Neuroinformatics Research
Research Proposal

Analysis of Functional Brain Connectivity using Graph Theory in Alzheimer's Disease

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Abstract

One of the most common causes of dementia is Alzheimer's disease (AD). Magnetoencephalography (MEG) recordings provide interesting information about the way neural oscillations are altered in patients suffering from this disorder. It is only recently that graph theory principles have been applied to the study of structural and functional connectivity in brain networks. This project aims to compute and compare functional connectivity graphs of control subjects and of patients suffering from AD and Mild Cognitive Impairment (MCI). Phase lag index is used to measure phase synchronisation between the MEG sensors. The obtained results give information about the connectivity strength between each pair of MEG channels. These in turn are used to build functional connectivity graphs for each subject. A number of graph features such as small-world topology, clustering coefficients and modularity will be compared between the subject groups. Classifiers such as support vector machines will be trained using the computed graph measures. This will allow categorisation of a new subject's recording into one of the AD, MCI or healthy control (HC) categories. The final purpose of the results is to contribute to the development of more accurate clinical diagnosis methods and to the design of better predictions about disease progression.

1. Background

AD is the most frequent cause of dementia [1]. It is also a significant economical burden to most countries and the costs are expected to grow remarkably by the year 2050, with 1 out of 85 people suffering from the disease [2]. AD can be placed in four categories: MCI, Mild and Moderate AD and Severe AD. The first stage is MCI with memory loss as the main symptom [3]. Early diagnosis allows more effective treatments as medication has a greater impact when started in advance and also allows patients to start planning a course of action with their families.

Magnetoencephalography (MEG) records perturbations that occur in the magnetic field produced by populations of neurons. The advantage of electrophysiological methodologies such as MEG is the high temporal resolution (1-100 Hz), whereas a caveat of the technique lies in the lower spatial resolution (order of millimetres or centimetres) [4].

Synchronised activity of groups of neurons gives rise to neural oscillations. Many cognitive functions have been linked to these patterns of activity [5]. It is thus believed that studying the brain from a network point of view would yield insight into its functioning. MEG recordings fulfil the

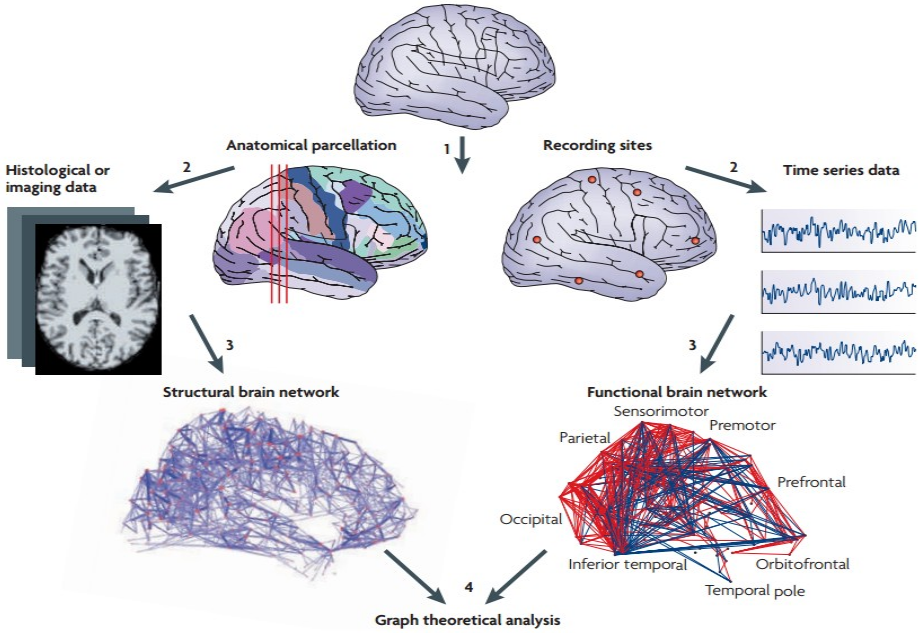
condition of recording brain activity at a global level. These recordings can be classified in different frequency bands: infraslow (<0.2 Hz), δ (0.2-3.5 Hz), θ (4-7.5 Hz), α and μ (8-13 Hz), β (14-30 Hz), γ (30-90 Hz) and high-frequency oscillations (>90 Hz) [4].

