Characterisation of Resting Brain Network Topologies across the Human Lifespan with Magnetoencephalogram Recordings: A Phase Slope Index and Granger Causality Comparison Study

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Abstract: This study focuses on the resting state network analysis of the brain, as well as how these networks change both in topology and location throughout life. The magnetoencephalogram (MEG) background activity from 220 healthy volunteers (age 7-84 years), was analysed combining complex network analysis principles of graph theory with both linear and non-linear methods to evaluate the changes in the brain. Granger Causality (GC) (linear method) and Phase Slope Index (PSI) (non-linear method) were used to observe the connectivity in the brain during rest, and as a function of age by analysing the degree, clustering coefficient, efficiency, betweenness, modularity and maximised modularity of the observed complex brain networks. Our results showed that GC showed little linear causal activity in the brain at rest, with small world topology, while PSI showed little information flow in the brain, with random network topology. However, both analyses produced complementary results pertaining to the resting state of the brain.

1 INTRODUCTION

The brain is the main hub of all intellectual activity, the coordination centre of all levels of conscious and subconscious movement as well as the interpretation centre of all activity (Fornito, et al., 2015; Rescorla, 2015). It is made up of soft nervous tissue and is one of the largest organs in the body (Orrison, 2008). Similarly, like any other organ in the body, the brain is subject to changes with age. Thus, many studies have been conducted in a bid to understand how the structure and function of the brain are affected by the ageing process throughout life (Lebel, et al., 2007; Schafer, et al., 2014).

Complex network analysis, a subset of methods from graph theory, has been successfully used to analyse multidimensional, multimodal systems containing various levels of directed, undirected, symmetric, and unsymmetrical connections (Chowdhury & Stauffer, 2000; Hsu, et al., 2003; Sporns, et al., 2004; Dehemer, 2010). At its core, a graph is defined as a mathematical representation of a network made up of nodes and edges. Graph theory principles, such as degree, clustering coefficient, betweenness centrality, efficiency, modularity, and maximised modularity, can be used to estimate robustly the structure of observed networks in the brain (Dehemer, 2010). Centrality measures such as degree and betweenness provide a description of local centrality and connectivity, segregation measures such as clustering coefficient provide a description of the subdivision within in a network, and modularity and maximised modularity provide a description of the overall structure of the detected graph network. Thus, centrality measures provide the intimate details of the structures alluded to by the topology analyses, and so enable robust descriptions of the observed network topologies (Bullmore & Sporns, 2009).

When applied to neuroscience, these graphs can be used to define robust estimates of structural, functional and anatomic networks present in the brain (Papo, et al., 2013; Fornito, et al., 2015). Many studies have been conducted to determine the changes in the brain at rest, task or due to pathology using

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functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), and electrocorticography (ECoG) to determine the changes in the brain either at rest, task or due to pathology (Ogawa, et al., 1990; Niedermeyer & Lopes da Silva, 2005; Jafarpour, et al., 2013).

A study performed by Goldenberg and Galvan (2015) using fMRI and dynamic causal modelling (DCM) revealed that in resting state, brain network topologies resembled small world architecture when studied using graphs theory. However, when the brain was studied using Pearson's Correlation, Cao et al. (2013) observed that the brain networks present in the brain throughout life, move from being local to distributed and revert back to having local functional structure. Furthermore studies performed by Huttenlocher, et al. (1982), Good, et al. (2001), Salat, et al. (2005), and Giedd and Rapoport (2010) show that changes in the brain networks were attributed to the maturation of nerve fibres, changes in myelination in the brain as it matures, synaptic pruning as well as changes in the dendrite structures throughout life.

