dHb into a calibration parameter is denoted as M and it is equal to $f\nu(0) \left(\frac{\text{CMRO}_2(0)}{\text{CBF}(0)} \right)^\beta$.

Substituting in (3.3) we get

$$B_t - 1 \propto M (1 - (\text{CMRO}_2(t) / \text{CMRO}_2(0)))^\beta \cdot (\text{CBF}(t) / \text{CBF}(0))^{\alpha-\beta} \quad (3.4)$$

BOLD signal change due to motor task B_{task} i.e. $\Delta\text{BOLD} / \text{BOLD}_{rest}$ can be written as:

$$B_{task} = M (1 - (\text{CMRO}_{2task} / \text{CMRO}_{2rest}))^\beta \cdot (\text{CBF}_{task} / \text{CBF}_{rest})^{\alpha-\beta} \quad (3.5)$$

For a scaling parameter it is assumed that there is no significant variation in CMRO_2 hence $r\text{CMRO}_2$ can be approximated to 1 hence BOLD signal change is given as:

$$B_{Scale} = M \cdot (1 - (\text{CBF}_{task} / \text{CBF}_{rest})^{\alpha-\beta}) \quad (3.6)$$

Where B_{Scale} is $\Delta\text{BOLD} / \text{BOLD}_{Scale}$ is BOLD signal change for any paradigm which gives intended scaling parameter.

After getting the responses during the different task performances, we can now do the scaling of the BOLD data due to motor task. A division of B_{task} by B_{Scale} gives the scaled response minimizing the effect of vascular changes present during the task. B_{Scale} can be any scaling parameter reaching the aimed effect. In the study, we used high frequency of Breathhold and Rest as well as low frequency of Breathhold to do scaling.

Changes in the BOLD activity can be realized by many parameters derived from the data. In time domain the parameter used to see changes was standard deviation (SD) of data while average of frequency fluctuation was used in frequency domain.

3.2 Data Acquisition

Siemens Allegra 3T MRI scanner was used for scanning all patients. Asymmetric head gradient coil and shielded radio frequency coil were the basic parts of the system. At the time of scan, patients were asked to lie in supine position i.e. on the back with face up. The heads were exactly in the middle of the gradient coil. Motion artifacts were reduced by providing foam padding between forehead and gradient coil. The echo-planar images are obtained with TR 2 sec and 64X64 matrix was used. 36 slices with the slice thickness of 2mm were obtained across the whole brain. A flip angle of 80° was used. Mid sagittal image was used to cover the motor cortex for functional imaging.

Number of healthy subjects who took part in the experiment was 14. A written consent was obtained from every subject once they were made aware of the procedure and nature of the experiment. All subjects performed three types of paradigms.

A) Breathhold Paradigm

Subject starts with the normal breathing and continues to breathe normally for 40 seconds. After 40 seconds, subject holds breath for 20 seconds continuously. This cycle is repeated 3 times and scan ends with 40 seconds of normal breathing. Whole scan lasts for 220 seconds for a single person.

B) Motor task Paradigm

This paradigm consist of simple task of tapping fingers of hand by your thumb starting from index finger to little finger whenever prompted to do so. This paradigm starts by the rest period of around 20 seconds and then subject is prompted to do task.

Subject performs finger tapping task for 20 seconds. It is followed by rest period of 20 seconds. Cycle of rest followed by task is repeated 4 times. Whole paradigm lasts for 90 seconds

C) Rest Paradigm

In Rest paradigm, subjects were asked to just close their eyes but not to go into sleep.

Rest state was done for 230 seconds.

3.3 Data Analysis

Once the data was collected, analysis had different steps. Flowchart showed in Figure 3.1 gives brief idea about the steps involved.