Studies have suggested that brain networks which play a role in memory are active in the resting state [6]. As brain diseases such as AD affect memory, more attention has been given to recordings made during this state. It is interesting to see how these oscillations differ between healthy people and patients suffering from AD or MCI.

1.1 Functional Connectivity Graphs

In [7], Sporns argues that graph theory can be used to provide quantitative analysis of brain networks. This would provide insights into characteristics such as network vulnerability which would allow us to predict how diseases may evolve in patients.

It is only recently that these mathematical concepts have been applied to brain networks [8]. A graph is simply a structure formed by a set of nodes or vertices and a set of edges which connect the former. In the context of brain graphs, the nodes denote anatomical regions and the edges reflect a connectivity function. Depending on the acquired imaging data, the connectivity function can be structural or functional. The former refers to physical or anatomical connections linking neural elements and is mapped using diffusion tensor imaging and tractography [9], while the latter refers to neurophysiological dynamics and is mapped using fMRI, EEG or MEG recordings. In *Illustration 1*, the general process of exploring brain networks with graph theory is shown.



1. Illustration: Structural and functional brain networks (from [13]) - In step 1, the network nodes are specified. These can be anatomical regions in case of diffusion tensor imaging or electrodes in case of EEG or MEG. In step 2, a measure of association between nodes is computed (e.g. spectral coherence for MEG electrodes). An association matrix is computed in step 3 which shows the connections between pairs of nodes. In step 4, graph measures are derived from the matrix computed in the previous step.

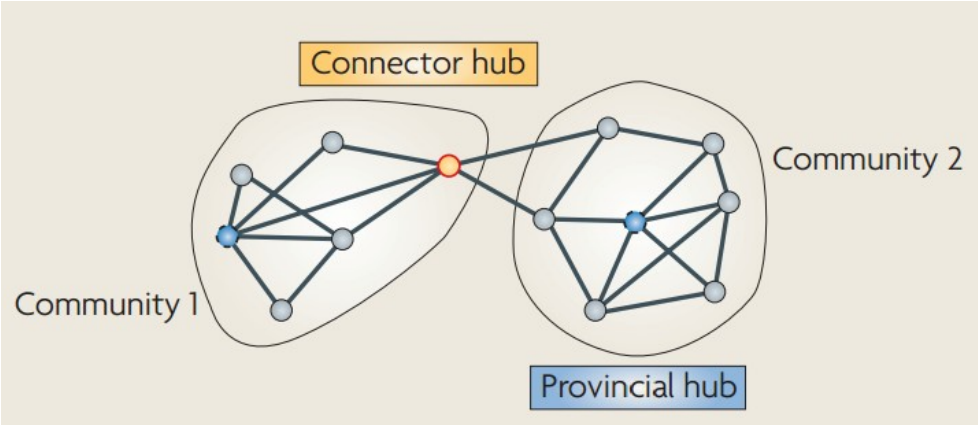
It is important to note that functional connectivity characterises statistical relationships, which means that it does not indicate causal effects of underlying neural structures [7].

Neural mass models use simplifications to model network dynamics. Alstott et al. [10] integrated previous structural connectivity data sets [11] and neural mass models [12] to create a computational model that can be used to explore the functional effects of brain lesions. They saw that removal of random nodes or of nodes with high degree does not have a high impact on node interactions, but deletion of high-centrality nodes (hubs) causes great network interference. The network characteristics examined in the current project can lead to more AD-targeted computational models for looking into different stage-specific scenarios of the disease.

1.2 Graph Analysis

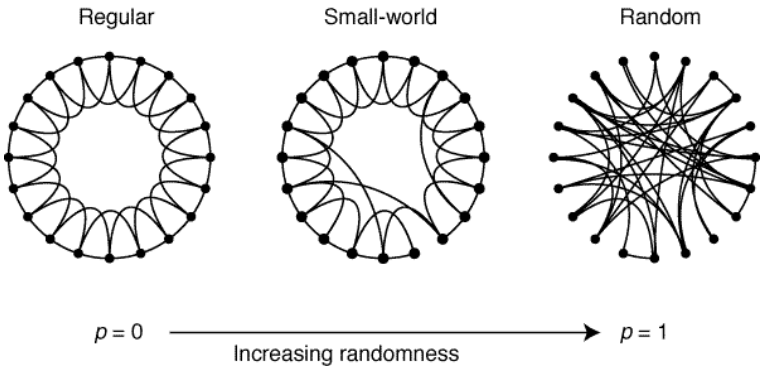
An overview of basic principles of graph theory can be found in the review [13].