Over the years, there has been a notable increase in the use of magnetoencephalograms (MEGs) to study the background activity of the brain. Magnetoencephalography is a non-invasive analysis technique used to record, reference free, the magnetic fields generated by electrical activity in the human brain (Gomez, et al., 2008; Escudero, et al., 2009; Jafarpour, et al., 2013). Due to the weak magnetic fields generated by the brain, large arrays of superconducting quantum interface devices (SQUIDs) immersed in liquid helium at 4.2K and below are used to record the brains activity in a magnetically shielded room to reduce contamination by environmental noise (Ahonen, et al., 1993; Stam, 2005; Carlson, et al., 2007).

With the advances in technology and a higher life expectancy, it becomes necessary to be able to map and define the changes that networks in the brain undergo throughout life. In so doing, this knowledge of healthy ageing could help in the early diagnosis of pathologies such as dementia and epilepsy as they can assist with the identification of activity lying outside the normal ranges defined by the healthy ageing brain networks.

The use of linear vs. non-linear analysis to accurately describe brain dynamics, has been under debate, with researchers using either branch of analysis to validate their preferences (Stam, 2005). Therefore, in this study, the use of both linear and non-linear methods to analyse the brain networks recorded using MEG was performed so as to determine if non-linear analysis is superior to linear analysis or if these analyses are complementary (Nolte, et al., 2010; Haufe, et al., 2012).

In this study, we examined MEG background activity in healthy subjects using GC and PSI. The main aim of this work was to test the hypothesis that linear analysis tools reveal less information when compared to non-linear analysis tools. The results from GC and PSI were then used in combination with network analysis tools to determine if the topology of the brain networks changed with age.

2 MATERIALS AND METHODS

2.1 Materials

MEGs were recorded in a shielded room using a whole head magnetometer with 148 channels (MAGNES 2500WH, 4D Neuroimaging) at 'Centro de Magnetoencefalografía Dr. Pérez-Modrego' (Madrid, Spain). The subjects lay comfortably in an awake relaxed state with eyes closed while 5 minutes of recording was acquired. The MEGs were recorded at sampling frequency of 678.17Hz using a hardware bandpass filter from 0.1 to 200Hz after which down sampling using Nyquist criterion followed to obtain a sampling rate of 169.55Hz. The MEG data were acquired from 220 subjects aged between 7 and 84 and were grouped according to age. Table 1 summarises the relevant information about the different age groups.

Table 1: Grouping of subjects according to age.

Group	Age	Subjects	Male	Female
1	7-10	12	7	5
2	11-20	27	11	16
3	21-30	39	15	24
4	31-40	30	19	11
5	41-50	15	9	6
6	51-60	22	12	10
7	61-70	44	12	32
8	71-80	27	12	15
9	81-84	4	1	3

2.2 Methods

2.2.1 Granger Causality

Granger causality (GC) is a linear asymmetric method used to predict causality between two simultaneously occurring signals. The results from the use of GC have been successfully used to characterise functional circuits in the brain by identifying regional

activations (Seth, et al., 2015). For instance, the study of lexical influences on speech perception performed by Gow et al. (2008) used GC to reveal the functional architecture of cognition. Furthermore the use of GC to analyse monkey brain dynamics has revealed causal relationships in the alpha, beta and gamma ranges (Friston, et al., 2013).

Though GC is a powerful analysis tool lying between fully model-free and light model dependent methods, it only models linear interactions (Bressler & Richter, 2014). Therefore, though the use of a higher model order can be used to try analyse non-linear systems, more often than not this leads to confound results (Gao, et al., 2015; Winkler, et al., 2015).