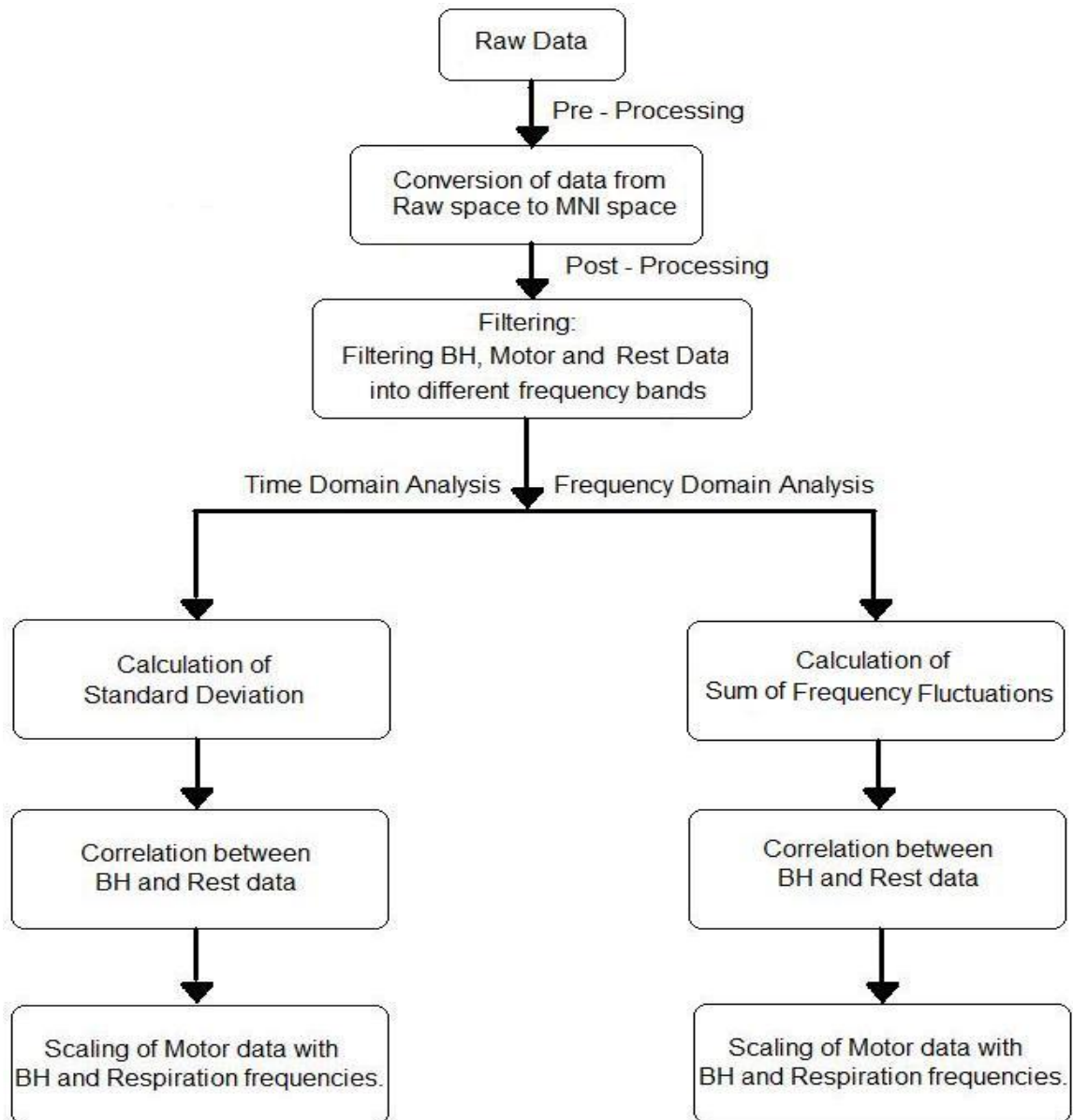


Figure 3.1 Flowchart of different steps involved in the processing of data.

3.3.1 Preprocessing

Analysis was done using MATLAB and AFNI (Cox, 1996). Data was acquired in raw space. Every subject has different brain size and shape hence we normalize the brain data to particular template given by Montreal Neurological Institute (MNI). It reshapes brain in a particular standard size.

3.3.2 Post-Processing

Different frequency components were taken into consideration in the study hence different datasets were filtered in high and low frequency bands with cut off frequencies determined by looking at the time series of the active voxels in frequency domain. Rest data was filtered in the bands of 0.01 to 0.1 Hz for low and 0.06 to 0.25 Hz for high frequency band. Breathhold data was taken from 0.015 to 0.06 Hz in the low frequency band and 0.06 to 0.25 Hz in high frequency. Motor data had frequency limits of 0.03 to 0.06 Hz for lower band and 0.06 to 0.25 for upper frequency data.

A new parameter like high frequency of a Rest was going to be used hence we checked the similarity between scaling parameter BH and rest by getting the correlations between them. Correlations were performed between SD of the datasets in the time domain and on frequency fluctuations amplitudes in frequency domain.

