

**FUNCTIONAL CONNECTIVITY DURING REST AND  
TASK: A STUDY BASED ON GRAPH THEORETICAL  
METRICS**

by

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Dedicated to Nazan Öncel songs and coffee beans...

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## ABSTRACT

### FUNCTIONAL CONNECTIVITY DURING REST AND TASK: A STUDY BASED ON GRAPH THEORETICAL METRICS

In this study, task-related network organization were examined, and the association between network integration at rest and cognitive performance was investigated using n-back task. Global efficiency, local efficiency and modularity were computed at rest and during n-back task. Task-related metrics were compared with resting state metrics to understand the neural mechanism underlying working memory. Correlations between resting state metrics and performance in the n-back task were computed to investigate the optimal topology. The results revealed that performing n-back task required a reorganization of resting state network. Task-related topology showed higher global efficiency and modularity , and lower local efficiency compared to rest. Moreover, it was reported that the resting state topology was an indicator of cognitive performance. Performance in n-back task was positively correlated with global efficiency, local efficiency and modularity of resting state network.

**Keywords:** Graph Theory, Resting State, Working Memory, Network Integration, Cognitive Performance.

## ÖZET

### ÇİZGE KURAMSAL METRİKLERE DAYALI BİR ÇALIŞMA: DİNLENME VE GÖREV SIRASINDA İŞLEVSEL BAĞLANTISALLIK

Bu çalışmada görev ilişkili network yapılanması incelendi ve dinlenme sırasındaki şebeke entegrasyonu ile bilişsel performans arasındaki ilişki n-back görevi kullanılarak araştırıldı. Dinlenme sırasında ve n-back görevi sırasında küresel verimlilik, yerel verimlilik ve modülerlik hesaplandı. N-back görevinin altında yatan nöral mekanizmayı anlamak için görevle ilişkili ölçümler dinlenme sırasındaki ölçümlerle karşılaştırıldı. Optimum dinlenme topolojisini araştırmak için dinlenme sırasındaki metriklerle n-back görevi performansı arasındaki korelasyonlar değerlendirildi. Sonuçlar gösterdi ki, n-back görevini yerine getirmek dinlenme şebekesinin yeniden yapılanmasını gerektirdi. Görev ilişkili topoloji dinlenmeye göre daha yüksek küresel verimlilik ve modülerlik, daha düşük yerel verimlilik gösterdi. Buna ek olarak, dinlenme topolojisinin bilişsel performans için bir gösterge olduğu bildirildi. N-back görevi performansı dinleme sırasındaki küresel verimlilik, yerel verimlilik ve modülerlikle koreledir.

**Anahtar Sözcükler:** Çizge Kuramı, Dinlenme Hali, Çalışma Belleği, Şebeke Entegrasyonu, Bilişsel Performans.

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## LIST OF SYMBOLS

$a_{ij}$	Entry of a binary connectivity matrix
$C$	Clustering coefficient
$d_{ij}$	Path length
$e_i$	Edge
$E$	Set of edges
$E_{glob}$	Global efficiency
$E_{loc}$	Local efficiency
$G$	Graph
$k_i$	Degree of the node $v_i$
$L$	Characteristic path length
$N$	Set of nodes
$Q$	Modularity
$v_i$	Node
$w_{ij}$	Entry of a weighted connectivity matrix
$\kappa$	Connection density

## LIST OF ABBREVIATIONS

ADHD	Attention Deficit/Hyperactivity Disorder
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
MEG	Magnetoencephalography
PET	Positron Emission Tomography
P-FIT	Parieto-Frontal Integration Theory
RSN	Resting State Network
WM	Working Memory

## 1. INTRODUCTION

Brain connectivity refers to three different aspects of brain organization: structural connectivity, effective connectivity and functional connectivity [1]. Structural connectivity corresponds to the network of anatomical connections. That network generally refers to white matter pathways linking regions in cerebral cortex and subcortex. Effective connectivity refers to the network of directed causal effects between neural elements [2]. Functional connectivity is a statistical concept depending on the temporal dependency between spatially remote neurophysiological events [3].

Various techniques are proposed to compute the functional connectivity from the time series data such as correlations, phase synchronization and mutual information. Time series data derived from different neuroimaging techniques such as functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) are used to compute this temporal dependency. All these techniques have their own specificities and sensitivities. For example, fMRI has good spatial resolution but poor temporal resolution. On the other hand, electrophysiological methods have better temporal resolution, but they have lower spatial resolution [4].

