FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) SIMULATOR

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KAMİL ARSLANKOZ

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FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) SIMULATOR

Submitted by **Kamil ARSLANKOZ** in partial fulfillment of the requirements for the degree of **Master of Science in the Department of Medical Informatics, Middle East Technical University by,**

Prof. Dr. Nazife BAYKAL ____________________
Director, **Informatics Institute**

Assoc. Prof. Dr. Yeşim AYDIN SON ____________________
Head of Department, **Health Informatics**

Assist. Prof. Dr. Didem GÖKÇAY ____________________
Supervisor, **Medical Informatics, METU**

Examining Committee Members

Assoc. Prof. Dr. Tolga Esat ÖZKURT ____________________
Medical Informatics, METU

Assist. Prof. Dr. Didem GÖKÇAY ____________________
Medical Informatics, METU

Assist. Prof. Dr. Aybar Can ACAR ____________________
Medical Informatics, METU

Dr. Emre BAŞESKİ ____________________
HAVELSAN

Dr. Nurcan TUNÇBAĞ ____________________
Medical Informatics, METU

Date: 07.07.2015

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Name, Last name : Kamil ARSLANKOZ

Signature :

ABSTRACT

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) SIMULATOR

ARSLANKOZ, Kamil

M.Sc., Department of Medical Informatics

Supervisor: Assist. Prof. Dr. Didem GÖKÇAY

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Functional magnetic resonance imaging (fMRI) utilizes the change in the oxygenation of blood to predict active areas in the brain. fMRI consists of multiple low resolution whole brain images, for which, the contrast difference in corresponding voxels among all images are studied. In this study, an fMRI simulator has been developed which generates customized 4D fMRI data that can be used as a ground truth for comparing/benchmarking different fMRI analysis methods. This simulator can be also used for educational purposes for hands-on study of several aspects of the fMRI time series. Some of the strengths of this simulator with respect to other simulators are as follows. The simulator is programmed in MATLAB and it contains a GUI which facilitates its use. It allows an atlas (ICBM) to generate multiple brain activations within pre-defined anatomical structures. It utilizes T2 MRI images to construct task related (event/block/mixed paradigms) or DMN (Default Mode Network) 4D fMRI data. It is capable of simulating the effects of head movement, habituation, scanner drift and Gaussian noise. The simulator completes realistic fMRI data generation on the order of minutes. The results produced by the simulator are analyzed by popular fMRI analysis tools, FSL and AFNI. The estimation of brain activations and the prediction of the embodied artifacts by FSL and AFNI matched the simulation parameters with great certainty, verifying the quality of the simulations.

Keywords: Functional Magnetic Resonance Imaging, fMRI Simulation, Artifact, Region of Interest (ROI), DMN (Default Mode Network)

ÖZ

FONKSİYONEL MANYETİK REZONANS GÖRÜNTÜLEME (FMRG) BENZETİCİSİ

ARSLANKOZ, Kamil

Yüksek Lisans, Tıp Bilişimi Bölümü

Tez Yöneticisi: Yrd. Doç. Dr. Didem GÖKÇAY

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Fonksiyonel manyetik rezonans görüntüleme (fMRG) kandaki oksijenlenme değişiminden yararlanarak beyindeki aktif alanları kestirir. fMRG düşük çözünürlüğe sahip tam beyin görüntülerini toplar ve beyin hacimlerindeki tekabül eden voksellerin kontrast farkını ölçer. Bu çalışmada, farklı FMRG analiz yöntemlerini karşılaştırmak/kıyaslamak için temel doğru olarak kullanılabilecek özelleştirilmiş 4B verisi üreten bir FMRG benzeticisi geliştirilmiştir. Benzetici, fRMG zaman serilerinin birkaç yönünün eğitimsel olarak çalışılması için de kullanılabilmektedir. Bu benzeticinin diğer benzeticilere kıyasla güçlü olduğu bazı yönler şunlardır: Benzetici, MATLAB ile programlanmıştır ve kullanımı kolaylaştıran bir grafiksel arayüze sahiptir. Önceden tanımlı anatomik yapılar içinde birden fazla beyin aktivasyonu oluşturmak için bir atlas (ICBM) kullanımını sağlar. Benzetici; T2 MRG görüntülerini, ilgilenilen alanı ve görev temelli (olay/blok/karma paradigmaları) ya da DMN

(Default mode network – Varsayılan mod ağı) temelli 4B fMRG verisi için kullanır. Benzetici; baş hareketlerini, alışkanlığı, tarayıcı sapmasını ve Gauss gürültüsünü benzetebilmektedir. Benzetici, dakikalar içerisinde gerçeğe yakın fMRG verisi oluşturabilmektedir. Benzetici tarafında oluşturulan sonuçlar yaygın kullanılan fMRG analiz araçları(FSL ve AFNI) ile analiz edildi. FSL ve AFNI tarafından beyin aktivitelerinin tahmin edilmesi ve içerilmiş artefaktların kestirimi, benzetici parametreleri ile yüksek bir kesinlikle örtüşmüştür, bu da benzeticinin kalitesini doğrulamaktadır.

Anahtar Kelimeler: Fonksiyonel manyetik rezonans görüntüleme, fMRG benzeticisi, artefakt, DMN (Default mode network – Varsayılan mod ağı).

In dedication to my dear daughters, Elif Deniz and Ayşegül Nehir. And to my wife.

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CHAPTER 1

INTRODUCTION

MRI is a widely used tool providing high resolution images with good contrast between different tissues. The fundamental mechanism behind MRI depends on the magnetic property of the hydrogen atom. Nucleus of a hydrogen atom behaves like a small magnet and nuclei can be manipulated so that they generate a signal that can be mapped and turned into an image.

The hydrogen molecules in our body align with the direction of strong magnetic field. When a radio frequency (RF) pulse is applied at the correct frequency, hydrogen molecules absorb their energy and create a signal that is detected by RF coils. By using 3 RF coils in x, y, z planes and changing RF frequency within short intervals, 3D MRI signal can be generated [1].

Functional MRI (fMRI) is a method which enables MRI to measure the neuronal (or glial) activity of the brain. When neuronal activity is increased, more oxygen is needed for those activated brain areas. In order to supply more oxygen, the blood flow to the active area increases. The oxygen is transferred to cells by hemoglobin molecules. The oxygenated (oxygen loaded) form of hemoglobin is called as oxyhemoglobin and deoxygenated is called as deoxyhemoglobin. Oxyhemoglobin is diamagnetic but becomes paramagnetic when deoxygenated. This magnetic behavior of deoxyhemoglobin leads to small differences in MR signal. The change in MR signal is dependent on the degree of oxygenation. Measuring MRI signal during this neuronal activity is called blood oxygenation level dependent (BOLD) imaging. During fMRI process, low resolution whole brain BOLD images (i.e. volumes) are collected several times to capture less than 5% increase in oxygeneation in active brain areas [2].

In order to analyze the fMRI data, several techniques have been developed. The developments of those techniques are mostly based on empirically gathered fMRI images. Since ground truth is not known with this empirical approach, it is difficult to measure the accuracy of the analysis method. This is also true for artifact removal algorithms since it is difficult to measure the artifacts within empirically gathered fMRI data. If we knew the ground truth data, then we could easily analyze the fMRI analysis algorithm results, compare/benchmark different fMRI analysis methods and develop new ones. However, the complexity of cognitive processes and background spontaneous activity of the brain hinders producing ground truth in actual brain images.

The motivation behind this thesis is generation of 4D fMRI data which facilitates use of a simulated ground truth for comparing/benchmarking different fMRI analysis methods. By using this ground truth, comparison of performance of new fMRI analysis methods may be possible. The simulator can also be used for educational purposes. For the ones who are interested in learning fMRI, this tool can be treated as an educational tool.

In this thesis, we developed an fMRI simulator which is capable of generating task related and resting state 4D FMRI data. The task related fMRI data generation consists of event, block and mixed design patterns whereas the resting state mode consists of default mode network (DMN) data generation. Habituation, scanner drift, noise and motion are the artifacts that can be added to fMRI signal.

For the task related fMRI data generation; the duration of experiment and TR value (time between consecutive 4D whole brain volumes) can be manipulated by the user. For DMN related data generation, the duration is designed to have a fixed value which is coming from resting templates but the TR value is user defined.

An important feature of the simulator is the ability to define different sets of ROIs for brain activity. For the task related fMRI data generation, 4 types of ROI selection was implemented to define the active voxels: ROI selection by drawing free form canvas, ROI selection by selecting a point of interest, ROI selection from atlas labels and finally the entire brain as a single ROI. Two types of activation patterns were designed: Event related and block activity patterns. By indicating active time points for events and active intervals for blocks, fMR time series can be generated. Mixed design was the combination of event and block activation design types. BOLD response shape and the amplitude of BOLD response are parametric within the simulator.

For the DMN related fMRI data generation, the active areas are limited to 6: Anterior Cingulate Cortex (ACC), Posterior Cingulate Cortex (PCC), Right Inferior Parietal Lobule (rIPL), Left Inferior Parietal Lobule (lIPL), Dorsomedial Prefrontal Cortex (dmPFC), Ventromedial Prefrontal Cortex (vmPFC). These brain areas are selected because of higher correlation with DMN activity. While generating DMN time series, template signals that are previously uploaded to fMRI data repositories are exploited. This way, DMN simulation is targeted to produce data close to real life conditions. In this mode, signal correlations with the chosen template signal and signal amplitudes are designed to be parametric.

Artifacts are defined as add-on components of the fMRI time series. Rigid body rotation and translation are implemented in 3D plane to accomplish motion artifact. The center of rotation and translation is selected as the middle voxel of the brain volume. Sudden motion changes or changes within an interval are also supported. For the scanner drift artifact; 1st, 2nd and 3rd degree polynomials are used. Gaussian white noise is used to add random noise to fMRI data. For the habituation artifact, the signal was decreased according to a parametrized habituation weight.

Overall, we created a user friendly fMRI simulator with features that are important for current cognitive neuroscience applications. The main difference between our simulator and the existing ones (Chris Rorden's fMRI Design Software [11], SimTB [13], POSSUM [12] and METU- fMRISim [14]) are as follows.

Chris Rorden's fMRI Design Software [11] is a tool for only designing an fMRI study, but it does not provide 4D fMRI output and artifacts cannot be defined with this simulator. SimTB [13] is an fMRI simulator which has the capability of creation and manipulation of spatial sources, block and event-related design experiments, inclusion of tissue-specific baselines and simulated head movement. It has a GUI to design and execute simulations. Unfortunately, SimTB calculates the time course of single axial slice. Besides, no artifact other than motion can be generated with SimTB. POSSUM (Physics-Oriented Simulated Scanner for Understanding MRI) is a tool for generating simulated MRI and fMRI images. POSSUM is developed under FSL (FMRIB's Software Library) [12]. POSSUM collects several MR parameters (relaxation times T1, T2*, spin density ρ, and chemical shift value δ), pulse sequence (RF angle, RF frequency bandwidth, RF center frequency), slice profile as well as a pre-generated 4D activation file from the user in order to simulate the fMR time series using a mathematical model (i.e. Bloch equations) rather than utilizing an algorithm. This is somewhat inconvenient because it requires deep knowledge on MR physics and it takes more than 40 hours to complete. With respect to artifacts, POSSUM is limited to use motion and noise artifacts. Finally, METU-fMRISim is an fMRI simulator capable of simulating block and event-related 4D fMRI data with several artifacts: motion, scanner drift, habituation and cardiac pulsation. However, it does not use a T2 weighted image as a baseline. It generates the fMRI data for a flat image which is registered to the T1 weighted anatomic image.

The layout of this thesis is as follows. In chapter 2, background and literature survey is presented. In chapter 3, methods which were used in order to implement this simulator are discussed. Chapter 4 and 5 consists of simulation results and conclusion parts respectively.

CHAPTER 2

BACKGROUND AND LITERATURE SURVEY

This chapter is composed of four sections: Functional Magnetic Resonance Imaging Process, fMRI design types, fMRI artifacts and existing fMRI simulators at present. In "Functional Magnetic Resonance Imaging Process" section; a general overview of fMRI is presented. In "fMRI design types" section; task related fMRI (block, event and mixed design types) and default mode network (DMN) related fMRI, which consists of spontaneous baseline brain activity are explained. In "fMRI artifacts" section, different types of fMRI artifacts are identified. In "fMRI Simulators at present" section, already developed fMRI simulators are described.

2.1 Functional Magnetic Resonance Imaging Process

The main principle of fMRI is based on detecting neuronal activity changes from differences in local concentrations of deoxyhemoglobin (dHb) and oxyhemoglobin (HbO2). Oxyhemoglobin is diamagnetic (i.e. does not change MRI signal) but deoxyhemoglobin is paramagnetic (i.e. changes MRI signal). When dHb decreases, the spoiled T2* signal increases, and this is detectable as a small signal intensity improvement. Because neural activity increases HbO2, the density of dHb in the bloodstream decreases, which in turn registers as an increased signal. "The BOLD Contrast refers to the difference in T2* signal between oxygenated (HbO2) and deoxygenated (dHB) hemoglobin." [3]. Figure 2-1 shows the BOLD response function of a single brain voxel assuming that a stimulus is presented a time zero causing the neuronal bed captured within the voxel to respond.

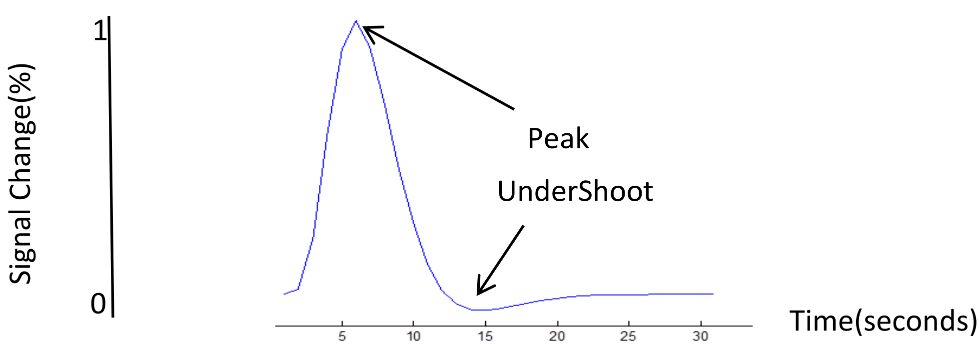


Figure 2-1 BOLD response function (Image adopted from [3])

From the figure above, we can see that the response cycle lasts for about 30 seconds. In the figure, stimulus is presented at time t=0. After stimulus is presented, an initial deep is observed at first. Then signal changes to its maximum value at about t=6. After that, undershoot occurs at about t=16 and signal returns to its initial state at t=30. [3]

In fMRI experiments, low resolution whole brain volumes (generally >100) are collected. Collection period of the entire brain volume is less than 3 seconds. The voxel sizes are typically between 2mm x 2mm x 2mm – 3mm x 3mm x 3mm [4]. In Figure 2-2, a sample event related fMRI experiment which has 2 stimuli conditions (red and green arrows stand for events of two different conditions) is shown. During the experiment, several 3D low resolution MRI scans of brain take place. In the figure below, there are n volumes of the brain MRI during a single fMRI scan. If the time between 2 consecutive volume scans is t_{volume} seconds, then experiment would last in n x t_{volume}seconds.

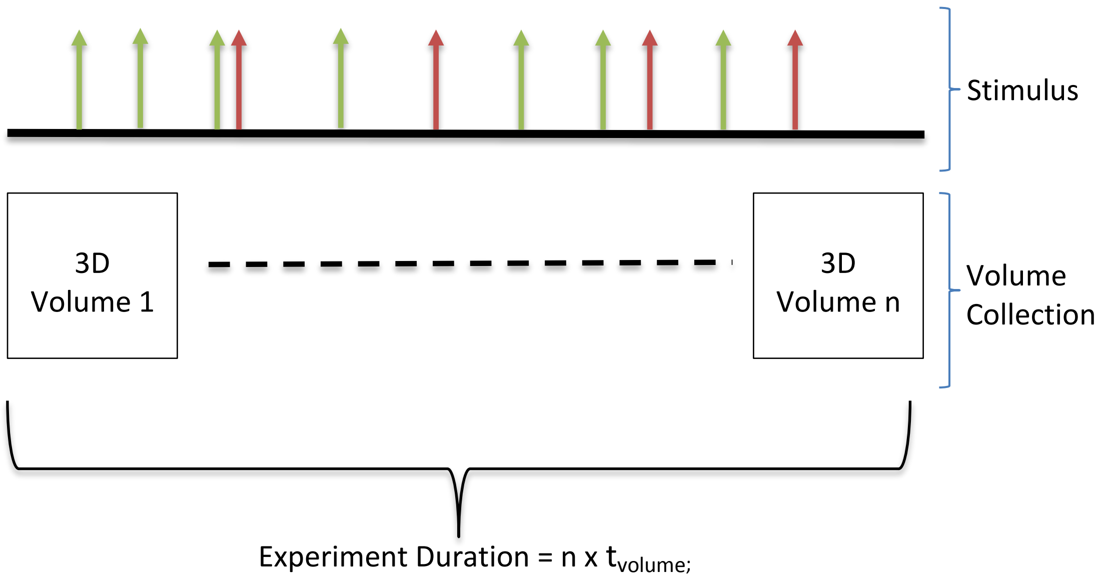


Figure 2-2 Sample fMRI experiment

(n: number of volumes, t_{volume}: Brain Volume collection time)

2.2 fMRI design types

In order to design fMRI experiments, several experiment design types are used. Block, event and mixed designs are well-known fMRI experiment design types used in fMRI studies.

2.2.1 Block design (epoch related)

For the block design, stimuli (many stimuli of the same type) are presented to subjects during ON periods and subject rests in OFF periods [3]. Sample block design can be seen in Figure 2-3. In the figure, ON and OFF periods are shown. Note that each ON period ends with an OFF period and vice a versa. A typical time frame for the blocks is on the order of 10-40 sec.

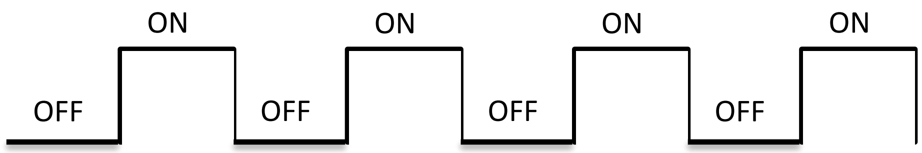
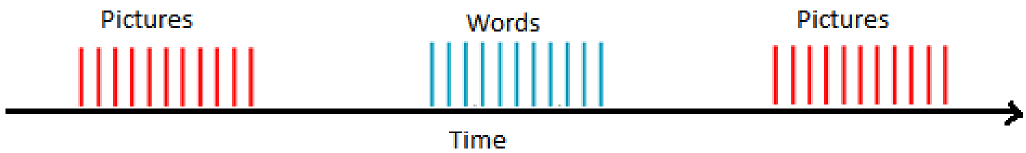


Figure 2-3 Block Design Pattern

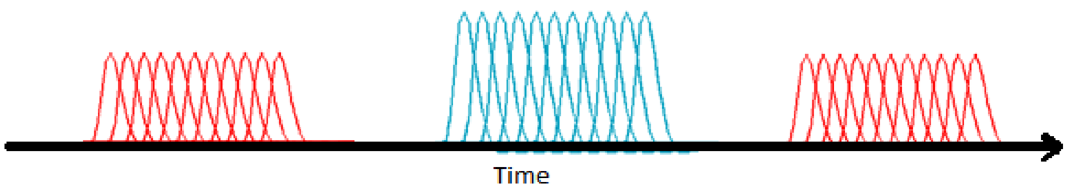
For the block design, more than one condition may also exist in an experiment [5]. A sample experiment showing more than one condition can be seen in Figure 2-4. In the figure, two conditions are tested: pictures (red blocks) and words (green blocks). In the figure it is seen that the HRF response to words is higher than pictures since the amplitude of HRF is higher for words. The Figure 2-4c is the sum of individual HRFs shown in Figure 2-4b.

Stimulus Event



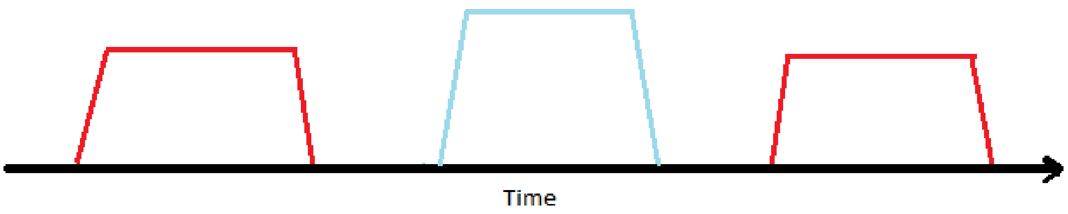
(a)

Individual HRF for each stimulus:



(b)

The sum of HRFs:



(c)

Figure 2-4 Sample Block Design with two experimental conditions

(Image adopted from [5])

With block design, hemodynamic responses of blocks can be compared to each other or compared to baseline (i.e. rest or OFF). Block design is not used to compare individual trials [5].

2.2.2 Event-related design

For the event related design, stimuli are presented at random times during the experiment. Sample event design can be seen in Figure 2-5. From the figure, it can be seen that the time difference between 2 consecutive events are not homogeneous during the experiment.

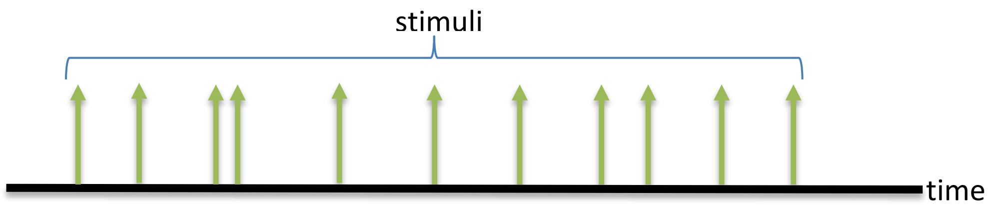


Figure 2-5 Event Related Design Pattern

In an event-related design, more than one condition may exist in the experiments [5]. A sample experiment showing more than one condition can be seen in Figure 2-6. In the figure, three conditions are tested which are shown in Figure 2-6a. The individual responses are shown in Figure 2-6b. In Figure 2-6b, it can be observed that Stimulus C has higher response that Stimulus A and Stimulus A has higher response than Stimulus B. Figure 2-6c is the sum of individual HRFs shown in Figure 2-6b.

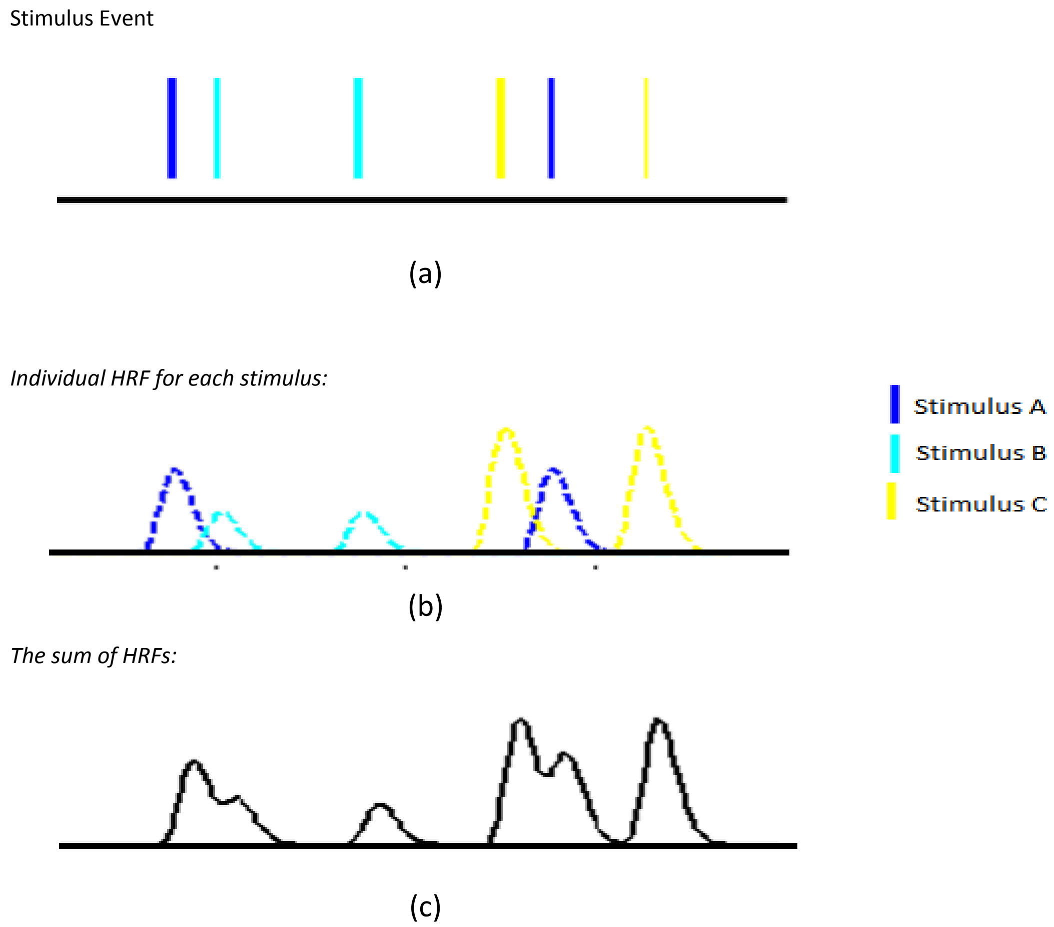


Figure 2-6 Sample Event-Related Design with three conditions (Image adopted from [5])

With event-related design it is possible to present stimuli in random order which is not possible with block design. [5]

Event-related design falls into two categories: slow event-related design and rapid event-related design. With slow event-related design, the stimuli are spaced far apart from each other to prevent overlap of their hemodynamic functions. In such a slow event-related design, time intervals between stimulus presentations range from 15-30 seconds as can be seen in Figure 2-7.

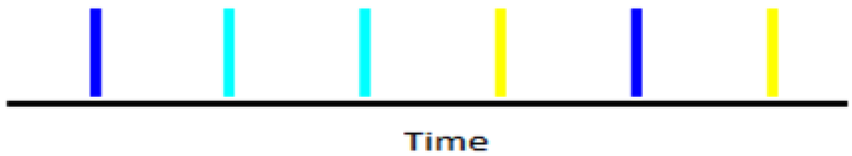


Figure 2-7 Sample Slow Event-Related Design (Image adopted from [5])

With rapid event-related design, the stimuli are close to each other and their hemodynamic functions overlap. Samples of rapid event-related designs can be seen in Figure 2-8. In Figure 2-8a, non-random and fixed ISI (inter stimulus interval) event related design is shown. It can be seen that the interval between 2 consecutive stimuli are same throughout the experiment. Such events are scheduled on the order of 1-3 sec in between. Also the order of stimuli is not random (i.e blue-cyan- yellow, blue-cyan- yellow, blue-cyan- yellow). In Figure 2-8b, random and fixed ISI (inter stimulus interval) event related design is shown. It can be seen that the interval between 2 consecutive stimuli are same throughout the experiment but the order of stimuli is random. In Figure 2-8c, jittered ISI (inter stimulus interval) event related design is shown. It can be observed that ISI is dynamic and order of stimuli is random.

