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Applying Dynamic Bayesian Networks to Infer Functional Connectivity in Event Related Design

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by

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ABSTRACT OF THE THESIS

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Various methods are used to infer functional connectivities between different regions of brain using functional Magnetic Resonance Imaging (fMRI) of brain. Most of these methods either assume a linear relationship between different areas of brain or they require a number of priors. Recently, use of Dynamic Bayesian Networks (DBNs) to infer functional connectivity using fMRI of brain, mainly in block design tasks, has gained ground. Though they are very effective in modeling non-linear relationships in time series data, there are several issues like getting stuck in local optima, the problem of discretisation, the processing and memory needed to solve DBNs increases exponentially as the number of nodes increase, initialisation, the requirement of a large sample for analysis to get statistically significant results.

We investigated the usage of DBNs for event related design and to what extent we can stretch in terms of number of nodes with the available softwares. We also came up with a novel way of using DBNs to make a comparative study between effective connectivity. We applied DBNs to face/scene memorisation task which has a event related design and presented the results.

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PREFACE

This is my Masters Thesis with the following objectives

- To Introduce Probability and Dynamic Bayesian Networks(DBNs) in a simple yet formal way to Computer Vision Students in the research group
- To give an introduction to functional Magnetic Resonance Imaging (fMRI)
- To present the research on using DBNs to extract the functional connectivies of brain from fMRI of brain Images
- This thesis will act as a guide to the students who would be working on further enhancement of the project

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I would like to thank Prof. Dimitris Samaras, my advisor who not only gave me an opportunity to work in this interesting project, but also was my mentor and had been patient in answering questions however elementary or tough they were. At times when I thought it can't be done he provided a direction without which I could nothave come this far. I would also like to thank Prof. Hoi-Chung Leung with whom I have collaborated in this work. She had been a source of information and inspiration for me. I am indebted to her for all the help she and her lab had provided me to get this thesis done. I would like to express my gratitude to Prof. Luis Ortiz and Prof. Tamara Berg who agreed to be on my thesis committee on a short notice. I would also like to thank Dr. Goldstein and her lab for letting me have hands on experience with fMRI data.

Jean Honorrio, Weidong Cai and Hwamee Oh are the three people whom I have pestered the most with questions regarding machine learning and fMRI processing. I am thankful to them for being so tolerant of me and for all the help I received from them. I would also like to thank Moieed Ahmed, Arvind Akella, Mayank Goswami, Sejal Magia, Guruswamy Namasivayam, Srivatsa Bhat whose laptops I have borrowed many times for running experiments and analysis of data. It will be sinistrous not to mention all the help I got from Mayank and Abhinav my apartment-mates who were ever ready to help me with any doubts in the mathematics part. A very special thanks to Alexandros Panagopulos another member from my lab, who had been my mentor from the time I joined the lab and had helped me in number of ways research, academic or otherwise.

Finally I would like to thank my parents, without their constant support and encouragement, I wouldn't even have come for graduate studies let alone do research.

CHAPTER 1

INTRODUCTION

Understanding the brain has been one of the most important objectives of science. We have advanced from the point of view that brain is just extra cranial stuffing, to the point where we know that it is the seat of intelligence and a myriad variety of scientific fields emerged to study various functionalities, anatomy and dysfunctions of the brain. Neuro-Imaging is one such field where images of brain taken using both invasive and non-invasive methods are studied.

Phrenology developed by German physician Franz Joseph Gall was one of the first to introduce the concept of localization in the brain. Phrenology is now considered defunct and a pseudo-science because it believed that brain areas have localised and specific functions, and that their size is proportional to a person's traits. And the personality trait of a person can be just measured by measuring the corresponding area of skull over the particular part of brain, since the size of brain would translate to measurable bumps on skull. Though phrenology has been labeled as a defunct science because it could notprove any of its beliefs, nevertheless it gave us the idea of localisation of functions in the brain.

Many brain studies based on lesions, and imaging techniques support the concept that neurons do not function individually but function as a group and localisation indeed happens in the brain Engel et al. [1997], Kami et al. [1995]. Functional neuro-imaging tries to measures the neuronal activity happening in different parts of brain. The reason it is preferred to other commonly used methods such as lesion studies, drug manipulations and recording electrical activity is that it is a non-invasive method of imaging. Thus can be used for studying human cognition and psychology with much lesser effect on the subjects participating in the studies.

Functional Magnetic Resonance Imaging(fMRI) is a non-invasive neuro-imaging technique that measures the activity of brain. fMRI is not only used in research studies to study cognition [Cabeza and Nyberg, 2000, Ochsner et al., 2002], it is also widely used in studying, understanding and diagnosing various disorders of the brain [Weiller

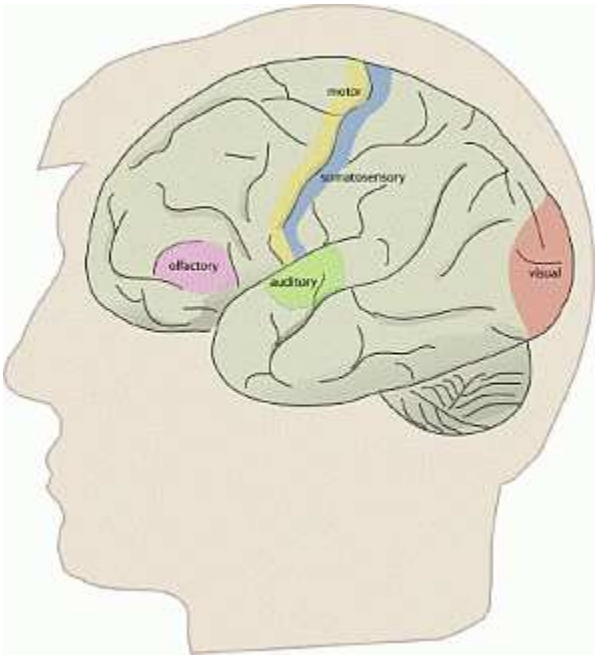

Figure 1.1: Localised areas of brain

et al., 2003, Kana et al., 2006, Rich et al., 2008]. Ungerleider and Haxby [1994], Porro et al. [1996] show that neurons not only form a group for performing a certain task, but there are certain areas in the brain that form a network to perform various tasks. Though the concept of functional connectivity is not totally well defined Horwitz [2003], for our purpose we can have a simplistic view of it as a measure of such interactions between various localised areas of brain. Weiller et al. [2003], Kana et al. [2006], Rich et al. [2008] show that the study of functional connectivity can be used to help diagnose some of the neuronal disorders like autism, parkinson's disease. Though there exists a number of methods to get the functional connectivities for fMRI images of brain [Friston et al., 2003, McIntosh and Gonzalez-Lima, 1994, Friston et al., 1997], they use several assumptions and require a lot of priors to get a measure of the functional connectivities.

In this project, I have applied Dynamic Bayesian Networks to find the functional connectivities of brain. DBNs were successfully applied in finding functional connectivities earlier [Zhang et al., 2005, Li et al., 2008, Rajapaksea and Zhoua, 2007] but there were several limitations such as only a small number of areas can be examined, also several properties of the data like convolution, discretization were overlooked. I applied DBNs to event related fMRI task design to make a comparative study of functional

connectivites related to areas of brain that are responsible for remembering faces and scenes. This kind of study can't be achieved by using existing methods like Dynamic Causal Modeling or Psychophysiological Interactions.

1.1 Organisation of the Thesis

The second chapter introduces the concept and techniques of Functional Magnetic Resonance Imaging. This chapter is particularly important for those people who are new to the field and who would be working the project later. The third chapter introduces dynamic Bayesian networks and graphical models in an informal manner. Fourth chapter gives an view of different methods used for finding functional connectivities. Chapter five gives a detailed description of all the experiments I have done, what softwares I have used and the results.The final chapter has conclusions and future work.

CHAPTER 2

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional Magnetic Resonance Imaging(fMRI) is a non-invasive neuro-imaging technique that is among the one of the more recently developed methods. Yet the underlying idea inferring brain activity by measuring changes in blood flow - is not new. The following account of an experiment performed by the Italian scientist Angelo Mosso can be found in William James The Principles of Psychology.[1]

> "The subject to be observed lay on a delicately balanced table which could tip downwards either at the head or the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system"

2.1 Basic Principle of fMRI

We need to take a brief look into the working of Magnetic Resonance Imaging(MRI) before understanding the functional imaging. Magnetic Resonance is based on the fact that the nucleus of an atom spins at certain frequencies, and if we generate an electro magnetic field of same frequency, energy is absorbed by the atom due to resonance.This absorbed energy can be measured, hence the name Magnetic Resonance Imaging. The measured absorbed energy is then translated by various procedures into a meaningful image. The key to MRI is that the signal from hydrogen nuclei varies in strength depending on the surroundings. This provides a means of discriminating between grey matter, white matter and cerebral spinal fluid in structural images of the brain.