Modern neuroimaging techniques provide large datasets of connectivity patterns [5]. In general, increase of large connection datasets in different scientific fields led us to create new methods to understand the complex systems [6, 7]. This motivation gave rise to the modern science of networks. Complex network analysis originated from graph theory which is a branch in mathematics.

Although graph theory is an area in mathematics, recent developments like small-world phenomenon was originated from sociology [8, 9], biology [10] and physics [11, 12]. The first and simplest organism investigated in terms of graph theoretical metrics was *Caenorhabditis elegans*. It was shown that the nervous system of this organism has a small-world topology [13]. Subsequent studies have been done on

different animals, including human [14, 15, 16].

Besides the investigation of brain diseases, high-level cognitive functions became an outstanding issue in connectivity researches. Several studies focused on the use of resting state functional connectivity in healthy and pathological brains [17, 18] and few of them investigated functional connectivity during various cognitive tasks [19]. Working memory (WM) is an important component for any cognitive function since it is necessary in information processing over time. In studies focusing on working memory, EEG is preferable due to its high temporal resolution.

## 1.1 Motivation

Brain graphs is an increasingly popular way of investigating the brain. Several studies have been performed to understand the normal brain organization and compare it to the pathological organization. However, studies on dynamic changes of these graphs during a cognitive task are limited. In addition, evaluating the relation between resting state functional network organization and performance following rest became an issue of investigation.

The main motivation of this thesis is to investigate the task-related changes in graph theoretical metrics during n-back task compared to rest, and analyse the association between resting state metrics and behavioral results. The major expectation is to test the hypothesis that graph metrics computed at rest can predict the performance.

## 1.2 Objectives

In this study, we investigated resting state functional connectivity and network reorganization during a working memory task. Participants performed a verbal n-back task which is commonly used in working memory studies. The correlation coefficient was used as a measure of functional connectivity. A single threshold was adjusted



according the predefined connection density. Graph theoretical metrics were computed and statistically analyzed. Our aim is to observe the dynamic changes in the network organization when the subject's mental state shifts from rest to conscious, effortful state. We also monitored the subjects responses in order to evaluate the relation between resting state connectivity and cognitive performance.

### **1.3 Outline of The Thesis**

The outline of the thesis is summarized as follows: Chapter 2 gives information about EEG technique, graph theory and graph theoretical studies focusing on functional connectivity. Concept of working memory is explained briefly. Finally, literature review is given on task-related changes in functional network and the relation between network organization and cognitive performance. In Chapter 3, the experimental design, preprocessing and analysis procedure are given in details. Behavioral and experimental results are presented in Chapter 4. In Chapter 5 and 6, discussion and conclusion are given respectively.

## 2. BACKGROUND AND LITERATURE REVIEW

### 2.1 EEG

Electroencephalography (EEG) is a non-invasive medical imaging technique to record the fluctuating electrical activity of brain structures along the scalp. Presynaptic neuron releases the neurotransmitters into the synaptic cleft. Neurotransmitters binds to receptors and opens the ion channels on the postsynaptic cell. Synchronised pyramidal cells produce potential difference. These potential differences in the cell membrane are recorded by scalp electrodes [20]. EEG reflects summed activity of large numbers of similarly oriented pyramidal neurons close to the recording electrode. Subcortical areas are much more difficult to detect than currents near the skull. Measurement is done in the microvolt range with millisecond resolution.

Volume conduction, which makes EEG signal detectable, can be defined as the transmission of electric fields from electrical generator through biological tissue towards the recording electrodes [20]. The activity generated from an arbitrary part of the brain spreads on wide areas. The underlying cause of the low spatial resolution of EEG is the volume conduction. In addition to this sprawling activity, the signal measured by an EEG electrode contains artifacts depending on muscle or eye movements [21].

The reconstruction of the primary currents is called the inverse problem of EEG. Since some potentials produced by these currents cancel each other out, it is mathematically impossible to localize the source of the electrical activity [22].

#### 2.1.1 Oscillations

In 1875, Richard Caton discovered the electrical nature of the brain from his experiments with rabbits and monkeys [23]. Hans Berger detected human brain waves

for the first time and called it electroencephalogram [24]. Berger realized that these brain waves were not entirely random, they had certain periodicities and patterns. He suggested that activity of brain waves changed in noticeable way when the participant's state of mind changed [25].