GC can be determined using the following equations where the univariate autoregressive model is used to calculate the regression of $p\,(t)$ which is added to the past values of $q\,(t)$. The model parameters a_{ij} are estimated using least squares method while the order is estimated using the Akaike and Bayesian Information Criterion (Akaike, 1974; Schwarz, 1978):

$$GC_{q\to p} = In\left(\frac{V_{p|\bar{p}}}{V_{p|\bar{p},\bar{q}}}\right) \quad (1)$$

$$V_{p|\bar{p},\bar{q}} = var\left(u_{pq}\right) \quad (2)$$

$$V_{q|\bar{p},\bar{q}} = var\left(u_{qp}\right) \quad (3)$$

$$V_{p|\bar{p}=var(u_p)V_{q|\bar{q}}} = var(u_q) \quad (4)$$

where var (.) is the variance over time and $p|\bar{p},\bar{q}$ is the prediction of $p\,(t)$ by the past samples of values of $p\,(t)$ and $q\,(t)$ and the residuals which depend on the past values of both signals are:

$$\begin{aligned} p(n) &= \sum_{k=1}^{X} a_{p|p,k}p(n-k) + \sum_{k=1}^{X} a_{p|q,k}q(n-k) \\ &\quad + u_{pq}(n) \\ q(n) &= \sum_{k=1}^{X} a_{q|p,k}p(n-k) + \sum_{k=1}^{X} a_{q|q,k}q(n-k) \\ &\quad + u_{qp}(n) \end{aligned} \quad (5)$$

The results of this analysis range from $0 \leq G_{p\to q} < \infty$, with the lower limit implying that the past of $p\,(t)$ does not improve the prediction of $q\,(t)$. However, the upper limit implies that the past of $p\,(t)$ improves the prediction of $q\,(t)$ therefore implying that q is causal to p (Niso, et al., 2013).

2.2.2 Phase Slope Index

Phase slope index (PSI) is a non-linear asymmetric method that makes use of the complex coherency function to detect synchronous statistically significant time delays between two signals (Niso, et al., 2013). By calculating a combination of both instantaneous and delayed causal relationships between two signals PSI can be used to determine the flow direction of information and thus can be used to determine the level of synchronisation in a network. The use of PSI has increased over the years. Nolte et al. (2010) applied PSI to EEG data and found that there was a net flow of information between default regions of the brain when the eyes are open. Furthermore, Rana et al. (2012) detected an increase in information flow in the brain at the onset of epileptic seizures using PSI. PSI can be determined using:

$$PSI = \Psi_{xy} = \frac{\widetilde{\Psi_{xy}}}{std(\widetilde{\Psi_{xy}})} \quad (6)$$

$$\widetilde{\Psi_{xy}} = \Im\left(\sum_{f\epsilon F} K_{xy}^{*}(f)K_{xy}(f+\delta f)\right) \quad (7)$$

Where $K_{xy}(f)$ is the complex coherence, δf is the frequency resolution, $\Im(.)$ is the imaginary part and F is the set of frequencies over which the slope is summed (Niso, et al., 2013).

In this study, the entire 5 minute length of recording was used un-epoched so as to extract as much information as possible. The data was filtered using an FIR bandpass filter with cut-off frequencies at 1.5 Hz and 40 Hz. Additionally, the HERMES toolbox was used to do the GC and PSI calculations on the data set (Niso, et al., 2013). Graph theory complex network analysis was then used to determine the connectivity of the brain networks. By evaluating the node degree, betweenness centrality, local (nodal) and global efficiencies, modularity and maximised modularity, the structure of the brain networks was inferred.

3 RESULTS

Before processing the MEG signals with GC and PSI. They were tested for stationarity using the augmented Dickey–Fuller test (ADF). To avoid the potential loss of information associated with the selection of a threshold that can be used to binarise the data for network analysis, the results presented below for both GC and PSI were saved as weighted data in adjacency matrices, after which they were combined with complex network analysis tools.

Figures 1 and 2 illustrate the results observed using GC and graph theory principles on the MEG dataset. Sparsely connected global networks with low

nodal degree, low clustering coefficient, and low betweenness were observed throughout life. Furthermore, low nodal and global network efficiencies were observed despite the maximised modularity results showing that the module topologies reflected ordered structures. Therefore, though the structure and number of identified modules changes throughout life, it was observed that the topology of these structures does not.