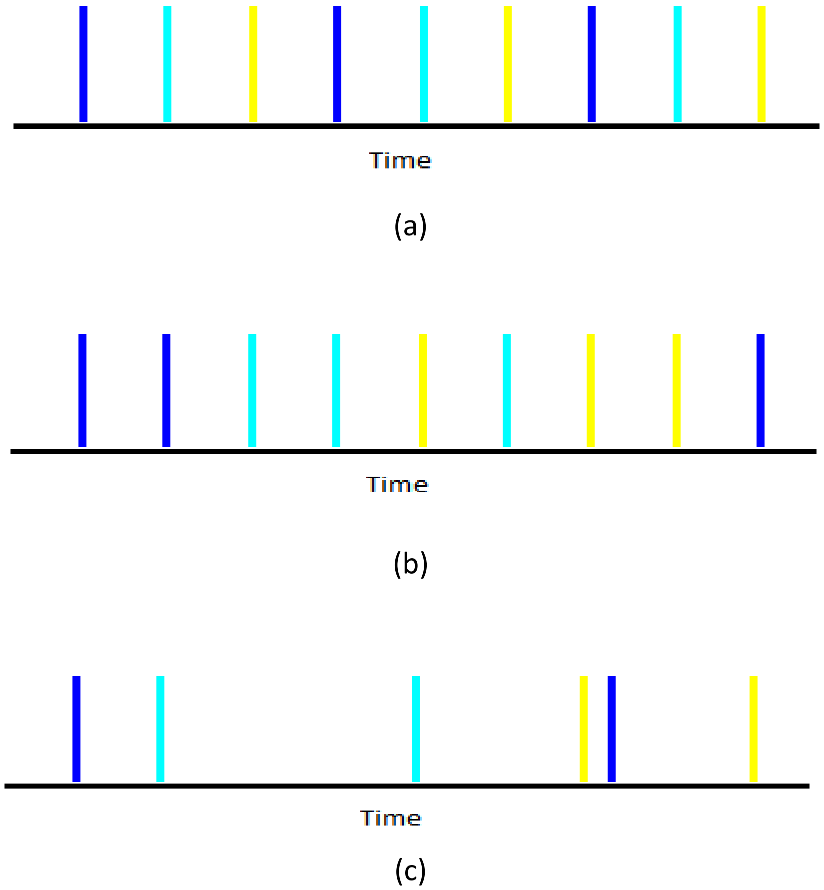


Figure 2-8 Sample Rapid Event-Related Design
(a: nonrandom and 3 seconds fixed inter stimulus interval, b: random and 3 seconds fixed inter stimulus interval, c: random and jittered inter stimulus interval) (Image adopted from [5])

2.2.3 Mixed design

Mixed design is the mixture of event-related design and block design [6] which can be seen in Figure 2-9. From the figure it can be seen that there are ON-OFF periods which is coming from the block related fMRI design. It can also be seen that during ON periods, 0 or more events exists which in turn is the nature of mixed design.

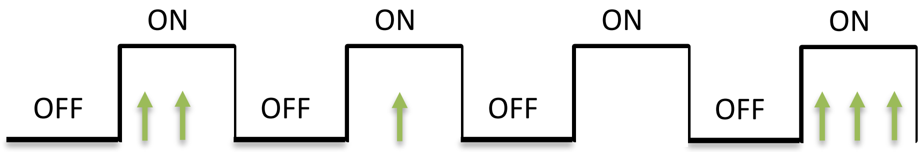


Figure 2-9 Mixed Design

2.2.4 Resting State fMRI - DMN

Most of the fMRI experiments are accomplished by doing an active task (like pushing a button) [28]. On the contrary, in resting state MRI (rsFMRI) experiments, data is collected while subject is doing nothing (i.e. resting). During this condition (i.e. doing nothing) different areas of brain may act together in synchrony. For functional connectivity, it is not a requirement for areas to be physically connected [28]. There may still be connectivity if there is synchronization between them.

DMN is one of the resting state networks. “Default mode” term was first used by Dr. Marcus Raichle in 2001 [28] [31]. During the rest, DMN network becomes active. But it becomes passive when a task is initiated.

The brain areas which are included in DMN are medial temporal lobe, the medial prefrontal cortex, and the posterior cingulate cortex, as well as the ventral pre-cuneus and parts of the parietal cortex [29]. These areas are mostly related with some kind of internal thoughts [28].

Because DMN is active at rest and due to the brain areas included in DMN; DMN is thought to be associated with introspective thought, including activities like daydreaming or retrieving memories [28].

In the study of Damoiseaux et al. [32], different kinds of coherent low-frequency fluctuations in the BOLD signal are identified across subjects. The study showed that the coherent fluctuations within DMN are very consistent and also very dynamic. The percentage BOLD signal change in these areas reach up to 2–3%, and areas with high mean percentage BOLD signal change also show high levels of consistency. As a result the signal being measured during resting state fMRI data acquisition is not an artifact caused by another physiological function [32].

Meta-analysis of the brain regions that are active during rest (passive state) indicate several correlated ROIs [34]. The first study was conducted by Shulman and colleagues (1997) [35] to determine the brain areas that are active during passive rest. In order to achieve this, the data of 132 normal adults were collected both active condition (stimulus was presented and subjects performed tasks) and passive condition (same stimulus was presented with no given task). Similar approach was used by Mazoyer et al. (2001) on 63 subjects [36]. These two analyses revealed consistent brain regions that are more active during passive condition than active condition.

2.3 fMRI artifacts

Some of the artifacts that are added onto the signal are due to physical strain of the device, and some of the artifacts are originate from the human subject being scanned.

2.3.1 Scanner drift

Scanner drift is mostly occurs because of the instability of gradient coils which causes a drift in magnetic field strength. This drift in magnetic field strength causes a drift in the acquired signal which is called "scanner drift") [7]. Figure 2-10 shows the sample scanner drift effect. From the figure, a linear drift (increase in baseline signal) in fMRI data can be observed easily as a baseline increase in the fMRI signal over time.

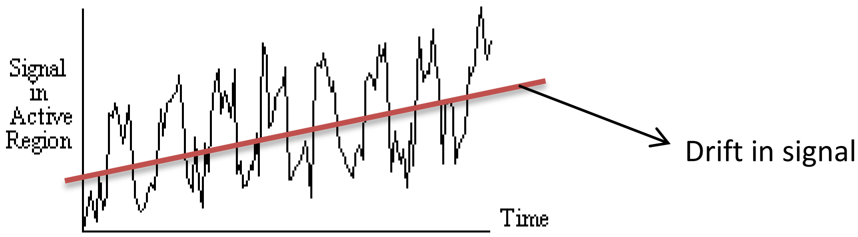


Figure 2-10 Sample scanner drift effect (Image taken from [8])

2.3.2 Habituation

"Neural responses tend to be stronger to novel information than to repeated information (for recent reviews, see Grill-Spector et al., 2006; Krekelberg et al., 2006; Schacter et al., 2007)" [9]. For this reason, BOLD increase in repeated tasks is much less compared to novel stimuli which can be observed in Figure 2-11. From the figure it can be seen that novel information has higher fMRI signal increase than repeated information. Although this is not an artifact, we incorporated such signal changes into our simulator as a manipulation similar to artifacts.

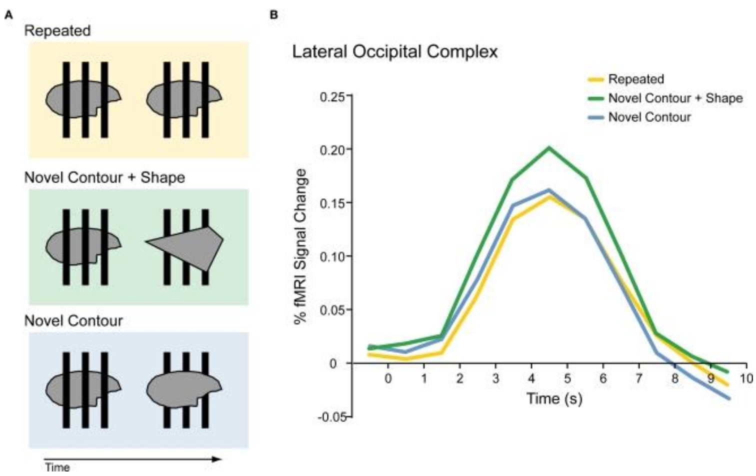


Figure 2-11 Habituation effect (Image taken from [9])

2.3.3 Subject Motion

Subject motion is an important artifact. Motion leads to abrupt signal intensity changes and it is sometimes indistinguishable from neuronal activity, if it occurs at task-related time intervals [10]. “Even relatively small motion (of the range much smaller than a voxel size e.g. 1.6-3.2 mm) can create serious artifacts due to the partial volume effects.” [3]

2.3.4 Gaussian White Noise [7]

All MR imaging can be affected by thermal noise. Thermal noise is mostly caused by electronics within the MR imaging device. Thermal noise may be added to or subtracted from the intensity resulting in a Gaussian distribution.

2.4 fMRI Simulators at present

2.4.1 Chris Rorden’s fMRI Design Software [11]

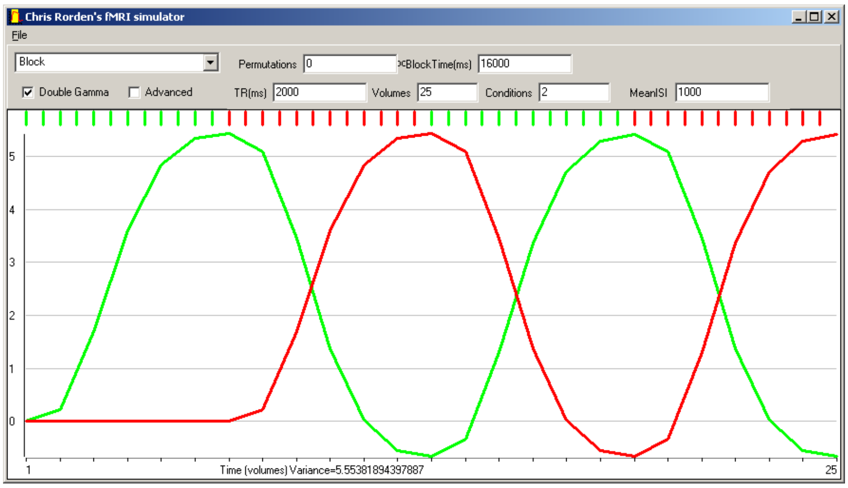


Figure 2-12 Chris Rorden’s fMRI Design Software GUI (Image taken from [11])

This software is a tool for just designing an fMRI study. The tool does not provide 4D fMRI output. It shows HRF time course of an experiment by using the settings (like TR, number of volumes, design type etc.) which are defined by user.

Block and event related BOLD responses can be viewed with the simulator. For the block design, the length of activation should be same for each stimulus (condition). For the event related design; fixed inter stimulus interval, exponential inter stimulus interval and random inter stimulus intervals are implemented. But the user has no control on the time of events.

2.4.2 POSSUM (Physics-Oriented Simulated Scanner for Understanding MRI) [12]

POSSUM is a tool for generating simulated MRI and fMRI images. POSSUM is developed under FSL (FMRIB's Software Library). In order to generate MRI data, POSSUM uses Bloch equations, as well as geometric definition of the brain. The GUI of POSSUM is given in Figure 2-13.

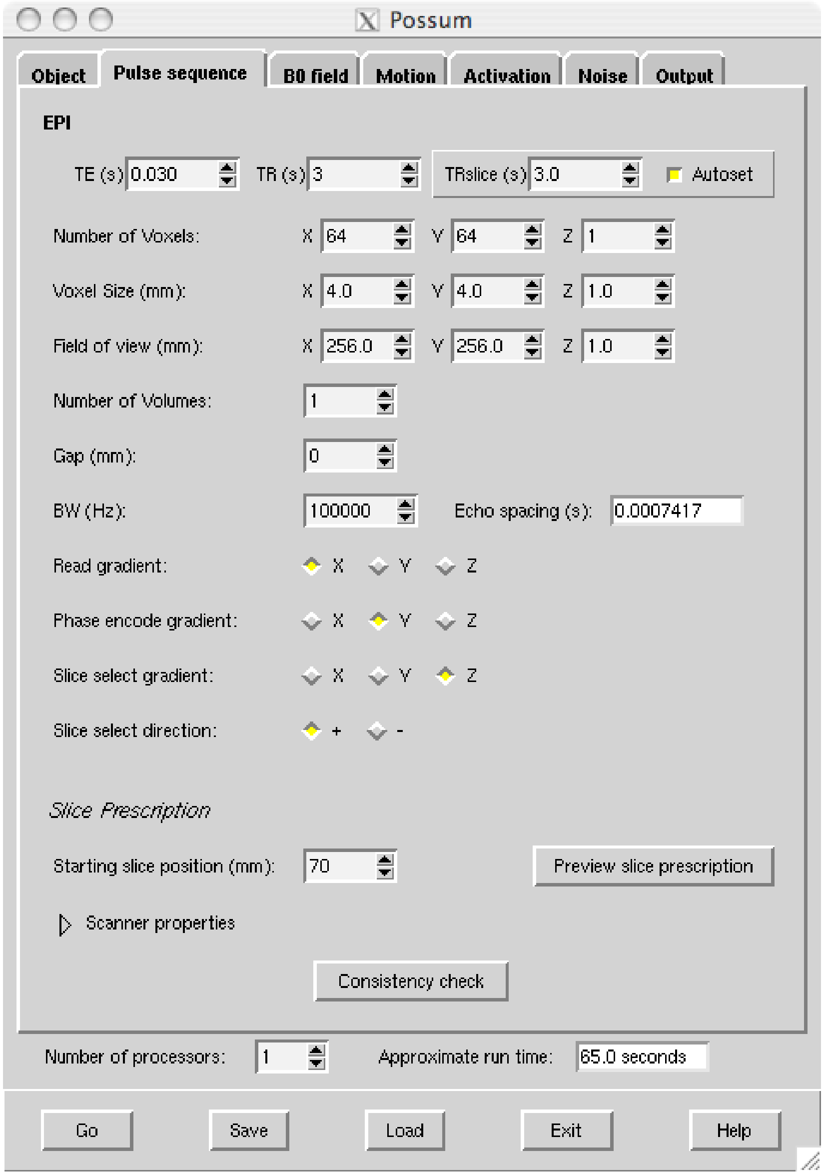


Figure 2-13 POSSUM GUI (Image taken from [12])

Some of the important parameters are as follows.

- Object: The input object is a 4D volume which is combination of 3D tissue type volumes. Each tissue type (CSF, white matter, grey matter etc.) is defined as a 3D image volume. 4D fMRI volume is created by combining these 3D volumes.

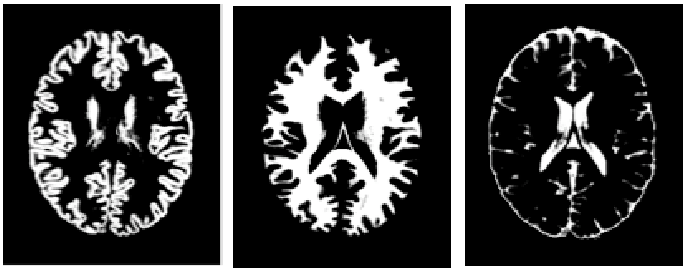


Figure 2-14 Sample tissue template

(grey matter, white matter and CSF from left to right) (Image taken from [12])

- MR parameters: The MR parameters for the Bloch equations[1] (relaxation times T1, T2*, spin density, and chemical shift value) are specified for each tissue type.
- Pulse sequence: The pulse sequence defines flip angle, RF frequency bandwidth, RF center frequency, read-out times, and gradient waveforms
- Slice profile: Describes the shape of the RF pulse in the frequency space.
- Motion sequence: The input motion sequence is defined in the simulator by an input file which specifies 7 parameters per motion: time, translation at each orientation and rotation at each orientation.
- B0 inhomogeneities: B0 inhomogeneities define distortion in the local magnetic field such as tissue-air interfaces

For generating a 4D dataset, time series must be obtained for each voxel. For this purpose, files can be prepared by drawing areas of interest in “fslview” and then creating a modulation time-course file which matches your experimental paradigm or existing FMRI files under $POSSUM can be used. In the 4D data, each object voxel has its own time-series of T2* changes. Instead of using 4D data, 3D T2* map and an extra file providing the scaling parameter can also be used. Sample scaling parameter file and 3D T2* can be seen in Figure 2-15 and Figure 2-16 respectively.

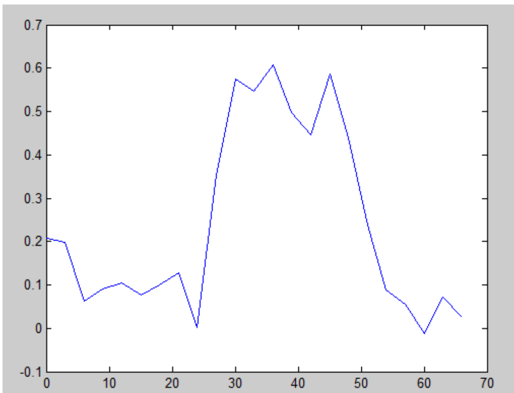


Figure 2-15 Sample scale parameter file generated from “$FSLDIR/data/possum” directory

[1] Bloch equations are as follows: $\frac{dM_x}{dt} = \gamma M_y B_0 - \frac{M_x}{T_2}$, $\frac{dM_y}{dt} = -\gamma M_x B_0 - \frac{M_y}{T_2}$, $\frac{dz}{dt} = -\frac{M_z - M_0}{T_1}$

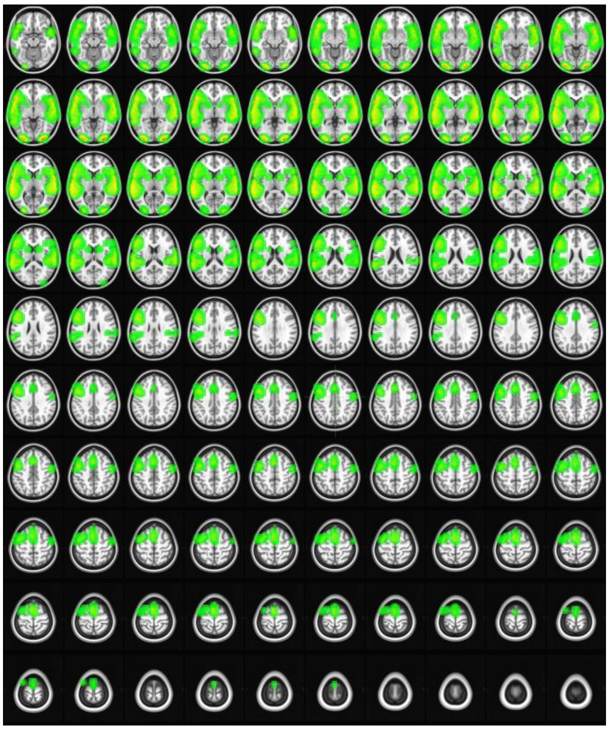


Figure 2-16 Sample 3D T2* map generated from "$FSLDIR/data/possum" directory

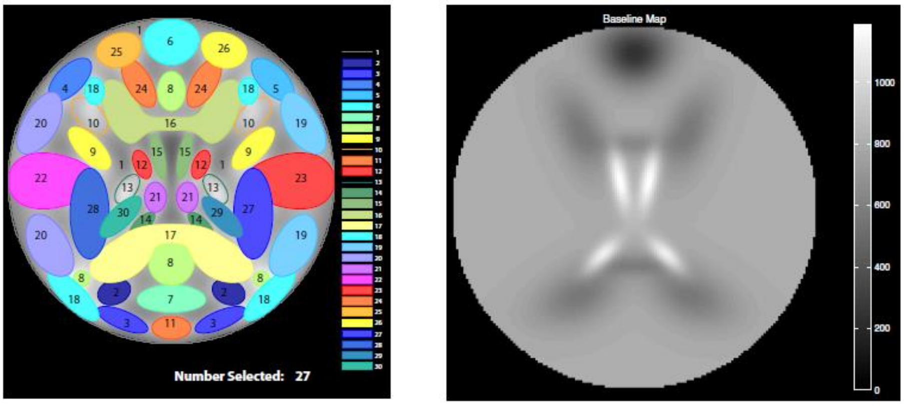
After running POSSUM, 4D fMRI data is generated as an output. In order to generate a time series of 100 fMRI volumes for 3 slices of 3mm thickness, with an output k-space matrix of 64 × 64 for each slice with no motion, it takes 42 hours 30 minutes on a single processor.

In order to run the POSSUM, the MR parameters should be defined at first. The MR parameters cannot be defined without deep knowledge on MR physics. Besides, activation file should be defined in order to define fMRI activation. For this, 4D or 3D+scaling parameter file should be prepared with other utilities. This means that POSSUM can be used efficiently only by professionals. Also with 3D+scaling file it is not possible to define different activations per ROI. For the artifacts; POSSUM does not take any artifact into account other than motion artifact. And it takes too much time to generate fMRI volumes. In sum, although POSSUM generates fMRI data by considering physics of the underlying measurements, it has several shortcomings for its use to mimic data obtained from a cognitive neuroimaging experiment.

2.4.3 A simulation toolbox for fMRI data: SimTB [13]

SimTB is an fMRI simulator which has the capability of creation and manipulation of spatial sources, block and event-related design definition, inclusion of tissue-specific baselines and simulated head movement. It has a GUI to design and execute simulations.

SimTB defines spatial maps (SM) which can be seen in Figure 2-17a. Components in SM are the components commonly seen in axial slices of real fMRI data. Components have default baseline values (see Figure 2-17b) which could be changed by user.



(a) (b)

Figure 2-17 SimTB spatial map (left), baseline map (right) (Images taken from [13])

In order to generate fMRI data; time courses (TC) of each component is calculated by convolution of task time series with hemodynamic model. Then TCs are multiplied with the baseline values of components. Motion and noise are added to get the final fMRI data. The result is 3D image where 2D square image (single slice) is convolved with hemodynamic model over the time which can be seen in Figure 2-18.

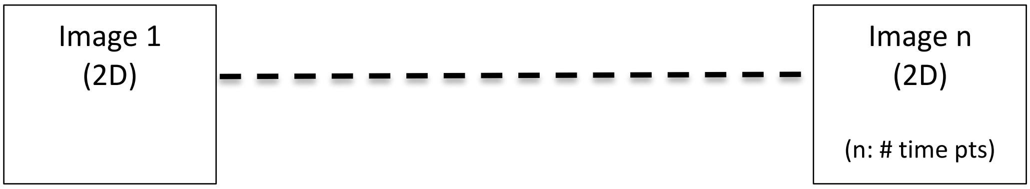


Figure 2-18 SimTB Image Series

As a result, SimTB does not generate 4D fMRI output. Instead, it generates 3D FMRI output where a single 2D slice is updated over the time to have 3D result.

2.4.4 METU-fMRISim [14]

METU-fMRISim is an fMRI simulator capable of simulating 4D fMRI data with several artifacts: motion, scanner drift, habituation and cardiac pulsation. The flowchart of METU-fMRISim can be seen in Figure 2-19 and the GUI of the simulator can be seen in Figure 2-20.

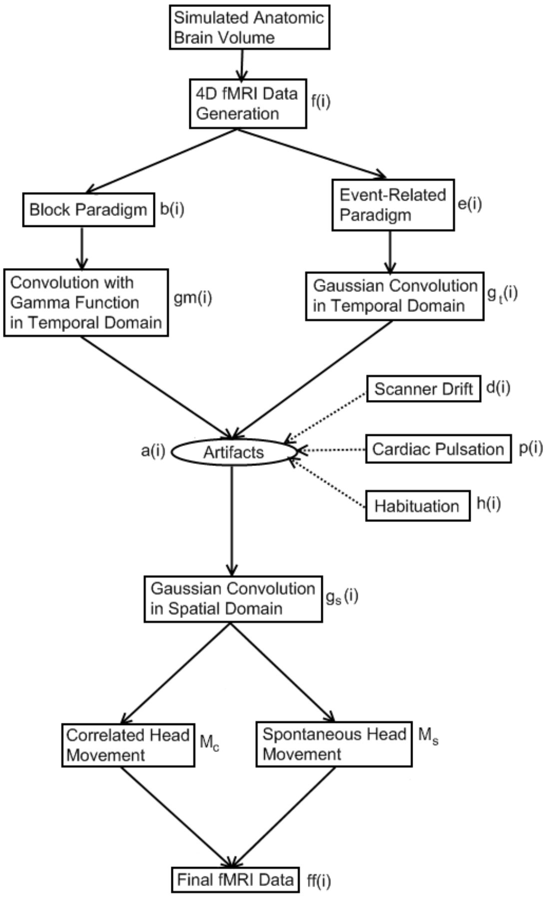


Figure 2-19 METU-fMRISim (Image taken from [14])

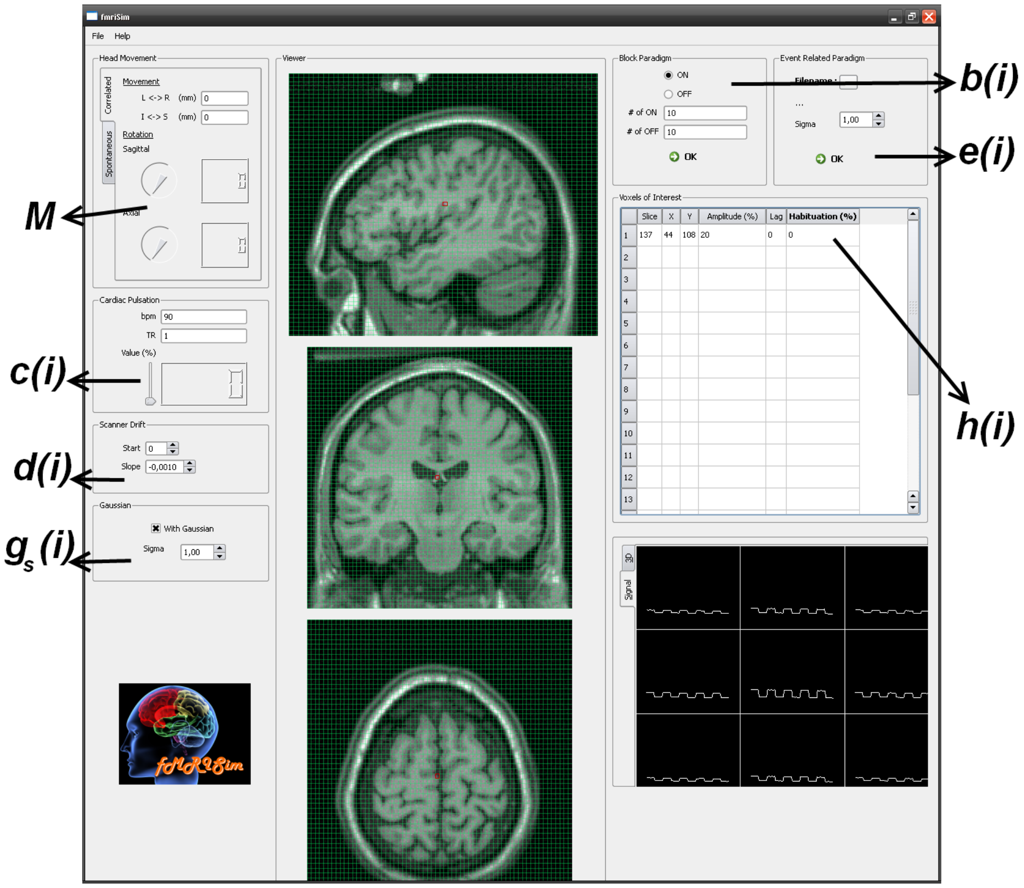


Figure 2-20 The main GUI of METU-fMRISim(Image taken from [14])
(b(i): block paradigm, e(i): event-related paradigm, g_s(i): Gaussian convolution, d(i):scanner drift, c(i):cardiac pulsation, h(i): habituation, M: motion)

In order to generate 4D fMRI data, time courses are calculated by convoluting HRF with task waveform (event or block designs are used to compute time series) and adding baseline value to the convolution result. Scanner drift, habituation and cardiac pulsation artifacts are added to the calculated time course signal. The resulting signal is then convolved in spatial domain with 3x3x3 Gaussian kernel. Final fMRI data is calculated after adding motion to convolved signal. METU-fMRISim uses the same baseline value for all voxels of the brain. However this is not true since each voxel may have a different offset value. For example voxels belonging to white matter and voxels belonging to gray matter have different intensities. Besides, it is very hard to define the ROI with this simulator. Also only one condition can be represented. For the block paradigm, the durations are same and only ON-OFF is handled. The amplitude of BOLD response cannot be defined with the simulator. In sum, the simulator has overbearing limitations.

CHAPTER 3

METHOD

This chapter includes 2 sections. In section 1, “Overview of the METU-fMRISim 2.0” is presented. In the “Overview of the METU-fMRISim 2.0” section; ROI Selection, HRF time course generation and 4D fMRI generation are explained. In section 2, METU-fMRISim 2.0 is compared with other fMRI simulators.

3.1 Overview of the METU-fMRISim 2.0

An fMRI simulator has been developed which is capable of generating 4D fMRI data based on user selected active voxels (ROI), experiment settings and artifacts.

In order to generate 4D fMRI data, 5 phases (Paradigm Selection, ROI Selection, HRF/DMN signal generation, Scanner Drift/Habituation artifacts addition and 4D fMRI generation) are followed in order. The overview of the simulator can be seen in Figure 3-1.