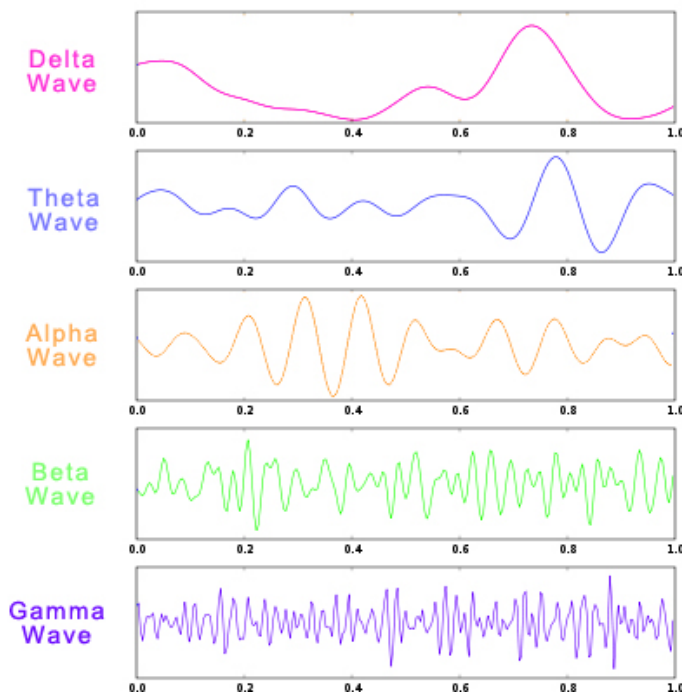


Figure 2.1: Different frequency bands.

The first frequency observed was in 10-hertz range, (8 to 12 Hz) which Berger named alpha. It was recorded during awake resting state with eyes closed. Alpha rhythm was seen in the posterior part of the brain. He reported how brain waves changed dramatically slower to faster when subject simply shifted from eyes closed to eyes open state. This faster frequency was named by Berger as beta activity. He also noticed the alteration of brain when attention is directed towards a cognitive task. When the subject sat with eyes closed, focusing on a math problem, brain waves shifted from alpha to beta rhythms [24]. Beta band is symmetrically distributed on both side of the brain and most evident frontally. It is also studied in relation to sensorimotor behavior [26].

Oscillations below the alpha band were divided into two range, delta (0 to 4 Hz)

and theta (4 to 8 Hz). Delta waves are prominent posteriorly in infants and decrease as getting older . Delta is seen normally in nREM sleep in adults and it is predominant frontally [27]. It is also found during continuous attention tasks. Theta is seen normally in young children and in drowsiness in adults. By development of special amplifiers and analysis techniques other oscillations were identified and named as beta (12 to 30 Hz )and gamma (above 30 Hz). Gamma activity is closely related to the integration of perceptions which is called 'binding problem' [28]. Besides the sensory responses, empirical findings contain cognitive gamma responses. EEG response to an external event Event-related potential (ERP) is an average EEG response a stimulus. Event-related oscillations (ERO) is also one of the most common methods used in memory studies. EROs can be defined as a reorganization of ongoing EEG rhythms. Studies focusing on encoding and retrieval processes mostly depends on EROs.

### 2.1.2 Oscillations and Working Memory

Alpha activity is seen during sensory, cognitive and motor processes [29, 30]. Although it was thought as idling rhythm at first, studies showed that alpha band is related to cortical communication and cognition [31, 32]. Alpha power is also modulated by memory load [33, 34, 35] and this rhythm has an important role in long-term memory processes [36]. There are two main hypothesis on function of alpha activity. According to first one, alpha band is directly related to process underlying WM maintenance [37, 38]. Second hypothesis emphasizes the effect of alpha activity on inhibition of task-irrelevant regions [39, 40]. Haegens et. al indicated that there was an increase in alpha activity except the regions of WM network during WM task [41].

Most of the studies focused on the relation between beta band and sensorimotor behaviors . For example, the decrease in theta power related to voluntary movements was shown [26]. On the other hand, there are empirical evidences on the role of beta activity in cognitive functions. Basile et. al indicated an increase of beta activity related to stimulus expectancy [42]. MacLean et al. reported the correlation between beta power and performance in the attentional blink test [43].

In 1972, the expression 'gamma-response' was used for the first time to explain the gamma activity to external stimuli in cats [44]. Different studies also reported 40Hz oscillatory responses to external stimuli in humans [45, 46]. Subsequent studies linked gamma activity to visual [47] and olfactory [48] senses.