3.3.2.1 Time Domain Analysis. Standard deviation (SD) was calculated for different frequency bands of the rest, breathhold and motor task data. SD correlation values for high frequency BH and Rest were very high as well as low frequency data. Cross correlation

between low frequency BH and high frequency Rest also showed good correlation. Similar trend was observed in the frequency domain correlations between BH and Rest.

Looking at the good correlation values between the BH and Rest datasets, Rest data was also used for scaling along with BH to scale task signal. Scaling was done with three parameters; low frequency BH, high frequency BH and high frequency Rest.

3.3.2.2 Frequency Domain Analysis. Spontaneous low frequency fluctuations were first observed during rest state by Biswal et al (1995). Zang et al (2007) developed a new parameter called Amplitude of Low Frequency Fluctuations (ALFF) to see the activation pattern in the resting state. Frequency estimation was performed on voxel-wise basis. In this study, data is divided in different high and low frequency components for rest, breathhold and motor. Using similar steps like ALFF calculation, amplitude of frequency fluctuations was calculated for different datasets. The steps to calculate amplitude include, first to get the data filtered for particular frequency range and then calculate the power spectrum of data. The square root of each of point in the power spectrum was calculated and then amplitude of each point i.e. every frequency present is added to get the measure of amplitude of frequency fluctuation for that particular voxel.

Amplitude of frequency fluctuation of task data was scaled. Low frequency amplitude of motor data was scaled with amplitudes of low frequency of BH, high frequency of BH and high frequency of Rest. A motor activation mask was calculated and applied on each of the scaled result.

CHAPTER 4

RESULTS

All the datasets were filtered in different frequency bands. As shown in Figure 4.1, the Breathold signal was separated into lower frequency bands and higher frequency bands.

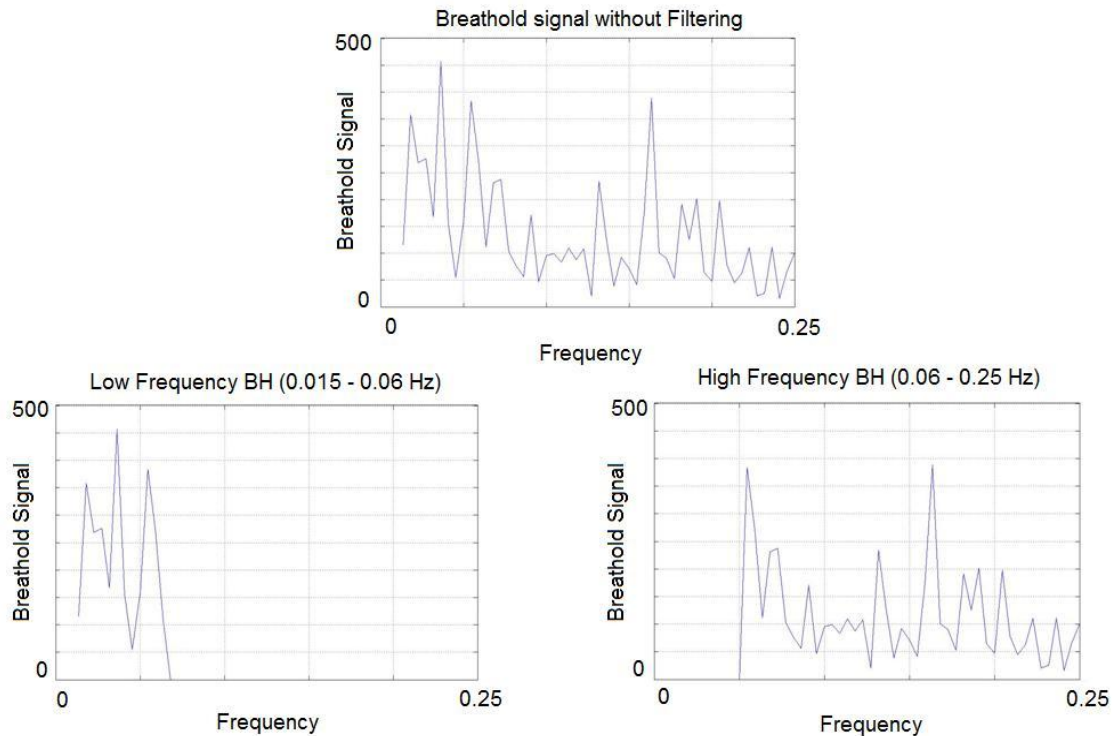


Figure 4.1 Fourier Spectrum of Breathold data. Data was filtered in low and high frequency datasets. Low frequency BH data had range of 0.015 Hz to 0.06 Hz while high frequency was ranging between 0.06 Hz to 0.25 Hz. The frequency cutoff was decided looking frequency distribution of original unfiltered data.