Figures 3 and 4 show a graphical representation of the observed results using PSI and graph theory on the MEG dataset. Densely connected global networks with high nodal degree, low clustering coefficient and high betweenness were observed throughout life. However, low network efficiency was also observed on both local (nodal) and global scales. Furthermore, the maximised modularity values for the brain networks were all high, i.e. >0.7, therefore implying that the structure of the identified modules were similar to random networks, a result echoed by the modularity analysis.

4 DISCUSSION

In this pilot study we explored the ability of GC and PSI to identify the structure of brain networks in MEG recordings of 220 healthy volunteers. The results obtained by applying GC and graph theory revealed that there is very little causal activity present in the brain during rest throughout life. These results complement those obtained by Stam et al. (2016) who observed that the brain at rest resembles a system that is in phase transition and thus, until an input disrupts the rest state, the system will remain in 'limbo'. Therefore, the presence of simple non-causal modules in the brain aide in maintaining this rest state to ensure that the brain operates optimally upon reception of an input.

It has been argued that PSI, being a non-linear analysis tool, reveals more information than a linear analysis tool. Nolte et al. (2010) observed in EEGs that PSI enabled them to determine robust estimations of the net flow of information between regions of the brain when eyes are open, while GC was not able to reveal this. Complementary to this study, Rana et al. (2012) also observed an increase in the information flow in the brain before the onset of an epileptic seizure using PSI, therefore suggesting that there is a net flow of information in the brain during task and pathology. Literature has shown that brain networks resemble small world network topology, however contrary to this, the results from this study have revealed that at rest, the brain networks resemble a more random topology. Rubinov et al. (2011) and Deco et al. (2013) suggested that the meaningful relation between structure and function can be identified when a system is near a critical state. Therefore, if the resting brain, which is assumed to be in a metastable state, is analysed using PSI, very little synchronisation between MEG channels, representing network nodes, can be observed, thus resulting in the complex brain network resembling a densely connected random network structure. With this in mind it is then plausible that in a healthy brain at rest, i.e. without mind wandering or daydreaming, there is no distinct flow of information between network nodes (Bullmore & Sporns, 2009; Rubinov, et al., 2011; Deco, et al., 2013).

The results obtained using GC and PSI, both reveal different aspects of the resting state brain networks. While GC showed the absence of Granger-causality between any of the brain regions, PSI revealed that there were no regions of the brain that exhibited efficient information flow.

Nevertheless both linear and non-linear approaches have shown that the brain has very low efficiency at rest and resembles a metastable state (Stam, et al., 2016). Evidently, the connectivity of the brain networks have shown that both linear and non-linear analysis tools show complementary information i.e. that there is very low causal activity in the brain at rest, and that though there are many paths for information flow in the brain, there is little observable net information flow at rest (Nolte, et al., 2010; Haufe, et al., 2012). Though PSI and GC revealed different network topological structures of the resting brain, the low granger-causal information present in the brain coupled with the difficulty in prediction of the direction of information flow in the brain, can be used in combination to give a more complete image of the metastable state of the brain at rest. Thus, the results from this study show that non-linear and linear analysis tool work hand-in-hand as they give complementary information about brain network topology at rest. Finally, this study was also observing if there were any changes in the topological structures of the resting brain throughout life. The results in Figure 1(e) show that the network topologies for all groups had maximized modularity<0.3, which implies that across all ages when analysed using GC the network topologies were all of simple network topology. Similarly, the results in Figure 2(e) show that the maximized modularity>0.7 thus implying random network topology for the PSI results across all groups (Dehemer, 2010). These results suggest that when analysed using GC and PSI there are no differences