In addition to sensory gamma responses there are studies focusing on cognitive gamma responses. The first study expressing the relationship between gamma activity and WM maintenance was done by Tallon-Baudry and colleagues [49]. They recorded cortical activity by EEG during performance of a visual delayed-match-to-sample (DMS) task and reported a continuous increase in gamma oscillations. Subsequent studies reported the supporting results for visuospatial [50] auditory [40] and somatosensory WM maintenance [41]. It has been shown that the strength of the gamma response was influenced by size, velocity, contrast and duration of the visual stimuli [51, 52]. Gamma activity was associated with feature binding as a result of the studies done with cats [53], monkeys [54] and humans [55]. Moreover, some studies linked gamma activity to attentiveness of the subject [56].

## 2.2 Graph Theory

Neuroscience showed fascinating improvement in 20<sup>th</sup> century [57]. In 2000, Eric Kandel was a recipient of the Nobel prize for explaining the molecular mechanism of memory storage in neurons. On the other hand, only few theories are available to investigate the high level functions and the most recent one is the graph theory.

The basic idea of the graph theory was introduced by Leonard Euler in 1737 to solve the Königsberg bridge problem [58]. The idea was a simplified representation of physical world in terms of nodes (vertices) and connections (edges). In 1959, Paul Erdos and Alfréd Rényi introduced the random graph model, however this model was not satisfactory to explain the most of the real world systems such as social networks [59]. Stanley Milgram was inspired by the idea of Hungarian writer Frigyes Karinthy. According to him two people can be connected to each other in a maximum of six

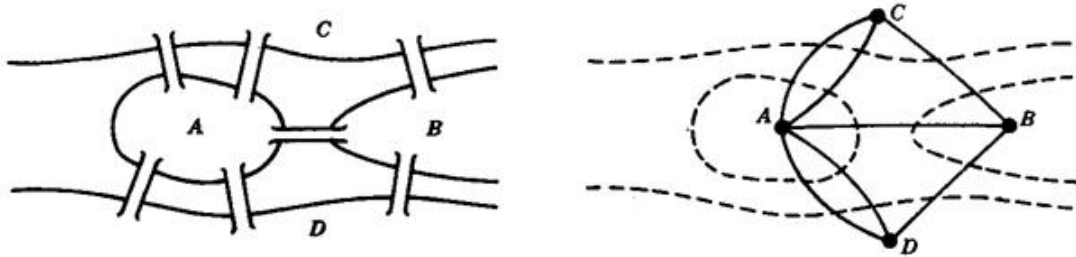


Figure 2.2: Königsberg in 1736 and Euler's graphical representation [58].

handshakes [60]. In 1967, Milgram confirmed that idea experimentally and introduced the "small-world" phenomenon [61]. Theoretical explanation did not appear until 1998. D. Watts and S. Strogatz proposed a generative model to explain the small world properties and introduced two metrics: characteristic path length and clustering coefficient [13].

In this model, there is a ring created over  $n$  nodes connected with its  $k$  nearest neighbors. Random number between 0 and 1 is drawn for each edge. Each edge is rewired with probability  $p$ : if the edge's random number is smaller than  $p$ , then the source vertex of the edge is kept fixed, and a new target vertex is chosen uniformly at random from all other vertices. For  $p = 0$ , the resulting network is totally regular. For  $p = 1$ , the resulting network is a random graph. For the intermediate values of  $p$ , the graph reveals a small-world architecture. It is clustered as a regular graph; however, it has a small characteristic path length, like a random graph.

### 2.2.1 Basic Concepts

A graph  $G(N, E)$  with  $n$  nodes and  $m$  edges consists of a set of vertices (nodes)  $N = \{v_1, v_2, \dots, v_n\}$  and edges (connections)  $E = \{e_1, e_2, \dots, e_m\}$ . The structure of the network is represented by a  $n \times n$  binary matrix  $A = \{a_{ij}\}$ , known as adjacency matrix. Its element  $a_{ij}$  equals 1, when there is an edge joining the node  $v_i$  to the node  $v_j$  and it is 0 otherwise ( $i, j = 1, 2, \dots, n$ ). All elements of the main diagonal equal to 0 ( $a_{ii} = 0$ ). Graphs can be classified as directed or undirected. Directed graphs give information on