Oxygen is delivered to neurons by haemoglobin in capillary red blood cells. When neuronal activity increases there is an increased demand for oxygen and the local response is an increase in blood flow to regions of increased neural activity [Roy and Sherrington, 1890]. Haemoglobin is diamagnetic when oxygenated but paramagnetic

[1]Courtesy of the National Library of Medicine.

Figure 2.1: Siemens Symphony MRI scanner

when deoxygenated. This difference in magnetic properties leads to small differences in the MR signal of blood depending on the degree of oxygenation. Since blood oxygenation varies according to the levels of neural activity these differences can be used to detect brain activity. This form of MRI is known as *Blood Oxygenation Level Dependent* (BOLD) imaging. In the next two sections of this chapter we will see how a neuronal signal or activity is transformed into a BOLD signal.

2.2 Neuronal to Hemodynamics

Since we want to measure the neuronal activity and we know that fMRI doesn't directly measure it, there is need to know how neuronal signal are generated and how they relate to what we measure in fMRI. The process of passing on the electrical signal from one neuron to another needs energy. The figure 2.2 shows the structure of a neuron and the parts it consists of. The inside of a neuron is maintained at -70 mVolts, which is called resting potential. When a neuron is excited because of another neuron or some stimulus, it gets activated and the potential difference changes to +40mVolts, which is called activation potential. Neuron propagate this signal(change in potential) from itself to another neuron through axons. See Figure 2.3

In the simplest model, to propagate the charge from one neuron to another, there is a need to move the Na_+, K_+, Cl_- and to some extent Ca_{++} ions in and out of the

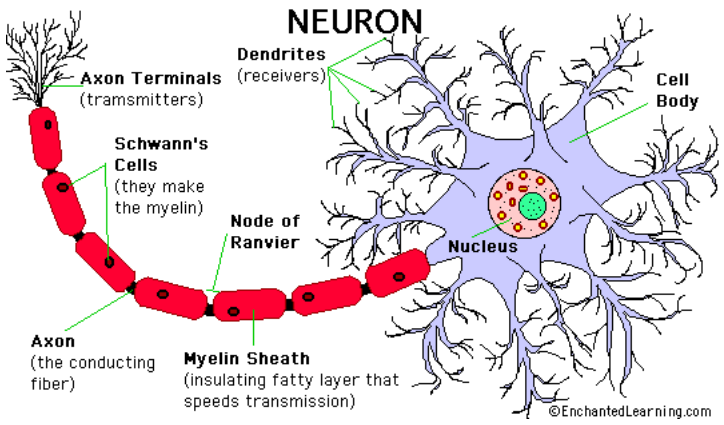

Figure 2.2: A neuron is organised into 3 parts. Dendrites integrate signals coming from other neurons via small gaps known as synapse. The soma, or cell body of the neuron contains a nucleus and organelles that support metabolic and structural properties of the neuron. Changes in the membrane potential of the neuron are signalled to other neurons by action potentials that travel along its axon

cell membrane. There are ion channels and pumps which help the influx and efflux of ions either to bring back the neuron to resting potential or to take it to action potential. The ion pumps need energy for their process and to generate the energy needed, glucose molecule combines with oxygen (this process is called aerobic glycosis) and releases the energy in the process of glycosis. This induces a change in the blood oxygenation level and that is how we can connect neuronal activity to hemodynamics.

2.3 Hemodynamics to Blood Oxygenation Level Dependent(BOLD) signal

There are various theories about neural activity translated to BOLD signal and there is no concrete evidence yet that neural activity is directly translated to BOLD signal, because some research suggests that there is also aneorobic glycosis that happens during the neuronal activity to run the ion pumps. Also there are theories that the signal we are imaging is due to oxygenated blood and not because of more the deoxygenated blood which acts as a deterrent to for creating contrast signal in MRI because of its paramagnetic nature. There are various models suggested by rigorous research such as Buxton and Frank [1997], Buxton et al. [1998], Chiha et al. [2001], Harel et al. [2002] which try to understand the underlying mechanism beneath fMRI signals. This is a nice

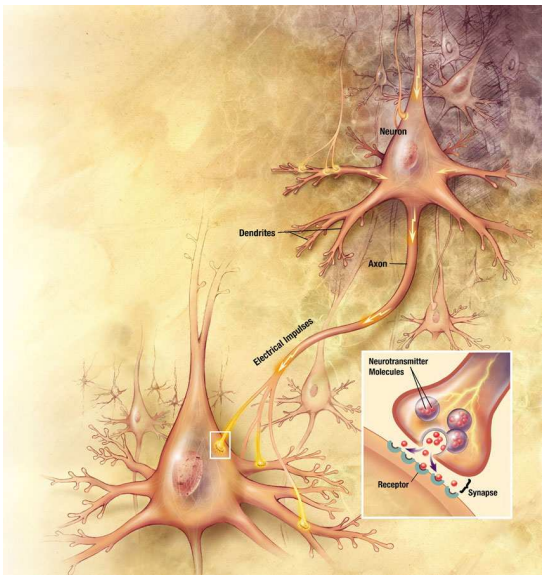

Figure 2.3: A figure showing the axon with the inset showing the synaptic cleft and neuro-transmitters

place to mention the chapter 6 and 7 of the book Huettel et al. [2004], which are a must read for anyone who would want to work on the project further. These chapters give a very insightful understanding of the way neuronal activity is performed and also current research related issues with using BOLD as an indication of neuronal response.

2.4 Preprocessing of Data

fMRI data is a 3D matrix of voxels repeatedly sample over time. The usual dimensions are around 64x64x20 and taken at around every 2 seconds. There are a series of operations that need to be done after image reconstruction from the scanner and before any statistical analysis. The following are the necessary preprocessing steps that are usually performed on fMRI raw data before any further analysis.

2.4.1 Slice Acquisition Time Correction

The data we see is 3 dimensional, but it is built by acquiring slices of two dimensions. Most fMRI machines use interleaved slice acquisition, which means if there are 20 slices to be acquired the odd numbered slices (1,3,5,7,9,11,13,15,17,19) are acquired in sequence first and then the even numbered slices(2,4,6,8,10,12,14,16,18,20). If the whole

process of acquisition takes a time of 1.5 seconds then there is a time lag introduced between every slice which needs to be corrected.

Temporal interpolation is one of the more common techniques used to correct the error introduced due to interleaved slice acquisition. This uses information from nearby time points to estimate the amplitude of the MRI signal. Various interpolation techniques like linear, spline, sinc functions are usually used. It should be noted that no technique can recover the lost information perfectly. Slice timing correction should be done before head motion correction.

2.4.2 Head Motion Correction

Head motion is one of the most damaging problem for fMRI studies. I have been a subject for one of the fMRI studies and it is inevitable that a person in the scanner can't stay still. The closed environment and the stress of doing the task in noise of scanner which usually one wouldn't expect unless he/she is used to will lead to small movements of head. Even a shift by 5mm will result in inconsistency in the borders. fMRI studies assume that each voxel in the brain corresponds to the same anatomical area in the brain, so if the subject moves his head each voxel's time course is derived from more than one anatomical area.

Usually problem with head motion can be prevented rather than solving it after the acquisition. There are various devices head restraint systems, vacuum packs, thermoplastic masks one can use to prevent head motion. But using such devices may prove counter productive because the subjects discomfort increases inside the scanner, which is already not a very nice place to be in and this might result in them leaving in between the tests or not coming for the tests. One simple but very useful technique is to place a tape on the head so that the subject can correct himself according to the tension in the tape.

A set of rigid body transformations can be used for motion correction. Since we can safely assume that brain doesn't change its shape for the short period of time inside the scanner, brain can be considered as a rigid body. The images acquired over time can be aligned spatially to the first image acquired by rotation and translation. A cost function can be defined with the rotation and translation as parameters and can be optimised used techniques like least-squared errors or expectation maximisation.

2.4.3 Fuctional-Structural Co-registration and Normalization

The two corrections mentioned above solve the spatial and temporal issue of ensuring that a single voxel represents the same part of the brain for the same subject. But researchers want to address two important issues : how does activity map into anatomy , and how consistent is that mapping across subjects, which can not be answered unless we make sure that every voxel used for analysis represents the signal from the same anatomical area of brain of all subjects. Since size of the brain varies largely according to the subject all of the images acquired are usually **normalised** in reference to a standard brain. Functional data is typically of low resolution, we often must map the functional data onto high-resolution and high-contrast structural images. Functional-structural co-registration and normalisation are the two most important pre-processing steps.

Most of the algorithms used for normalization do a decent job, but as with all optimization algorithms (optimization of cost function which would lead to normalization)there is a chance that it might get stuck in local optima, so it is always better to check one the software package does the normalisation for you. Also it is advisable to adjust the brain images by the user before using the computerised algorithms because giving prior information for algorithm reduces the chance of getting stuck in local optimas.