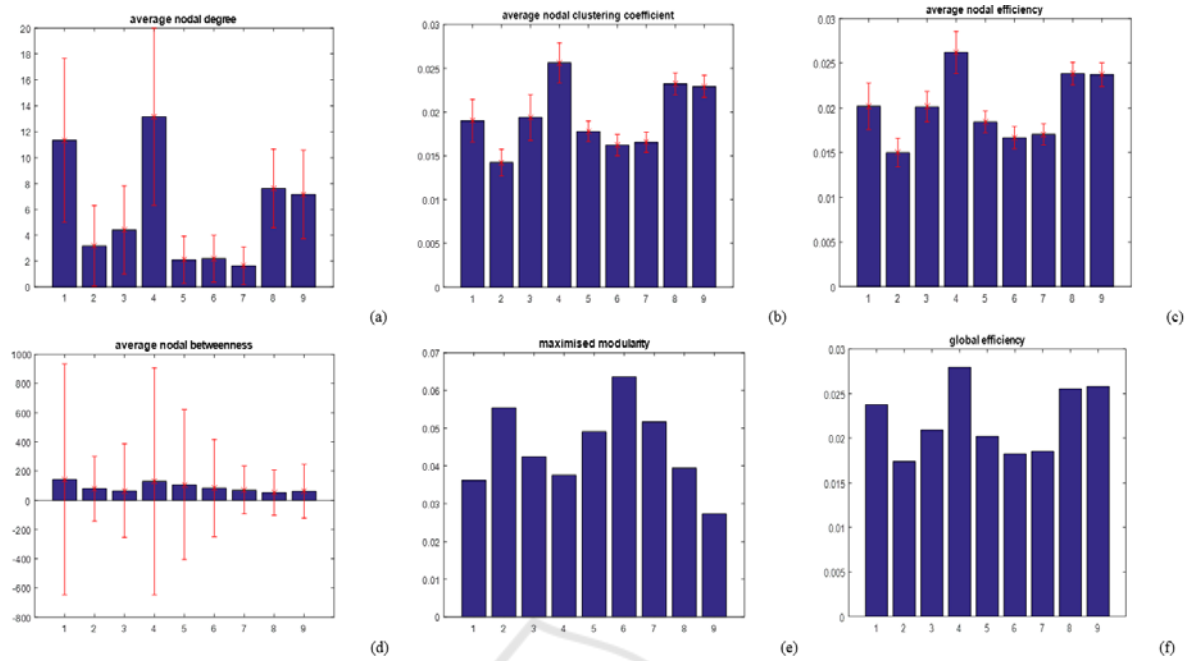

Figure 1: Averaged results for analysis performed using Granger Causality for (a) nodal degree, (b) clustering coefficient, (c) local efficiency, (d) betweenness, (e) maximised modularity and (f) global efficiency, with the error bars representing the standard deviation for each group (where the numbers on the x axis represent the subject group number i.e. 1 represents group 1).