A basic graph measure is the node degree. This refers to how many connections or edges link a node to the rest of the network. Nodes also have a measure of centrality. This refers to the number of shortest paths between the other pairs of nodes in the network that pass through a specific node. Nodes with a high measure of centrality are critical for fast communication. Hubs are nodes with either high degree or high centrality. Hubs and modules for a small graph are given in *Illustration 2*.



2. Illustration: Hubs and modules (communities) (from [13]) - The connector hub coloured in orange bridges two modules. The node in blue is a provincial hub because of its tendency to attach to nodes within a single module.

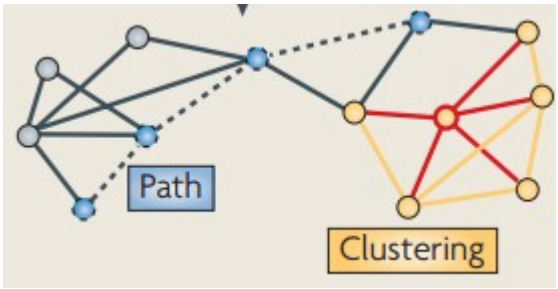
It has been suggested that brain networks have reached a balance between infrastructure costs (building and maintaining paths) and high connectivity. This equilibrium of high clustering and short paths is referred to as a "small world" model. The term was introduced by Watts and Strogatz [14]. This means that although most nodes have a small number of connections, they are still linked to distant nodes by a small number of edges. This is hypothesised to underlie information transfer and fast local computation and integration of results in the overall network [13]. In the picture below (*Illustration 3*), the small-world network is compared to the two other basic network types.



3. Illustration: Basic network types (from [14]) - Each node of a network is initially connected to its 4 neighbours. The network is highly clustered and most path lengths between nodes are high. With a probability p we disconnect edges and attach them to random nodes. If p is 1, all of the edges will be reconnected which results in a random network. This kind of network lost the high clustering property. For values of p between 0 and 1, the network maintains the high clustering quality and exhibits small path lengths.

Graph analysis of AD brain networks is still in its infancy. Studies concerned exclusively with AD can be found in [15] and [16]. In a very recent review, Tijms et al. [17] analysed the findings of 13 studies that addressed AD from a graph theory perspective. They found that a decrease and reorganisation of connectivity occurs in AD graphs. Although the studies found common graph characteristics, there are instances where some properties are inconsistent across results.

Two standard graph measures are the clustering coefficient and the average path length. The clustering coefficient is a common method of measuring local segregation. This refers to how densely connected is a node relative to the node's neighbours. A high coefficient characterises a cluster, while a low one indicates sparseness between neighbours. Previous studies have reported that clustering coefficients decline in AD graphs [15], [18]. The figure below illustrates a cluster.



4. Illustration: Path and cluster in a graph (from [13]) - A path is the sequence of edges connecting two nodes. Directly connected nodes form a cluster.

The shortest path length refers to the minimum number of edges between two nodes. The unnormalised path length was reported to be consistently increased in AD because of a decrease in connectivity. The normalised path lengths (divided by average path length of a random graph) were inconsistent [17].

A graph is said to have high modularity if the graph is formed of subgraphs (modules) that have high intraconnectivity and low interconnectivity (connection between the subgraphs). Only one study looked at network modularity in AD and found fewer modules in AD networks. [19] Also, in this study, increased modularity was found in the theta band. Intramodular connectivity was the same compared to control groups, but intermodular connectivity was affected. This suggests that a decrease in connector hubs occurred.

The study by Stam ([20]) was one of the earliest studies which showed that functional connectivity networks of healthy subjects have the small-world network property. All studies reviewed in [17] reported that the AD networks have the small-world property and three studies out of the 13 described a decline in the small-world value in AD networks, presumably because of the increase in path length.

Another characteristic that was only explored in one fMRI study [21] and one MEG study [18] is the Eigenvalue centrality (EC) measure. [22] This is used to identify hub nodes which previous studies report to be vulnerable in AD [29].

The authors of [17] suggest that a possible cause for the incompatibilities between studies is the lack of standardised methods for building these types of graphs. Another cause may be the small sample sizes used in the studies. It is proposed that for a study which aims to compare 3 groups (e. g. AD, MCI and control groups), larger sample sizes are required.