2.4.4 Spatial and Temporal Filtering

Filters are techniques used in signal processing to remove or retain particular frequencies in a signal. They can also be used to remove noise from a signal. Filters can be used in any dimensional space. For our purpose in fMRI we can use them on 1d time course of a voxel or on 2/3d images of the scans. Filters here are usually necessary to remove uninteresting variations in data that can be attributed to noise.

Usually in toolkits that process fMRI data we need to set the threshold for filtering. **Nyquist Sampling Theorem** helps us to set the threshold for a temporal filter. **Nyquist Sampling Theorem** essentially says that to retain all the information about a continuous signal when discretising it, if the frequency of the continuous signal X then sampling it at $2X$ will do our task of preserving the signal. How is this useful to us ? If we are taking a scan of brain every 2 seconds and the experiments continue for 5 mins. We have 150 scans in all. So if we set the threshold to be 300, that means we can have all the signal from fMRI and any frequencies which is above is cut. As a rule of thumb

$filterthreshold = 2 * thetotalnumberofscans.$

Smoothing or spatial filtering is the last preprocessing step that is performed on the fMRI data. There are various smoothing filters that one can use such as mean filter, median filter, but the most preferred one is Gaussian filter and in the preprocessing step we need to set size of the Gaussian filter for the tool kit. Again spatial filtering or smoothing is used to remove the noise or to filter out any high frequency components.

2.5 Experimental Design

This is the most important section that one needs to understand to find and analyse functional connectivities. The main aim of experiments related to fMRI is to see what parts of brain are active when performing particular tasks in different sets of subjects. To see how the functioning of a drug addict is different from that of a normal person, or what are the different areas in the brain that are activated when doing simple tasks with right hand and how are the areas different when performing the same task with left hand etc. The best experimental design is such that it will be able to answer the aim of the study and also minimize number of experimental subjects and experimental trials per subject. **Block Design** and **Event Related Design** are the two main design paradigms that neuorscience researchers are currently using for fMRI studies. The usual pattern of experiments is the subject is given a task to do, this task can range from being very simple task (e.g. to press a button when you see something on screen), to very complex task depending on what the neuroscience researcher wants to find. The way you present the tasks to the subject is what describes a design.

2.5.1 Block Design

In this kind of design the user is given a same tasks to be done under similar condition in blocks. To press a button or not to depending on the cue given at the beginning with the motivation of 3 monetary conditions.

- Block 1(60 seconds) - Press a Key or abstain from pressing depending on the cue shown (45 cents reward each time if correctly done)
- Rest (35 Seconds)
- Block 2(60 seconds) - Press a Key or abstain from pressing depending on the cue shown (1 cent reward each time if correctly done)

- Rest (35 Seconds)
- Block 3(60 Seconds) - Press a Key or abstain from pressing depending on the cue shown (0 cent reward each time if correctly done)
- Rest (35 Seconds)

Task from Goldstein et al. [2007]. This task is used analyse decreased sensitivity to money in cocaine users. So each block consist of different monetary conditions and evaluate the subjects performance.

Finding functional connectivities in such a design is relatively easier because in each block according to our hypothesis there are certain areas of brain that are active only because of the experimental condition and the fMRI signal do not have convolution effect because of other conditions.

2.5.2 Event Related Design

Event related design is more challenging to deal with when finding functional connectivities. In this design instead of one block having the same condition, the subject is given tasks to perform in events continuously with a small interval between each task. This is called Inter Stimulus Interval(ISI). This becomes even more challenging when there are two different events which come at random. The reason why this is challenging is because when the ISI is small and two different events are present after one another, the signals from the event at $t-1$ convolve with signal from events at t.

Though it is difficult for finding functional connectivities nevertheless event related design is gaining popularity. Burock et al. [1998] shows how one can exploit the advantages of event related design. Friston et al. [1999], Dale [1999] givens an insight into when event related design is preferred.

Chapter 11 of Huettel et al. [2004] gives more insightful look into both the block design and event related design.

2.6 Notes

Before starting to work on the project I would suggest to read Functional Magnetic Resonance Imaging by Scott A. Huettel and Allen W.Song and Gregory McCarthy. Reading the book would not only give a perspective of fMRI but also gives knowledge of data that one would be dealing with. It would be a nice idea to perform all the

preprocessing steps in SPM [Friston et al., 1995] as you go on reading the preprocessing steps.

CHAPTER 3

DYNAMIC BAYESIAN NETWORKS

As mentioned earlier the aim of this project is to find the functional connectivities between the areas of brain using fMRI data. By connectivities we mean the causal information between the ROIs. We have already seen that fMRI is a time series where at regular intervals we have a snapshot of brain. Dynamic Bayesian networks provide a easy way to encode the causal information in time series data (Ghahramani [1998] and the references within).

Dynamic Bayesian networks are a type of **graphical models** that can be used for making probabilistic inferences.[1] A graphical model is a family of probability distributions defined in terms of a directed or undirected graph. The nodes in the graph are identified with random variables, and joint probability distributions are defined by taking products over functions defined on connected subsets of nodes.

In most of the real scenarios the observations are not related to each other deterministically, also there is added uncertainty resulting from the availability of data, noise in the data and the fact that there can always be a mismatch between the true process and our model. In such cases probability theory helps us define the non-determinism and randomness in a model. Jordan [2004] gives a very good introduction to graphical models.

Probabilistic graphical models are graphs in which nodes represent random variables, and the (lack of) arcs represent conditional independence assumptions. Hence they provide a compact representation of joint probability distributions. Undirected graphical models, also called Markov Random Fields (MRFs) or Markov networks, have a simple definition of independence: two (sets of) nodes A and B are conditionally independent given a third set, C, if all paths between the nodes in A and B are separated by a node in C. By contrast, directed graphical models also called Bayesian Networks or Belief Networks (BNs), have a more complicated notion of independence, which takes into account the directionality of the arcs, as we explain below.

[1] For a basic introduction on probability refer Appendix A

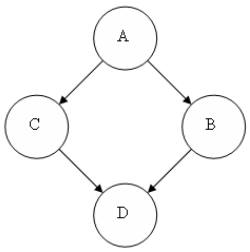

Figure 3.1: The conditional probabilities of Random variables A,B,C,D which are nodes can be encoded using graphs like these.

Undirected graphical models are more popular with the physics and vision communities, and directed models are more popular with the machine learning and statistics communities. (It is possible to have a model with both directed and undirected arcs, which is called a chain graph.). Although directed models have a more complicated notion of independence than undirected models, they do have several advantages. The most important is that one can regard an arc from A to B as indicating that A "causes" B. From figure 3.1 we can infer that $P(D|A,B,C) = P(D|B,C)$. Also in terms of causality we can say that A causes B and C which in turn are the cause for D.

Now that we have a general idea of how conditional independencies can be encoded using a graph, we can now move on to see how to encode the causal information for time series using Dynamic Bayesian Networks. We need to know few definitions for that

- N^{th} **order Markov Chain:** If X_t describes the state of a process at time t. N^{th} order Markov Chain assumes that X_{t+1} can be described by $X_t, X_{t-1}, X_{t-2}, ..., X_{t-N+1}$, and it is independent of $X_1, X_2..., X_{t-N}$

Assuming that our model follows N^{th} order Markov Chain Property, DBNs try to maximise

$$P(X_t|X_{t-1}, X_{t-2}, ...X_1) \tag{3.1}$$

since our model follows N^{th} order Markov Chain Property, the above equation will be reduced to

$$P(X_t|X_{t-1}, X_{t-2}, ...X_{t-N+1}) \tag{3.2}$$

There are two problems associated with DBNs

- Parameter Estimation: Here we already know the conditional independencies and from the data we learn the strength of each arc (easier)

- Structure Learning: In this case we don't know what the conditional independencies are, so we need to estimate the structure which is a tougher problem. In our case we need have to use the Structure Learning because we are trying to find the causal relations which are nothing but conditional independencies. In the next section we will learn why structure learning is a tough problem and the algorithm Simulated Annealing that BANJO uses for structure learning.

3.1 Structure Learning

There are two ways find the structure from the observed data. The first class consists of constructive methods based on the examination of various constraints that must hold over the conditional dependences and independences computable from the empirical probability distributions on the variables represented in the data [Spirtes and Glymour, 1999, Spirtes and Scheines, 1993].

The second class of algorithms consists of strategy that searches for a network that seek to maximise some scoring function that describes the ability of network to explain the observed data [Friedman et al., 1998]. The example below gives an intuition why searching is a hard problem

Suppose there are N nodes and we are trying to find a network under Order-1 Markov Chain assumption (the simplest one possible). There are N^2 possible connection between instances at time t and $t+1$. These N^2 can give rise to 2^{n^2} networks in all making the sample space exponential and which in turns makes the searching problem a hard one. For more a formal proof see Chickering et al. [1994], which shows that discovering a highest scoring network is NP-hard. So heuristic methods are preferred to exhaustive search strategies.