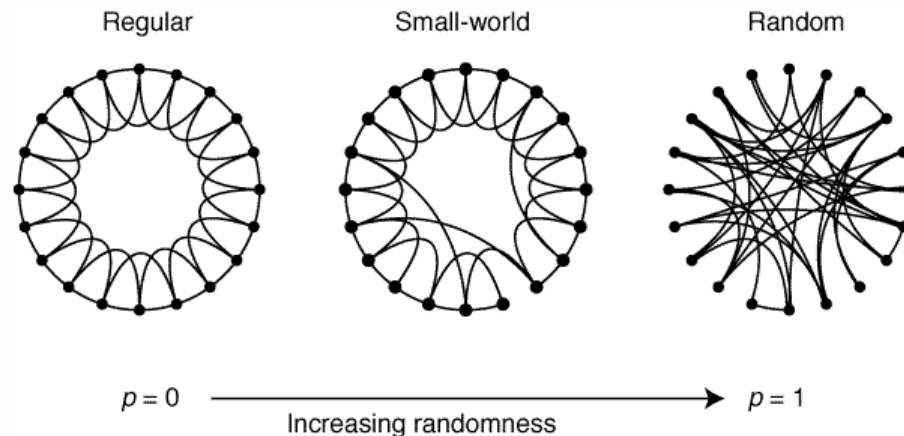


Figure 2.3: Watts and Strogatz (Small World) Model [13].

the direction of the relation. In the case of undirected networks the adjacency matrix is symmetric. Alternative to binary graphs, networks can be represented as weighted graphs depending on the intensities of the links in the network. A weighted graph is represented in terms of its weight matrix  $W = \{w_{ij}\}$ . Each element  $w_{ij}$  shows the weight of the connection from node  $v_i$  to node  $v_j$ .

*Connection density*  $\kappa(G)$  corresponds to the ratio of existing to possible links in the network. The *degree*  $k_i$  of a node  $v_i$  is defined as the number of its neighbours. The *strength*  $s_i$  is the sum of the weights of all edges attached to the node  $v_i$  for weighted graphs.

*Path length (distance)*  $d_{ij}$  between two nodes  $v_i$  and  $v_j$  is the shortest length that has to be travelled to go from  $v_i$  to  $v_j$ . There are two different definitions of path length according to the network type: transportation or communication networks. In the case of transportation networks, path length  $d_{ij}$  is defined as the smallest sum of the weights:  $d_{ij} = \min \sum_{i,j \in N} w_{ij}$ . On the other hand, since the intensity, strength or efficiency of the connection is inversely proportional to weight in communication network, path length is computed as:  $d_{ij} = \min \sum_{i,j \in N} \frac{1}{w_{ij}}$ . The average path length between all pairs of nodes is the *characteristic path length*.

*Efficiency* metric was introduced by Latora and Marchiori to measure how efficiently the nodes transfer information through the network [62]. It is computed from the distance matrix  $D$  containing path lengths of each pair of nodes. The efficiency  $e_{ij}$  is inversely proportional to the path length  $d_{ij}$ :  $e_{ij} = \frac{1}{d_{ij}}$ . If there is no relation between two nodes  $v_i$  and  $v_j$ ,  $d_{ij} = \infty$  and  $e_{ij} = 0$ . The measure *global efficiency* is closely related to the average inverse path length.

Since the global efficiency is also defined for disconnected graphs, local organization of the graph  $G$  can be characterized by computing the efficiency of subgraph  $G_i$  for each node  $v_i$ . The global efficiency of the neighborhood subgraph  $G_i$  of the node  $v_i$  gives the local efficiency of that node. *Local efficiency* of the network is the average of these local efficiencies [62]. The local efficiency of the subgraph  $G_i$  shows how efficient the communication is between the first neighbors of  $v_i$  when the node  $v_i$  is removed.

Clustering coefficient gives information about the level of local connectedness. In binary graphs, clustering is quantified by the ratio of the existing edges  $e_i$  between the node's neighbors and the total number of possible connections between these neighbors. It may also be expressed as the fraction of triangles containing the node  $v_i$ , to the maximum possible number of such triangles. There are different generalizations for weighted graphs.

*Modularity* is a method for subdividing the network into non-overlapping modules. Any module contains a densely connected subset of the all nodes and nodes in the modules are sparsely connected to nodes in other modules. It corresponds to an estimate of the difference between the number of intra-modular edges and the expected number in a null model given by a randomized network of the same size. Modularity reflects the quality of a module structure, investigates the organization across sub-networks.