Rest and Motor data were also filtered in the similar way to low and high frequency bands. Higher frequencies mainly represented the respiration frequencies.

These filtered signals were correlated to each other in time domain and frequency domain.

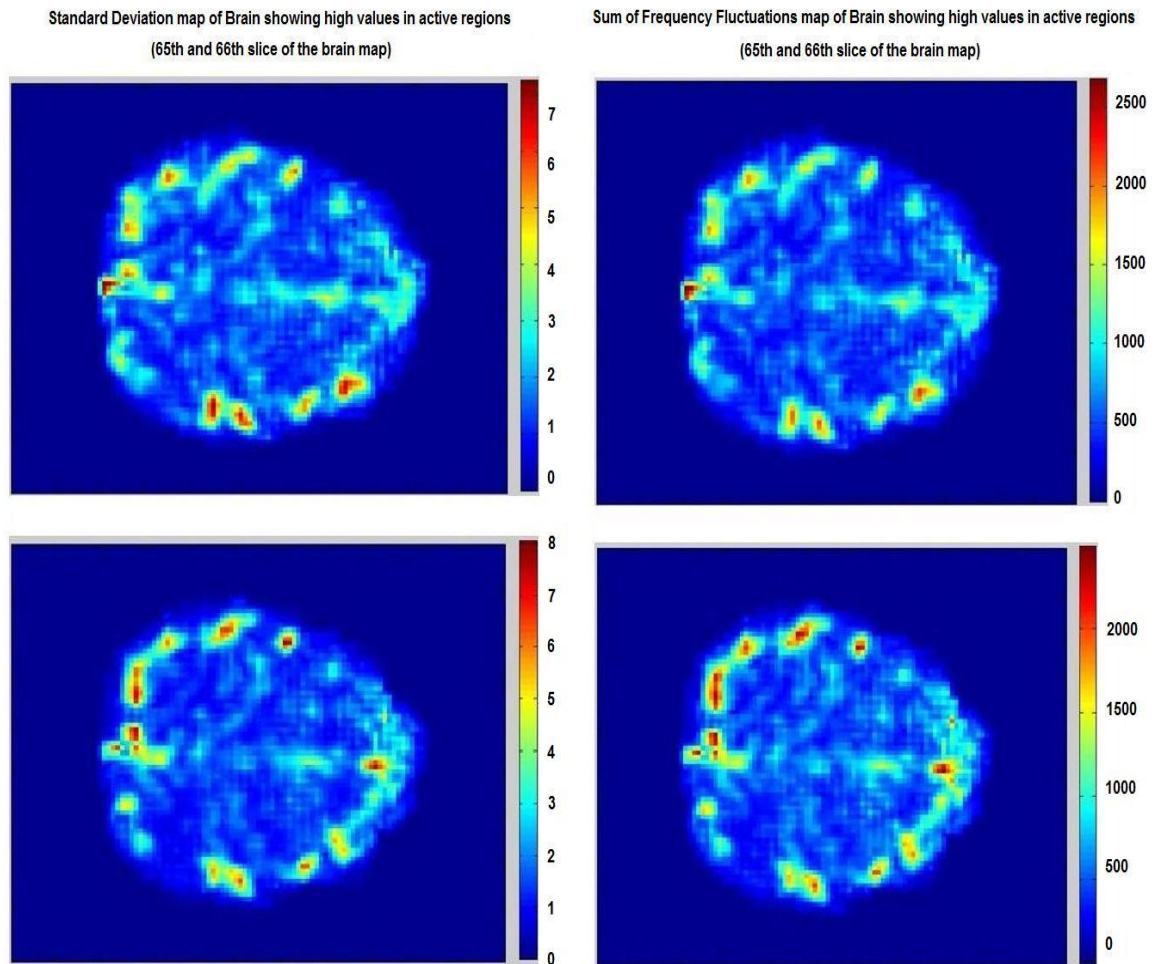


Figure 4.2 Brain maps for standard deviation and sum of frequency fluctuations showing high values in the active areas. 65th and 66th slice of the brain showing left and right motor cortex areas.