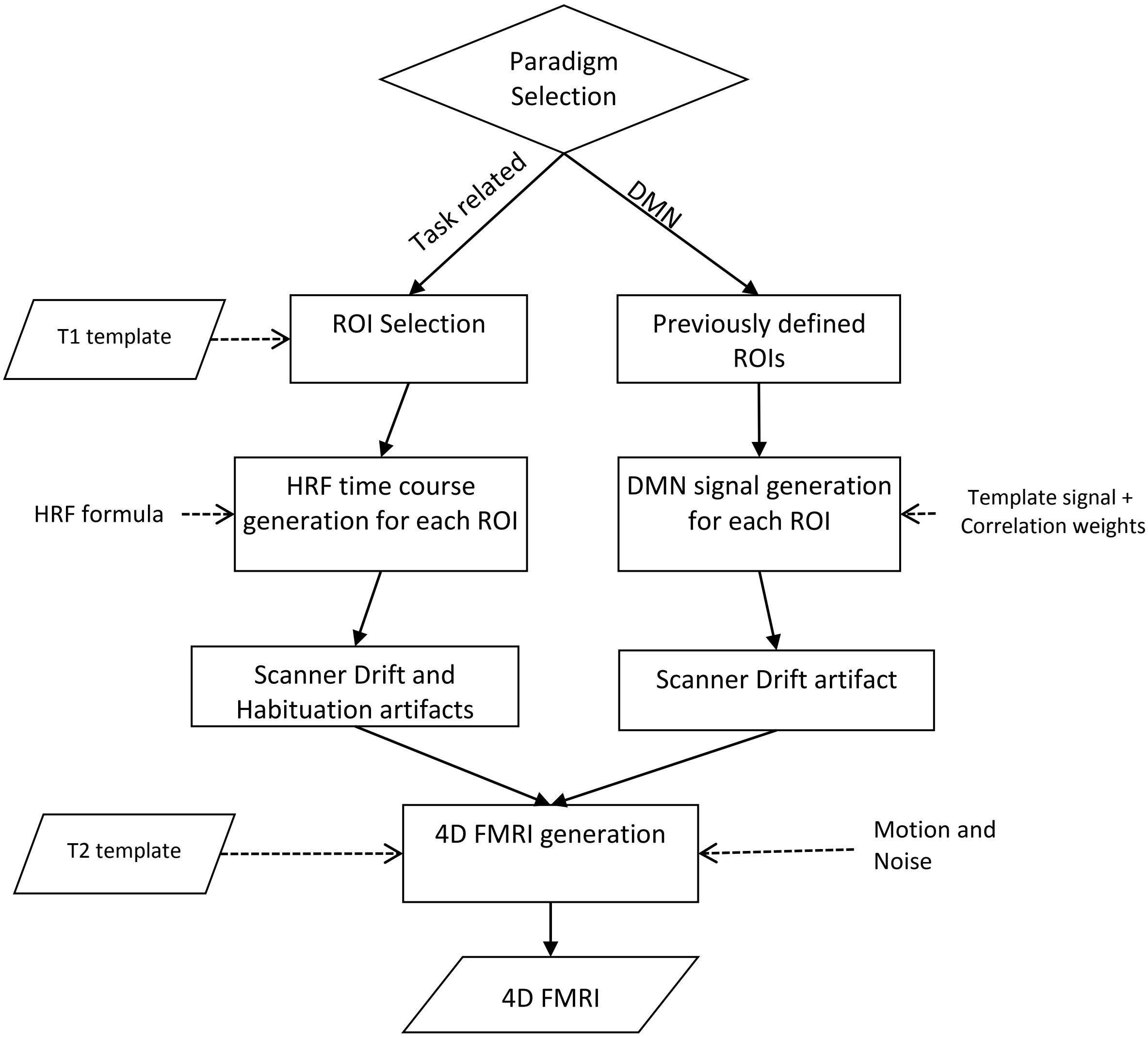


Figure 3-1 Overview of the simulator

The GUI of the simulator can be observed in Figure 3-2. In the GUI, there are 4 major parts: Experiment Settings (in blue), Task Related (Event, Block and Mixed) FMRI Data (in green), Default Mode Network (DMN) Related FMRI Data (in yellow), artifacts definition (rigid motion, noise and scanner drift – shown in red) and 4D fMRI generation (in black). The details of the simulator GUI is described in later sections.

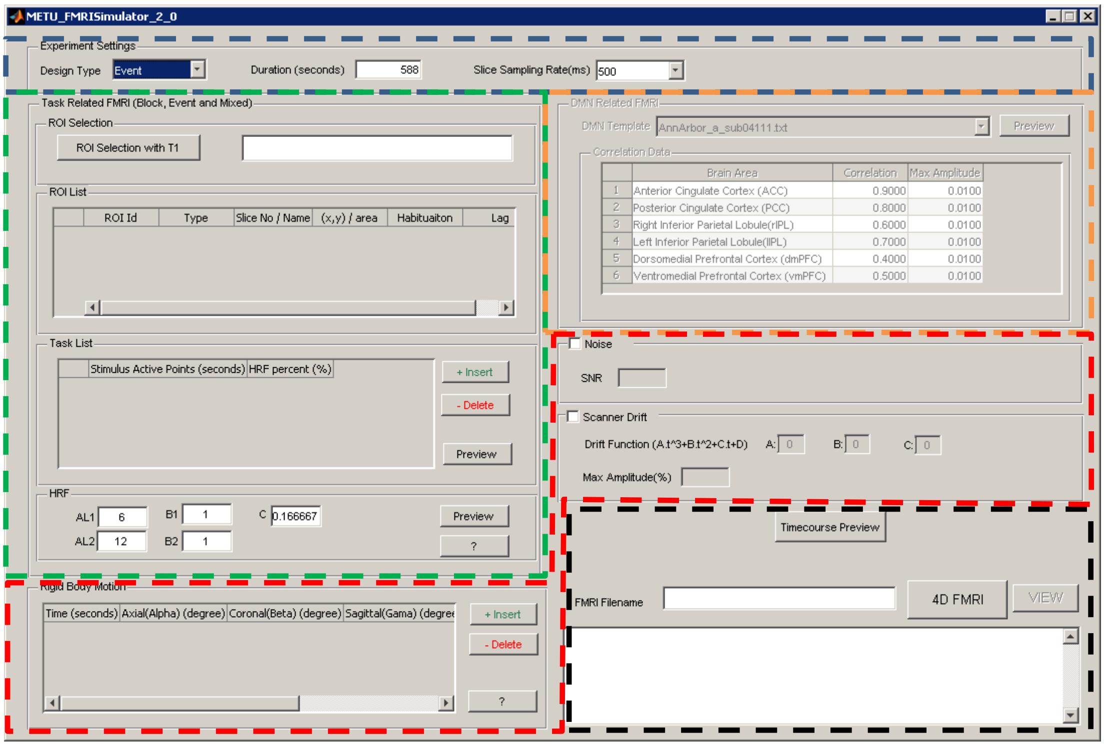


Figure 3-2 Simulator GUI

3.1.1 Task Related (Event, Block and Mixed) FMRI Data

3.1.1.1 ROI Selection

In order to generate task related fMRI data, ROI should be defined since only voxels within an ROI will have hemodynamic activation. By using 3D T1 template file [4], T1 Template Label Definition file [15] and 3D T1 Template label file [15]; the user defines ROI either “by drawing on T1 slices”, “by selecting previously defined brain areas from a labeled template” or selects “whole brain” as ROI. After ROI is defined, it is saved by user. In the saved ROI file; values greater than “1” corresponds to active voxels and “0” corresponds to passive ones. Figure 3-3 describes the overall flowchart of ROI Selection.

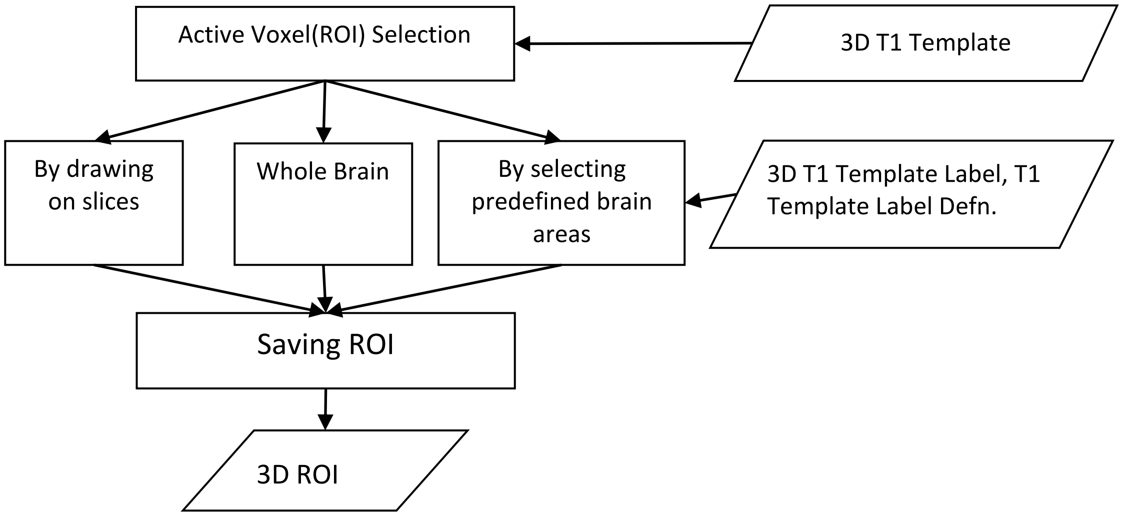


Figure 3-3 ROI Selection flowchart

The GUI of ROI Selection can be observed in Figure 3-4. In the figure, there are 4 major parts: Top (red dashed lines) is the sagittal, axial and coronal views, bottom (blue dashed lines) is the ROI selection types, middle (green dashed lines) is list of selected ROIs and bottom right (black dashed lines) is file name to be saved.

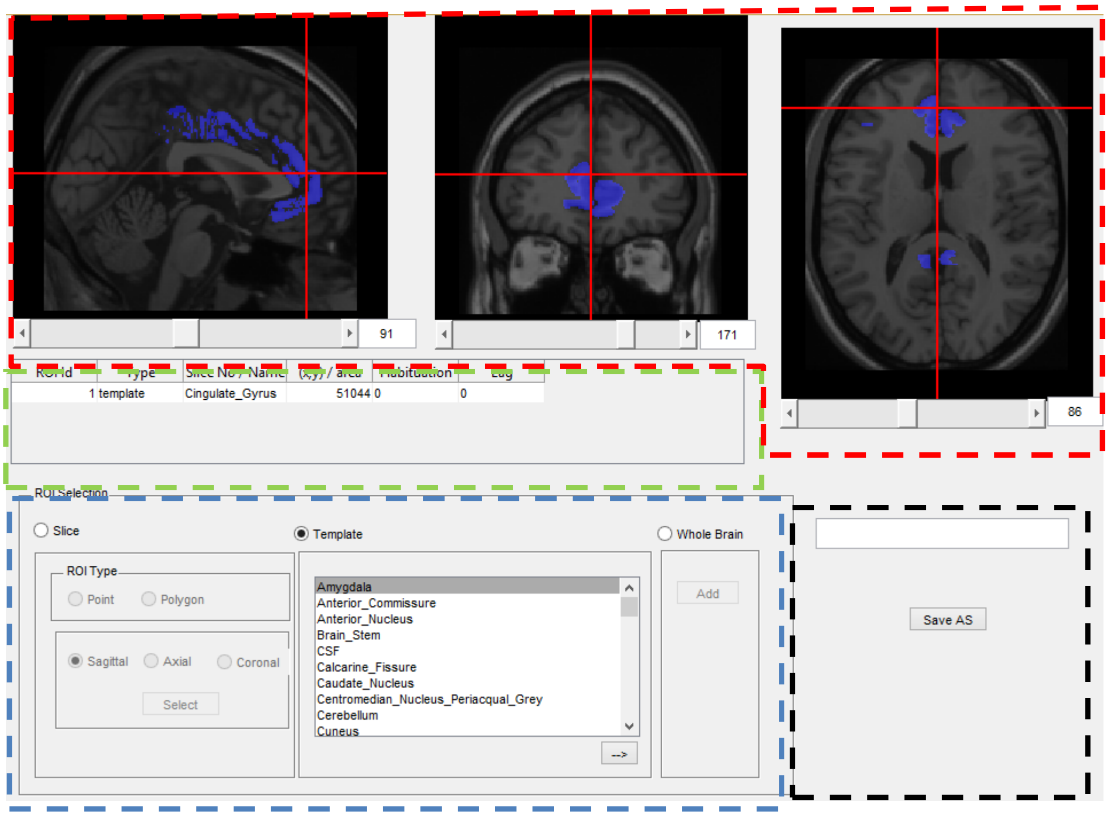


Figure 3-4 ROI Selection GUI

3.1.1.1.1 ROI Selection by drawing polygon/point on the slices

The type of ROI could be either Point or Polygon. For the point case; user selects a single active voxel by pressing mouse button on the selected slice (sagittal, coronal or axial). If the selection is Polygon, then user defines edge points by pressing mouse on the selected slice (sagittal, coronal or axial). For both cases, selected voxels are shown in blue. Polygonal and Point selection can be defined on multiple slices so that user can define any number of polygons/points on any slices. For example, a polygonal area is selected on the sagittal slice in Figure 3-5.

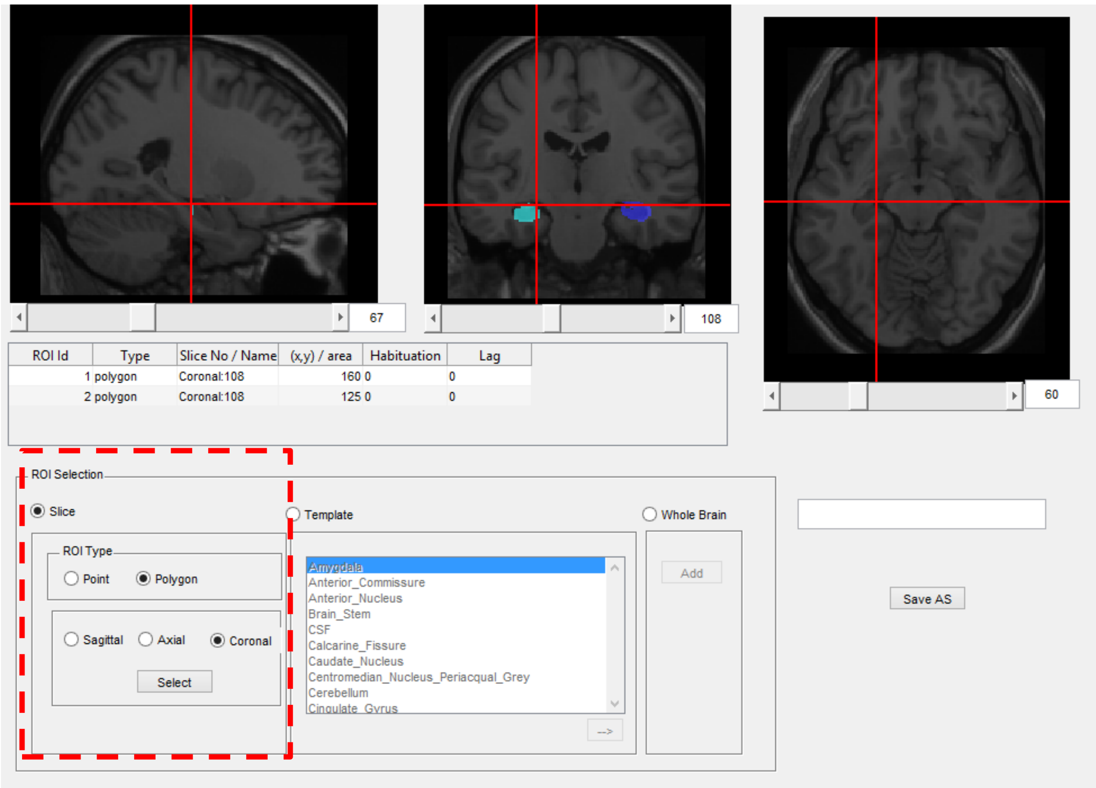


Figure 3-5 ROI Selection by drawing on the slices

3.1.1.1.2 ROI Selection by previously defined brain areas

Predefined brain areas are selected from ICBM as templates "T1 Template Label Definition file" [15] and their associated anatomical labels are defined in "3D T1 Template Label" image file [15]. In the "T1 Template Label Definition" file, each brain area is associated with a numeric value which is referencing to the "3D T1 Template Label" image file. Since 3D T1 Template Label and 3D T1 Template image files are registered to each other, the corresponding voxels of brain areas could be identified in 3D T1 Template image.

Sample T1 label definition, 3D T1 labels and 3D T1 template are shown for a 3x3 area in a single slice in Figure 3-6. As can be seen "Amygdala" is labeled as "240" in Template Label Definition file. When we look at the 3D T1 Template Label image file, we can see that the voxel at the top-right most is associated with Amygdala label. Since 3D T1 Template Label and 3D T1 Template are registered to each other we can easily say that the intensity value of 254 is a voxel from Amygdala.

Amygdala	240
…	…
Putamen	14
….	….

T1 Template Label Definition

1	14	240
3	8	14
5	23	32

3D T1 Template Label

1234	1846	254
300	76	1745
123	432	487

3D T1 Template intensities

Figure 3-6 Sample T1 Label Definition, T1 Labels and T1 Template

Predefined templates are listed in the ROI Selection GUI which can be seen as the red colored area in Figure 3-7. In order to select brain area(s) as ROI, user selects active brain area and presses "→" button. The selected brain area is shown in blue on the GUI which means that those voxels will have neuronal activity.

For example "Hippocampus" is selected in Figure 3-7 and shown in blue. It means that voxels of Hippocampus will have neuronal activity only.

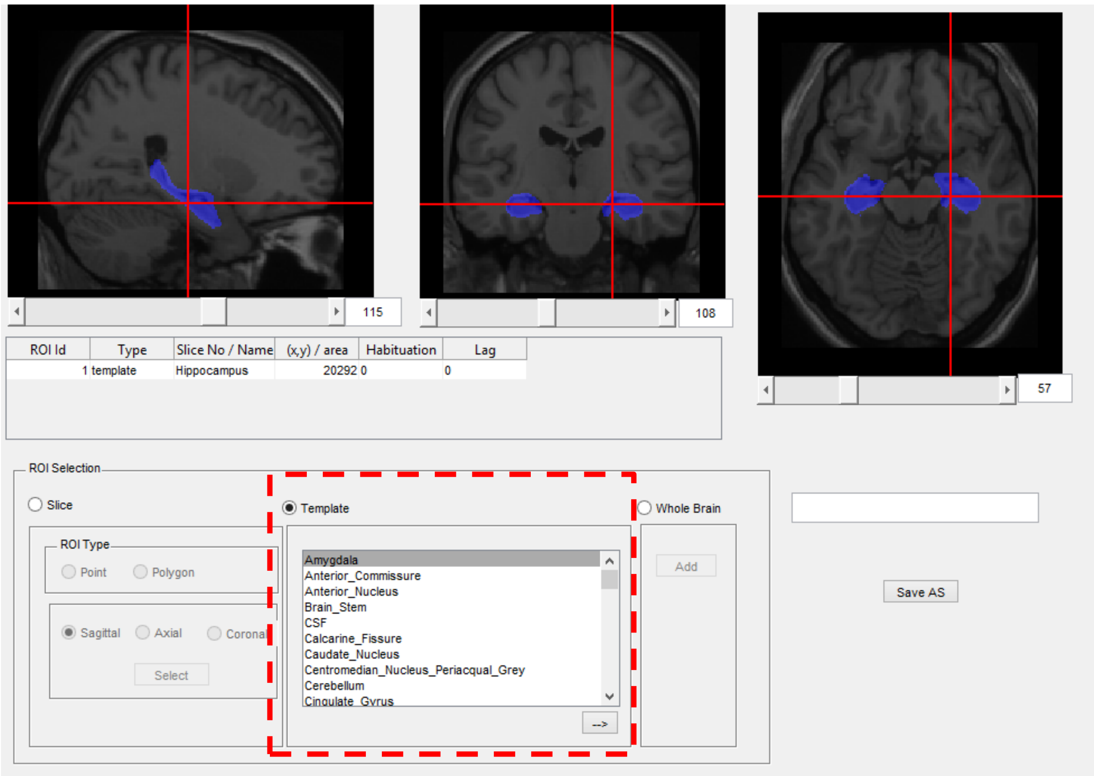


Figure 3-7 ROI Selection by using Brain Areas

3.1.1.1.3 ROI Selection-Whole Brain as ROI

The whole brain can also be defined as a ROI. In order to select whole brain as a ROI, “Whole Brain” radio button selection is selected and “Add” button is pressed. In Figure 3-8, whole brain is selected as a ROI.

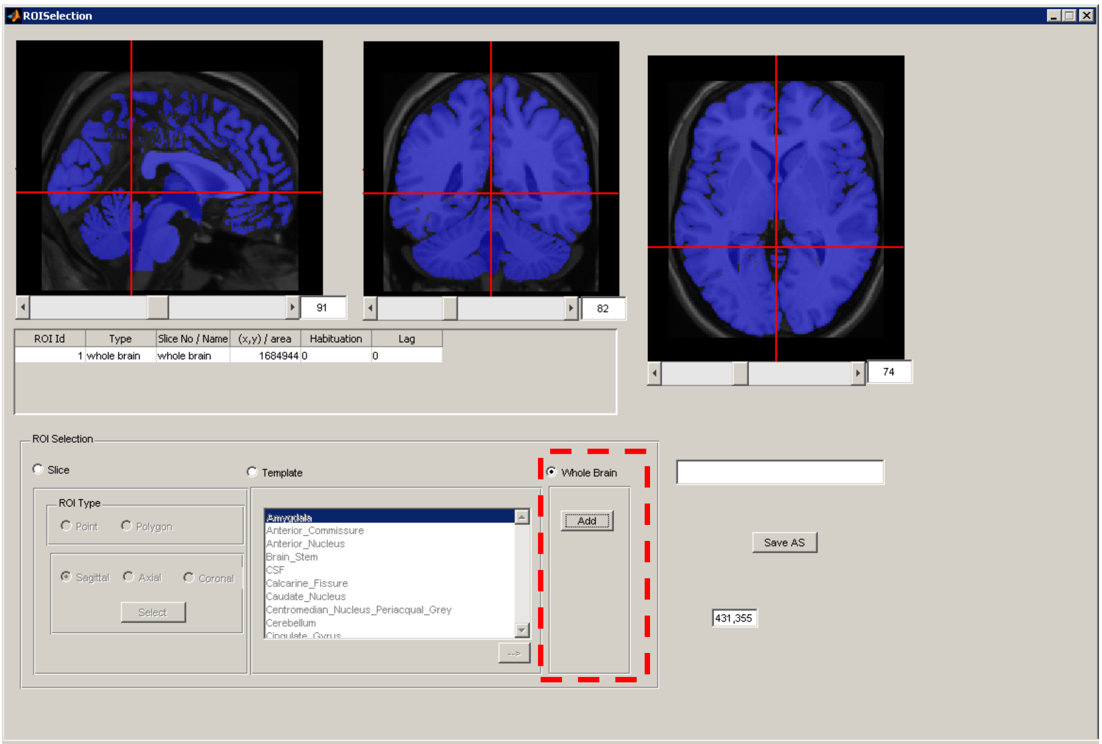


Figure 3-8 ROI Selection - Whole Brian as ROI

3.1.1.2 HRF Time Course Generation

Figure 3-9 describes the overall flowchart of HRF time course generation. According to the figure, stimulus function can fall into category of Event, Block or Mixed paradigms. At first task waveform is generated by using experiment duration and paradigm type values. Task waveform consists of the time spots of previously assigned stimulus conditions. It is the basic design of the experiment. Then resulting ideal fMRI signal is obtained by convolving the task waveform with HRF function as described in section 3.1.1.2.2. Then Gaussian White noise and Scanner Drift/Habituation artifacts are added onto this ideal signal to make it closer to the observed fMR time series which includes artifacts.

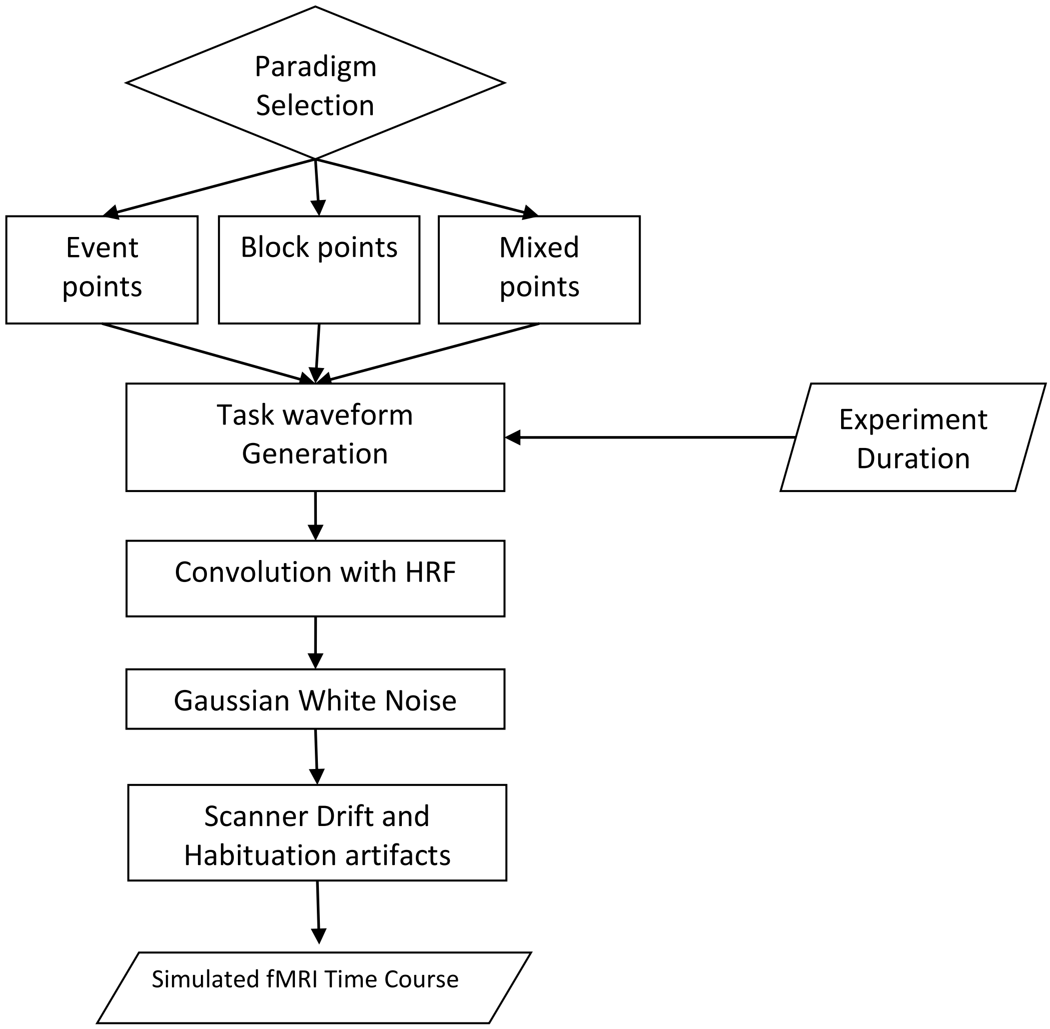
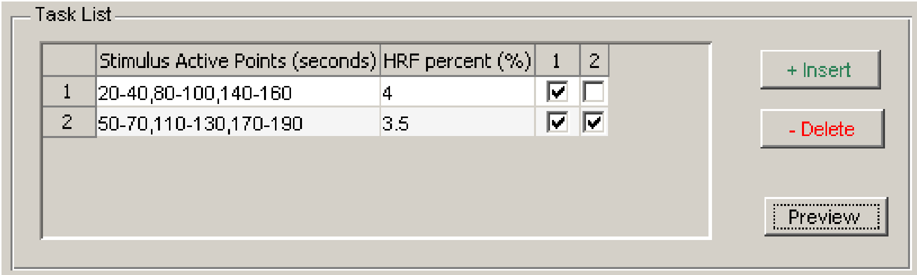


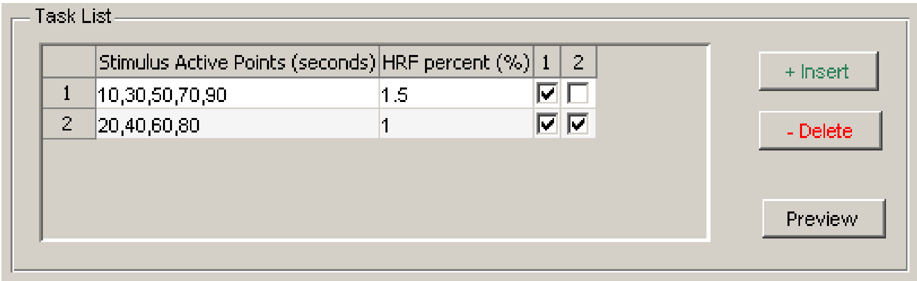
Figure 3-9 Flowchart o HRF time course generation

3.1.1.2.1 Stimulus Function

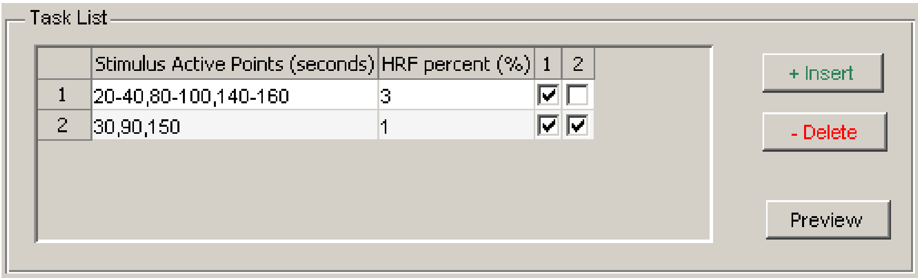
There are 3 types of task waveforms that can be defined: Event, Block and Mixed. As shown in Figure 3-10a and Figure 3-10b, event points are entered with comma separated and blocks are entered in "a-b" form where a is the starting time and b is the ending time in seconds (blocks are also separated with comma). For the mixed design (as shown in Figure 3-10c), user can enter the values in block and event type formats at the same time. When the user presses the Preview button, stimulus function can be seen as a plot.