In summary, network-based biomarkers have gained popularity in recent years. The review by Horwitz and Rowe [23] outlines the relevancy of network analysis of neuroimaging data in the investigation of neurodegenerative disorders. There is evidence that imaging networks can help in discriminating between diagnoses [24] and in gaining understanding of disease neuropathophysiology [25] and disease progression [26]. As within the realm of AD research literature individual studies focused only on assessing a few graph measures [17], the proposed project aims to address this gap by describing a relatively large dataset of AD, MCI and HC with a comprehensive set of graph characteristics.

2. Goals

The present data analysis project aims to answer the research question:

What are the identifiable differences in functional brain connectivity between populations of AD, MCI and control subjects?

To answer this question, functional connectivity graphs of patients (AD, MCI) and HC subjects are proposed to be compared as part of this project. The piece of research would supplement the current literature by providing more advanced graph statistics that have been little investigated in the past. This would be relevant for predicting how the disease might progress and may contribute to the development of more focused clinical treatments targeted to certain regions of the brain. The processing pipeline developed in this project might also be used to create new longitudinal studies that will compare connectivity graphs for the same patients throughout time.

Partial Objectives

- signal processing: compute correlations between the pairs of MEG sensors
- graph analysis: compute functional connectivity graphs and graph measures
- classification: train classifiers using graph measures as features to categorise recordings of new subjects in one of the AD, MCI or HC categories

3. Methods and Predicted Results

3.1 Dataset

The dataset proposed for this study is the same one used in [27]. The study involved resting state MEG recordings from 80 patients: 36 diagnosed with AD (mean age 74.06, standard deviation 6.95), 18 with MCI (mean age 74.89, standard deviation 5.57) and 26 control subjects (mean age 71.77, standard deviation 6.38). The recordings were performed by using an MEG with 148 channels and are 5 minutes long at a sampling frequency of 169.54 Hz. Mini-mental state examination (MMSE) test scores have also been collected for each of the patients. These reflect the cognitive abilities of the subjects [28].

3.2 Signal Processing

The data will be processed in a similar fashion to the one employed in the study by Stam et al. [29]. In the data preprocessing stage, artefacts caused by events such as eye movements or heartbeats need to be removed. In the case of heartbeat artefacts, removal can be done using independent component analysis. The method has been previously described and applied in [30]. Subsequently, the recordings will go through a filtering process where a Fourier transform would be used to ignore frequencies outside the main spectral bands that are to be studied (delta, theta, alpha, beta and gamma). The inverse Fourier transform would be then used to obtain the filtered signal with original phase information. The results would then be band-pass filtered for each of the main frequency bands.

A 148x148 adjacency matrix illustrating the connectivity strength between each pair of MEG channels would be then constructed, as the MEG device has 148 channels. Similarly to [29], the phase lag index (PLI) [31] would be used to populate the connectivity matrix. PLI is a measure of the asymmetry of the distribution of phase differences between two signals. The problem of volume conduction consists in the fact that EEG or MEG sensors in proximity may register activity from the same source which would lead to false correlations. Compared to previous methods, PLI is much less affected by this problem. A traditional metric which can also be used to inspect the relationship between two signals is the spectral coherence [32]. If phase differences cannot be successfully identified with PLI, then coherence will be used as a fallback method.

3.3 Graph Analysis

The adjacency matrices corresponding to the different frequency bands would be analysed using the open-source Brain Connectivity Toolbox (BCT) written in Matlab [33]. This allows computation of complex network features and comparison with existing datasets included in the toolbox. The

project aims to apply the graph measures explained in section **1.2** (**Graph Analysis**) to the previously described dataset.

Clustering coefficients measure how much nodes in a graph are clustered together. It is predicted that in AD and MCI graphs a decline in the average clustering coefficient would be found. This would be in agreement with previous studies [15], [34].

It is also worth exploring how the normalised path lengths are affected in MCI and AD patients, as studies reported inconsistent results. The relationship between path length and small-world property has also been superficially investigated in MCI and AD patients [17].

EC is another measure that has been poorly explored in the past. The only MEG study that assessed this measure ([18]) had only 18 AD patients (vs 36 in the dataset mentioned at the beginning of the section) and 18 controls (vs 26 in the same dataset). Also, the correlations between the MEG channels were computed using the Synchronisation Likelihood (SL) instead of the proposed PLI. SL is more prone to be affected by the volume conduction effect than the PLI measure [29].

The dataset of this project can provide insights into modularity statistics not only in AD patients, but also in MCI patients. To my knowledge no previous study explored modularity in the latter category.