Small-worldness requires clustered local connectivity and few connections between clusters mediating a short path length in the graph [13, 63], alternatively high local ( $E_{loc}$ ) and global efficiency ( $E_{glob}$ ). It has been shown that structural and func-



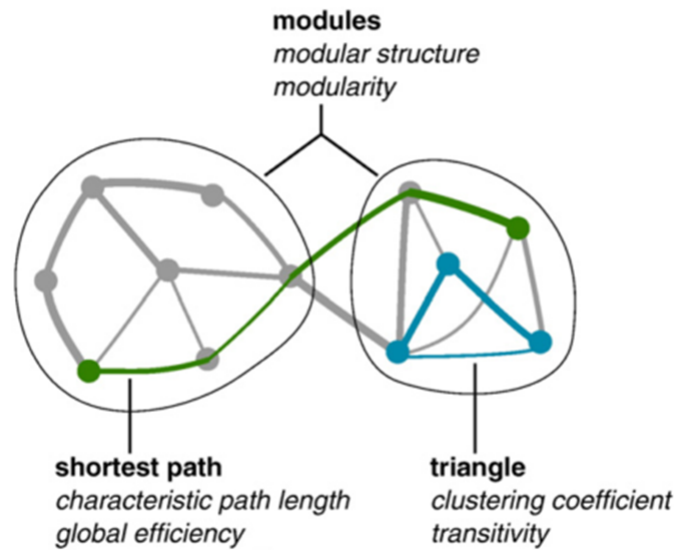


Figure 2.4: Metrics [5].

tional brain networks satisfy the properties of being a small-world network [64, 64, 65]. Researchers supposed that brain network has likely evolved to optimize information processing [63].

## 2.3 Graph Theoretical Studies in Neuroimaging

### 2.3.1 Functional Neuroimaging of Cognition

Researchers have long studied for individual differences in cognitive ability. Although it is difficult to agree upon the concept of intelligence, APA published the following definition according to current studies: "Individuals differ from one another in their ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought". Traditional approach to understand the human intelligence is to decompose the cognitive functions into elementary cognitive components and to investigate the features of these components such as capacity, speed and accuracy. For the first time, Galton thought that speed of these elementary cognitive components

was a sign of individual differences in cognitive ability [66]. This idea was revived by Hick and Roth as a mental speed approach to human intelligence [67].

Empirical results indicating the negative correlation between the reaction time (RT) and intelligence strengthened the idea that physiological properties of the brain could be the reason of altered the speed of information processing [66]. This idea became the base of the researches on possible relations between biological events and individual differences in cognitive ability. The first generation studies focused on latency parameters derived from EEG. Results on ERP supported the mental speed approach to human intelligence [68, 69].

In the course of time, different neuroimaging techniques such as positron emission tomography (PET scan) and functional magnetic resonance imaging (fMRI) have been used to understand the biological basis of intelligence. Many studies have related intelligence to whole brain size, thickness of cortical layer, white matter volume and gray matter volume [70, 71, 72]. An important PET study done by Haier showed that there was an inverse relationship between glucose consumption during an intelligence test (Raven's Advanced Progressive Matrices) and participant's performance. He formulated the neural efficiency hypothesis of intelligence which predicts that lower and more focused cortical activation reflects higher neural efficiency [73]. Hence, brighter intelligent individuals are expected to have lower brain activation during task and easier tasks are expected to require less brain activation in comparison with difficult tasks.

Spearman realized that almost every cognitive tests tended to correlate with each other. He introduced the term general factor of intelligence ' $g$ ' as a predictor of cognitive ability [74]. Jung and Haier (2007) reviewed 37 neuroimaging studies on the location of  $g$  in the brain [75]. They proposed the Parieto-Frontal Integration Theory of intelligence (P-FIT). According to this theory, intelligence does not have a center in the brain. Individual differences in cognitive ability is related to variations in a brain network. The network was distributed among the dorsolateral prefrontal cortex, the parietal lobe, the anterior cingulate, the temporal and the occipital lobes. In addition to the structural based studies, [76, 77, 78, 79] functional based studies

using various effortful tasks showed correlations between IQ and specific brain regions containing the frontal, parietal, temporal and occipital lobes [80, 81, 82]. Most studies of human intelligence have been conducted in the context of two basic theories: the neural efficiency hypothesis and the P-FIT of intelligence.

The fluid and crystallized intelligence model introduced by Cattell (1943) was improved by Horn (1976) [83, 84]. Fluid intelligence is characterized by abilities to analyze novel problems, identify patterns and relationships and is assessed as the core concept determining Spearman's g-factor. Crystallized intelligence is the ability to use skills, knowledge, and experience and it is responsible for accessing information from long term memory [83]. Although this theory did not support the integrative general factor of intelligence [85], the distinction between fluid and crystallized abilities became important in exploring the individual differences. Fluid intelligence is related to integrity and function of the lateral prefrontal cortex [86, 87]. On the other hand, crystallized intelligence is localized to more parietal and posterior regions of the brain [86]. Friedman et al. (2006) demonstrated that updating of WM was related to both types of intelligence [88].