As seen in the Figure 4.2 the high values of the standard deviation and sum of frequency fluctuations are seen in the active regions like, left and right motor cortex. Some of the edges show high value and areas due to hemodynamic activity also show high values.

4.1 Correlation

Correlation of SD was very high between BH and high frequency of Rest. Average correlation between low frequency of BH and high frequency Rest was 0.81 while between high frequency of BH and Rest had average correlation of 0.92 while low frequencies of Rest and BH had average of 0.87. Correlation of amplitude of frequency fluctuations for Rest and Breathhold was observed. High frequency data of both rest and breathhold correlated nicely (Avg. $R = 0.62$) while low frequency data of BH also had a high correlation value (Avg. $R = 0.63$) with Rest. Even though cross correlation of rest high frequency and breathhold low frequency was little less (Avg. $R = 0.56$), good correlation indicated the similarity between the data sets hence possibility of presence of hemodynamic component in the higher frequency part of the rest i.e. respiration frequencies. These results were reproducible for every subject. [Table1 and 2]

Table 4.1 Table of Correlation between Standard Deviations of Different High and Low Frequency Datasets of Breathhold and Rest

	Rest low frequency Vs. BH low frequency	Rest high frequency Vs. BH high frequency	Rest low frequency Vs. BH high frequency	Rest high frequency Vs. BH low frequency
BH002	0.8482	0.8946	0.7904	0.8327
BH003	0.8491	0.8974	0.8177	0.7715
BH004	0.8493	0.9274	0.7550	0.7642
BH005	0.8313	0.9166	0.8481	0.7709
BH007	0.8783	0.9343	0.8613	0.8201
BH008	0.8894	0.9557	0.8455	0.8198
BH009	0.9144	0.9509	0.8706	0.8271
BH010	0.8809	0.9254	0.8193	0.7598
BH014	0.8218	0.9292	0.7976	0.8271
BH015	0.8818	0.8906	0.8632	0.8405
BH018	0.8281	0.9023	0.8046	0.7784
BH019	0.8840	0.9044	0.8315	0.8050
BH020	0.8970	0.9190	0.8666	0.8368

TABLE 1

Table 4.2 Correlation for Sum of Frequency Fluctuations for Different Frequency Bands of Breathhold and Rest

	Rest low frequency Vs. BH low frequency	Rest high frequency Vs. BH high frequency	Rest low frequency Vs. BH high frequency	Rest high frequency Vs. BH low frequency
BH002	0.5960	0.5315	0.5674	0.5032
BH003	0.6306	0.5781	0.5902	0.5313
BH004	0.6387	0.6600	0.5630	0.5767
BH005	0.6334	0.5457	0.6089	0.4918
BH007	0.6368	0.7221	0.6267	0.6588
BH008	0.5429	0.6214	0.5097	0.5523
BH009	0.6313	0.6965	0.6050	0.6276
BH010	0.6453	0.6633	0.5960	0.5705
BH014	0.6068	0.6472	0.5875	0.5940
BH015	0.6426	0.5405	0.6106	0.5182
BH018	0.6232	0.5767	0.6217	0.5181
BH019	0.6606	0.6528	0.6081	0.6112
BH020	0.6519	0.5960	0.6191	0.5584

TABLE 2

As you can see in the Table 4.1, correlation between breathhold and rest is high. The frequency domain correlations [Table 4.2] are not as high as SD but they give the similar indications as the time domain correlations. Figure 4.3 shows the correlation for a

typical subject for both SD and frequency fluctuation average. Breathold low frequency SD has the correlation of value 0.77 with Rest high frequency SD and in frequency domain they give correlation of 0.49. Power of breathold low frequency is greater than respiration frequencies in rest making shift of datapoints towards the breathold axis.