(a)



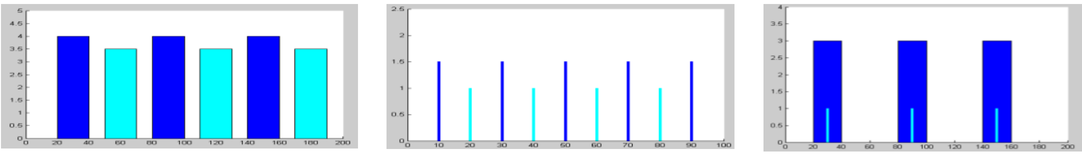
(b)



(c)

Figure 3-10 Task List Window for Block (a), Event (b) and Mixed (c) Designs

Figure 3-11a , Figure 3-11b and Figure 3-11c are the samples of task waveforms for block, event-related and mixed design types respectively. In Figure 3-11a, there are 2 conditions for the block design. The amplitudes of HRF response of conditions are 3.5 and 4%. From the figure it is seen that the dark blue colored condition will have a higher HRF response. In Figure 3-11b, 2 conditions for an event related fMRI design is shown. The amplitude of HRF responses are 1.5 and 1% for dark blue and light blue respectively. In Figure 3-11c, mixed design is shown. It can be seen that there are 2 conditions for mixed design. One for the block design and the other for the event related design. The amplitude of block is 3% and event is %1. During the experiment, a single event occurs during the active blocks.



(a) (b) (c)

Figure 3-11 Stimulus Function for Block (a), Event (b) and Mixed (c) Designs

3.1.1.2.2 Hemodynamic Response Function (HRF)

The HRF acts as an impulse response function in generating ideal (i.e. expected) fMRI time series from a given task waveform. A task waveform can be thought as a combination of several impulses. The HRF is a linear combination of two Gamma Functions is shown below:

$$HRF(t) = \frac{t^{\alpha_1 - 1}\beta_1^{\alpha_1} e^{-\beta_1 t}}{\Gamma\,(\alpha_1)} - c\,\frac{t^{\alpha_2 - 1}\beta_2^{\alpha_2} e^{-\beta_2 t}}{\Gamma\,(\alpha_2)}$$

where t references time, α_1 = 6, α_2 = 16, $\beta_1 = \beta_2$ = 1 and c = 1/6 [16]. Γ represents the gamma function. Following figure is the plot of HRF.

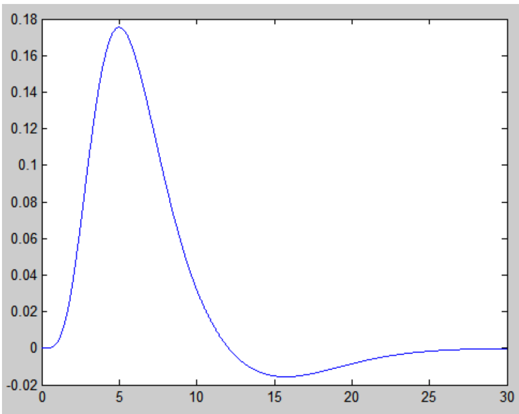


Figure 3-12 HRF plot

The HRF formula is used to simulate the HRF time course of block, event and mixed designs which is described in the section below.

3.1.1.2.3 Ideal fMRI response

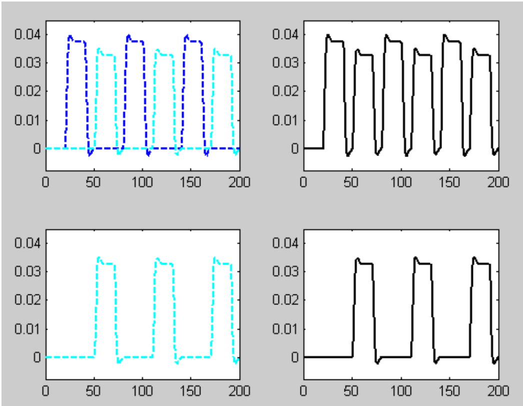
The ideal fMRI response, HC, for a given task waveform, fs is calculated by using the formula below:

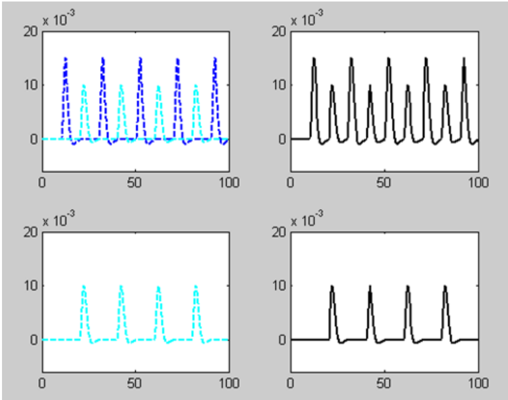
$$\mathrm{TC(fs(x))} = \mathrm{fs(x)} * HRF$$

where "*" is the convolution operator.

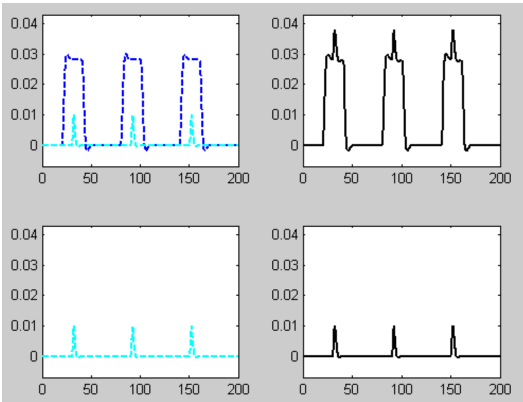
In order to see the HRF time course, user presses Preview button under "Time Course" pane which is shown in Figure 3-13.

Figure 3-13 HRF Time Course Preview GUI





(a) **(b)**



(c)

Figure 3-14 HRF Time Course – Block (a), Event (b), Mixed (c)

Figure 3-14a shows the HRF time course of block paradigm. The corresponding task waveform is the one shown in Figure 3-11a. From the figure we can see that the amplitude of the time course is close to %3.5 and %4.

Figure 3-14b shows the HRF time course of event-related paradigm. The corresponding stimulus function is the one shown in Figure 3-11b. From the figure we can see that the amplitude of the time course is close to %1.5 and %1".

Figure 3-14c shows the HRF time course of mixed paradigm. The corresponding stimulus function is the one shown in Figure 3-11c. From the figure we can see that the amplitude of the time course is close to %3 for blocks and %1 for events.

3.1.2 Default Mode Network (DMN) Related fMRI Data

3.1.2.1 DMN Template Generation

In order to generate signal templates for DMN Related fMRI Data Generation, resting state fMRI data of 397 subjects were downloaded from the nitrc web site [19]. Table 3-1 describes the source of data, number of subjects per source and TR values about downloaded rsfMRI scans.

Table 3-1 Subject count and TR values of downloaded rsfMRI datasets

Data Source Laboratory	Number of Total Subjects	TR Values (sec)
AnnArbor	22	2
Baltimore	23	2.5
Bangor	20	2
Berlin_Margulies	26	2.3
Cambridge_Buckner	48	3
Dallas	24	2
Leipzig	37	2.3
Oxford	22	2
Pittsburgh	17	1.5
Atlanta	28	2
Beijing_Zang	40	2
Cleveland	17	2.8
Newark	19	2
NewYork	41	2
Taipei	13	2

In the table above, there are 15 laboratories which provided resting state fMRI data. The number of subjects and TR values of fMRI scans per laboratory can also be seen in the table.

After that each subject was registered to MNI 152 Coordinate Space [20] having 4mm*4mm*4mm voxels. Then, for each subject, the mean signal was calculated for 6 brain areas which are Anterior Cingulate Cortex (ACC), Posterior Cingulate Cortex (PCC), Right Inferior Parietal Lobule (rIPL), Left Inferior Parietal Lobule (lIPL), Dorsomedial Prefrontal Cortex (dmPFC), Ventromedial Prefrontal Cortex (vmPFC). After that the mean signal was interpolated to have TR values of 0.5 second. Then subjects which have signal drift were removed from data set. After removal, 212 subjects remained to be template candidate.

In order to identify the template subject for each laboratory, normalized correlation matrixes were calculated for each laboratory as follows: In order to calculate the correlation matrix, the paired normalized correlations of the DMN signals between the subjects within a laboratory are calculated. Then normalized correlation values in the correlation matrixes [-1 1] were transformed into [100 0] interval where 0 stands for positive maximum correlation and 100 for negative maximum correlation. This [100 0] interval is interpreted as the "distance" between 2 values. After that, transformed scores (distances) were summed for each subject as seen in Table 3-2. The subject having minimum distance is selected as the template among several subjects for that laboratory. The chosen template subject has the representative data, because his/her rsfMRI data has the highest correlation with that of other subjects.

Table 3-2 Correlation matrix between subjects of a specific laboratory (transformed scores)

Laboratory $_{1..M}$	**Sub$_1$**	**Sub$_2$**	**...**	**Sub$_N$**
Sub$_1$	score$_{11}$	score$_{12}$	...	score$_{1N}$
Sub$_2$	score$_{21}$	score$_{22}$	...	...
...	...	...	...	...
Sub$_N$	score$_{N1}$	score$_{N2}$	...	score$_{NN}$
SUM	**score_sub$_1$=** $\sum_{i=1}^{N} \boldsymbol{score_{i1}}$	**score_sub$_2$=** $\sum_{i=1}^{N} \boldsymbol{score_{i2}}$	**...**	**score_sub$_N$=** $\sum_{i=1}^{N} \boldsymbol{score_{iN}}$

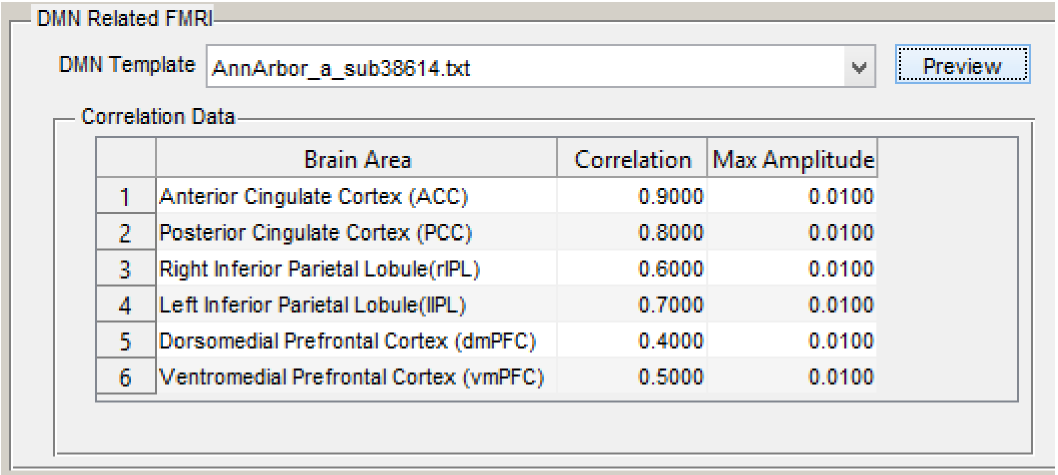
N: subject count for a laboratory, Sub$_i$: individual subjects

Selected template subject for a laboratory: min (score_sub$_x$) where x=1: N

Signals of selected template for each laboratory can be seen in APPENDIX B: DMN TEMPLATES.

3.1.2.2 DMN fMRI Generation

As described in the previous section, there are 6 brain areas in which DMN related fMRI is generated. In order to calculate a separate template signal for each brain area, correlation values under Correlation Data Section shown in Figure 3-15 is used. As a result, DMN resting state signal in each of the 6 areas exhibit a different correlation coefficient with the chosen template signal.



	Brain Area	Correlation	Max Amplitude
1	Anterior Cingulate Cortex (ACC)	0.9000	0.0100
2	Posterior Cingulate Cortex (PCC)	0.8000	0.0100
3	Right Inferior Parietal Lobule(rIPL)	0.6000	0.0100
4	Left Inferior Parietal Lobule(lIPL)	0.7000	0.0100
5	Dorsomedial Prefrontal Cortex (dmPFC)	0.4000	0.0100
6	Ventromedial Prefrontal Cortex (vmPFC)	0.5000	0.0100

Figure 3-15 DMN Related FMRI Data section

To calculate a resting-state correlated signal for a brain area (x: correlation value of one of the brain areas shown in Figure 3-15.)[21]

1. Mean and standard deviation of template signal (template_signal) is calculated.
2. Gaussian random normally distributed signal (random_signal) is generated having equal mean and standard deviation with template signal.
3. Then Cholesky decomposition, CHOL, of the matrix $\begin{bmatrix} 1 & x \\ x & 1 \end{bmatrix}$ is calculated where x is the desired correlation (For example x is 0.9000 for ACC in Figure 3-15). The Cholesky decomposition of $\begin{bmatrix} 1 & x \\ x & 1 \end{bmatrix}$ is in the form of $\begin{bmatrix} 1 & A \\ 0 & B \end{bmatrix}$
4. Then M= $\begin{bmatrix} template\_signal \\ random\_signal \end{bmatrix} x \begin{bmatrix} 1 & A \\ 0 & B \end{bmatrix}$ is calculated by multiplying $\begin{bmatrix} template\_signal \\ random\_signal \end{bmatrix}$ matrix with the matrix calculated at step 3 above ($\begin{bmatrix} 1 & A \\ 0 & B \end{bmatrix}$).
5. Correlated signal is the second row element of matrix which is template_signal*A+ random_signal*B

For example, Figure 3-16 shows original signal and generated signal which is 60% correlated with original signal.

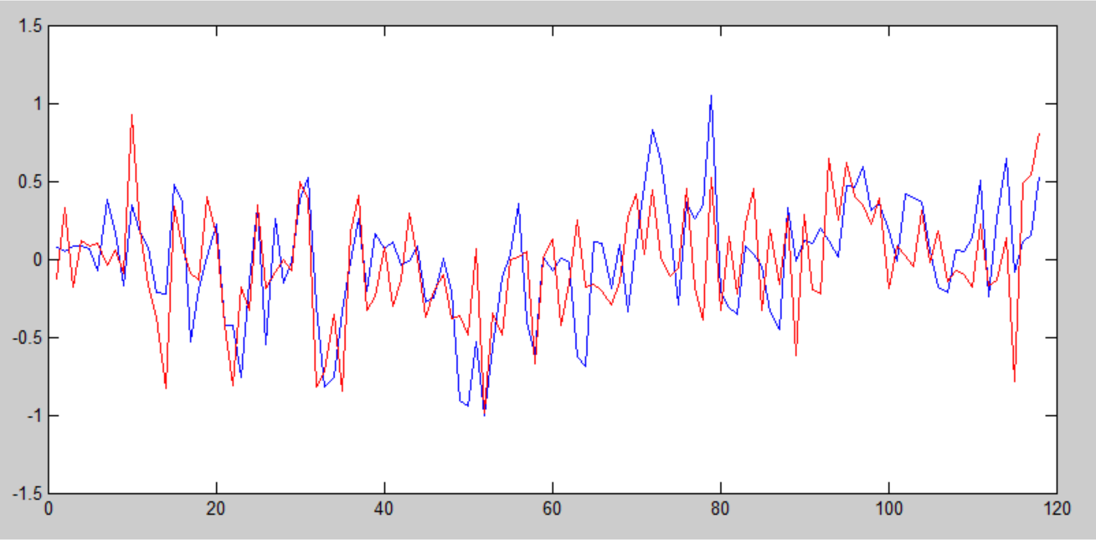


Figure 3-16 Correlated signal generation - blue: original signal, red: generated signal (60% correlation)

3.1.3 Scanner Drift Artifact

Scanner Drift Artifact is calculated by using the formula below:

$$TC_{sda}(\mathrm{t}) = \mathrm{TC}(\mathrm{t}) \times (1 + \tan SDA \times \mathrm{t})$$

where TC(t) is the value of the ideal fMRI series at time t and SDA is the Scanner Drift Artifact value.

Figure 3-17 shows the Scanner Drift Artifact Definition GUI and Figure 3-18 shows Scanner Drift added signal.

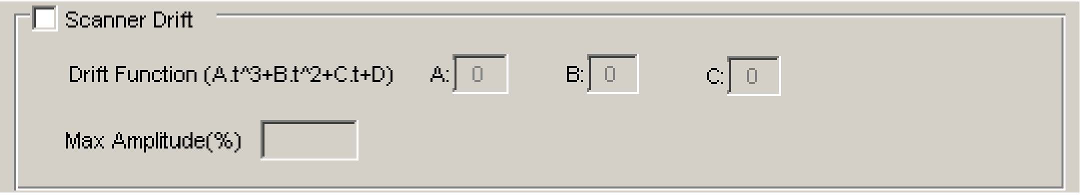
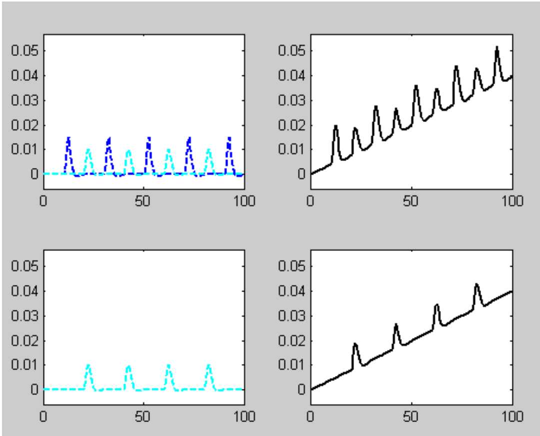
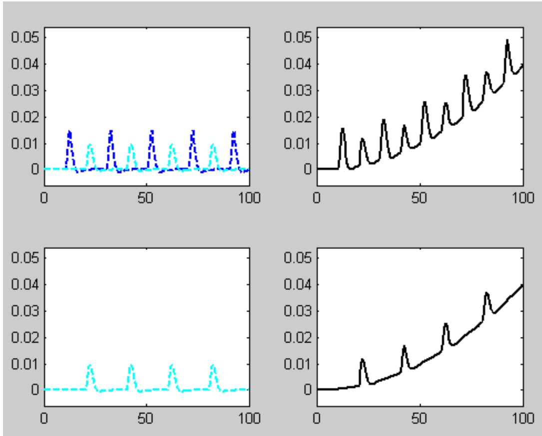
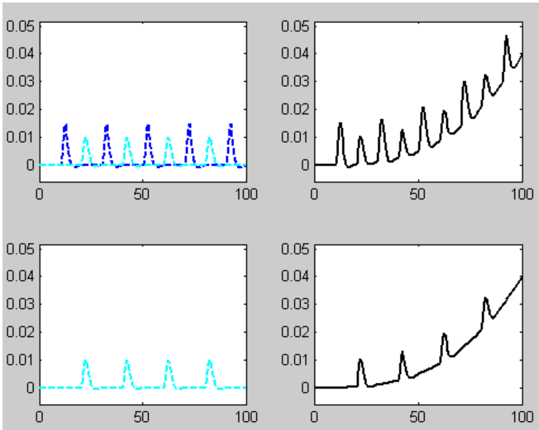


Figure 3-17 Scanner Drift Artifact Definition GUI





(a) **(b)**



(c)

Figure 3-18 Ideal fMRI time series (blue) and added scanner drift artifact (black)

(a) 1st degree,(b) 2nd degree and (c) 3rd degree scanner drift signal

In Figure 3-18, 3 types of scanner drift are shown: 1st, 2nd and 3rd degree scanner artifacts. In Figure 3-18a, scanner drift calculated by using 1st degree polynomial is shown. From the figure, it is seen that the fMRI time course increases over the time linearly since 1st degree polynomial is used. In Figure 3-18b and Figure 3-18c, scanner drifts calculated by using 2nd and 3rd degree polynomial are shown. From the figures it is seen that the shapes of fMRI time course fits 2nd degree polynomial and 3rd degree polynomial respectively.

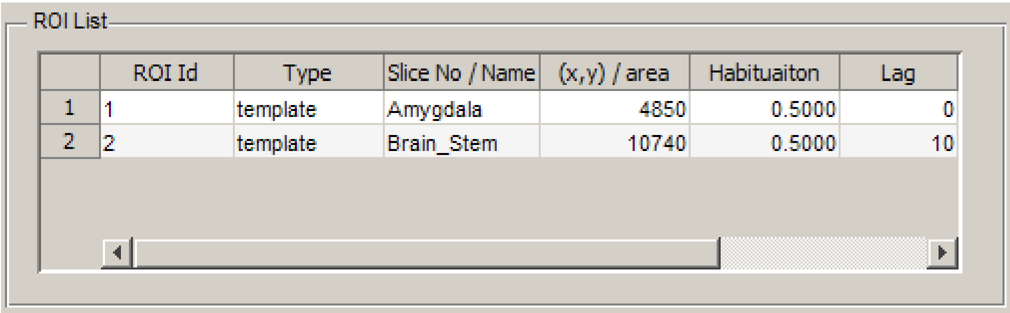
3.1.4 Habituation Artifact

Habituation Artifact is calculated by using the formula below:

$$TC_{ha}(\mathrm{t}) = \mathrm{TC(t)} \times (1 - \tan HA \times \mathrm{t})$$

where TC(t) is the ideal fMRI time course value at time t and HA is the Habituation artifact value.

Figure 3-19 shows the Habituation Artifact Definition GUI and Figure 3-20 shows Habituation Drift added signal. Habituation value in this figure is the percentage of the signal decrease over the time. Lag is the shift of the time course in time in seconds. For example 10 seconds lag means that the time course will be shifted 10 seconds. This effect can be seen in the bottom part of Figure 3-20 where the time course is shifted to right with an amount of 10 seconds.


ROI List

	ROI Id	Type	Slice No / Name	(x,y) / area	Habituaiton	Lag
1	1	template	Amygdala	4850	0.5000	0
2	2	template	Brain_Stem	10740	0.5000	10

Figure 3-19 Habituation Artifact Definition GUI

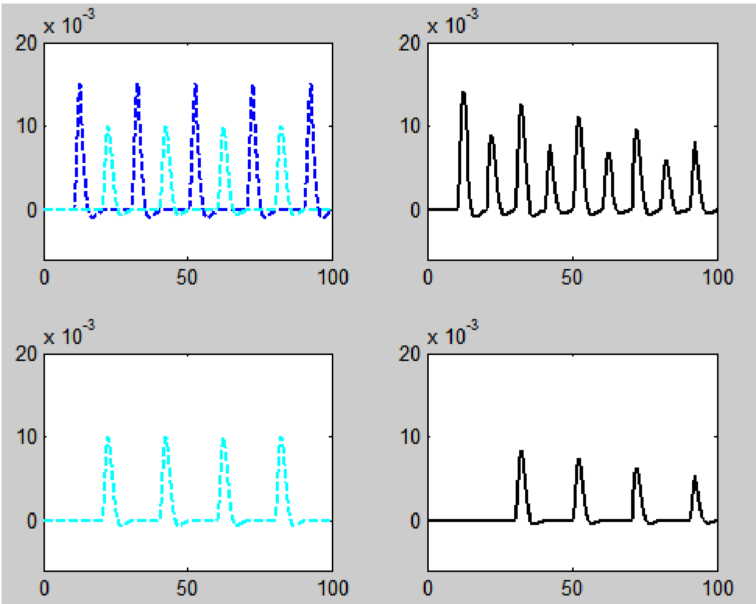


Figure 3-20 Habituation artifact added HRF time course

In Figure 3-20, it can be observed that the hemodynamic response decreases over time which is the effect of habituation. The lag can be observed at the bottom of the figure. The bottom left (cyan dashed) is the original signal whereas the bottom right (black) is the lagging signal. It can be easily seen that the HRF time course is shifted right which described the lag effect.

3.1.5 Gaussian White Noise

Gaussian White Noise is calculated by using the formula below where noise is just normally distributed pseudorandom values with equal length of signal.

$$Power_{signal} = \left(\sqrt{\sum signal^2}\right) / Length_{signal}$$

$$Power_{noise} = \left(\sqrt{\sum noise^2}\right) / Length_{signal}$$

$$Signal_{result} = signal + noise \times \left(Power_{signal}/Power_{noise}\right)/SNR$$

where $Power_{signal}$ is the signal power, $Power_{noise}$ is the noise power and $Signal_{result}$ is the final signal calculated.

Figure 3-21 shows the Noise Definition GUI and Figure 3-22 shows Noise added signal.

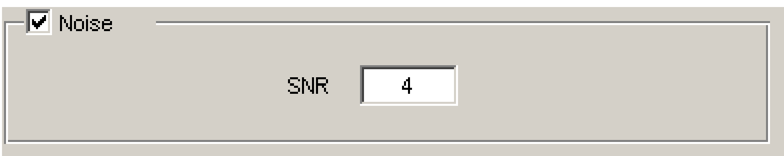


Figure 3-21 Noise Definition GUI

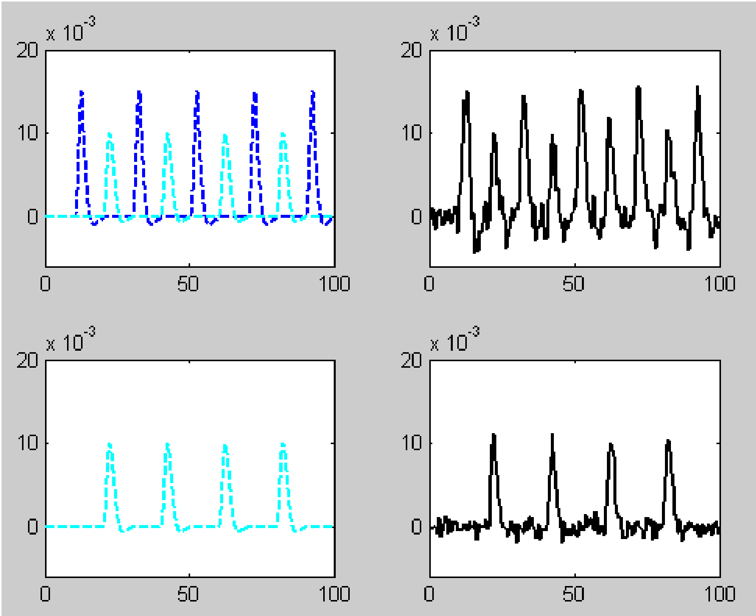


Figure 3-22 Noise added HRF time course

In Figure 3-22, left side of the figure is the original signals and right side is Gaussian White Noise added signals.

3.1.6 4D fMRI Generation

Figure 3-23 describes the overall flowchart of fMRI time course generation. The 3D ROI and HRF Time course are the ones that were described in section 3.1.1.1 and 3.1.1.2. By using T2 template [17], 3D ROI and HRF time course 4D fMRI data was generated. In order to generate 4D fMRI data following formula is used:

$$\mathrm{4DfMRI(t)} = \mathrm{T2} \times (1 + \mathrm{ROI} \times \mathrm{HRFT(t)})$$

where 4DfMRI is the 4D fMRI data, T2 is the 3D T2 template[17], ROI consists of active voxels described in section 3.1.1.1 and HRFT is the HRF time course described in section 3.1.1.2.

After generation of 4D fMRI data, motion artifact is added to 4D fMRI data which is described in section 3.1.6.