If the evaluation of scoring function is decomposable a local change (addition, addition deletion of a node) in the model results in a local change in the scoring function which makes the search strategy much easier. The general approach for heuristic algorithms is to propose a structure, evaluate it using a decomposable scoring metric, perform a local and change and evaluate the new network to see if the score increases or decreases. Keep repeating this method until a network structure with maximum score is found. But this heuristic search strategy is called hill climbing and would often result

in getting stuck at local optima.

To avoid getting stuck in local optimum, a more general version can be used called Metropolis wherein the random local operation is implemented if it increases the score, as before, but is also implemented with a certain probability p if it does not (setting $p = 0$ yields the previous greedy random algorithm).

The Metropolis search strategy forms the basis of a more complicated search strategy known as simulated annealing, so named because it operates in a manner analogous to the physical process of annealing. During the search process, the Metropolis algorithm is run as a subroutine at various temperatures T. The prevailing temperature and the score difference between graphs determine the transition probability p within Metropolis, with higher temperatures indicating more permissive transitions. Initially, the temperature is set very high (allowing almost all changes to be made), but is gradually reduced according to some schedule until it reaches zero, when p is also zero, at which point the Metropolis subroutine is equivalent to the greedy random algorithm. The schedule that the temperature is constrained to follow can be varied to produce different kinds of search algorithms including ones that allow for re-annealing after the temperature becomes sufficiently low. Hartemink [2001], Metropolis et al. [1953], Hastings [1970] can be referred for more detailed description of scoring functions Metropolis algorithm and simulated annealing algorithms.

CHAPTER 4

PREVIOUS WORK

There have been various methods introduced to find the underlying functional connectivities from functional images of brain images. The mapping methods have greatly changed from Structural Equation Modeling (SEM) McIntosh and Gonzalez-Lima [1994], which does not consider the data to be time series and requires a prior model, to vector auto regressive models Roebroeck et al. [2005] which explores directed influences in neuronal population and Friston et al. [2003] which not only considers the neural influences to be non-linear, but also fits a forward model from neuronal activity to *functional magnetic resonance imaging* (fMRI) *bold oxygenation level dependent* (BOLD) signal.

One common point to be noted for all these approaches is that they assume the connectivities between different areas of brain to be deterministic plus a noise component, meaning same response will generate the same network with same strength of connections. The correctness or incorrectness of this assumption has not yet been tested. In this section we will discuss four approaches Structural Equation Modeling, Granger Causality,Pyschophysiological Interactions, Dynamic Causal Modeling.

4.1 Structural Equation Modeling(SEM)

Covariance as a tool had been successfully used to analysis and gain insight into functioning of brain [Aertsen et al., 1987, Gevins and Cutillo, 1993, Gevins et al., 1985]. McIntosh and Gonzalez-Lima [1994] applied SEM on covariances based on time-integrated activity of measures of ensembles of brain regions.

Expressed in terms of neural systems, a measure of covariance represents the degree to which the activities of two regions are related to one another, or how they vary together, A high covariance between areas A and B means that if area A increases its activity, so too will B (in the case of a positive covariance). Covariances are studied in many scientific disciplines, but in neural systems, covariances of activity have a special meaning. The dependent variables (regional activity of brain areas) are anatomically

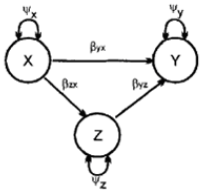

Figure 4.1: X,Y,Z are covariances of the areas we want to analysis and the βs are the influences they have on each other which are represented by the directional arrows. (Figure taken from McIntosh and Gonzalez-Lima [1994]) .

connected to one another, while in other disciplines, such as social science, there may be no a priori connective relationships between dependent variables.

Assume we are analysing 3 areas and we know the network structure. Let X, Y, Z be the covariances of the 3 areas we are analysing. The structure in 4.1 can be represented by equation 4.1 .

$$\begin{bmatrix} X \\ Z \\ Y \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ \beta_{z,x} & 0 & 0 \\ \beta_{y,x} & \beta_{y,z} & 0 \end{bmatrix} \begin{bmatrix} X \\ Z \\ Y \end{bmatrix} + \begin{bmatrix} \psi_x \\ \psi_z \\ \psi_y \end{bmatrix} \tag{4.1}$$

Given the interconnections among neural elements and that regional activity in the central nervous system is mainly determined by afferent influences, the changes in functional relationships among brain regions can only be quantified by covariance analyses.

This method assumes that we already know the structure that is formed and then analysis the strength of the connections or the influence that one area has on another which is believed to be linear the figure 4.2 below summarises the SEM process applied to infer connectivities.

In conclusion, the SEM method applied to infer brain network tries to see the linear dependencies of covariances of brain areas on each other given a prior network.

4.2 Granger Causality and Vector Autoregressive Modeling

This method in some sense is the extension of SEM. It considers the sequence of fMRI measures of regions of interest x_i as components of a discrete vector time series $X[n] = (x_1(n), ..., x_m(n))'$ where n represents time and there are m regions of interest [Roebroeck et al., 2005].

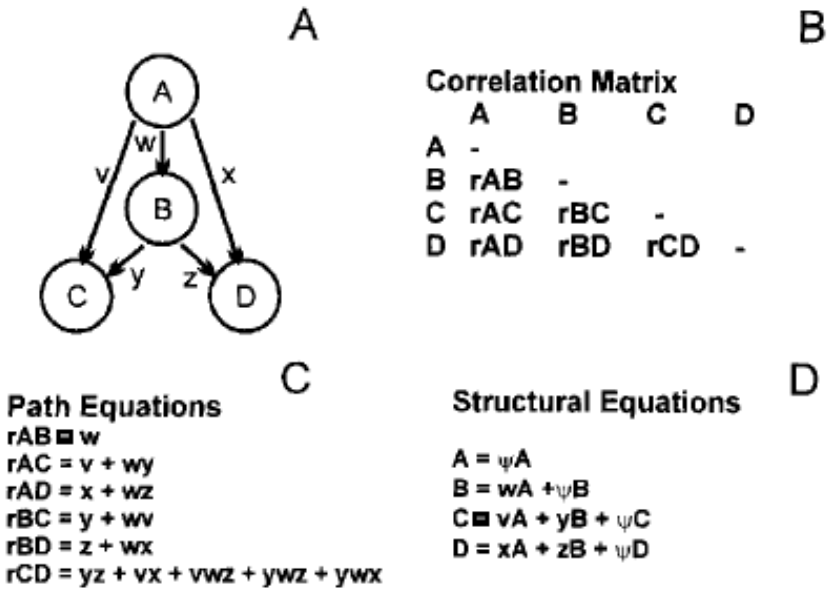

Figure 4.2: Schematic representation of methods involved in structural equation modeling of a neural system. **A:** Path diagram of a simple network with four brain regions (A, B, C, D) and their anatomical connections (indicated by arrows). **B:** The information about the correlations of activities between regions is used in conjunction with the path diagram (A) to calculate the strength of influences through the connections, known as the path coefficients (v, w, x, y, z). **C:** Path equations show how the correlations between regions can be decomposed to solve for the path coefficients. **D:** Structural equations show the variance in activity in each region as a function of the weighted variance of other brain regions and a residual influence (indicated by ψ). These residuals are not shown in A and C for simplicity.(Figure taken from McIntosh and Gonzalez-Lima [1994]).

Taking the temporal structure of signal time-courses into account is related to our commonsense concept of causality: causes always precede effects. Something in the future cannot cause something in the past or present. All events taking place at a certain point in time must have had their cause at an earlier stage. These considerations have led econometrist Clive Granger to propose a definition of causality for temporally structured data, i.e., time series [Granger, 1969a,b]. Conceptually, it amounts to the following: if a time-series y causes (or has an influence on) x, then knowledge of y should help predict future values of x. Thus, causality (or influence) is framed in terms of predictability. More in detail, given two discrete time-series x and y, we say that y Granger causes x if we can predict the current value of x, x[n] using past values of x and y (i.e., the information set $D = y, x = y[n-1], [n-2], ..., x[n-1], x[n-2], ...$ better than we can when using past values of x alone).

The influence measure $F(x, y)$ is the sum of three components: the linear influence from x to y denoted by $F_{x \to y}$, the linear influence from y to x denoted by $F_{y \to x}$, and the instantaneous influence between x and y denoted by $F_{x,y}$. The measure can be defined using the residual cross-covariance matrices of the following three VAR models involving the K-dimensional series x[n] and L-dimensional series y[n]. Roebroeck et al. [2005] gives a more indepth view of the method and its application.

The important point to note here is the extension of linear models from a static to dynamic scenarios. In contrast to SEM the time series was never considered for analysis except for building the covariance matrices, which is considered in granger causality analysis. However the two main assumptions that the connections between areas are deterministic and that they are linearly dependent still hold even for this method.

4.3 Psychophysiological Interactions(PPI)

The novelty in PPI is that it tries to model the hemodynamic responses in one area of brain as an interaction between hemodynamic response in another area and some experimental conditions based on the design of the task [Friston et al., 1997]. The contribution of one area to another can be greatly influenced by the experimental conditions. This is modeled in terms of PPI.