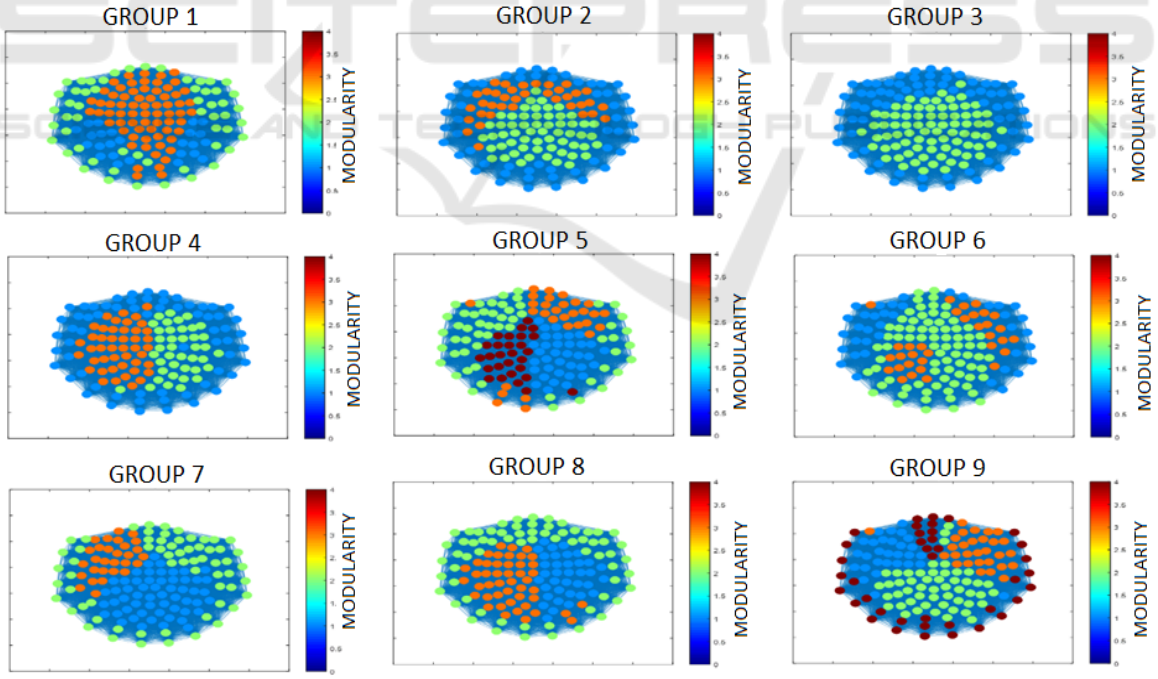

Figure 2: Modularity results obtained after using GC to determine the different clusters detected in the brain resting state network, as well as their location.

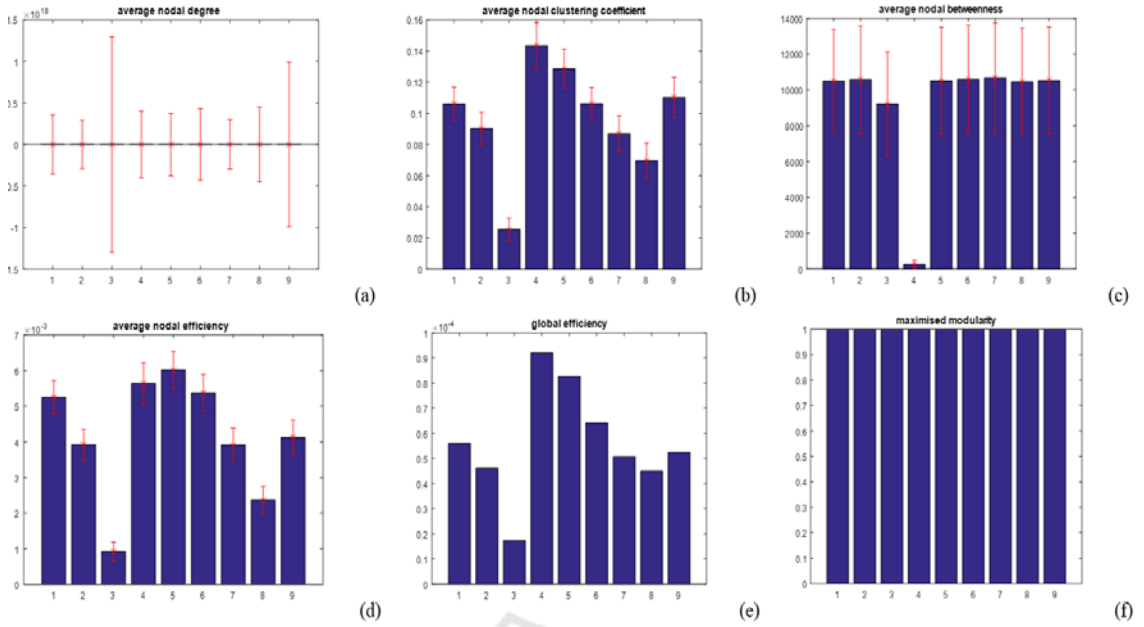

Figure 3: Averaged results for analysis performed using Granger Causality for (a) nodal degree, (b) clustering coefficient, (c) local efficiency, (d) betweenness, (e) maximised modularity and (f) global efficiency, with the error bars representing the standard deviation for each group (where the numbers on the x axis represent the subject group number i.e. 1 represents group 1).