It is clear that WM is one of the most strongly related cognitive functions to cognitive ability [89, 90]. Although it has been determined that WM and intelligence have the same underlying processes [91, 92], there are studies arguing that these two concepts are not identical [93, 94]. However, researchers still try to understand how related they are [95, 96].

Colom and his colleagues gave subjects a broad range of cognitive tasks to complete and demonstrated that there was correlation between cognitive performance on WM tasks and g [97]. They focused on the WM components to explore the reasons behind this correlation. Their results gave short term storage processes an important role in intelligence [98]. On the other hand, Engle and Kane suggested executive WM component as a core concept of WM related to intelligence [92, 96].

**2.3.1.1 Working Memory.** Memory is the process in which information is encoded, stored, and retrieved [99]. In 1898, W. James hypothesized that memory may consist of more than one component. In subsequent years, as a result of empirical evidences, two basic components emerged: short-term memory (STM) and long-term memory (LTM). The modal model suggested that memory processing starts with sensory registration and passes through short-term storage [100]. Short-term storage is crucial for the transmission to the third component, long-term storage.

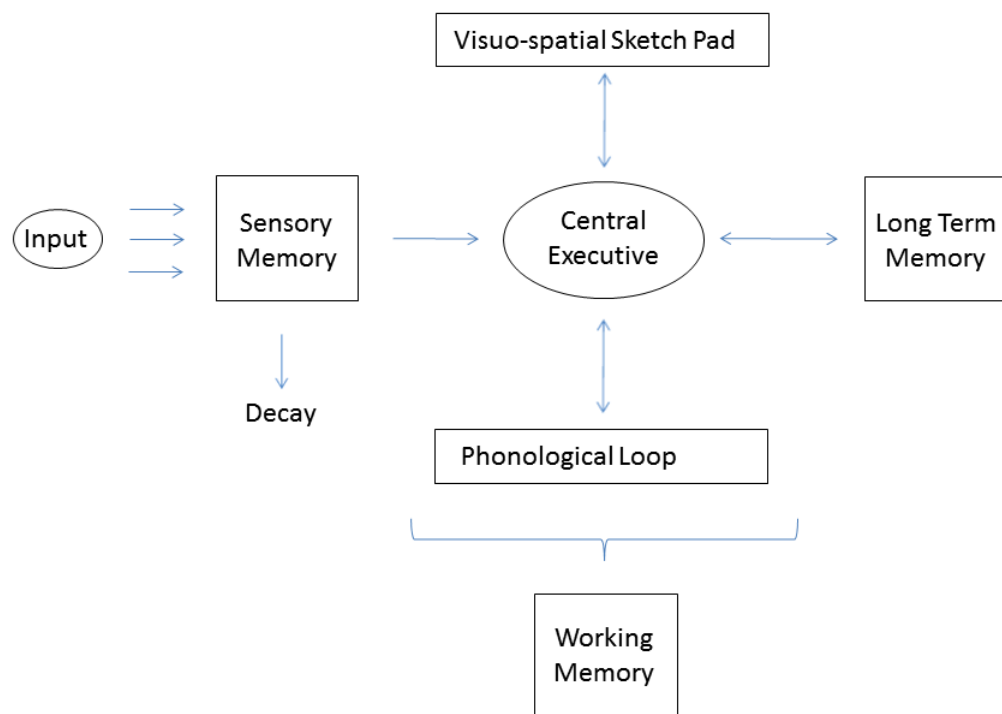


Figure 2.5: Baddeley's working memory model [101].

The next step was the introduction of the term 'working memory' [101]. Baddeley and Hitch proposed a multicomponent model for working memory (WM). It was responsible for not only storage but also processing. The model contains a central executive as an attention controller and at least two slave systems: phonological loop and visuo-spatial sketch pad. These two systems are related to verbal and visuospatial stimuli. Tasks involving the phonological loop generally activate left hemispheric brain areas, whereas the visuo-spatial sketch pad is primarily associated with the activity in right hemisphere [102, 103]. Traditionally, the frontal lobe activity was related to

cognitive functions; however, recent studies showed that cognitive functions rely on a distributed fronto-parietal network in addition to the prefrontal activity [104, 105].

In 1929, Lashley claimed that memories are scattered across the entire brain instead of being concentrated in specific regions [106]. Hebb claimed that information processing depends on activity of distributed neurons [107]. The transition from single neuron dynamics to the dynamics of neural ensembles can be seen in the studies published between 1960 and 1971 [108, 109]. According to an fMRI study on effects of verbal WM load and visual attention load, there was a common network including parietal and occipital cortices, thalamus, and the cerebellum activated by increased cognitive load [110].