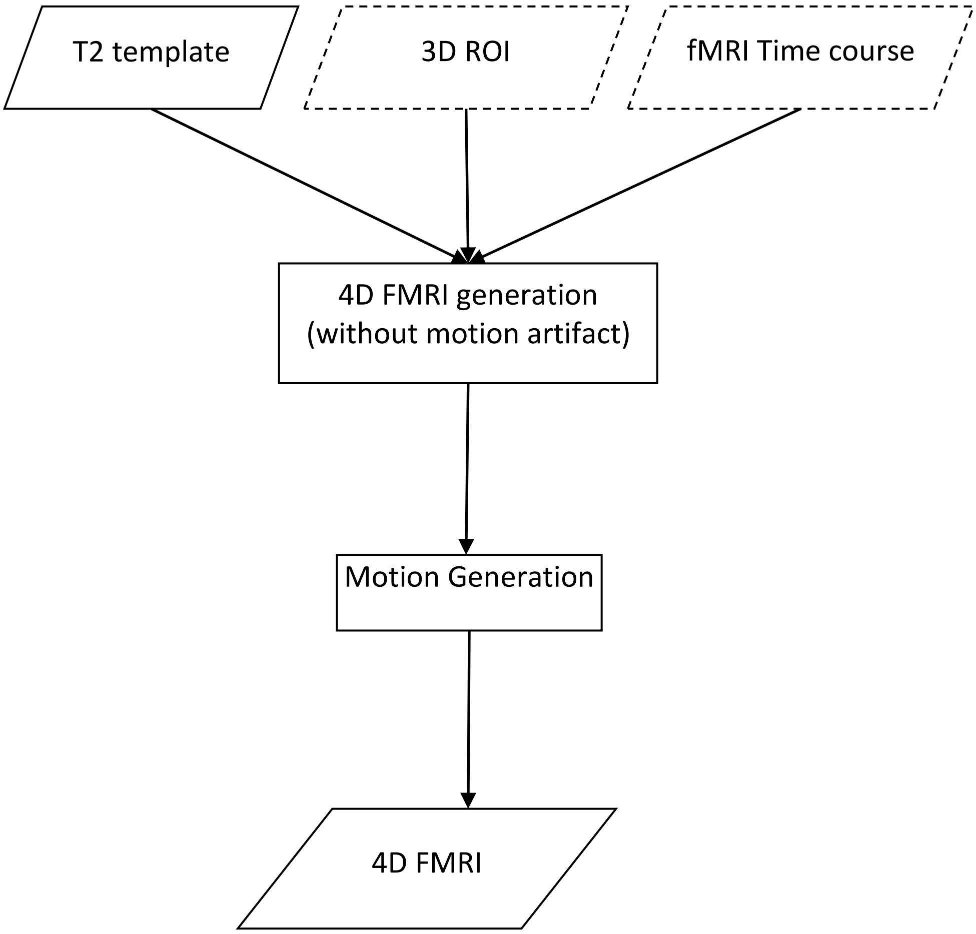
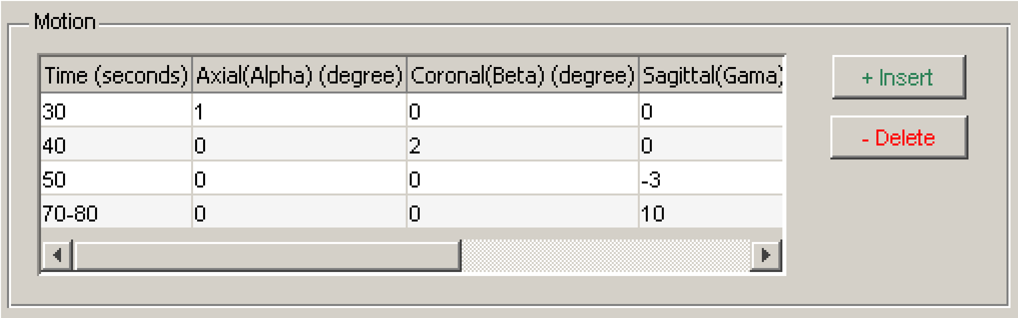


Figure 3-23 4D FMRI Generation

3.1.6.1 Rigid Body Motion Artifact

Motion artifact is the rigid body rotation and translation of the head in sagittal, axial and coronal planes. The rotation and translation can be any combination of these 3 planes in + or - directions. The unit of motion is degree per second. Rotational point is the middle of sagittal, axial and coronal planes.

Figure 3-24 is an example of how rotation is entered. As seen from Figure 3-24, there are four rotations. At 30th second, head is rotated at 1 degree in the axial plane. At 40th second, head is rotated at 2 degrees in coronal plane. At 50th second, head is rotated negative (opposite) 3 degrees in sagittal plane. In the end, there is total of 10 degrees rotation in 70-80 second time frame which means that head is rotated in sagittal plane at 10 degree/(80-70)second= 1 degree per second.



Time (seconds)	Axial(Alpha) (degree)	Coronal(Beta) (degree)	Sagittal(Gama)
30	1	0	0
40	0	2	0
50	0	0	-3
70-80	0	0	10

Figure 3-24 Motion Artifact

Rotation and translation in 3D planes are explained in Figure 3-25 and Figure 3-26 respectively.

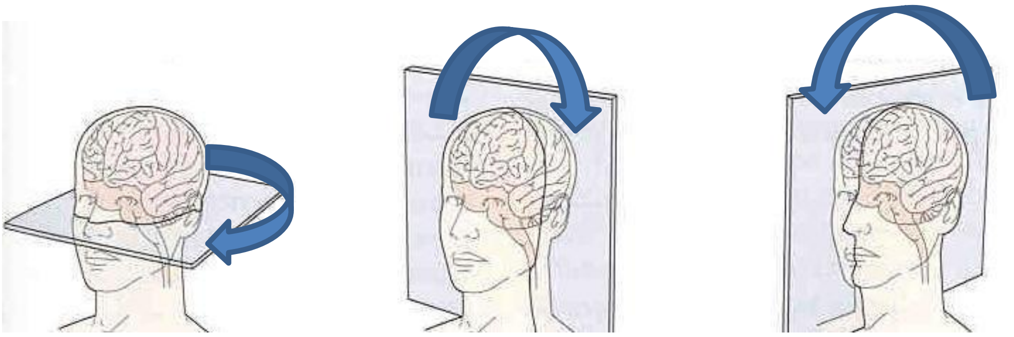


Figure 3-25 3D Rotation planes
(Left: Axial rotation, Middle: Coronal rotation, Right: Sagittal rotation)
(Image taken from http://www-psych.stanford.edu/~kalina/BB)

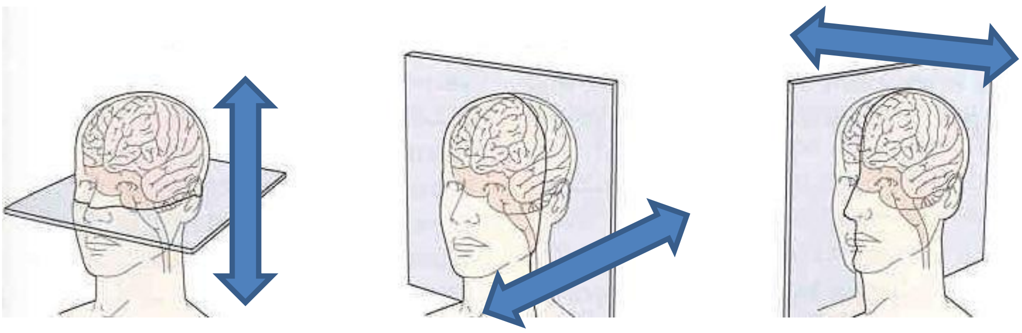


Figure 3-26 3D Translation planes
(Left: Axial translation, Middle: Coronal translation, Right: Sagittal translation)
(Image taken from http://www-psych.stanford.edu/~kalina/BB)

3.1.7 Development Environment

MATLAB was used as the programming language. In order to read/write ANALYZE and NIFTI files, NIFTI Tools (Copyright 2009 Jimmy Shen) was used.

T1 template, T1 template labels and T2 atlas used within this application were downloaded from http://www.loni.usc.edu/atlases website.

3.1.8 Boundary Conditions

There are some boundary conditions which should be taken into account when running the simulator. The boundary conditions have been described in Table 3-3

Table 3-3 Boundary Conditions of the Simulator

Field/Data	**Boundary**
Experiment Length	Experiment length should not exceed 30 minutes
Block Length	For the block design, block length should be in between 20-30 seconds
Block Design HRF Amplitude Percent	For the block design, HRF Amplitude Percent should not exceed 5%
Event Design HRF Amplitude Percent	For the event-related design, HRF Amplitude Percent should not exceed 2%
Output voxel size	Output voxel size in the simulator is fixed 4mm X 4mm X 4mm.
Time resolution	Time resolution within the simulator is 0.5 seconds. Motion and tasks can be defined in the simulator is in the increments of 0.5 seconds.
Habituation Percentage	Habituation percentage is expected to be in between 0-1
Lag	Lag is expected to be in between 0-30 seconds
Scanner Drift	Expected to be in between 0-1
Scanner Drift Maximum Amplitude	Expected to be in between %1-%10
Noise SNR	Value greater than 0
Rotation	Values are in degrees. Expected to be in between 0-5 degrees
Translation	Values are in voxels. Expected to be in between 0-5 voxels (0-20mm).

3.2 Comparison with Other simulators

3.2.1 Comparison with POSSUM

In POSSUM, in order to generate fMRI data, the MR Parameters (relaxation times T1, T2*, spin density ρ, and chemical shift value δ), pulse sequence (RF angle, RF frequency bandwidth, RF center frequency), slice profile and 4D activation file should be provided. MR Parameters and pulse sequence parameters can only be defined with deep knowledge on the MR physics. 4D fMRI Activation file should also be defined in order to run POSSUM. With our simulator, 4D activation is handled by providing ROI and the shape of HRF which could be defined by the user. For the artifacts, POSSUM is limited to use motion and noise artifacts whereas our simulator also simulates drift and habituation artifacts. Running POSSUM takes too much time (For 100 fMRI volumes with 3 slices of 3mm thickness, with an output k-space matrix of 64 × 64 for each slice with no motion, it takes 42 hours 30 minutes on a single processor) whereas fMRI data generation finishes in minutes with our simulator. Since POSSUM is generating data by solving Bloch equations and T2* is generated as output, it is expected for data generation to take hours. But in our simulator we are using real T2 data and adding 4D activation and artifacts on top of T2 values. This is the reason of why generation of fMRI data with our simulator lasts in minutes.

3.2.2 Comparison with SimTB

SimTB is an fMRI simulator which has the capability of the creation and manipulation of spatial sources, block and event-related design types definition, inclusion of tissue-specific baselines and simulated head movement. It has a GUI to design and execute simulations.

SimTB calculates the time course of single axial slice. For this reason, it generates 3D result whereas our simulator generates 4D whole brain FMRI data. Besides, no artifact other than motion can be added with SimTB.

3.2.3 Comparison with Chris Rorden's fMRI Design Software

This software is a tool for designing an fMRI study. Tool does not provide 4D fMRI output and artifacts cannot be defined with this simulator. It only shows HRF time course of an experiment by using the settings (like TR, number of volumes, design type etc.) which are defined by user.

Block and event related BOLD responses can be viewed with the simulator. As a result, this software can only be used for designing fMRI experiments.

3.2.4 Comparison with METU-fMRISim

The major difference between the METU-fMRISim and the method described here is that; there is a baseline level of intensity throughout the whole brain in METU-fMRISim. However this approach is not correct since each voxel in fMRI has its own baseline intensity value produced from T2* weighted images. The intensity of the fMRI signal must be the original T2* intensity plus activation related intensity. With our approach, we are using T2 image modality as underlying baseline value and adding hemodynamic response to this baseline value to create fMRI signal for each voxel.

ROI selection by using previously defined brain areas is another major strength of this study. This mechanism is added to simulator since it is not easy to identify brain areas by drawing them with user effort. Now, there is capability to select brain areas (those brain areas are defined in a 3D template label file) as a ROI and BOLD activation in those selected areas will take place in the output fMRI data only.

HRF function in METU-fMRISim cannot be changed by the user. But in our simulator, it can be changed by changing the coefficients of the HRF function.

Mixed design paradigm is also added which does not exist in METU-fMRISim.

Default Mode Network rsfMRI data generation is another major functionality which is added with this method.

Cardiac pulsation artifact which exists in METU-fMRISim is not implemented within this study. As a future study, physiological noises like cardiac pulsation can be added to this simulator.

CHAPTER 4

RESULTS

4.1 Verification of Generated Activity

In order to test the activity results of the simulator, an fMRI experiment design was setup and corresponding 4D brain volume was generated. Then generated 4D brain volume was analyzed by 3dfim [25] utility of AFNI [23] (This utility return correlation of the generated time series in a voxel with the ideal task waveform. Higher correlation coefficient means that there is more probability for that voxel to have neuronal activity). Given the ROI for which fMRI signals are generated during the experiment, thresholding is done to decide 'active' voxels. Higher thresholds for the correlation coefficient –such as 0.5- reveal active voxels. We found Jaccard indexes [26] between the entire ROI for which simulation is done and those voxels AFNI returned as 'active' after thresholding, to verify that the fMRI activity we created is detectable.

Jaccard index between the ROI, A, in the simulator and voxels, B, detected by AFNI is calculated as follows:

$$J(A,B) = \frac{A \cap B}{A \cup B}$$

Where A and B are sets, ∩ is the intersection operation, ∪ is the union operation and J(A,B) is the Jaccard result. In our case, intersection and union are the number of intersecting and union voxels between the ROI in the simulator and voxels detected by AFNI.

4.1.1 Verification for Sample Block Design

In order to generate the block paradigm fMRI time series, the parameters in Table 4-1 were used. From Table 4-1, it can be observed that experiment duration is 300 seconds. Volumes are sampled at a rate of 3 seconds/volume. So there are 100 whole brain volumes at the end of experiment. Activity starts at 20th seconds and ends in 280th seconds. The HRF signal increase is 4% and the activation will take place in amygdala.

Table 4-1 Block Design FMRI Simulation Parameters

Duration (seconds)	300
Sampling Rate (TR) (milliseconds)	3000
TASK	Activity: [20-40,60-80,100-120,140-160,180-200,220-240,260-280], HRF Percent: 4
ROI	Amygdala

After the fMRI data was generated, it was loaded into AFNI to see the time course of the voxels. Figure 4-1 is the screenshot of 9 neighbor active voxels' time series. It can be seen from the figure that there are 7 ON and 8 OFF periods which corresponds to the task identified in Table 4-1. For this reason, we confirm that the simulator generated these ON-OFF periods correctly.

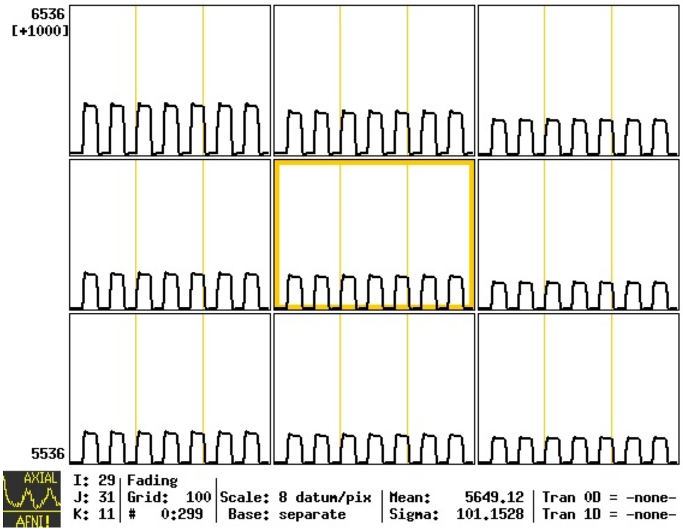


Figure 4-1 Block Paradigm time course

After visual inspection, generated fMRI data was analyzed by AFNI 3dfim utility. The result of the analysis and the ROI selected from the simulator can be seen in Figure 4-2. The red colored areas are the active voxels according to fMRI analysis. The yellow colored areas are the active ROI areas depicted by the user during the simulation run.

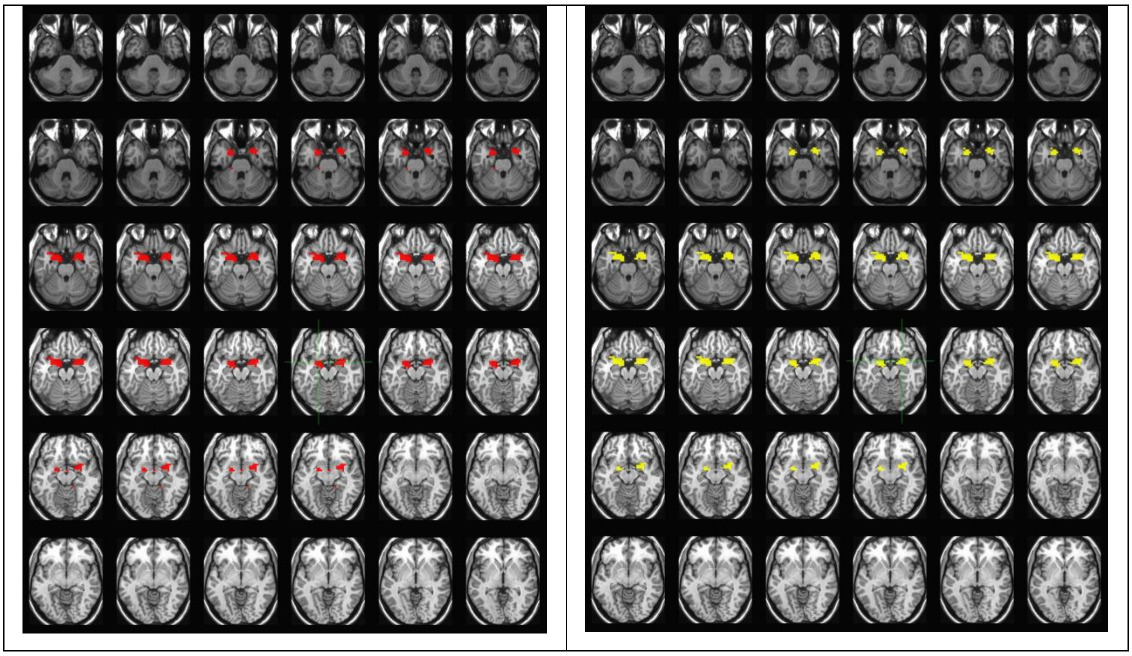


Figure 4-2 Block design FMRI analysis result (left) and ROI defined in the simulator (right).

From the Figure 4-2, it can be easily observed that the ROI and fMRI analysis results are having higher intersection. Also “Jaccard Index” is used to compare the results. The Jaccard Index calculated between ROI in the simulator and voxels detected by AFNI is 1 which means that voxels detected by AFNI is fitting over the voxels defined in the simulator with 100 percent correctness.

4.1.2 Verification for Sample Event Design

In order to generate the event paradigm fMRI, the values at Table 4-2 were used. From Table 4-2, it can be observed that experiment duration is 300 seconds. Volumes are sampled at a rate of 3 seconds/volume. So there are 100 whole brain volumes at the end of experiment. Activity starts at 30^{th} seconds and ends in 270^{th} seconds. The HRF signal increase is 2 % and the activation will take place in amygdala.

Table 4-2 Event Related FMRI Simulation Parameters

Duration (seconds)	300
Sampling Rate (TR) (milliseconds)	3000
TASK	Activity: [30,60,90,120,150,180, 210, 240, 270] HRF Percent: 2
ROI	Amygdala

After generating the fMRI data, it was loaded into AFNI to see the time course of the voxels. Figure 4-3 is the screenshot of 9 neighbor active voxels’ time series. As it can be seen from the figure, there are 9 events which correspond to the task identified in Table 4-2.

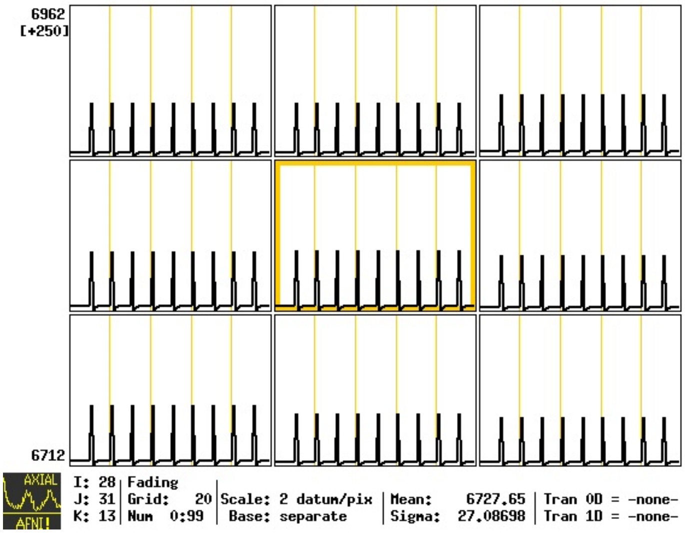


Figure 4-3 Event Paradigm time course

Generated fMRI data was then analyzed by AFNI 3dfim utility. The result of the analysis and ROI selected from the simulator can be seen in Figure 4-4. The blue colored areas are the active voxels according to fMRI analysis and the yellow colored areas are the active ROI areas depicted by the user during the simulation run.

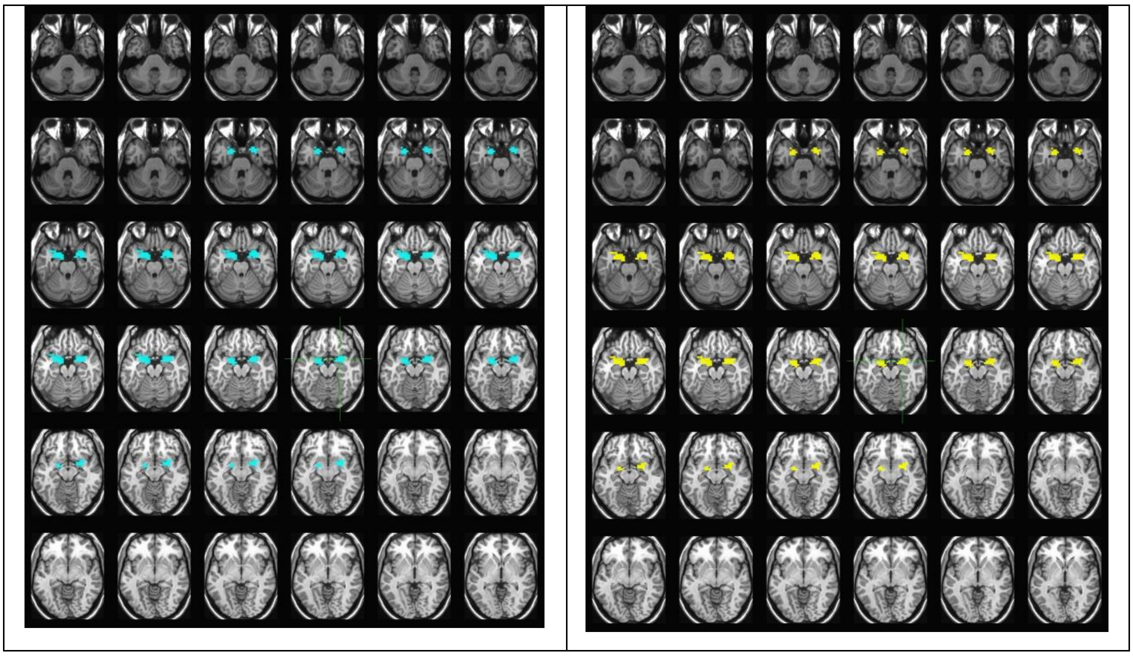


Figure 4-4 Event related FMRI analysis result (left) and ROI defined in the simulator.

From Figure 4-4, it can be easily observed that the ROI and FMRI analysis result are having higher intersection. Also "Jaccard Index" is used to compare the results. The Jaccard Index calculated between ROI in the simulator and voxels detected by AFNI is 1 which means that voxels detected by AFNI is fitting over the voxels defined in the simulator with 100 percent correctness.

4.2 Verification of Motion Artifact

In order to verify the motion introduced by the simulator, AFNI 3dvolreg [27] utility was used for both rotation and translation effects. If we can detect the motion by AFNI similarly, then the simulator has done its job in terms of motion generation.

4.2.1 Rotation

In order to verify the rotation effect, rotations described in Table 4-3 was generated with the simulator. In order to test the axial, coronal and sagittal rotations, simulator was re-run 3 times. In each run, rotations listed in Table 4-3 took place on only one of the planes (axial, coronal or sagittal).

Table 4-3 Rotation data generated with Simulator

Time of rotation (seconds)	Rotation (degree)
10	1
20	-1
30	3
40	-3
50	5
60	-5
70	10
80	-10
90	20
100	-20

Then 3dvolreg utility was used to identify the rotations in each plane. The rotations that were performed via simulation and the corresponding 3dvolreg calculated results can be seen in Table 4-4. From the table, it can be seen that rotation performed by the simulator and AFNI 3dvolreg utility calculated values are close to each other. Therefore we can conclude that the motion artifacts generated by the simulator are acceptable.

Table 4-4 Rotation Artifact Results

Time of rotation (seconds)	Axial/ Sagittal/ Coronal Rotation via Simulator (degree)	Axial Rotation calculated by AFNI 3dvolreg (degree)	Sagittal Rotation calculated by AFNI 3dvolreg (degree)	Coronal Rotation calculated by AFNI 3dvolreg (degree)
10	1	0.7401	0.7580	0.7453
20	-1	-0.7401	-0.7580	-0.7453
30	3	2.9152	3.0013	3.0038
40	-3	-2.9152	-3.0013	-3.0038
50	5	4.9822	4.9645	4.9569
60	-5	-4.9822	-4.9645	-4.9569
70	10	10.0036	9.9986	9.9849
80	-10	-10.0036	-9.9986	-9.9849
90	20	20.0232	19.9972	19.9955
100	-20	-20.0232	-19.9972	-19.9955

4.2.2 Translation

In order to verify the translation effect, translations described in Table 4-5 was generated with the simulator. In order to test the axial, coronal and sagittal translations, simulator was re-run 3 times. In each run, translation listed in Table 4-5 took place on only one of the planes (axial, coronal or sagittal).

Table 4-5 Translation data generated with Simulator

Time of translation (seconds)	Translation (mm)
10	4
20	-4
30	-8
40	8
50	12
60	-12
70	-16
80	16
90	20
100	-20

Then 3dvolreg utility was used to identify the translations in each plane. The translations that were performed via simulation and the corresponding results estimated by 3dvolreg can be seen in Table 4-6. From the table, it can be seen that translation performed by the simulator and AFNI 3dvolreg utility calculated values are so close to each other.

Table 4-6 Translation Artifact Results

Time of translation (seconds)	Axial/ Sagittal/ Coronal Translation via Simulator (mm)	Axial Translation calculated by AFNI 3dvolreg (mm)	Sagittal Translation calculated by AFNI 3dvolreg (mm)	Coronal Translation calculated by AFNI 3dvolreg (mm)
10	4	4.0249	4.0264	4.0210
20	-4	-4.0249	-4.0264	-4.0210
30	-8	-8.0488	-8.0511	-8.0399
40	8	8.0488	8.0511	8.0399
50	12	12.0673	12.0682	12.0598
60	-12	-12.0673	-12.0682	-12.0598
70	-16	-16.0425	-16.0913	-16.0729
80	16	16.0425	16.0913	16.0729
90	20	20.1095	20.0978	20.0747
100	-20	-20.1095	-20.0978	-20.0747

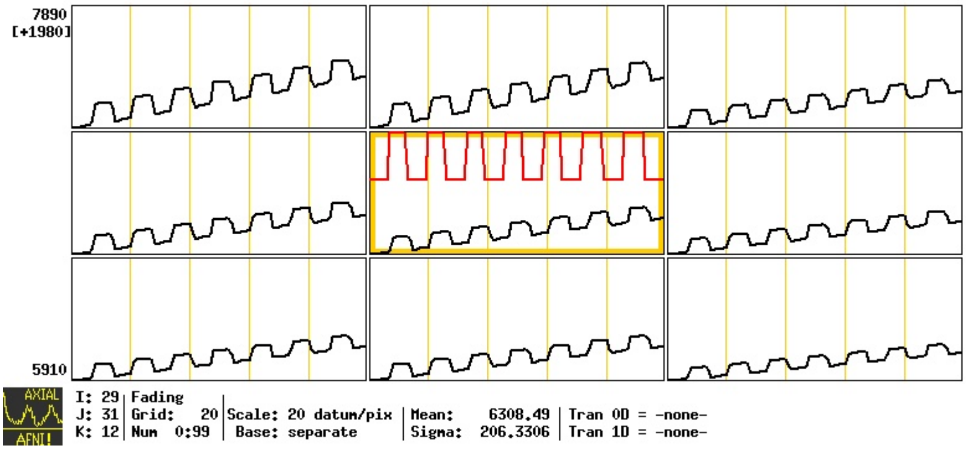
4.3 Verification of Drift Artifact

In order to generate the drift artifacts, the values at Table 4-7 were used. This verification is done only by visual inspection, not quantitatively.