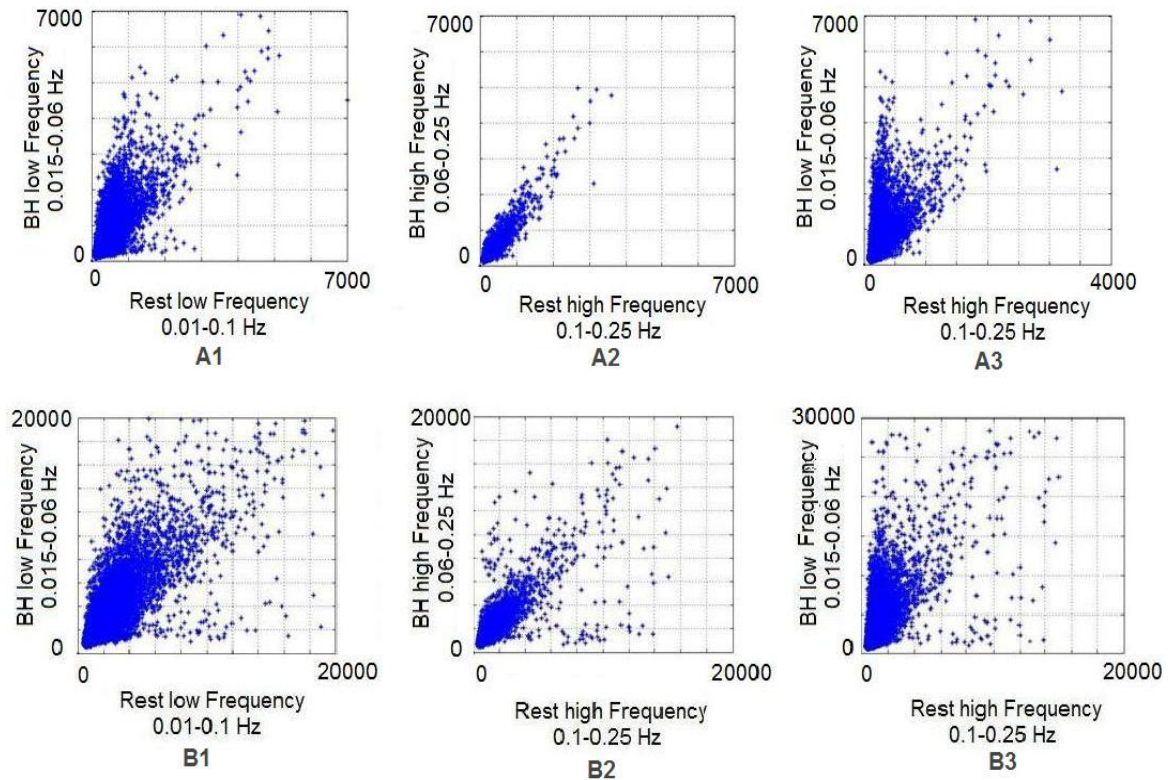


Figure 4.3 Correlation of low and high frequency datasets of rest and breathold.

- SD correlation of rest and breathold data. A1 has the correlation value of 0.83, A2 has correlation value of 0.88 and A3 has a correlation value of 0.77
- Sum of frequency fluctuations correlation of rest and breathold data. B1 has the correlation value of 0.63, B2 has correlation value of 0.55 and B3 has a correlation value of 0.49

4.2 Motor Data Scaling

Active areas for Motor were observed throughout the right and left motor cortex as expected. Breathold task showed activation in the major part of the brain especially in the gray matter. It was assumed that during the breathold, metabolic activity is not very

significant hence this activation is due to hemodynamic activity. Using the map of the activation in motor areas, a mask was created.

Standard deviation was the parameter used to scale the task data in time domain. Motor data was scaled with high frequency of breathhold and rest as well as low frequency of breathhold. After scaling, data was multiplied by the mask of motor activation. The average SD of motor data before any scaling was 0.8067 ± 0.1867 ; it reduced to 0.3067 ± 0.1702 when scaled with low frequency breathhold. It reduced to 0.3629 ± 0.2918 and to 0.3282 ± 0.0671 when scaled with high frequency with breathhold and high frequency of rest respectively.

Average of frequency fluctuation scaled data in the frequency domain and it followed by multiplication of motor mask to every scaled data. The amplitude of Fourier transform is very high making the sum of fluctuations very high but after scaling they come down in very small range. Low frequency BH has a higher power hence scaling task data by it reduces the power of task more than high frequency of BH or Rest. The regions of activation observed after scaling were very similar.