Let us consider modeling x_i the hemodynamic responses in area i as an interaction between some experimental condition g_e and hemodynamic response x_k of another area in the brain. PPI can be summarised by the equation below

$$x_i = x_k \times g_e \cdot \beta_i + [x_k g_e G]\beta_G + e_i \tag{4.2}$$

The term $x_k \times g_e \cdot b_i$ represents the psychophysiological interaction between the physiological activity in region k and some psychological or experimental parameter of the experimental design g_e and is constructed by multiplying the two effects.

The main contribution of this method is that it introduced a way to include a parameter that can integrate the effects of experimental design into the analysis.

4.4 Dynamic Causal Modelling

All the methods presented till this point to find functional connectivities assumed a linear dependency model between the areas of the brain. DCM approaches the problem in 3 different ways when compared to earlier methods.

- The influence that areas have on each other is non-linear and bilinear models can be used to model them
- DCM calls upon the same experimental design principles to elicit region-specific interactions that we use in experiments to elicit region-specific activations
- DCM appends a forward Hemodynamic Model that transforms neuronal activity to the BOLD signal that fMRI measures [Friston et al., 2000]

It is to be noted that the deterministic part of the assumption that the earlier two methods had is still there for DCMs.

DCM is used to test the specific hypothesis that motivated the experimental design. It is not an exploratory technique; as with all analyses of effective connectivity the results are specific to the tasks and stimuli employed during the experiment. In DCM,s designed inputs can produce responses in one of two ways. Inputs can elicit changes in the state variables (i.e., neuronal activity) directly. For example, sensory input could be modeled as causing direct responses in primary visual or auditory areas. The second way in which inputs affect the system is through changing the effective connectivity or interactions. Useful examples of this sort of effect would be the attentional modulation of connections between parietal and extrastriate areas. Another ubiquitous example of this second sort of contextual input would be time. Time-dependent changes in connectivity correspond

to plasticity. Figure 4.3 shows a graphical representation of an experimental design used by DCM.

Each region of interest is represented by five state variables

- One corresponding to neural activity and
- Four corresponding to the forward hemodynamic model:
  - Vasodialatory Signal,
  - Normalised Flow,
  - Normalised Venous Volume, and
  - Normalised DeoxyHemoglobin Content.

Let $z = (z_1, z_2...z_n)$ be the n neuronal states. The interactions between them are modeled by the equation 4.3.

$$z_{t+1} = Az_t + \Sigma u_j B_j z_t + Cu \tag{4.3}$$

Equation 4.3 is the bilinear equation with A representing the interactions between neuronal states, B_j representing the combined effects of inputs u and neuronal states z and, C represent how much the inputs directly influence the neuronal states. Various constraints on A and B are used as priors to estimate the parameters. Friston et al. [2003] has more information on solving the equation, appending the hemodynamic forward model and experimental evaluation and results for DCMs.

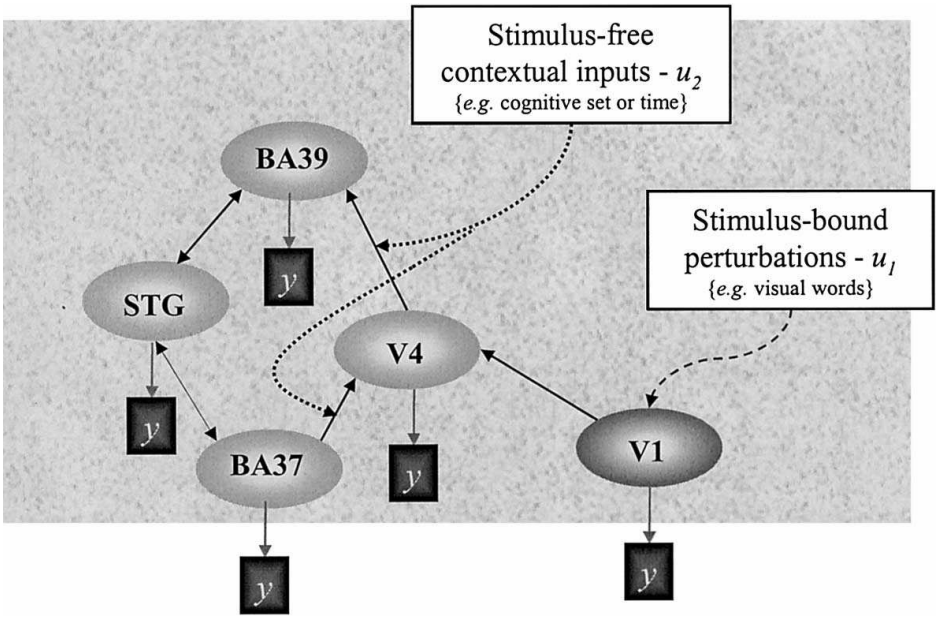

Figure 4.3: This is a schematic illustrating the concepts underlying dynamic causal modeling. In particular it highlights the two distinct ways in which inputs or perturbations can elicit responses in the regions or nodes that compose the model. In this example there are five nodes, including visual areas V1 and V4 in the fusiform gyrus, areas 39 and 37, and the superior temporal gyrus STG. Stimulus-bound perturbations designated u1 act as extrinsic inputs to the primary visual area V1. Stimulus-free or contextual inputs u2 mediate their effects by modulating the coupling between V4 and BA39 and between BA37 and V4. For example, the responses in the angular gyrus (BA39) are caused by inputs to V1 that are transformed by V4, where the influences exerted by V4 are sensitive to the second input. The dark square boxes represent the components of the DCM that transform the state variables z_i in each region (neuronal activity) into a measured (hemodynamic) response y_i. (Figure taken from Friston et al. [2003])

CHAPTER 5

DYNAMIC BAYESIAN NETWORKS(DBNS) FOR FINDING AND ANALYSIS FUNCTIONAL CONNECTIVITIES

We have seen three different methods in the previous chapters that can be used for analysis the functional connectivities from *functional magnetic resonance imaging*(fMRI) of brain images. All three methods have limitations of assuming hat the interactions between areas in the brain are linear and deterministic or they need a lot of prior knowledge to learn the functional connectivities. Though *dynamic causal modeling*(DCM) allows non-linearity to certain extent, it is limited in the sense that non-linearity is modeled only between the input stimulus and brain areas. Assuming the interactions among brain regions is deterministic is another severe limitation that these methods suffer.

Deterministic interactions between areas of brain means, for the same input stimulus the brain areas are expected to be activated the same amount and the strength of the connections between different areas will be the same [Friston et al., 2003]. There has been no hard evidence for this assumption. In addition even though we give the same input stimulus there is always the chance of the subject doing different things that may interfere with the input stimulus leading to more or less activations and different connection strength than the expected ones. So there is a need to introduce a model than can handle the uncertainties in the data collected.

As discussed in chapter 3, *dynamic Bayesian networks*(DBNs) can model uncertainty in terms of conditional probabilities and also can handle non-linearity in data [Smith et al., 2006]. So DBNs can be used to analyse of functional connectivities from fMRI of brain images.

5.1 Task Description

There are studies that determine the involvement of prefrontal and visual association regions during selective information processing by examining brain activity in correspondence to specific versus nonspecific memory cues during a delayed recognition task. It

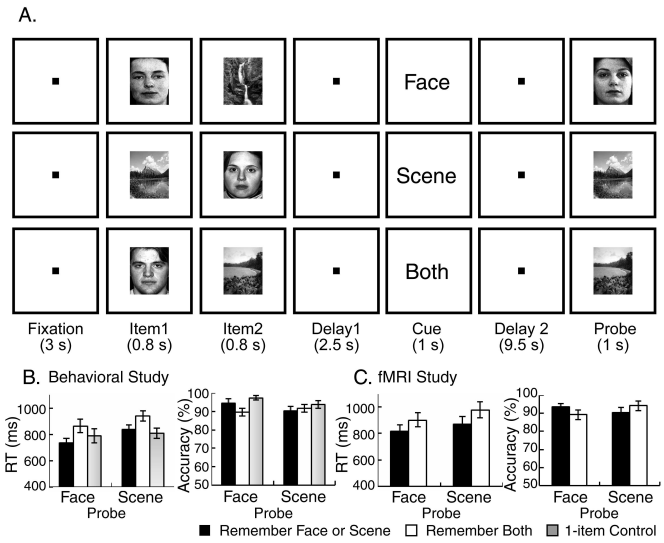

Figure 5.1: Task Design for Face/Scene Analysis, Courtesy: Ms Hwamee Oh

was expected that if a region is involved in selective maintenance, its activity would be correspondingly greater to the relevant specific cue than to the nonspecific cue. [Oh and Leung, 2008]

In this study areas related to remembering and recognising faces vs Scenes are examined. The figure 5.1 gives a description of the main task.