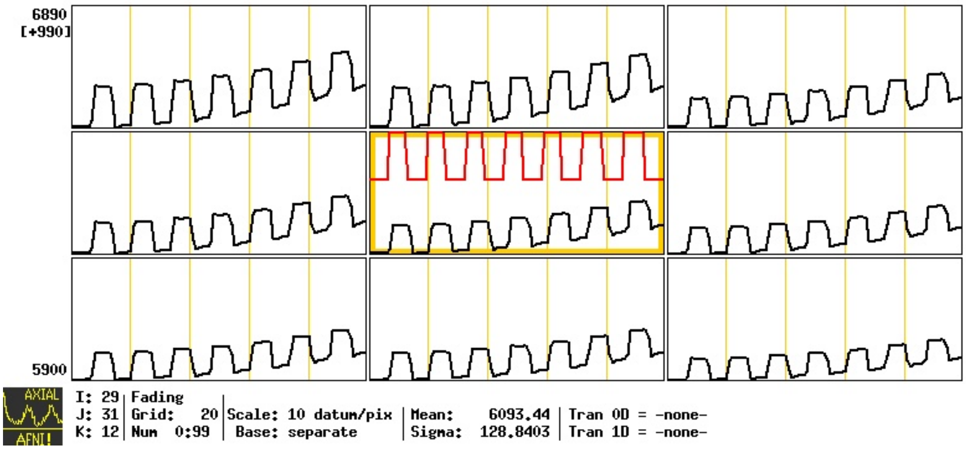
Table 4-7 Drift Artifact Parameters

Duration	300
Sampling Rate (TR)	3000
TASK	Activity: [20-40,60-80,100-120,140-160,180-200,220-240,260-280], HRF Percent: 4
ROI	Amygdala

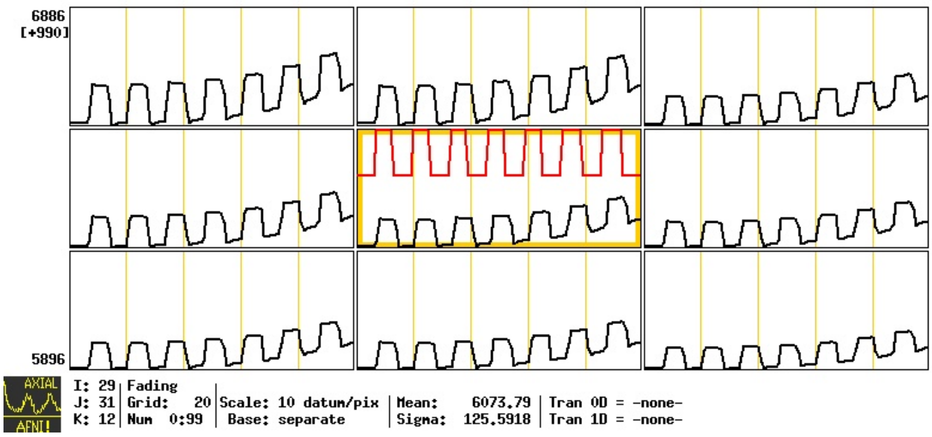
3 types of drift artifacts were added to the fMRI data: 1st order, 2nd order and 3rd order. After generating the data, it was loaded in AFNI to see the time course of the voxels. Figure 4-5a, Figure 4-5b and Figure 4-5c are the screenshots of 9 neighbor active voxels' time series for 1st order, 2nd order and 3rd order drift artifacts respectively. From the figures it can be seen that the baseline of signals contain the desired drift function shapes. The ideal task waveform is drawn in red color to indicate the signal without a drift.



(a)



(b)



(c)

Figure 4-5 1st, 2nd and 3rd order drift artifacts (a, b, c respectively)

4.4 Verification of Habituation

In order to generate the drift artifacts, the values at Table 4-8 were used. This verification is done only by visual inspection, not quantitatively.

Table 4-8 Habituation Artifact Parameters

Duration	300
Sampling Rate (TR)	3000
TASK	Activity: [20-40,60-80,100-120,140-160,180-200,220-240,260-280], HRF Percent: 4, Habituation Ratio:0.3
ROI	Amygdala

After generating the FMRI data, it was loaded into AFNI to see the time course of the voxels. Figure 4-6 and Figure 4-7 are the screenshot of 9 neighbor active voxels' time series for habituation artifacts with no lag and 10 seconds lag. In Figure 4-6 it can be seen that HRF response is decreasing. This is the required effect. In Figure 4-7, HRF response is decreasing as it is in Figure 4-6 except with a signal shift in the time. The ideal task waveform is drawn in red color to indicate the signal without habituation and lag.

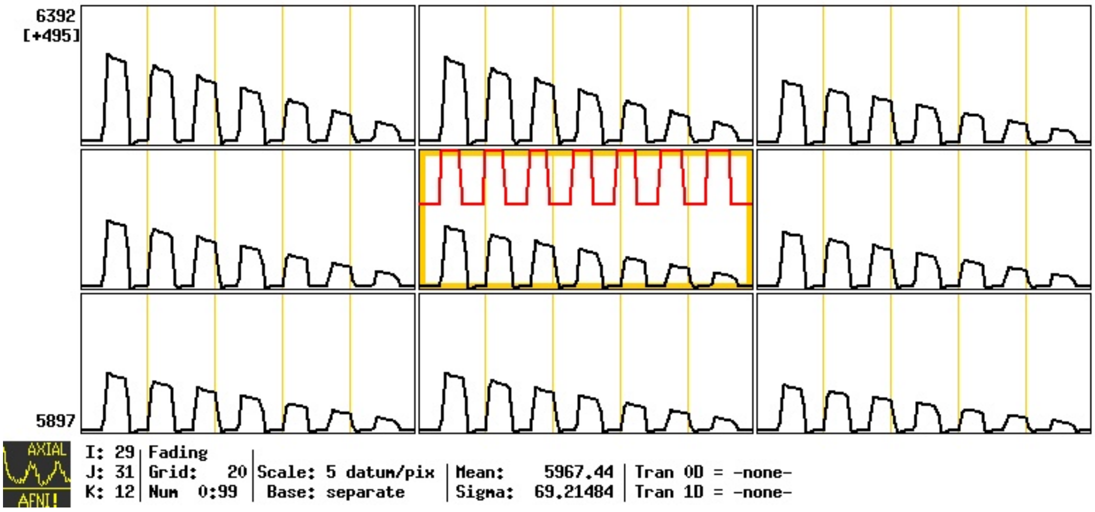


Figure 4-6 Habituation artifact – no lag

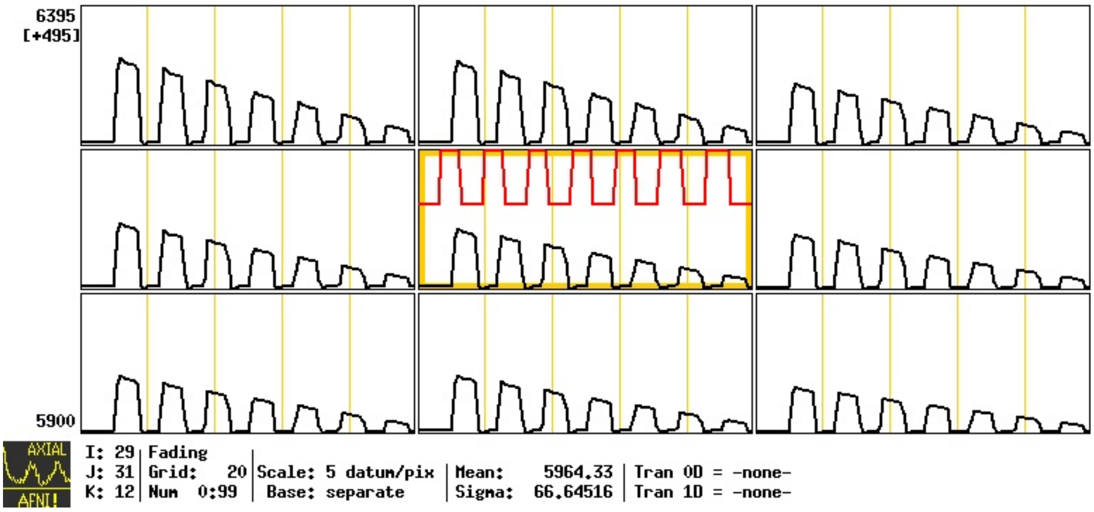


Figure 4-7 Habituation artifact – 10 seconds lag

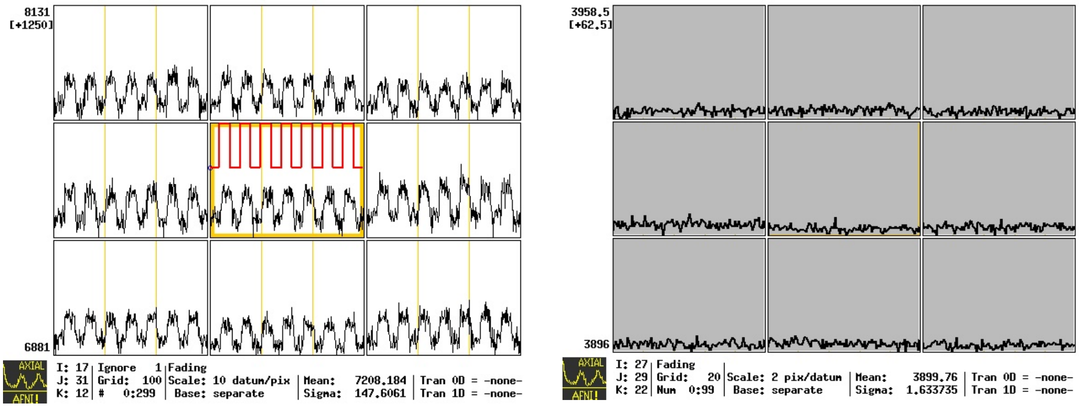
4.5 Verification of Noise

In order to generate the Gaussian noise artifact, the values at Table 4-9 were used. This verification is done only by visual inspection, not quantitatively.

Table 4-9 Motion Artifact Parameters

Duration	300
Sampling Rate (TR)	1000
TASK	Activity: [20-40,60-80,100-120,140-160,180-200,220-240,260-280], HRF Percent: 4
ROI	Amygdala
SNR	10

After generating the fMRI data, it was loaded into AFNI to see the time course of the voxels. Figure 4-8a is the screenshot of 9 neighbor active voxels' time series and Figure 4-8b is the screenshot of passive ones. From the figures noise added signal can easily be observed in comparison to the ideal task waveform given in red in Figure 4-8a. From the figure, noise can be easily observed when ideal and noisy signal are compared.



(a) (b)

Figure 4-8 Noise added signal ((a) active voxels, (b) passive voxels)

4.6 ICA Analysis on Task Related FMRI Data

Under this section, fMRI data generated by our simulator was analyzed by using Independent Component Analysis approach. This way, we can verify the added noise artifacts as independent time series. For this, FSL Melodic [22] utility was used. Independent components and their time courses are shown on each sub section.

4.6.1 ICA Analysis on Rigid Body Motion Artifact Signal

ICA Analysis was done on a block designed fMRI data (8 OFF- 7 ON blocks, each 20 seconds) where only one 2 degree axial rigid body rotation exist at about 20th seconds. ICA analysis was resulted to have 8 components. Among these components, 7 components are describing the motion [33] on mostly inactive areas (especially on the boundary of brain) and 1 component is describing the motion [33] on active area. From Figure 4-9 it can be seen that, the spatial distribution of component 1 is mostly at the boundary of the brain. By looking at Figure 4-10a-g, an abrupt change on the normalized responses exist at about 20th seconds which describes the motion effect.

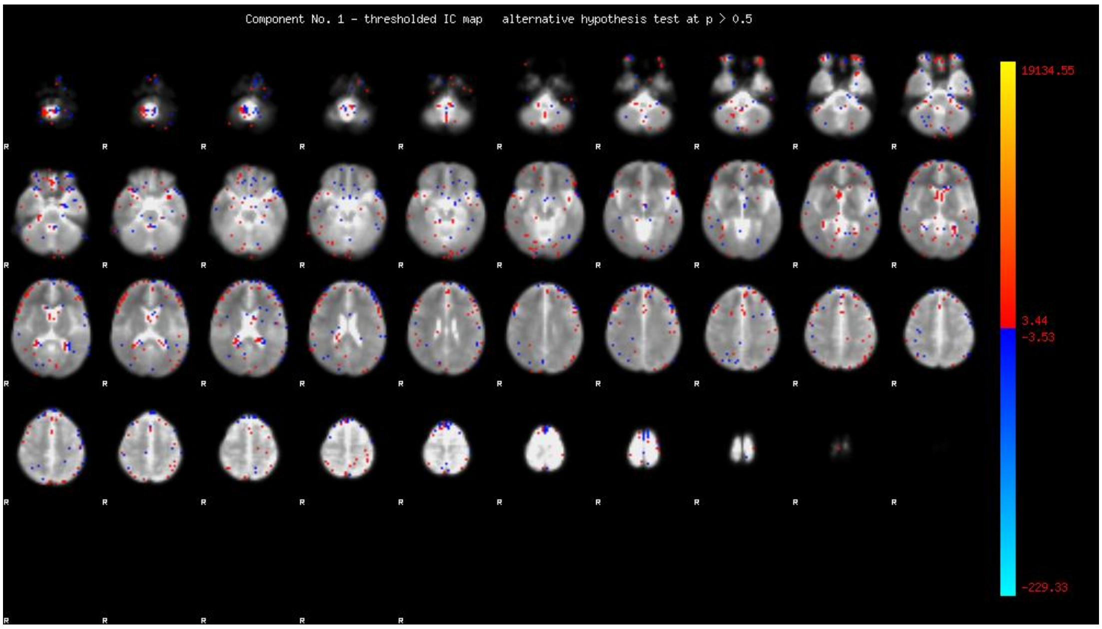
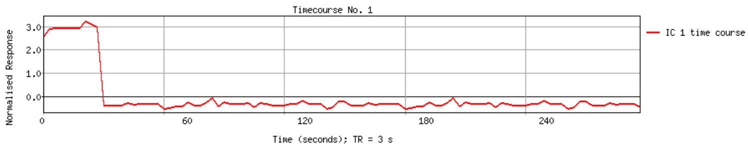
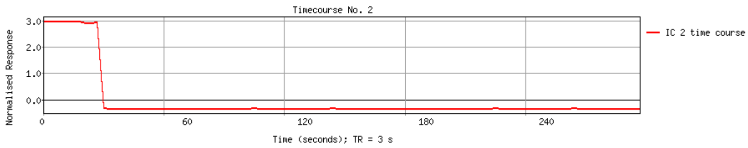


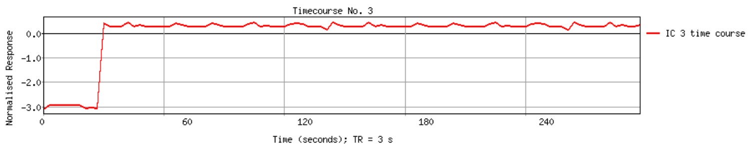
Figure 4-9 IC map of Component 1



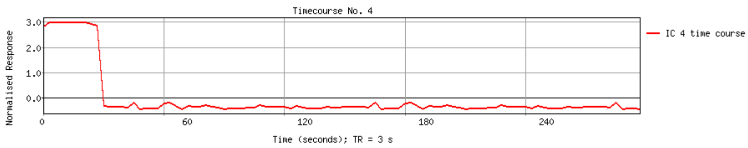
(a)



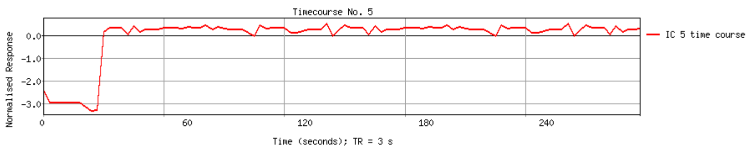
(b)



(c)



(d)



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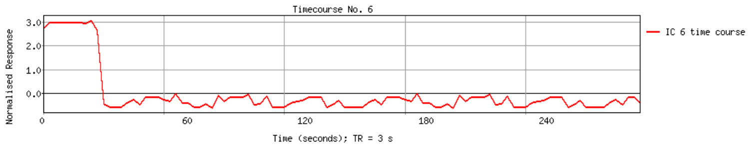
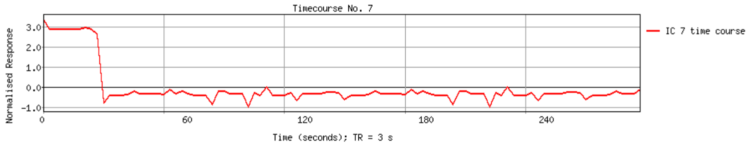


(f)



(g)

Figure 4-10 Time courses of Components 1-7 (a-g in order)

IC (independent component) map Component 8 is shown in Figure 4-11. By looking at the figure, active brain areas (amygdala) can easily be observed. Also the time course of component 8 shown in Figure 4-12 clearly represents the task design (8 OFF and 7 ON blocks). Unfortunately, ICA analysis was unable to get rid of the abrupt head motion at the 20th second of the experiment. This is unexpected, but it is the responsibility of the fMRI analysis toolkit to perform that action. This concludes our verification of the motion artifact of the simulator with ICA.

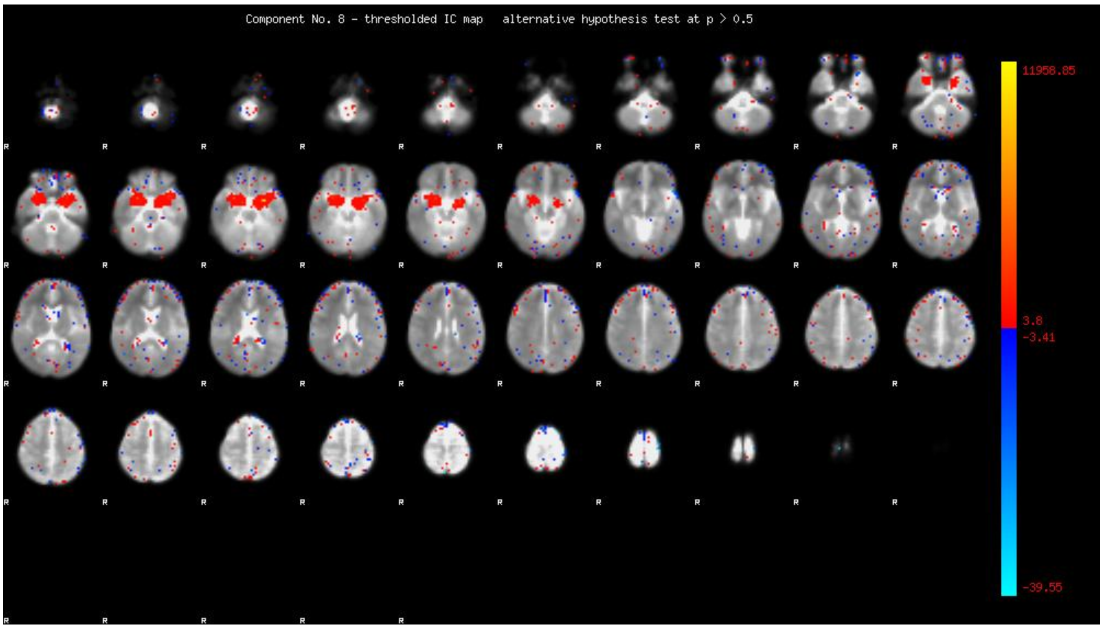


Figure 4-11 IC Map of Component 8

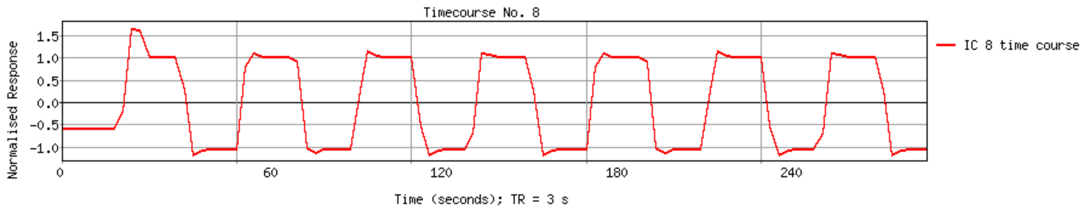


Figure 4-12 Time course of Component 8

4.6.2 ICA Analysis on Drift and Noise Artifact Added fMRI Data

Again, ICA Analysis was done on a block designed FMRI (8 OFF- 7 ON blocks, each 20 seconds) data which scanner drift and noise artifacts added. ICA analysis was done with FSL MELODIC utility which resulted with 21 independent components. The drift effect can be observed in Figure 4-13 and Figure 4-14. In Figure 4-14, the drift in signal can be observed easily describing the scanner drift artifact [33].

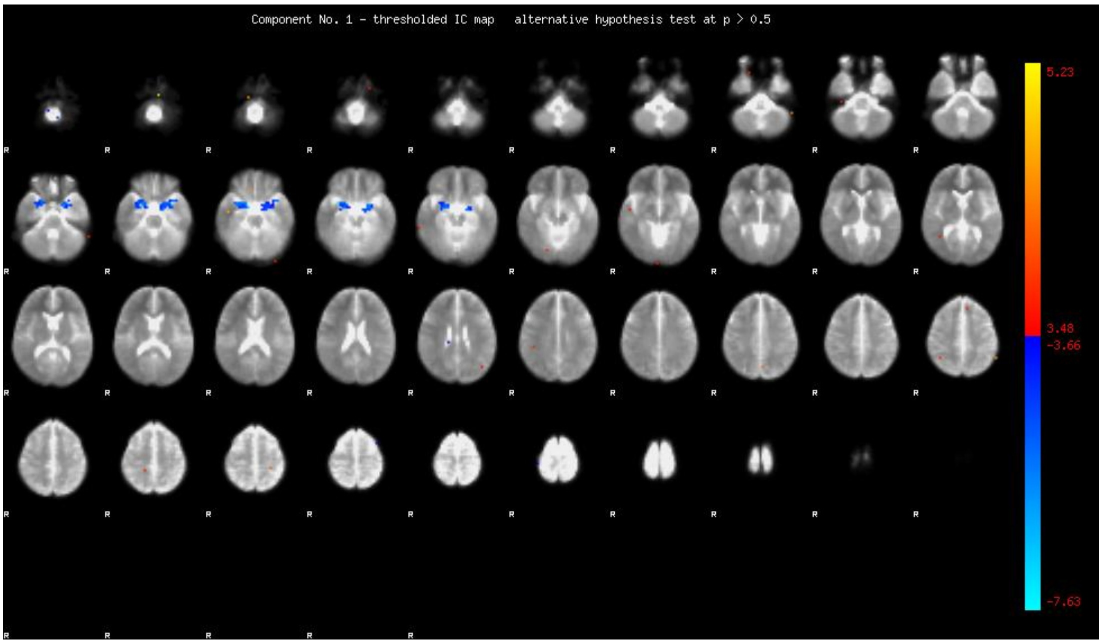


Figure 4-13 IC Map of Component 1

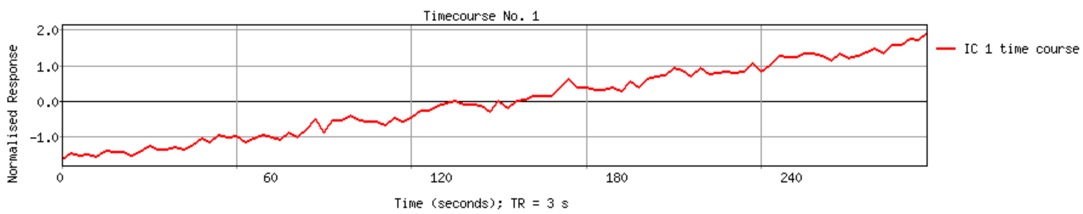


Figure 4-14 Time course of Component 1

The second component is describing the activity itself which can be seen in Figure 4-15 and Figure 4-16. In Figure 4-15, the spatial map of active area (amygdala) can be observed. In Figure 4-16, the time course of component 2 is seen. From the figure the block design can easily be observed. The result is as expected since we can see 8 OFF and 7 ON blocks in the figure.

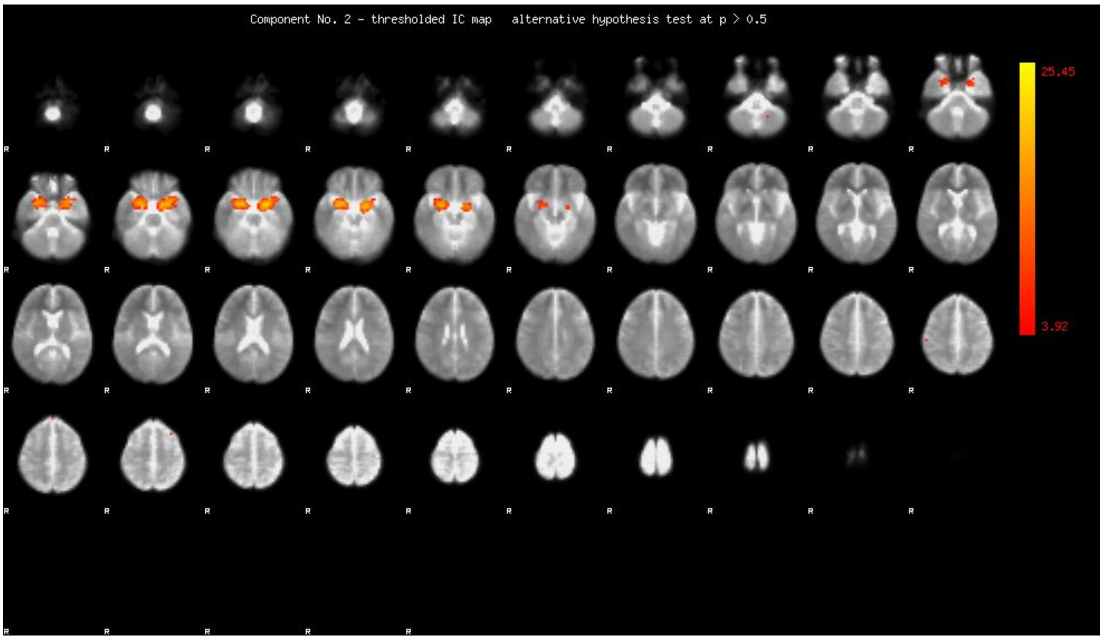


Figure 4-15 IC Map of Component 2

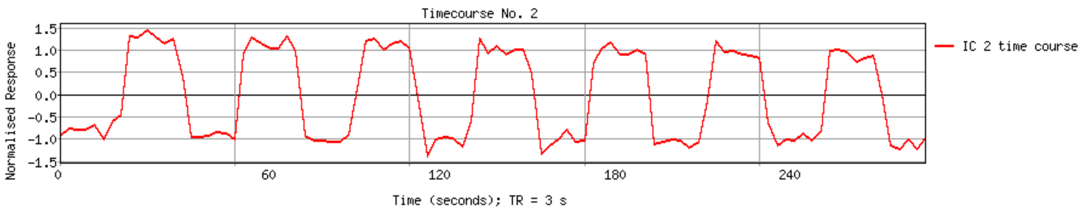
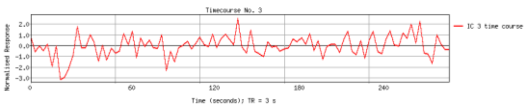
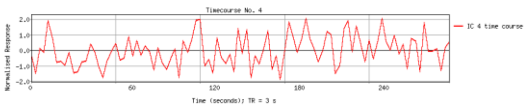


Figure 4-16 Time course of Component 2

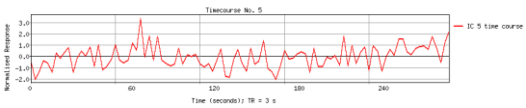
Components 3-21 describe the Gaussian noise components [33] of ICA analysis which can be seen in Figure 4-17.