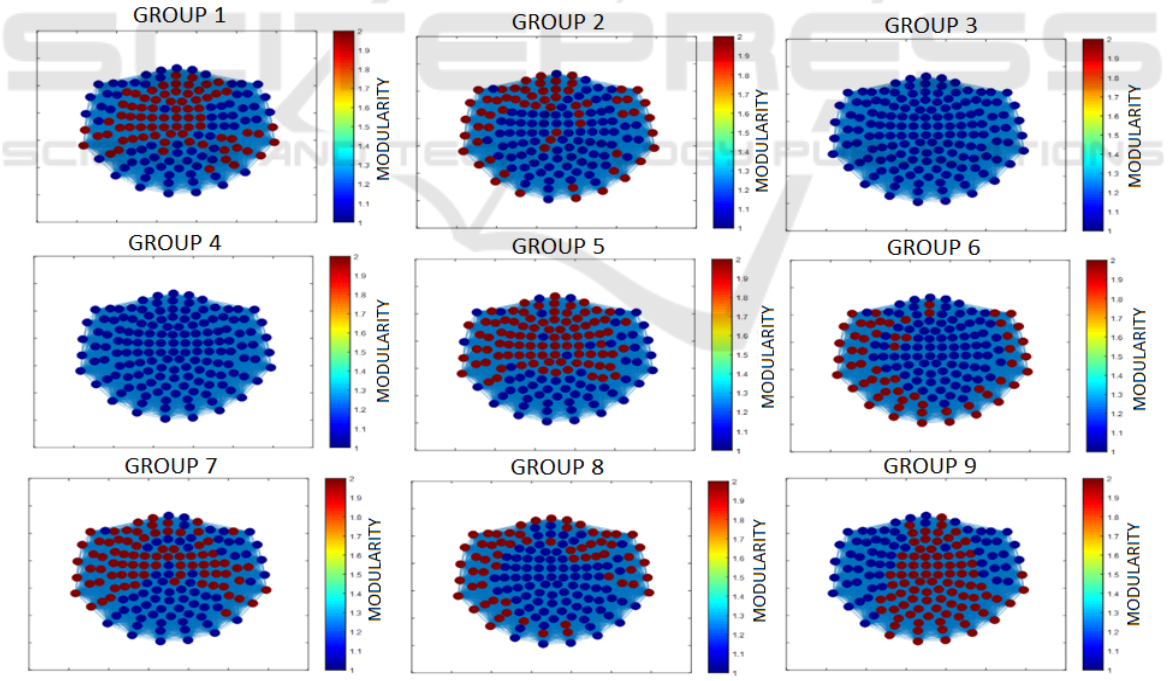

Figure 4: Modularity results obtained after using PSI to determine the different clusters detected in the brain resting state network, as well as their location.

in network topology throughout life.

Some limitations of the study should be mentioned. Firstly, the groups did not contain similar number of subjects with group 7 having 44 subject and group 9 only 4. Thus, the results for the latter group may not be conclusive. Furthermore, analysis

was done using only two methods, and so more methods should be used to explore the MEG background activity of the brain. Thus, future lines of research will include further signal processing using methods such as synchronisation likelihood, transfer entropy and mutual information so as to obtain a more complete description of the MEG background activity with ageing. In addition, statistical analysis will be performed to ascertain the significance of the obtained results.

5 CONCLUSIONS

A study of brain network topology was conducted using granger causality and phase slope index, in combination with graph theory, on data acquired from MEG recordings. The results observed showed that both linear and non-linear analysis tools reveal different complementary aspects of brain connectivity.

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