The localizer task was used to determine brain regions that show greater responses to faces in comparison to scenes, and vice versa. It was in 1-back task format, where one determines whether or not the current stimulus matches the last stimulus. Our task had 8 alternating blocks (4 face blocks and 4 scene blocks). Each task block was 16 sec long and they were separated by a 16-sec fixation period. Within each task block, 8 visual images were sequentially presented, each for 800 msec, with a 1.2 sec inter scan interval (ISI).

5.2 Aim

For the above task it was determined that left and right *Face Fusiform Areas*(FFA) are the regions associated with remembering and recognising faces, while left and right *Parahippocampal Place Areas*(PPA) are the regions associated with scenes. Twelve subjects participated in the experiment, PPI analysis is done for each of the subject for

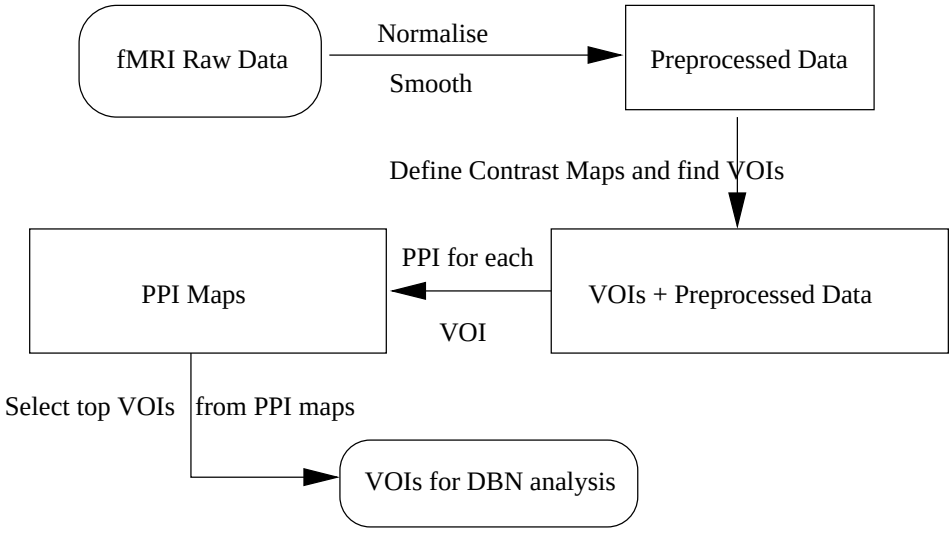

Figure 5.2: Pipe Line for processing the fMRI data

each of the l/r FFA, l/r PPA and the 9 areas with highest linear correlation obtained are used for DBN analysis. The figure 5.2 summarises all the steps done to get the data for DBN learning. The next sections describes DBNs used for the analysis of data and the results section contains the co-ordinates for the regions found using PPI maps.

5.3 Method

Range of the *blood oxygenation level dependent* (BOLD) signal that fMRI measures is different for different areas of the brain and also for different subjects. We need to make sure that normalisation be done separately for all the subjects for different regions. The plots in figure 5.3 of raw signal indicates the differences in range of bold signal. If we normalise over all the subjects and areas together, then discretisation based threshold the areas with lesser range of activations will not show up and lead to spurious results.

Since the software packages available for DBNs BNT toolkit by Murphy [2001] and Banjo by J.Hartemink and et. al [2005] can only handle discretised multivariate distributions, we need to discretise the BOLD signal values. This discretization usually depends on the experimental data we have. There is no particular way of discretising that is better. Though Friedman and Goldszmidt [1996] has described a method for automatic discretisation of data, it can handle only minimum description length(MDL) as a scoring metric. For this analysis normalisation and discretisation are handled at the

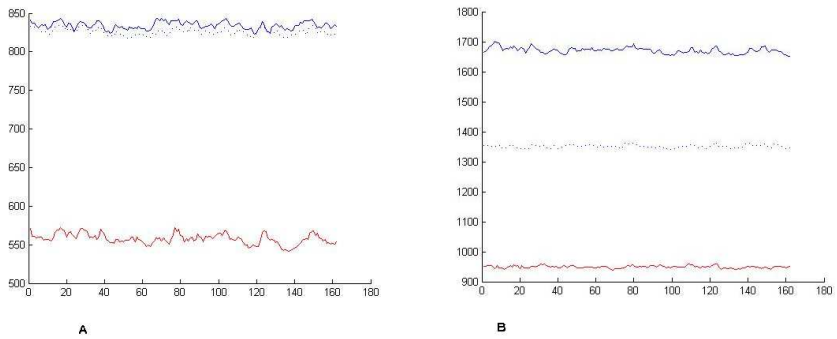

Figure 5.3: **A**: The plot of Left Visual Cortex(Blue Line), Left Motor Cortex(Dotted Line), Left PreMotor(Red Line) area for **Subject 1**, showing the difference in range of bold signal for different areas in the same person. **B:** The plot of Left Visual Cortex(Blue Line), Left Motor Cortex(Dotted Line), Left PreMotor(Red Line) area for **Subject 13**.

same time by doing a local discretisation. If t_i and t_j respectively are the starting and ending times of to a particular event. The fMRI data between t_i and t_j are considered separately for each subject for each ROI and discretised into 3 equal intervals so the data will have a value of 0,1,2. Different sized intervals have been tried and the one giving most meaningful results was taken.

One of the main disadvantage of DBNs is that the learning methods can get stuck in local minima whatever methods we use for searching [Ortiz, 1998]. There is not enough data to have statistically significant results which is another issue for using DBNs. Though simulated annealing theoretically guarantees convergence to global minima, often impractical because it takes too long to converge. The final structure found is mainly influenced by the initialisation. In our case there are 4 regions in the brain lFFA,rFFA,lPPA,rPPA and we need to know how strongly are these connected to 9 other regions. The knowledge about other connections is not significant. So each of these 4 region is initialised to have the other 9 regions as parents and given to the DBNs to analyse the connections.

The influence score metric developed in Yu et al. [2004] is used to finally get the strength of each connection. The sign of the influence score is ignored, because we consider inhibition and excitation as equal influence. The scores for left and right FFA are added to get a score for FFA and similarly the scores for left and right PPA are added to get a score for PPA. Because the influence score is calculated as a difference of

cumulative probabilities and the left and right PPA and FFA are assumed to independent and their influence score are added directly.

A voting system is developed to combine the scores for each area for all subjects, so that a comparative study can be performed. Let s_{ffa} represent the influence score for FFA and s_{ppa} represent the influence score for PPA for a particular subject for a particular region, and for a particular condition. If there is no connection then it is represented with a -1. The algorithm presented in figure 5.4 assigns labels that will be later used for weighted voting. Once labels are assigned for each area for each subject a value of 3,2,1,0 are assigned for GRE,EQL,LES and None respectively, and these values are summed over all subjects.

if $s_{ffa} \neq -1 and s_{ppa} \neq -1$ **then**
  if $s_{ffa} > s_{ppa}$ **then**
    $area_{ffa} = GRE;$
    $area_{ppa} = LES;$
  else if $s_{ffa} == s_{ppa}$ **then**
    $area_{ffa} = EQL;$
    $area_{ppa} = EQL;$
  else
    $area_{ffa} = LES;$
    $area_{ppa} = GRE;$
  end
else if $s_{ppa} = -1 and s_{ffa} > -1$ **then**
  $area_{ffa} = GRE;$
  $area_{ppa} = None;$
else if $s_{ffa} = -1 and s_{ppa} > -1$ **then**
  $area_{ffa} = None;$
  $area_{ppa} = GRE;$
else
  $area_{ffa} = None;$
  $area_{ppa} = None;$
end

Figure 5.4: Labeling Algorithm

Table 5.1: Table showing the regions and co-ordinates from PPI analysis for lFFA

ROI	X	Y	Z
vmSFG-r	9	21	51
ldmSFG-r	18	6	66
vlFG-l	-39	21	3
MFG-l	-42	30	21
dIPL-l	51	-39	42
dIFG-l	-39	9	21
lIOG-r	27	-87	3
Cblm-l	-36	-72	-33
mIOG-r	12	-96	0

5.4 Results and Discussion

Tables 5.1,5.2,5.3 and 5.4 give co-ordinates and regions that we found using PPI for lFFA,rFFA,lPPA,rPPA respectively.There are four ways in which we can classify the regions found.

- Type 1 : Areas that influence FFA more during face related events and PPA more during scene related events can be classified as **task related**.
- Type 2 : Areas that influence FFA more than PPA during face and scene related events, can be classified as **FFA related** areas.
- Type 3 : Areas that influence PPA more than FFA during face and scene related events, can be classified as **PPA related** areas.
- Type 4 : Areas that influence PPA more during face related events and FFA more during scene related events, can be classified as those that help in inhibiting the PPA during face related events and FFA during the scene related events, **inhibitory areas**.