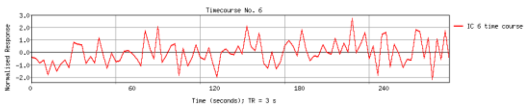
(a)



(b)



(c)



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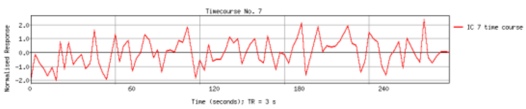

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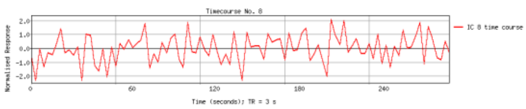

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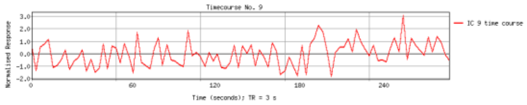
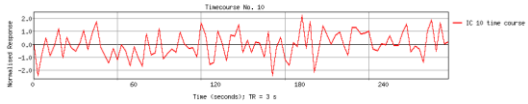


(g)



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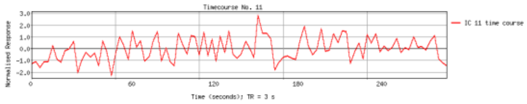
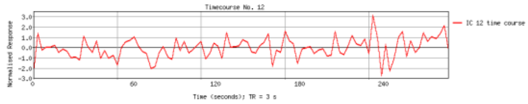


(i)



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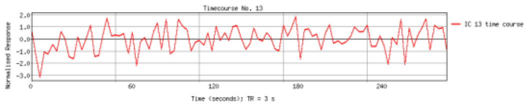

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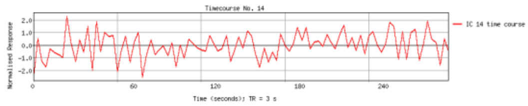
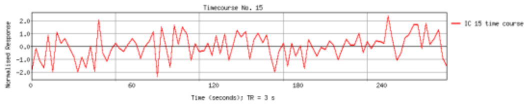
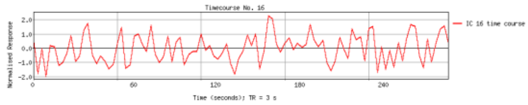


(a)



(a)



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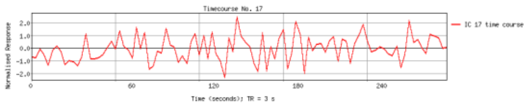
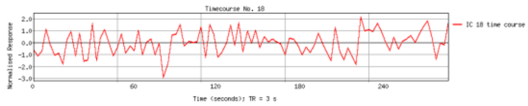


(m)



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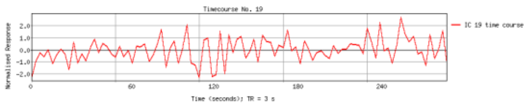
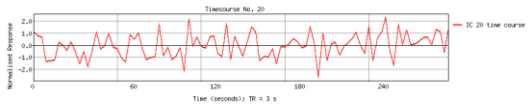
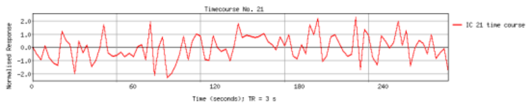


(o)



(p)



(q)

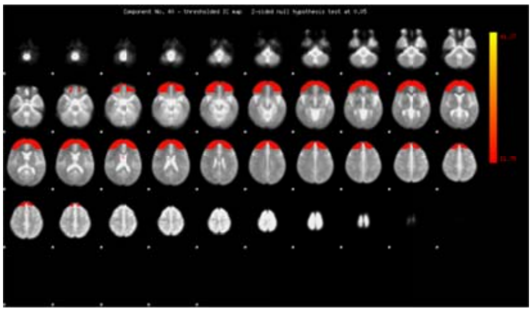
Figure 4-17 Time courses of Components 3-21 (a-q in order)

This concludes our ICA verification of active task fMRI data generation.

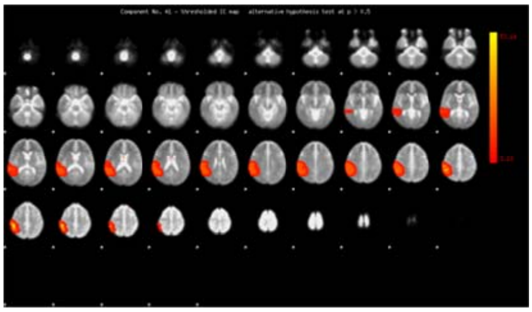
4.7 ICA Analysis on DMN Related fMRI Data

DMN Related fMRI data was generated with the simulator and FSL Melodic was used to analyze the generated fMRI. For the DMN generation, 0.90 is used as the correlation values for DMN data generation from template.

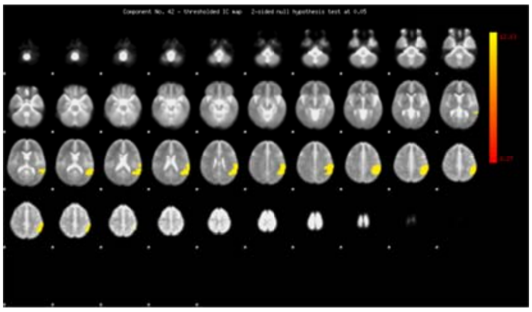
The analysis resulted with 44 independent components. Among them, the significant ones which are components 40, 41, 42, 43 and 44 were shown with respect to their anatomical localization in Figure 4-18a, Figure 4-18b, Figure 4-18c, Figure 4-18d and Figure 4-18e respectively. From the figures, it can be seen than each of the 6 ROIs used for DMN generation are picked up by ICA. This verifies the DMN data generation fairly well.



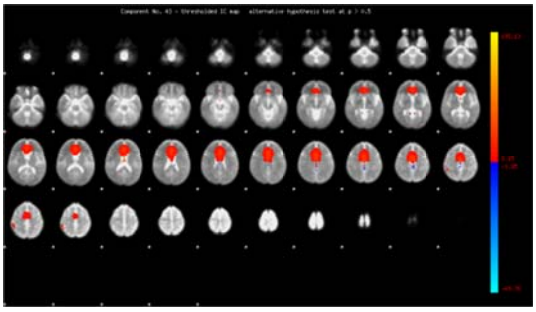
(a) dmPFC



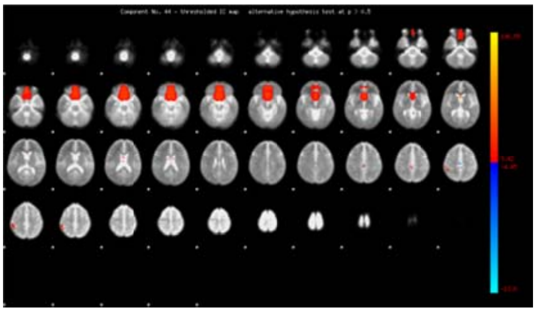
(b) right IPL



(c) left IPL



(d) ACC+PCC



(e) vmPFC

Figure 4-18 Components 40-44

After independent components are analyzed, their correlations with each other are calculated as seen in Table 4-10. From the table it can be seen that the correlations are in between 0.13-0.65. Most of the values in Table 4-10 are greater than 0.40 which means that these areas are the describing Default Mode Network. We cannot explain the low correlation value between rIPL and vmPFC which is 0.13. This will be investigated later in a more detailed quantitative study.

Table 4-10 Correlation of DMN components 40-44

Brain Area	Posterior Cingulate Cortex (ACC+PCC)	Right Inferior Parietal Lobule(rIPL)	Left Inferior Parietal Lobule(lIPL)	Dorsomedial Prefrontal Cortex (dmPFC)	Ventromedial Prefrontal Cortex (vmPFC)
Posterior Cingulate Cortex (ACC+PCC)	1.00	0.48	0.63	0.62	0.55
Right Inferior Parietal Lobule(rIPL)	0.48	1.00	0.48	0.48	0.13
Left Inferior Parietal Lobule(lIPL)	0.63	0.48	1.00	0.65	0.48
Dorsomedial Prefrontal Cortex (dmPFC)	0.62	0.48	0.65	1.00	0.53
Ventromedial Prefrontal Cortex (vmPFC)	0.55	0.13	0.48	0.53	1.00

CHAPTER 5

DISCUSSION AND CONCLUSION

The motivation behind this thesis is the generation of 4D fMRI data which can be used as a ground truth for comparing/benchmarking different fMRI analysis methods. By using this ground truth, development of new fMRI analysis methods may take place. Such a simulator can also be used for educational purposes. In order to fulfill these aims, an fMRI simulator has been designed and implemented. The simulator is capable of generating active task data in block, event-related and mixed designs, as well as resting state data of the default mode network. Habituation, scanner drift, noise and motion are the artifacts that can be added to the fMRI signal so that a realistic signal similar to those produced by an MR scanner can be generated.

There are various fMRI simulators at the present: Chris Rorden's fMRI Design Software [11], SimTB [13], POSSUM [12] and METU- fMRISim [14]. Chris Rorden's fMRI Design Software [11] is a tool for only designing an fMRI study, but it does not provide 4D fMRI output and artifacts cannot be defined with this simulator. SimTB [13] is an fMRI simulator which has the capability of creation and manipulation of spatial sources, block and event-related design experiments, inclusion of tissue-specific baselines and simulated head movement. It has a GUI to design and execute simulations. Unfortunately, SimTb calculates the time course of single axial slice. Besides, no artifact other than motion can be generated with SimTB. POSSUM (Physics-Oriented Simulated Scanner for Understanding MRI) is a tool for generating simulated MRI and fMRI images. POSSUM is developed under FSL (FMRIB's Software Library) [12]. POSSUM collects several MR parameters (relaxation times T1, T2*, spin density ρ, and chemical shift value δ), pulse sequence (RF angle, RF frequency bandwidth, RF center frequency), slice profile as well as a pre-generated 4D activation file from the user in order to simulate the fMR time series using a mathematical model (i.e. Bloch equations) rather than utilizing an algorithm. This is somewhat inconvenient because it requires deep knowledge on MR physics and it takes more than 40 hours to complete. With respect to artifacts, POSSUM is limited to use motion and noise artifacts. Finally, METU-fMRISim is an fMRI simulator capable of simulating block and event-related 4D fMRI data with several artifacts: motion, scanner drift, habituation and cardiac pulsation. However, it does not use a

T2 weighted image as a baseline. It generates the fMRI data for a flat image which is registered to the T1 weighted anatomic image.

With the strengths and weaknesses of the existing fMRI simulators in mind, we implemented an fMRI simulator in MATLAB which is easy to use with the GUI, capable of generating most artifacts in the scanner environment for both task based and resting state conditions, and able to complete within minutes. This simulator uses a T2-weighted image as baseline in the fMRI time series and the ICBM atlas as the high resolution anatomic image, so that the activity profiles can be complemented with pre-defined ROIs in the ICBM atlas. In our approach, we are using the T2 image modality as underlying baseline value for the fMRI time series so that hemodynamic response is added to the T2 intensities to create the fMRI signal. ROI selection by using previously defined brain structures from the T1 weighted atlas is another strength of this study. This mechanism is added to the simulator since it is inconvenient to identify brain areas as ROIs manually traced by the users. This way, multiple brain activity spots can be generated to facilitate functional connectivity analyses.

We can briefly state the overall functionality of the fMRI simulator as follows. For the task related fMRI data generation; the duration of experiment and TR value (time between consecutive 4D whole brain volumes) are designed to be changed by the user. For DMN data generation, the duration is designed to have fixed value which is coming from resting templates whereas TR value is user defined. For the task related fMRI data generation; 4 types of ROI selection was implemented to define the active voxels: ROI selection by drawing free form canvas, ROI selection by selecting point, ROI selection from atlas and whole brain as ROI. Two types of activation patterns were designed: Event and block related activity patterns. Definition of the activation pattern within the simulator is implemented by entering active time points for events and active intervals for blocks to have ease of use. Mixed design is the combination of event and block activation design types. BOLD response shape and the amplitude of BOLD response are parametric within the simulator. For the DMN related fMRI data generation, 6 fixed brain areas are designed to have activity only (Anterior Cingulate Cortex, Posterior Cingulate Cortex, Right Inferior Parietal Lobule, Left Inferior Parietal Lobule, Dorsomedial Prefrontal Cortex, Ventromedial Prefrontal Cortex. These brain areas are selected because of higher correlations reported in the literature. For these brain areas 15 previously collected fMRI datasets from the real fMRI scans are exploited. New signal correlations with the template signal and new amplitudes can be explored by adjusting the GUI parameters.

In terms of artifacts, rigid body rotation and translation were implemented to simulate sudden motion changes or slow changes within a time interval. The scanner drift artifact, Gaussian white noise, cognitive habituation and lag are other artifacts that can be utilized. All these artifacts are generated by manipulating several parameters, such as polynomial order and SNR.

The quality of the data generated by our toolbox is tested thoroughly using AFNI and FSL utilities. 4D fMRI data which is defined by a task waveform is viewed by AFNI and the activity within ROI is observed. AFNI 3dfim utility output is then compared with the ROI specified during simulation through Jaccard index. The generated activity and the estimated activity in AFNI had maximum overlap with respect to Jaccard index for types of active tasks (i.e. Block and Event –related). DMN results are verified with FSL Melodic utility to determine ICA components. The results showed that the ROIs constructed with simulation to contain DMN activity had been assigned meaningful signal-related ICA components.

The artifacts are also tested thoroughly by AFNI and ICA. Simulated fMRI motion artifact was analyzed by AFNI 3dvolreg utility. When the motion is inserted by simulation and the ones that are estimated by AFNI 3dvolgreg utility were compared, the difference was negligible. Similarly, ICA was able to pick up an abrupt motion as a separate component, verifying that a detectable motion is being generated by our simulator. When a simulated fMRI dataset is fed into ICA, drift and Gaussian noise artifacts are identified as separate components and the main task time series is separated out, proving that these artifacts are detectable by mainstream fMRI data processing utilities.

In the future, our simulator can be enhanced to add some other MRI and fMRI artifacts such as cardiac pulsation. Also T1, T2 and atlas images can be customized to make the simulator work with user defined images. Instead of using Cholesky Decompositon to generate correlated signal with respect to template, the simulated and correlated DMN signal could be generated by using the power spectrum of the average DMN.

In this thesis it was our aim to produce a fast and easy to use fMRI simulator to facilitate benchmarking fMRI analysis tools by generating realistic fMRI data to serve as ground truth. Our simulator will be available for public use through our website in the short-term future.

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APPENDICES

APPENDIX A: USER MANUAL

A.1 Simulator Startup

In order to startup the FMRI simulator, “METU_FMRISimulator_2_0” command should be entered in the MATLAB command window. After entering the command, Figure A-1 is displayed.

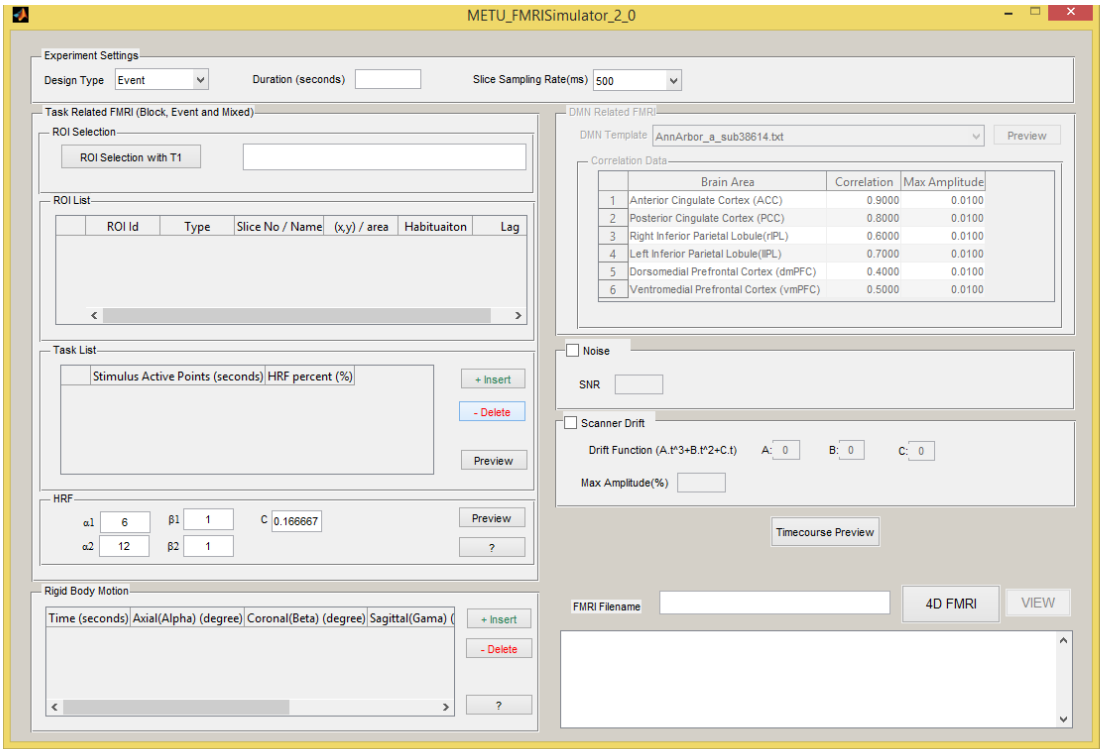


Figure A-1 FMRI Simulator Main Window screenshot

After that, design type (Event, Block, Mixed and DMN) should be selected. If the design type is task related (i.e. not DMN) then duration and slice sampling rate (500, 1000, 1500, 2000, 2500 and 3000 ms) should be entered in the window. If design type is DMN, then duration is entered automatically by the simulator but slice sampling rate should be entered manually.

A.2 Task Related FMRI Window Section

In order to design task related FMRI study, then the fields shown in Figure A-2 should be provided. Below is the order of operation:

1. **ROI Selection:** In order to define the ROI which identifies active voxels, "ROI Selection with T1" button should be pressed. In that case, ROI Selection window will be opened which is described in section A.2.1. After ROI selection has been made, ROI file name will be shown in the text field next to "ROI Selection with T1" button.
2. **Task (activity) Definition:** In order to enter the stimulus active points "+ Insert" button should be pressed. This adds a new row to the Task List table. For the event related FMRI design, stimulus values should be entered in the form of "e_1,e_2,e_3…e_n" where e_x is the time that event has occurred. For the block FMRI design, the values should be entered in the form of "s_1-e_1, s_1-e_2, s_3-e_3… s_n-e_n" where s_x-e_x is the time interval that defines the active period for the block. For the mixed design, stimulus can be either in the form of event or block. After activity definition, HRF percent should be entered too. Tasks stimulus points can be viewed by pressing "Preview" button. Figure A-3 is an example task stimulus activity.

3. **HRF formula definition:** HRF formula definition could be changed by the user. When the user changes the values, HRF time course can be previewed by pressing the "Preview" button. Figure A-4 is an example plot of HRF Time Course. Besides, HRF formula can be viewed by pressing "?" which results the window shown in Figure A-5 to be displayed. The simulator will use the parameters defined in this section to generate 4D FMRI data.

4. **Task-ROI association:** In order to define which task will be associated with which ROI, user should select related ROIs from Task List or select related tasks from ROI List by using the checkboxes residing at the end columns. For example in Figure A-2, Task 1 is associated with ROI 1 (Amygdala) and ROI 2 (Anterior Nucleus) whereas Task 2 is associated with only ROI2 (Anterior Nucleus). This means that, the HRF time course of Task1 will be added to ROI 1 and ROI 2 but Task 2 will be added to ROI 2 only.

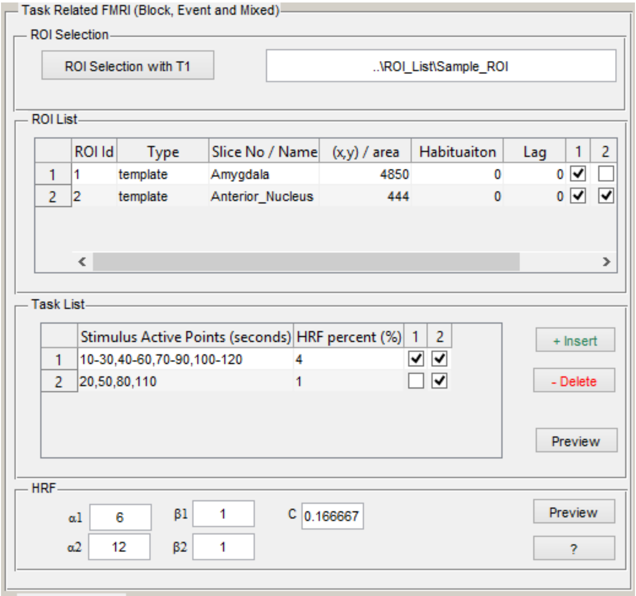


Figure A-2 Task Related FMRI Section

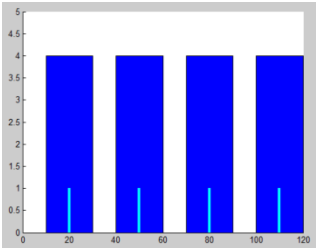


Figure A-3 Stimulus Active Points

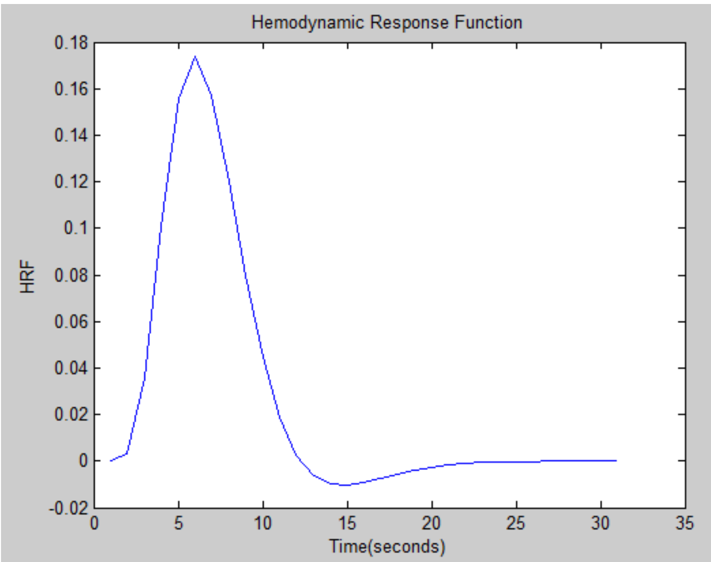


Figure A-4 HRF Time Course

$$HRF(t) = \frac{t^{\alpha_1 - 1}\beta_1^{\alpha_1} e^{-\beta_1 t}}{\Gamma\,(\alpha_1)} - c\,\frac{t^{\alpha_2 - 1}\beta_2^{\alpha_2} e^{-\beta_2 t}}{\Gamma\,(\alpha_2)}$$

Figure A-5 HRF Formula Help Window

A.2.1 ROI Selection Window

In order to open the ROI Selection window, “ROI Selection with T1” button should be pressed. ROI Selection window can be observed in Figure A-6. 3 types of ROI selection is available to the user: User defined (either point or polygon) ROIs, ROI selection from template and whole brain as ROI (The details are provided in subsequent sections). The user selects/draws related ROIs with these 3 selection types, fills the ROI Selection filename and presses “Save As” button to save ROIs.

A.2.1.1 User defined ROI selection

In order user to select a user defined (user drawn) ROI, “Slice” selection should be selected on ROI Selection section. Then ROI type and plane should be selected. After that, related slice should be selected by using the arrow keys or by selecting a point on the planes. Then ROI should be drawn on the selected slice of the selected plane. When ROI selection is made, the information of selected ROI will be shown in ROI list and ROI will be visible with a color attached.

A.2.1.2 ROI selection from template

In order user to select a ROI from template, “Template” selection should be selected on ROI Selection section. After that, related ROI should be selected from the list and “→” arrow button be pressed. When ROI selection is made, the information of selected ROI will be shown in ROI list and ROI will be visible with a color attached.

A.2.1.3 ROI selection as a whole brain

In order user to select whole brain as a ROI, “Whole Brain” selection should be selected on ROI Selection section. After that “Add “button should be pressed. When ROI selection is made, the information of selected ROI will be shown in ROI list and ROI will be visible with a color attached.

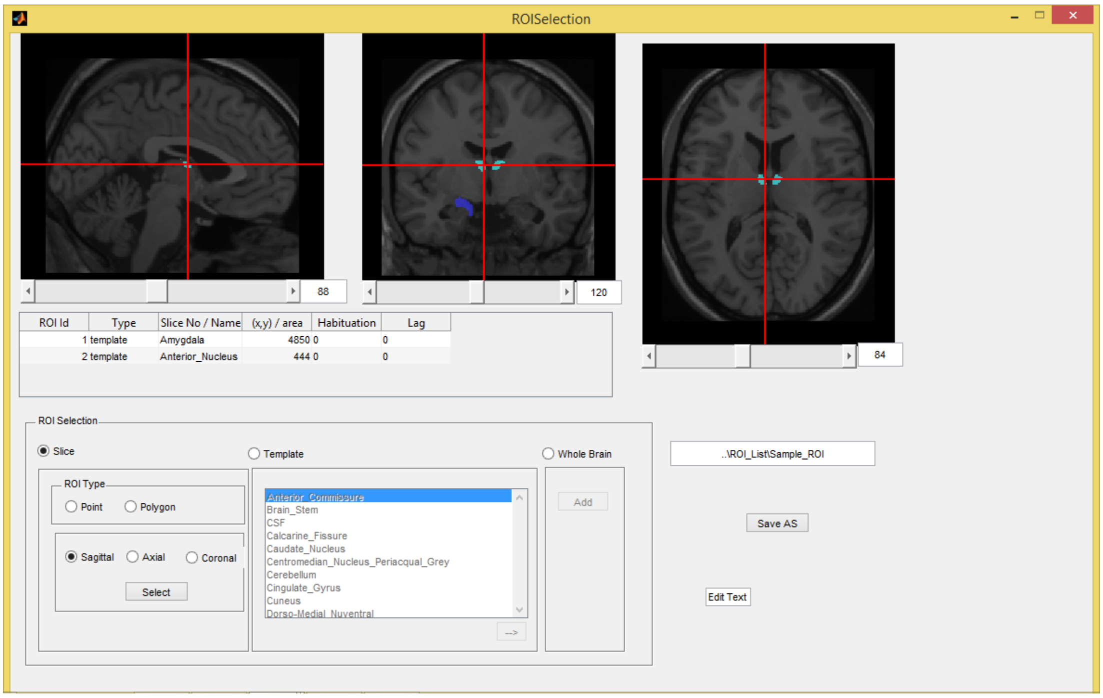
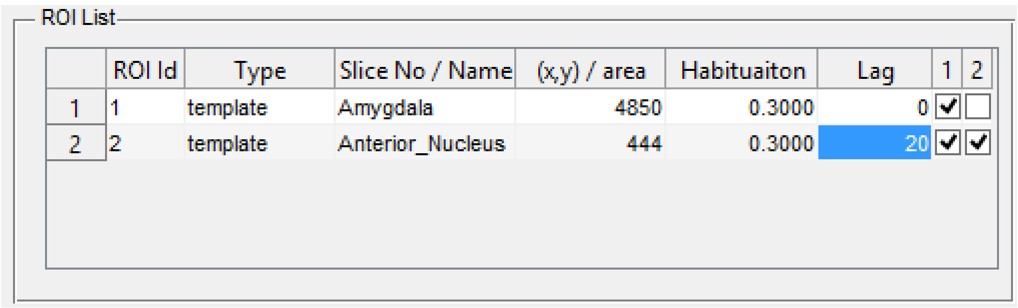


Figure A-6 ROI Selection window

A.2.2 Habituation Artifact

In order to add habituation artifact, “Habituation” and “Lag” fields shown inFigure A-7 should be provided. HRF time course of habituation artifact added signal can be seen in Figure A-8. Habituation is slope of decreased HRF signal in degrees and lag is the latency of HRF in seconds.