3.4 Classification

Support vector machines (SVMs) are a type of supervised machine learning algorithm that can be employed to classify a subject's previously unobserved data into a predefined category [35]. The algorithm is trained on a set of pairs of feature vectors with corresponding categories. In the current setting, a feature vector is composed of an individual’s graph measures computed in the previous step. The set of categories is AD, MCI or HC.

SVMs were chosen because of their high accuracy and popularity in previous AD literature. For a review of studies using this method, please see [36].

Prior to training the classifier, two steps need to be performed:

3.4.1 Feature extraction and feature selection

Feature extraction represents the process of transforming the initial data into a set of features that the SVM can use as input. This has been done in the graph analysis step with the resulting graph measures. Feature selection can refer to selecting those features that are most discriminating in choosing which category the feature vector belongs to. For example, knowing that hub regions are more vulnerable in AD, we can define regions of interest around those areas within the graphs and just supply the measures computed from those regions to the classifiers, hoping to increase prediction accuracy. Feature selection can also refer to feature elimination, which looks at removing redundant or uninformative attributes with the goal of increasing accuracy and decreasing algorithm learning time.

3.4.2 Training and Testing

SVMs can inherently discriminate between two classes. As a feature vector can be assigned to three possible categories (AD, MCI, HC), a multiclass SVM classification problem is identified. This problem is overcomed by training binary classifiers between every pair of classes (AD vs MCI, AD vs HC, MCI vs HC). Each of the classifiers assigns a given vector to a class and the class with most assignments is the final predicted class. This is also called pairwise classification. Another option would be the “1 vs all” method in which the classifier with the highest decision function value chooses the final class. We would choose the former option, as this is the one implemented in libraries that support SVM training such as WEKA [37] or LIBSVM [38]. It has also been shown that training time is shorter in the “1 vs 1” method [39].

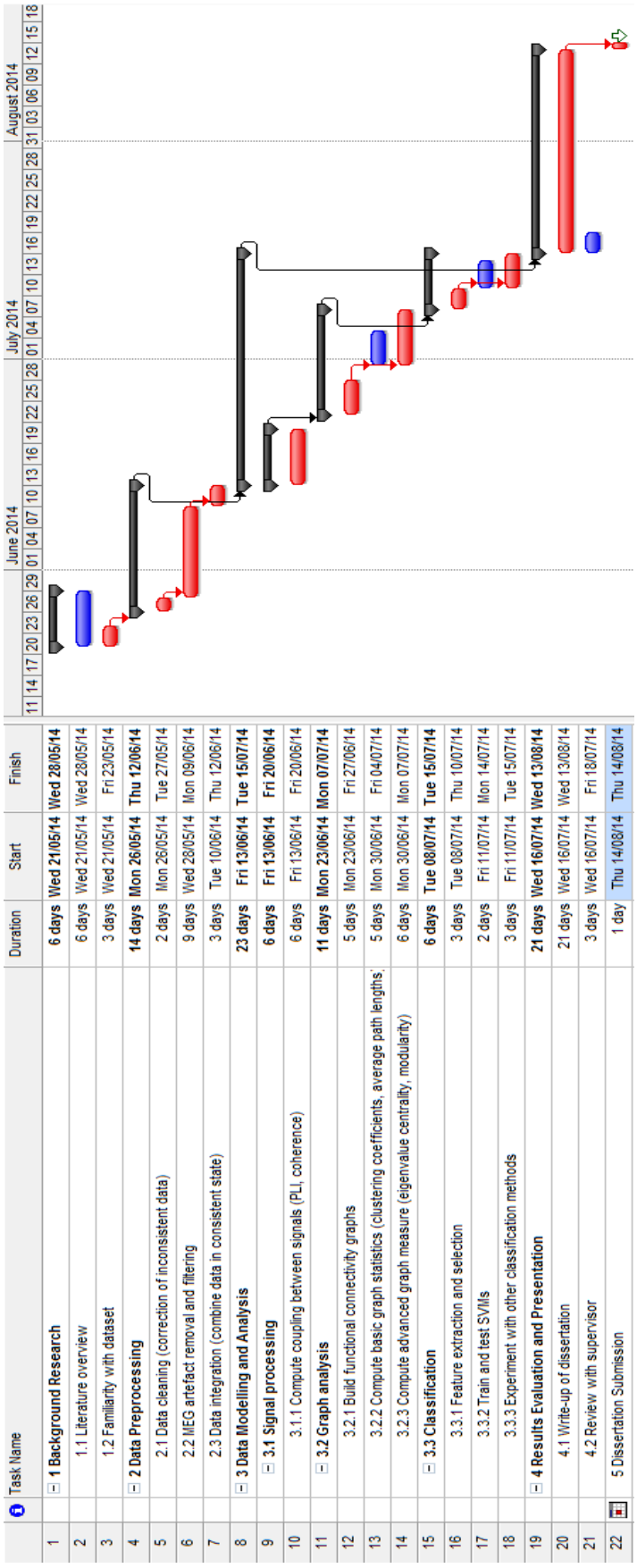
In the testing phase, we asses the performance of the trained algorithm on new data. In order to ensure generalisability, the testing data must not overlap with the training data. “Leave-one-out” cross-validation can be used to train the SVM on all data except one feature vector which will be used for testing [40]. An estimate of the classifier’s accuracy is obtained by repeating the process for each feature vector in the dataset.