The table 5.5 gives a list of areas for all the four types, which were found by using the influence score [Yu et al., 2004] and voting algorithm that was described in the previous section.

mIOF is found to be one of the areas in brain responsible for active memory [Johnson et al., 2007], which supports the fact that it is task specific, which we found in this analysis. One interesting pattern we can see from the table 5.5 is that right side of

Table 5.2: Table showing the regions and co-ordinates from PPI analysis for rFFA

ROI	X	Y	Z
dmSFG-r	3	9	63
vIFG-r	30	21	-15
dIFG-l	-39	6	21
mSFG-l	-12	6	60
ldmSFG-r	15	6	66
cblm-l	-39	-72	-30
vIFG-l	-42	18	3
dIFG-r	45	12	21
SFS	-27	6	57

Table 5.3: Table showing the regions and co-ordinates from PPI analysis for lPPA

ROI	X	Y	Z
IOG-r	24	-81	-15
FG-l	-39	-45	-24
IOG-l	-18	-93	-3
LG1-r	9	-78	18
LG2-r	27	-60	-18
IPL-l	-33	-45	45
SFS-r	30	3	51
put-l	-21	15	-6
mSFG-l	-3	-3	69

Table 5.4: Table showing the regions and co-ordinates from PPI analysis for rPPA

ROI	X	Y	Z
FG-r	39	-72	-21
SPL-l	-18	-69	48
mSFG-r	3	6	60
insula	-27	27	0
SFS-r	39	0	57
IOG-l	-30	-81	12
SFS-l	-24	0	54
dIFG-l	-48	6	30
MFG-r	-39	30	24

Table 5.5: A table showing the classification of brain areas related to face and scene processing into four categories that we defined

TYPE	Areas related to face and scene processing
Task related	mIOG-r, dIFG-r, mSFG-r
FFA related	vmSFG-r, ldmSFG-r, mSFG-l, SFS, put-l
PPA related	vIFG-l, dmSFG-r, vIFG-l, FG-r, IOG-l, insula
Inhibitory Areas	MFG-l, dIPL-l, SPL-l, SFS-l

the brain seems to be more of task related and the left side of the brain is involved in inhibitory control. There are studies on inhibition and active memory on face/scene related design [Johnson et al., 2007, Gazzaley et al., 2005], but the observation that right side of the brain is involved in task related activity and left side of the brain in inhibition has not been researched much. So our observation needs to be researched more before establishing a concrete result.

The role of mSFG(pre-SMA) was not clear in [Oh and Leung, 2008], but in this type of analysis it seems to be task specific when having an influence on the FFA or PPA, since it had a greater influence on FFA during face related activity and greater influence on PPA during scene related activity.

The fact that we are able to separate the task related areas and inhibitory areas is novel, since all the previous studies [Oh and Leung, 2008, Johnson et al., 2007], just saw the how the activations of the regions are modulated during the specific events but never didn't study the influence of the regions on FFA or PPA to compare them. But there is a need for further investigation about the this kind of categorisation.

There is experimentation done on the robustness of the algorithm , do we get the same results with noise added, what kind of results we may get if we remove one subject from the analysis are some of the issues regarding the usage of the proposed analysis that are need to be addressed.

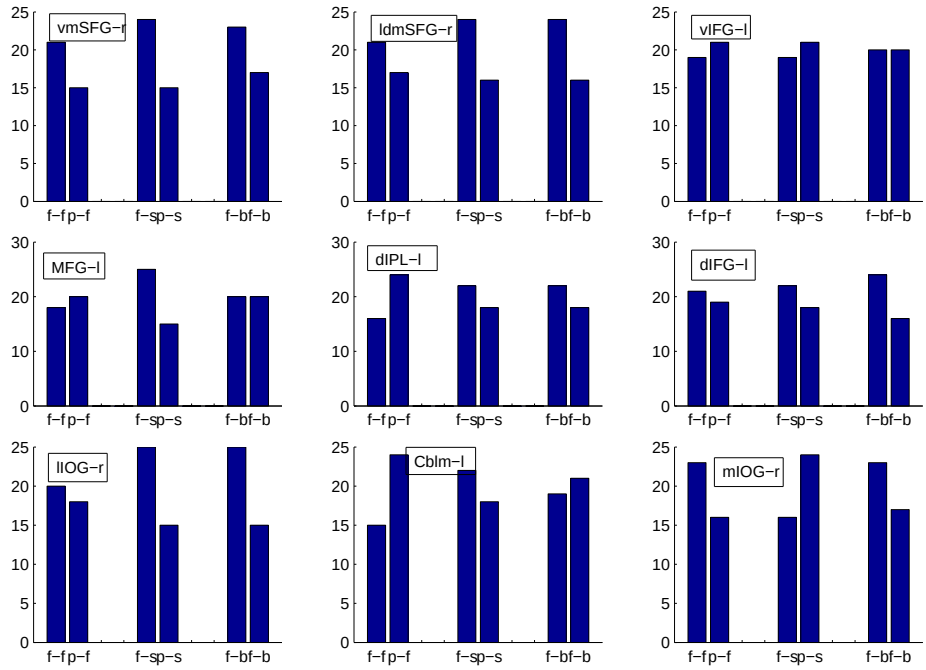

Figure 5.5: This figure shows the different areas correlated with lFFA that PPI analysis resulted in and those were used for DBN analysis. The y-axis plots the weighted vote measure which we developed.The labels on the x axis of each histogram correspond to FFA in face events(f-f), PPA in face events(p-f), FFA in scene events(f-s), PPA in scene events(p-s), FFA in both events(f-b), PPA in both events(p-b).

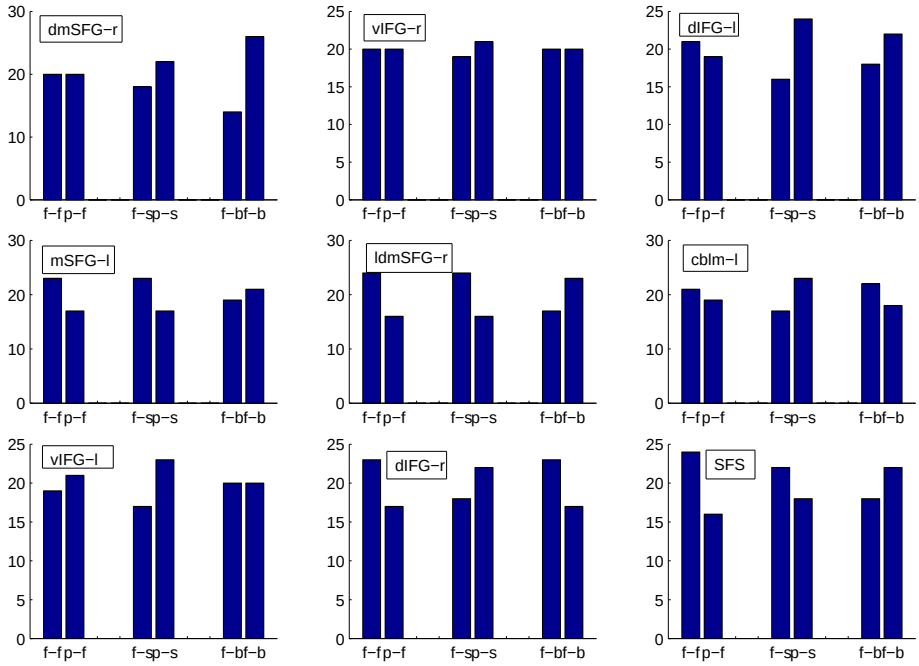

Figure 5.6: This figure shows the different areas correlated with rFFA that PPI analysis resulted in and those were used for DBN analysis. The y-axis plots the weighted vote measure which we developed. The labels on the x axis of each histogram correspond to FFA in face events(f-f), PPA in face events(p-f), FFA in scene events(f-s), PPA in scene events(p-s), FFA in both events(f-b), PPA in both events(p-b).

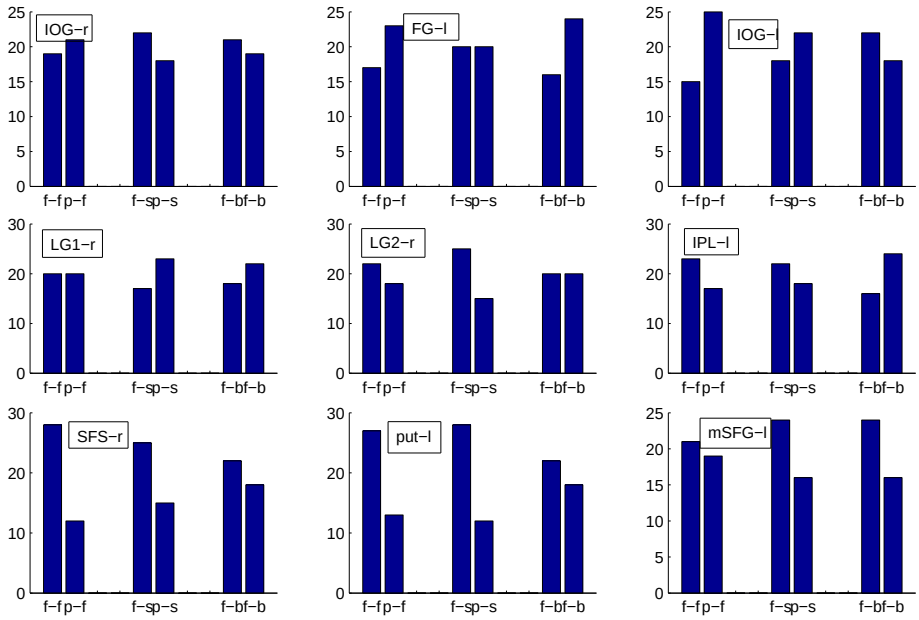

Figure 5.7: This figure shows the different areas correlated with lPPA that PPI analysis resulted in and those were used for DBN analysis. The y-axis plots the weighted vote measure which we developed. The labels on the x axis of each histogram correspond to FFA in face events(f-f), PPA in face events(p-f), FFA in scene events(f-s), PPA in scene events(p-s), FFA in both events(f-b), PPA in both events(p-b).