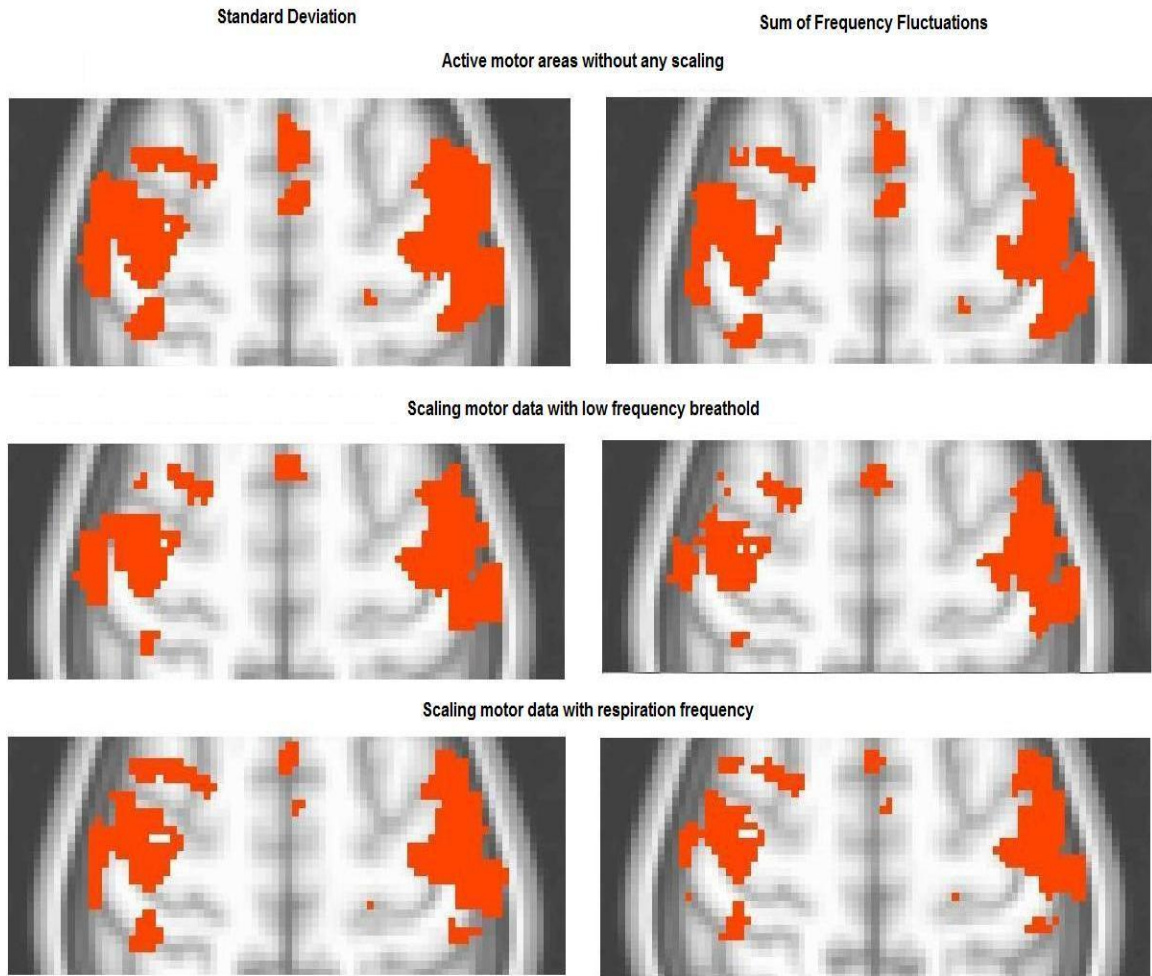


Figure 4.4 Active areas in the motor region without and with scaling of low frequency Motor data with different parameters for a typical subject. Areas show spatial reduction after scaling.

Standard deviation is used for scaling in time domain while sum of Frequency fluctuations is used in frequency domain for scaling. As you can see in the Figure 4.4 the activation regions are reduced. The amplitude of motor activation reduces. The signal reduces by 62% for low frequency breathold and 59 % for the high frequency rest data in case of standard deviation. Sum of frequency fluctuations reduce to 0.79 when scaled with low frequency breathold signal and 0.86 when scaled with respiration frequency.