Further investigations of the classification stage will be made in later phases of the project.

3.5 Summary

In conclusion, the project is made up of 3 stages. In the first stage, signal processing is used to derive functional connectivity between different brain regions. In the second stage, graph theory is employed to compute graph characteristics which are subsequently used for comparing functional connectivity between the AD, MCI and HC populations. Lastly, classifiers are trained using the graph measures as features with the purpose of assigning new unseen subject observations to one of the 3 categories.

4. Project Plan



	Task Name	Duration	Start	Finish
1	**1 Background Research**	**6 days**	**Wed 21/05/14**	**Wed 28/05/14**
2	1.1 Literature overview	6 days	Wed 21/05/14	Wed 28/05/14
3	1.2 Familiarity with dataset	3 days	Wed 21/05/14	Fri 23/05/14
4	**2 Data Preprocessing**	**14 days**	**Mon 26/05/14**	**Thu 12/06/14**
5	2.1 Data cleaning (correction of inconsistent data)	2 days	Mon 26/05/14	Tue 27/05/14
6	2.2 MEG artefact removal and filtering	9 days	Wed 28/05/14	Mon 09/06/14
7	2.3 Data integration (combine data in consistent state)	3 days	Tue 10/06/14	Thu 12/06/14
8	**3 Data Modelling and Analysis**	**23 days**	**Fri 13/06/14**	**Tue 15/07/14**
9	**3.1 Signal processing**	**6 days**	**Fri 13/06/14**	**Fri 20/06/14**
10	3.1.1 Compute coupling between signals (PLI, coherence)	6 days	Fri 13/06/14	Fri 20/06/14
11	**3.2 Graph analysis**	**11 days**	**Mon 23/06/14**	**Mon 07/07/14**
12	3.2.1 Build functional connectivity graphs	5 days	Mon 23/06/14	Fri 27/06/14
13	3.2.2 Compute basic graph statistics (clustering coefficients, average path lengths)	5 days	Mon 30/06/14	Fri 04/07/14
14	3.2.3 Compute advanced graph measure (eigenvalue centrality, modularity)	6 days	Mon 30/06/14	Mon 07/07/14
15	**3.3 Classification**	**6 days**	**Tue 08/07/14**	**Tue 15/07/14**
16	3.3.1 Feature extraction and selection	3 days	Tue 08/07/14	Thu 10/07/14
17	3.3.2 Train and test SVMs	2 days	Fri 11/07/14	Mon 14/07/14
18	3.3.3 Experiment with other classification methods	3 days	Fri 11/07/14	Tue 15/07/14
19	**4 Results Evaluation and Presentation**	**21 days**	**Wed 16/07/14**	**Wed 13/08/14**
20	4.1 Write-up of dissertation	21 days	Wed 16/07/14	Wed 13/08/14
21	4.2 Review with supervisor	3 days	Wed 16/07/14	Fri 18/07/14
22	5 Dissertation Submission	1 day	Thu 14/08/14	Thu 14/08/14

5. Budget

I request a total of £87.02. At the recommendation of my supervisor, an external hard drive should be purchased (Western Digital 2TB Elements). It's main purpose is to store data backups associated with the research project. It will also be used for transferring data between computers. Lastly, the hard drive is suitable for encryption to prevent unauthorised access. This is necessary as the project involves medical data.

Budget Item	Amount
Western Digital 2TB Elements Portable Hard Drive (ebuyer.com)	£87.02
	Total: £87.02

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