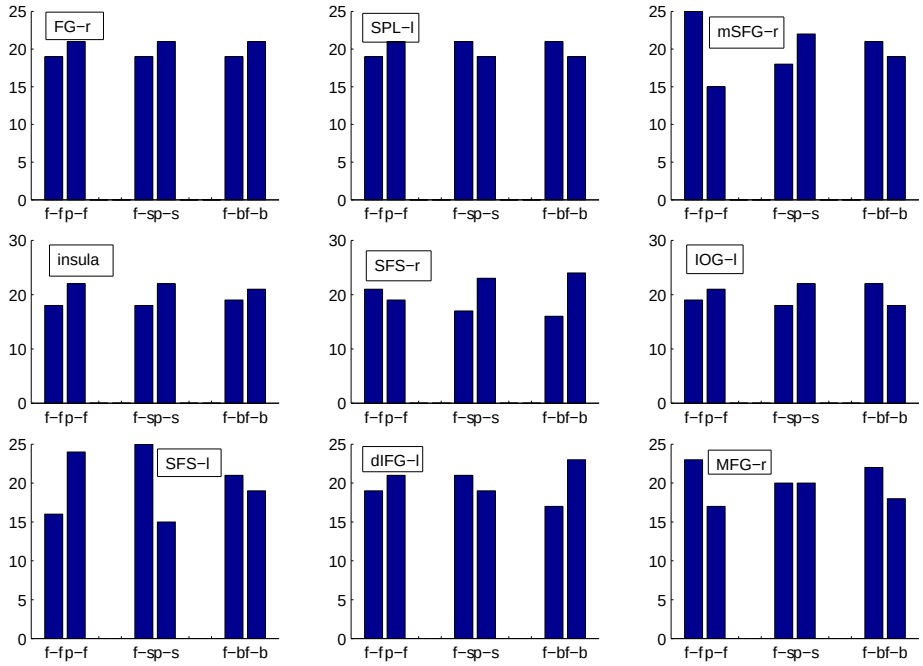

Figure 5.8: This figure shows the different areas correlated with rPPA that PPI analysis resulted in and those were used for DBN analysis. The y-axis plots the weighted vote measure which we developed. The labels on the x axis of each histogram correspond to FFA in face events(f-f), PPA in face events(p-f), FFA in scene events(f-s), PPA in scene events(p-s), FFA in both events(f-b), PPA in both events(p-b).

CHAPTER 6

CONCLUSIONS AND CONTRIBUTIONS

6.1 Conclusions

The new method found can be used to do a comparative strength between brain areas. Though structure learning algorithms for Dynamic Bayesian Networks can be stuck in local optima they can be used for finding connectivities between brain areas with good initial structures. As stated earlier a great amount of validation needs to be done before saying anything about the results.

6.2 Contributions and Future work

Dynamic Bayesian Networks in combination with Pyschophysiological Interactions(PPI) are used to make a comparative study of brain areas related to Fusiform Face Area(FFA) area that processes face information and Parahippocampal Place Area (PPA) place that processes scene information. A new approach to combine results from multiple subjects is developed using the influence score metric which is defined by Yu et al. [2004]. Some areas that conditionally influence FFA, PPA are found and some areas which are specific to task are discovered.

There is no scheme for validating the results, so the first step would be to find methods to validate the results. Anatomical correctness of the connections between the areas found should be evaluated by the psychologists and neurologists. Schemes like leave one out validation should be done to see how variant or invariant the Dynamic Bayesian Network structures found by the structure learning algorithm. A statistical way to combine the results from different subjects should be utilized rather than using a simple voting system. The robustness of the analysis to noise should be looked into. The usage of Cross Validation as an evaluation metric in place of using BDe owing to the less amount of data available, should be investigated.

The limitation of heuristic structure learning methods is that they are impractical for searching for a global optima with the computers systems we have. Using a super

computer for learning can be used to search for a larger portion of sample structure space which can lead to global optima.

Decreasing the search space from exponential to some small n_{th} degree polynomial will reduce the complexity of search space, which can be one more way of solving the problem of getting stuck in local optima. If we can manage to decrease the search space by imposing some conditions we can have the data better modeled. Decreasing the search space would also mean the results we get can be more statistically significant. Using partially observable models with hidden states we can try to find the neural connectivities instead of the BOLD signal functional connectivities. These are few steps which can be considered for future work.

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APPENDIX A

PROBABILITY

If you are familiar with concepts of probability you can skip this chapter. However since it is a small one you can skim through it just to remind yourself of the concepts.

Probability is a mathematical model to describe uncertainty. The two main elements of a Probabilistic Model are

- The sample space Ω, which is the set of all possible outcomes of an experiment
- The **probability law** which assigns a non-negative number $P(A)$ to a set A of possible outcomes that will tell us the certainty or uncertainty A happening.

The probability of an event A occurring is defined as

$$P(A) = \frac{|A|}{|\Omega|} where || - cardinality \tag{A.1}$$

A.1 Probability Axioms

The theory of probability is based on certain axioms.

- **Nonnegativity** $P(A) \geq 0, \forall A$
- **Additivity** If A and B are two disjoint events, then the probability of their union satisfies

  $$P(A \cup B) = P(A) + P(B) \tag{A.2}$$

  The equation below is more general form given $A_1, A_2, A_3...$ are disjoint events

  $$P(A_1 \cup A_2 \cup A_3.....) = P(A_1) + P(A_2) + P(A_3)..... \tag{A.3}$$

- **Normalisation** The probability of entire sample space Ω equals 1, i.e. $P(\Omega) = 1$

A.2 Conditional Probability

Understanding Conditional Probability is the most important to interpret and know Dynamic Bayesian Networks. It is very simple but powerful concept. Conditional Probability provides us with a way to reason about the outcome of an experiment, based on partial information. Here are few examples

- You see the grass wet what are the chances that the sprinklers were on or what are the chances that it rained.
- In a word game you know that the first letter is Q what are the chances that second letter is U
- You see a face in a photo what are the chances that it is one of your friends
- You know that there are 6 carbon atoms in a compound what are the chances that it is benzene

The Conditional Probability of an event A given, event B is defined as

$$P(A|B) = \frac{P(A \cap B)}{P(B)} \tag{A.4}$$

A.3 Total Probability Theorem

Let $A_1, A_2, A_3....A_n$ form a partition of the sample space which implies

$$\Sigma_{i=1}^{n} A_i = \Omega \tag{A.5}$$

$$A_i \cap A_j = \Phi, \forall i \neq j \tag{A.6}$$

$$P(A_i) \geq 0, \forall i \tag{A.7}$$

Then for any event B we have

$$P(B) = P(A_1 \cup B) + P(A_2 \cup B) + P(A_3 \cup B)... + P(A_n \cup B) \tag{A.8}$$

$$P(B) = P(A_1)P(B|A_1) + P(A_2)P(B|A_2) + P(A_3)P(B|A_3) + ...P(A_n)P(B|A_n) \tag{A.9}$$

A.4 Bayes Rule

From the definition of conditional probability and total probability theorem we have the Bayes rule which is

$$P(A_i|B) = \frac{P(A_i)P(B|A_i)}{P(B)} \tag{A.10}$$

$$P(A_i|B) = \frac{P(A_i)P(B|A_i)}{P(A_1)P(B|A_1) + P(A_2)P(B|A_2) + P(A_3)P(B|A_3) + ...P(A_n)P(B|A_n)} \tag{A.11}$$

A.5 Random Variable

The outcome of an experiment (the domain of a sample space Ω) need not always be numerical. It is always helpful to associate a numerical value of interest with such experiments. Even if the outcome of an experiment is numerical it will always be helpful if we can map the numerical value to another real number. **Random Variable** is a function that maps the outcome of an experiment to a real number.

Properties and Concepts related to Random Variables

- A random variable is a real-valued function of the outcome of the experiment
- A function of a random variable defines another random variable
- A random variable can be conditioned on an event or another random variable

Bertsekas and Tsitsiklis [2002] can be used for further reference.