CHAPTER 5

DISCUSSION AND CONCLUSION

5.1 Discussion

Activation doesn't reflect just the neuronal activity but also hemodynamic activity also BOLD signal contains a non neuronal component representing the vascular activity in the brain. Scaling the fMRI data with a component representing vascular characteristics will give a good suppression of vascular activity. Hypercapnia induces the effect similar to hemodynamic activity whereby there is a vascular change without a significant change in neuronal activity. CO₂ dilates the blood vessels effectively and induces a signal change. Hence it represents the respiration induced signal and has been routinely used for scaling. Hypercapnia involves inhaling CO₂ gas mixture and subject has to wear a mask. It is sometimes very uncomfortable to subjects. Population of old subjects or very young subjects often find it difficult to do this procedure. One more issue of vascular compliance comes into feature with these populations as signal intensity and the noise levels become different for different parts of the brain and it changes according to age also. Breathhold gives alternative to hypercapnia as it also has the similar effects induced. It includes holding breath for a long duration like 18-20 seconds. It also increases CO₂ concentration and induces BOLD response similar to the one due to inhaling CO₂. Subjects show good cooperation for breathhold as it is more comfortable than wearing a mask. Breathhold has become very popular to do scaling of task induced data with its advantages over hypercapnia but while performing breathhold; it is a possibility that, due to extended period of holding breath, body feels a deficiency of air. This is called air

hunger and it acts like a cause for a neural stimulus. Hence the BOLD signal might not contain activations only due to breathhold but also due to air hunger.

However, in certain patient population, breath holding is not feasible. Old populations, most of the time, have problems holding their breath for periods like 18-20 seconds and patients with impaired respiratory functions have an added risk, if doing breathhold. Stroke patients are also not eligible to do breathhold. They already have an interrupted blood supply to brain. Holding breath might do some additional damage to the brain tissues. Looking at these populations, breathhold might not be a good option.

Issues associated with hypercapnic scaling reveal a need of alternative method which not only shows similar vascular effects but also not much dependant on subject cooperation as well as compliance. Higher frequency components (> 0.1 Hz) during rest contain respiratory frequencies. In this study, hypothesis was tested that respiratory frequencies can be similar to hemodynamic response signal produced during breathhold and can be used effectively to scale the task induced fMRI signal. In this study, a data of motor task, breathhold and rest was divided into low and high frequency data by looking at the frequency domain.

Experiment was done using two parameters of the data. First is standard deviation (SD) of data and other is sum of frequency fluctuation of data. Former is used as time domain parameter while later being frequency domain parameter. These parameters represent change in BOLD amplitude and frequency respectively and sites of activation will show greater value for these parameters.

Correlations were done in time and frequency domain. Both showed good relation between respiration frequencies and breathhold frequencies. This high frequency data at

rest showed high correlation with low frequencies of breathhold (avg. $R^2=0.8056$) as well as high frequency data of breathhold (avg. $R^2=0.920$) when compared the standard deviations while comparing the sum of frequency fluctuations, high frequency rest data gave average correlation of 0.63 with low frequency breathhold and average correlation of 0.62 with high frequency breathhold.

Good correlation value between breathhold frequencies and respiration frequencies in time as well as frequency domain gives an indication that vascular component are present in respiration frequency band.

Breathhold shows hemodynamic activity without significant task related changes. Hence it is a very effective method for scaling of task induced data. Here, scaling of motor data was done using the respiration and its results were compared to low and high frequency breathhold. Scaling actually involved division of motor low frequency and different parameters like rest and breathhold. All the scaling results are pushed through motor activation mask to remove some of the unwanted pixels at the boundary of brain.

The results are very similar when compared. Since breathhold has its power mostly in the low frequency, it shows greater magnitude reduction for BOLD changes than high frequency but regions are similar. The motor region without any kind of scaling shows higher values but once the scaling is done, change in the BOLD signal on average reduced by 62% for breathhold low frequency scaling and it reduces by 55% and 59% when scaled by high frequency breathhold and respiration frequencies respectively in case of standard deviation. Scaling using sum of frequency fluctuations showed large reduction in the signal, when divided. Average BOLD signal in this case was 0.79 for low

breathhold scaling and it was 0.62 and 0.86 for scaling with high breathhold and respiration data respectively.

5.2 Conclusion

High correlation values between breathhold and rest data in both time and frequency domains suggested that high frequency band of rest data i.e. respiration frequencies show variation dependence on hemodynamic changes. Scaling was done using established breathhold parameter and with new parameter as high frequency data of rest i.e. respiration frequencies. Reduction in amplitude of activation was comparable. Areas of activation also reduced eliminating some of the false positive area. The scaling done for both showed very similar results. Based on the outcomes experiment it is suggested that respiration frequencies in can be a good alternative of for breathhold frequency and scaling can be effectively done in the frequency domain. Along with standard deviation, sum of frequency fluctuation can also be considered as an activation indicator in brain during any task.

Importantly, a parameter, that can be obtained without giving any discomfort to the patient and also without an additional breathhold scan. Respiration can be used to scale the data and remove the unwanted signal due to hemodynamic changes.

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