	ROI Id	Type	Slice No / Name	(x,y) / area	Habituaiton	Lag	1	2
1	1	template	Amygdala	4850	0.3000	0	✓	
2	2	template	Anterior_Nucleus	444	0.3000	20	✓	✓

Figure A-7 Habituation Artifact Definition

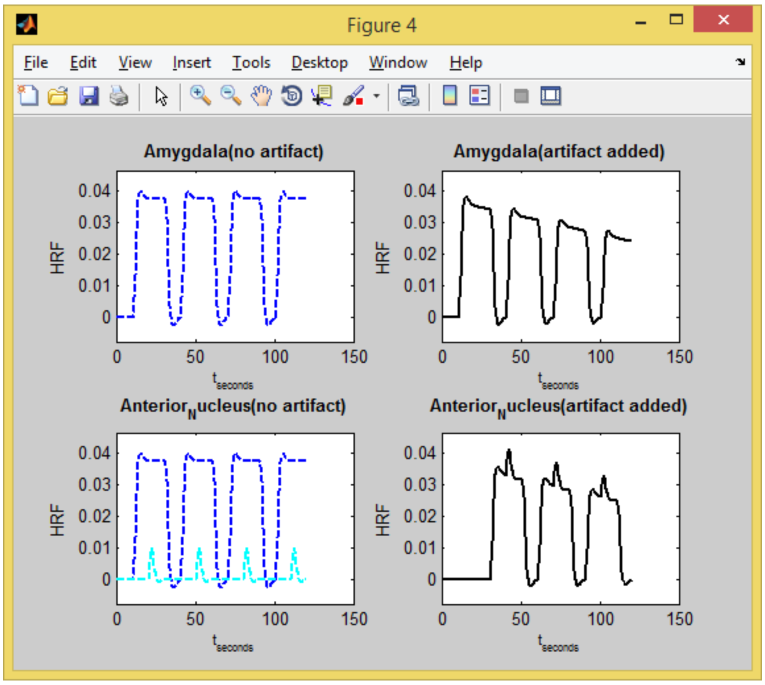


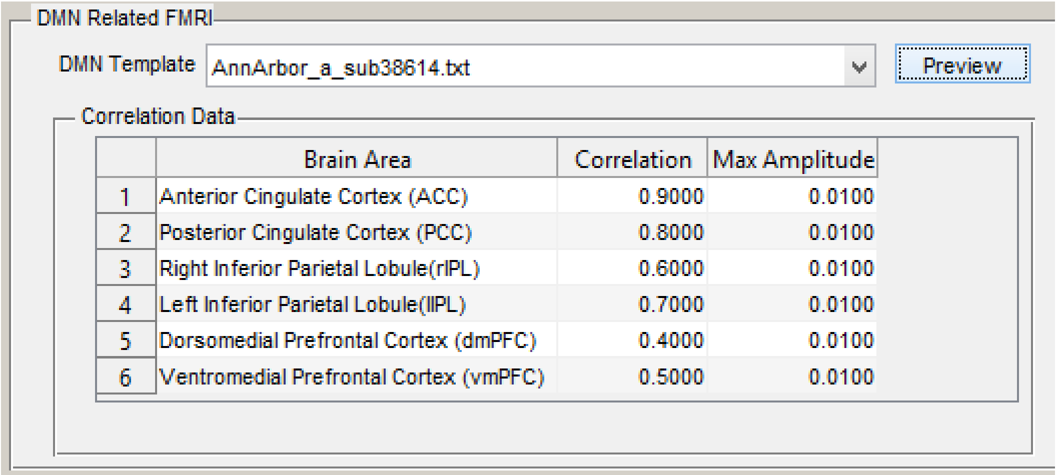
Figure A-8 HRF time course of habituation artifact added signal

A.3 DMN Related FMRI Window Section

In order to design DMN related FMRI study, then the fields shown in Figure A-9 should be provided. Below is the order of operation:

1. **DMN Template Selection:** DMN Template should be selected from “DMN Template” list. “Preview” button can be pressed to view DMN Template. An example DMN Template is shown in Figure A-10.

2. **Correlation Data Entry:** Correlation data for each 6 previously defines brain areas should be entered in the Correlation Data section. Correlation is the correlation of the resulting signals for that brain area with the signals identified in selected template. Max amplitude is the maximum amplitude of resulting signal.



	Brain Area	Correlation	Max Amplitude
1	Anterior Cingulate Cortex (ACC)	0.9000	0.0100
2	Posterior Cingulate Cortex (PCC)	0.8000	0.0100
3	Right Inferior Parietal Lobule(rIPL)	0.6000	0.0100
4	Left Inferior Parietal Lobule(lIPL)	0.7000	0.0100
5	Dorsomedial Prefrontal Cortex (dmPFC)	0.4000	0.0100
6	Ventromedial Prefrontal Cortex (vmPFC)	0.5000	0.0100

Figure A-9 DMN Related FMRI Section

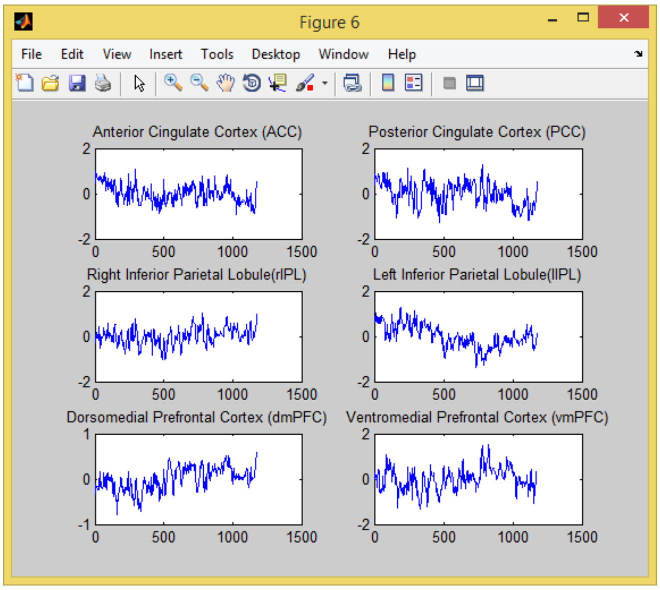


Figure A-10 Sample DMN Template Signal

A.4 Motion Artifact

In order to add motion artifact, then the fields shown in Figure A-11 should be provided. To add a motion (either rotation or translation) “+ Insert” button should be pressed. This adds a new row to the Motion List table. Then time of motion effect should be defined. Time can be in the form of “t” or “t1-t2” where t, t1 and t2 are the time in seconds. If the format is “t” then it means that there is sudden motion at t second. If the format is “t1-t2” then it means that there is a continuous motion from t1 to t2. For example in Figure A-11, there is negative 3 degree rotation at axial plane at 10th second and there are total of 10 degree rotation in the coronal plane between 20th and 29th seconds which means 1(10/(29-20+1)) degree coronal rotation per second from 20th to 29th seconds. Translations can be added in the same way as rotations.

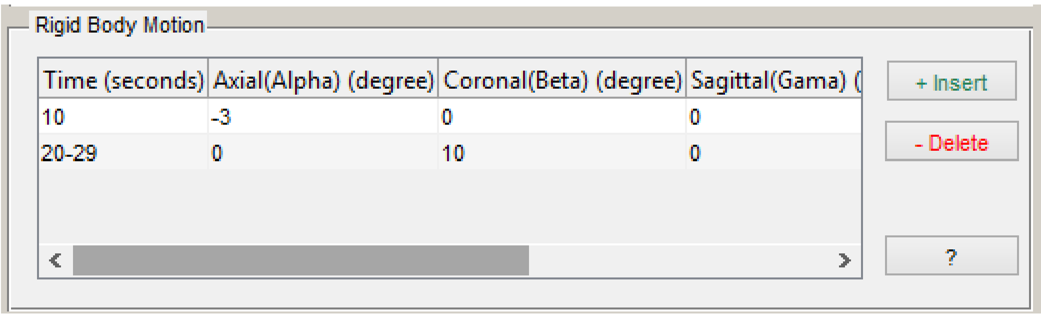


Figure A-11 Rigid Body Motion Artifact Definition Section

A.5 Gaussian White Noise

In order to add Gaussian white noise, then “Noise” checkbox should be selected and SNR value should be entered as shown in Figure A-12. HRF time course of noise added signal can be seen in Figure A-13.

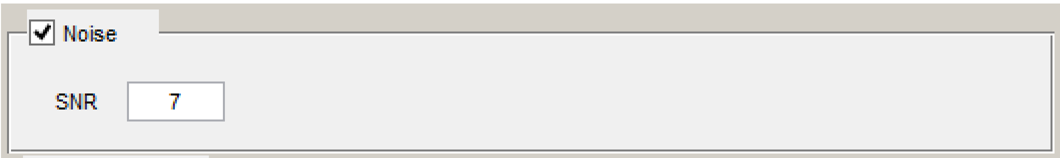


Figure A-12 Gaussian White Noise Definition Section

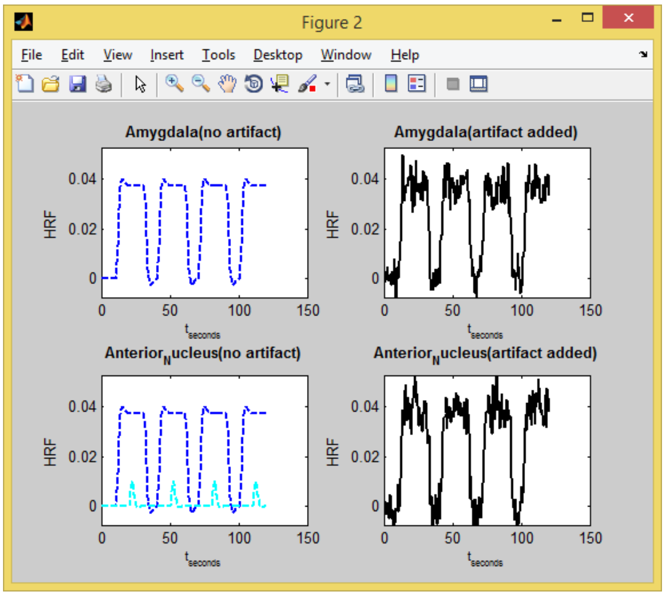


Figure A-13 HRF time course of noise added signal

A.6 Scanner Drift Artifact

In order to add scanner drift, then “Scanner Drift” checkbox should be selected and drift function coefficient and max amplitude of drift should be entered as shown in Figure A-14. HRF time course of drift added signal can be seen in Figure A-15.

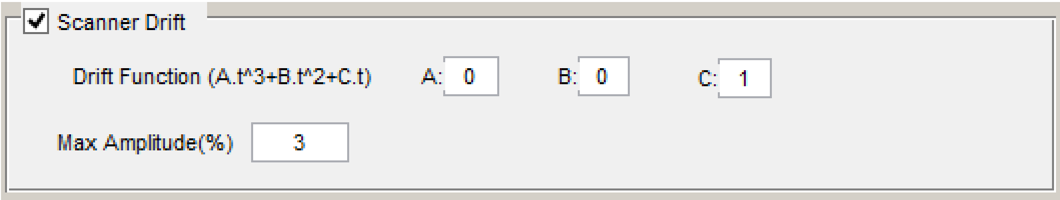


Figure A-14 Scanner Drift Artifact Definition Section

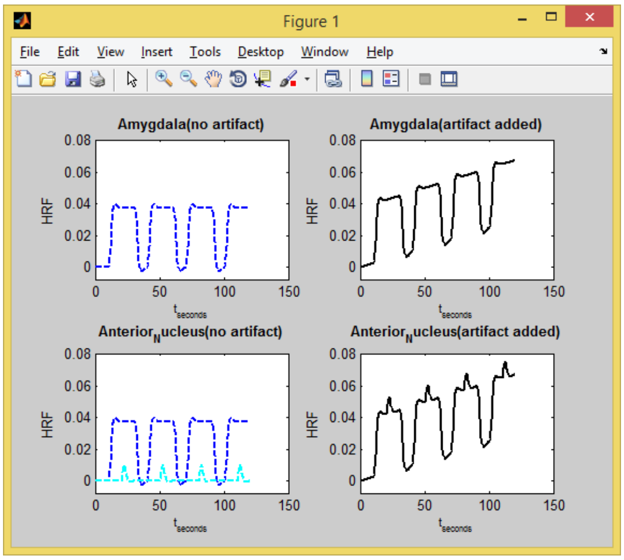


Figure A-15 HRF time course of drift added signal

A.7 HRF Time Course Preview

In order to see the HRF time course, "Timecourse Preview" button should be pressed. This opens HRF Time Course window as shown in Figure A-16. Each row in this window represents a ROI. For example in this figure, there are two ROIs which are Amygdala and Anterior Nucleus. On the window, left side represents the BOLD response without artifacts and artifact added signal is shown on the right. For example on the second row left side in Figure A-16, there are two stimuli as shown in blue and cyan. On the right is the linear summation of stimuli and added artifacts (noise + drift in this example).

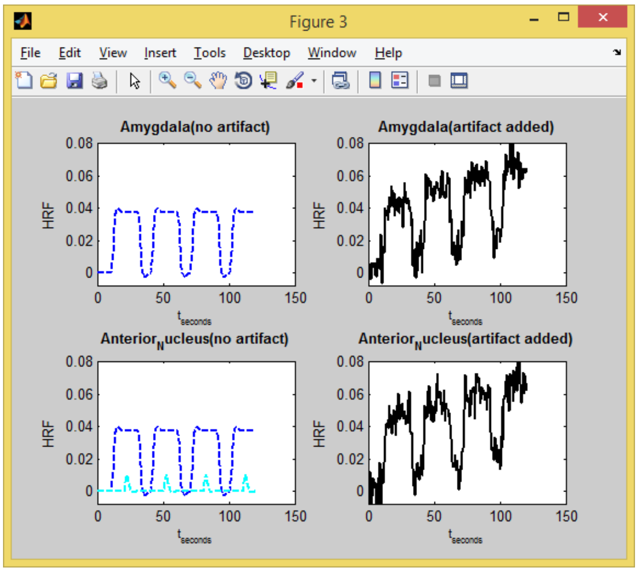


Figure A-16 HRF time course of drift+noise added signal

A.8 4D FMRI generation

In order to generate 4D FMRI data, FMRI Filename is entered and "4D FMRI" button is pressed. A popup window is displayed when data generation is completed.

A.9 Viewing the FMRI Results

In order to view 4D FMRI data, "VIEW" button should be pressed. This opens the FMRI Viewer window as shown in Figure A-17. In this window, 3 planes are shown: sagittal, axial and coronal. Also each ROI is represented with a color. When user selects a voxel, the time course of selected voxel is displayed at the bottom of the window.

For example, two ROIs exist in Figure A-17: amygdala (cyan) and anterior nucleus (blue). A voxel from amygdala has been selected and the time course of selected voxel is shown at the bottom.

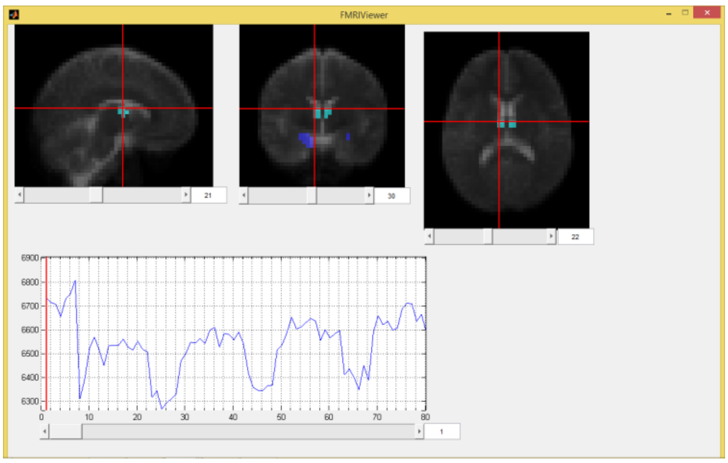
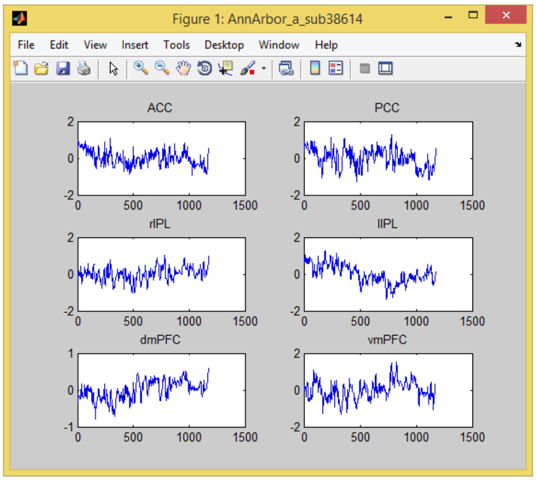
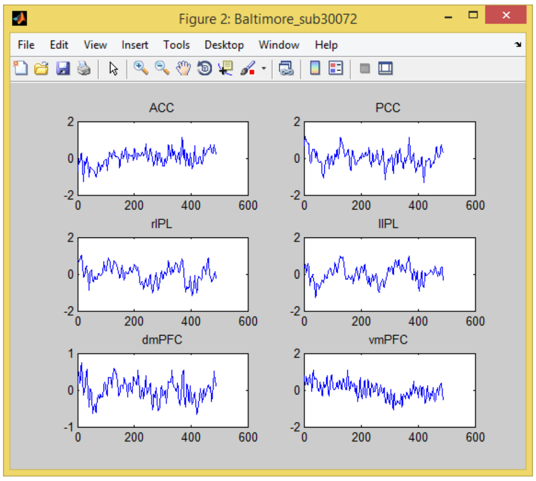


Figure A-17 FMRI Viewer window

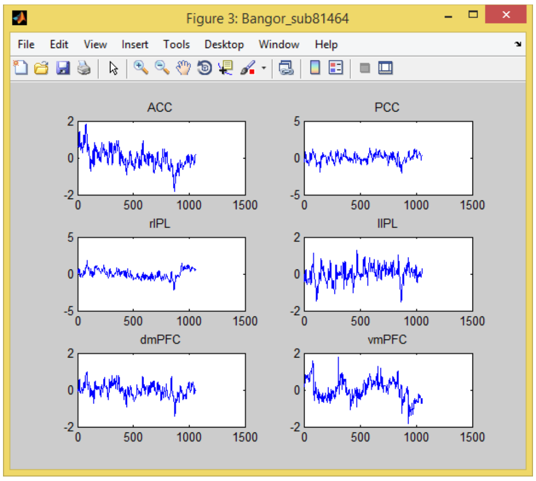
APPENDIX B: DMN TEMPLATES



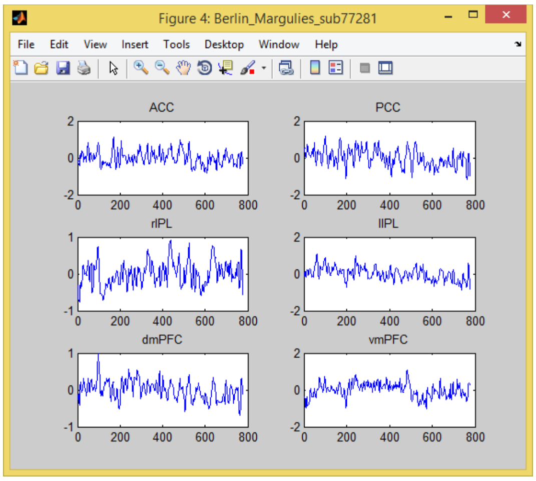
(a) AnnArbor



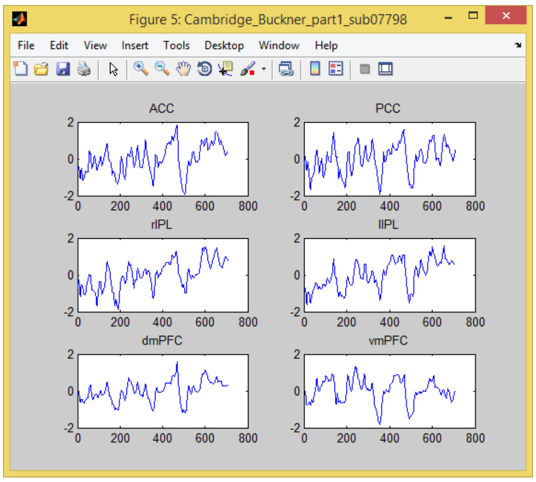
(b) Baltimore



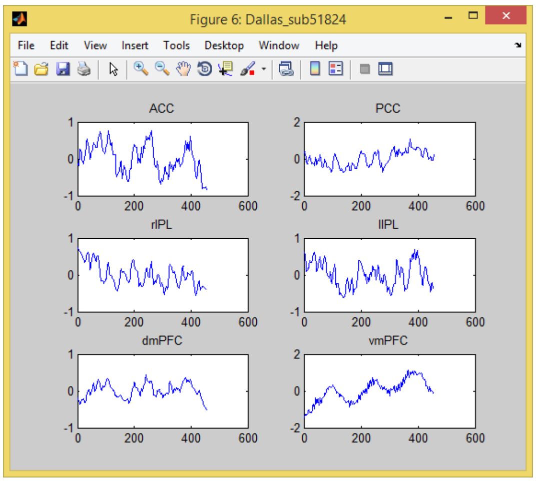
(c) Bangor



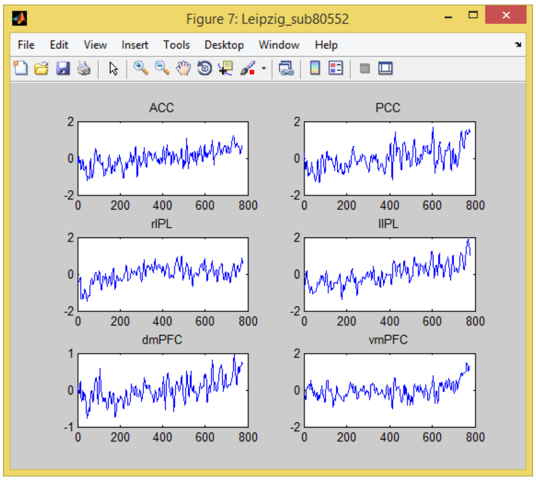
(d) Berlin



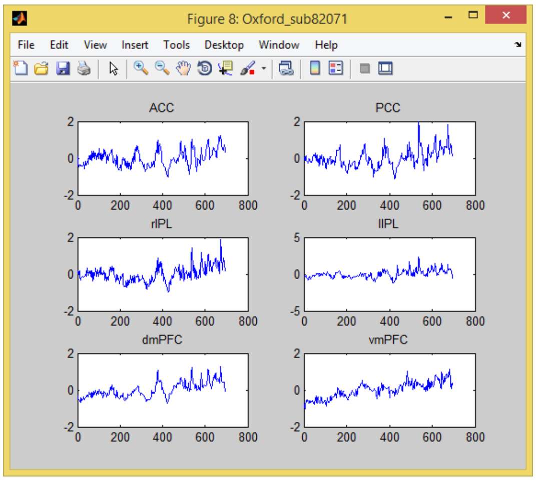
(e) Cambridge



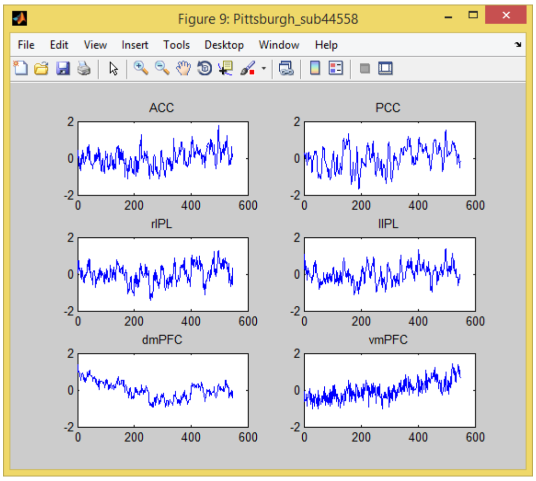
(f) Dallas



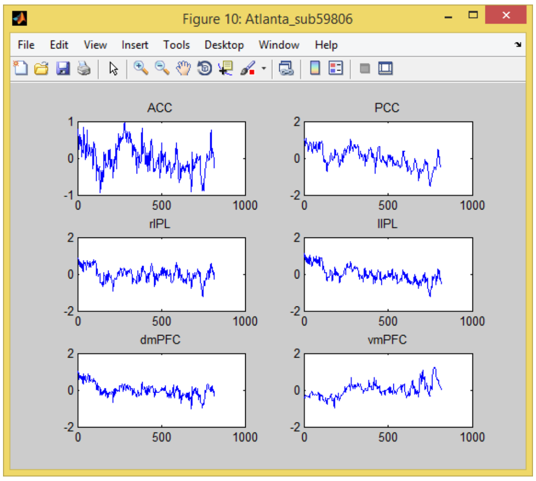
(g) Leipzig



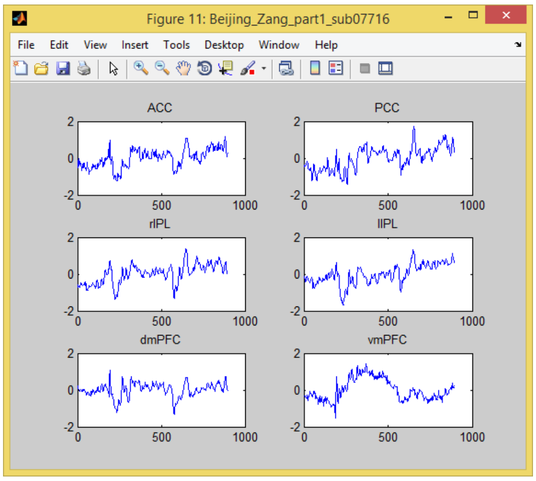
(h) Oxford



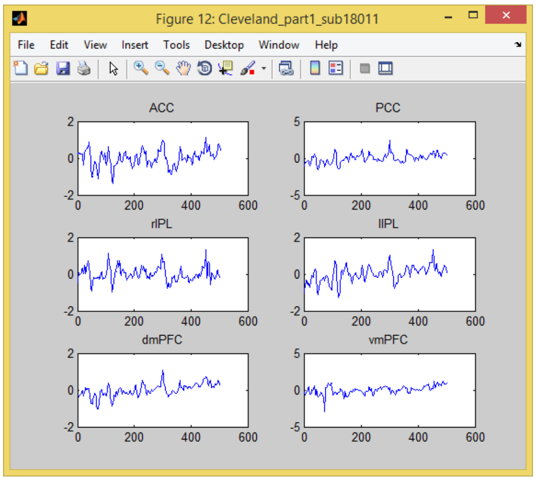
(i) Pittsburgh



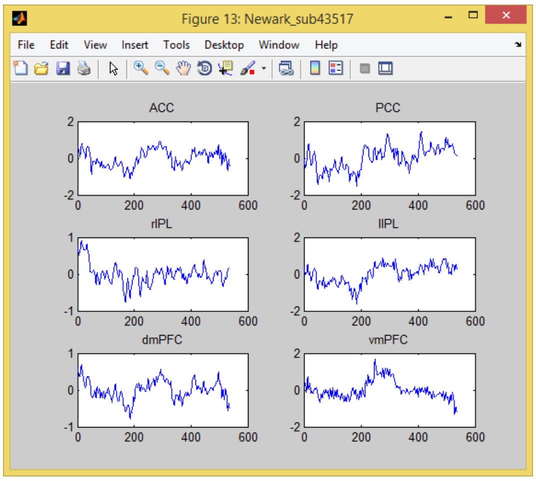
(j) Atlanta



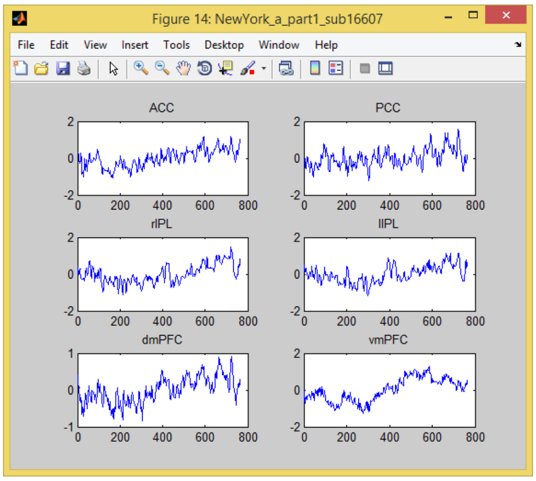
(k) Beijing



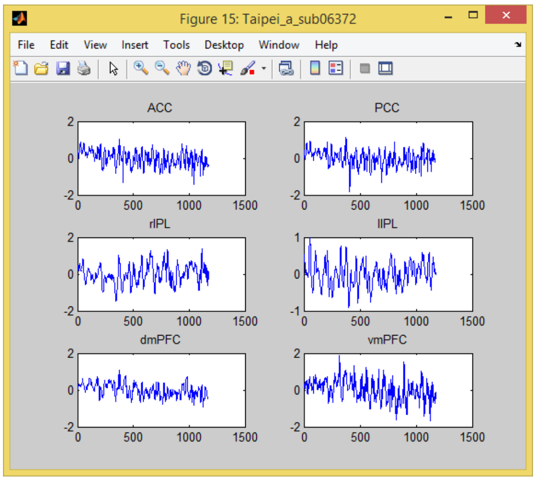
(l) Cleveland



(m) Newark



(n) Newyork



(o) Taipei

Figure B-1 DMN Templates