### 2.3.2 Graph Theory in Functional Connectivity Studies

In general, there are four basic steps that can be followed to investigate structural and functional brain connectivity network:

- (1) Defining the network nodes.
- (2) Choosing a measure of the relation between these nodes.
- (3) Generating an association matrix and thresholding the matrix.
- (4) Graph theoretical analysis [5].

In most of the studies, a threshold has been applied to each element of the association matrix to obtain a binary adjacency matrix. Even though using a binary matrix is a valid way to investigate the network characteristics, it has several drawbacks such as waste of information available in the weights, disconnected nodes when the threshold is too high and arbitrary threshold choice [65].

Weighted characterization may be useful to understand the different aspect of network organization. Weak and non-significant links can be the noise in the data and they may be regarded as a sign of connectivity. A weight threshold is often applied to the association matrix to disregard these links [5].

**2.3.2.1 Thresholding.** Generally, there are two approaches to thresholding: searching for a single optimal threshold and evaluating network properties across varying threshold.

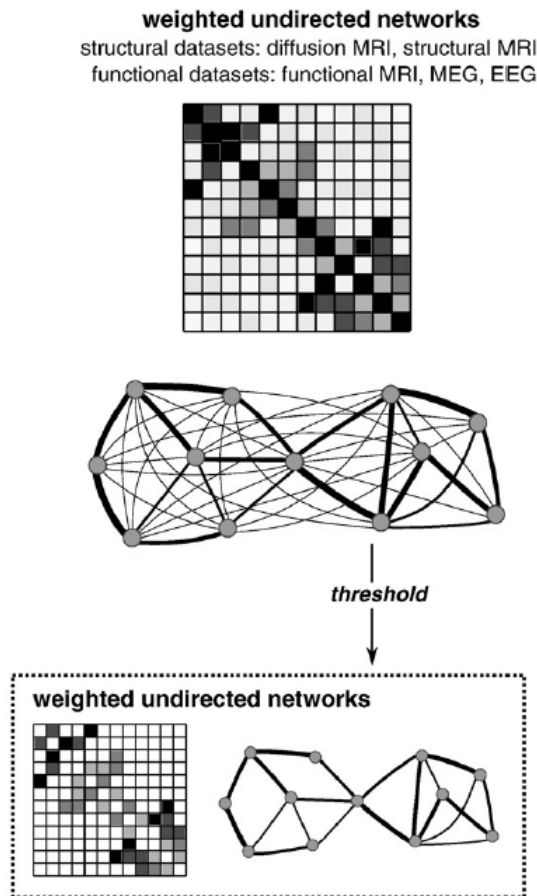


Figure 2.6: Basic steps to derive the connectivity from structural and functional datasets [5].

The threshold is adjusted as a function of connection density [111]. For non-random networks, topology of the network is more clearly delineated when connection density less than about 0.5. Increasing connection density induces an increase in global and local efficiency. To evaluate the small-worldness of the experimental network, it is compared to regular and random networks with same connection density. The characteristics of small-worldness can be regarded as a local efficiency greater than the local efficiency of a random graph and a global efficiency about the same as the global efficiency of a random graph [112].

Due the evaluation of random graphs generated over a range of connection densities, it has been shown that the network fragmented into a giant connected component and a number of smaller components, at a critical connection density. This percolation threshold is defined as the lowest connection density at which there exists a giant component [111].

**2.3.2.2 Comparing Brain Graphs.** In order to compare networks, there are two main rules to be followed [113]. The graphs must have the same number of node and the same number of edge.

**2.3.2.3 Different Organization Levels.** Graph theoretically, information processing in the brain can be investigated in different organization levels; global, intermediate and local [114]. Global efficiency and characteristic path length are the metrics giving information about functional integration. They both can be used for understanding the dynamics of the whole system and they are negatively related to each other. Networks with the short characteristic path length (or with high global efficiency) support parallel information processing of the whole system [62, 115]. Achard and Bullmore argued the superiority of global efficiency over characteristic path length as a global measure [116].

Modularity gives information about integration ability of the network on intermediate level. In modular graphs, many connections within modules represents higher clustering coefficient than random graph of the same size and density. On the other hand, only few connection between modules satisfy the short-cuts in small-world organization. Hence, the modular systems tend to be small-world networks; however, not all small-world networks are modular. Modularity is related to robustness of the network and it is also shown that higher modularity simplifies behavioral adaptation [117, 118]

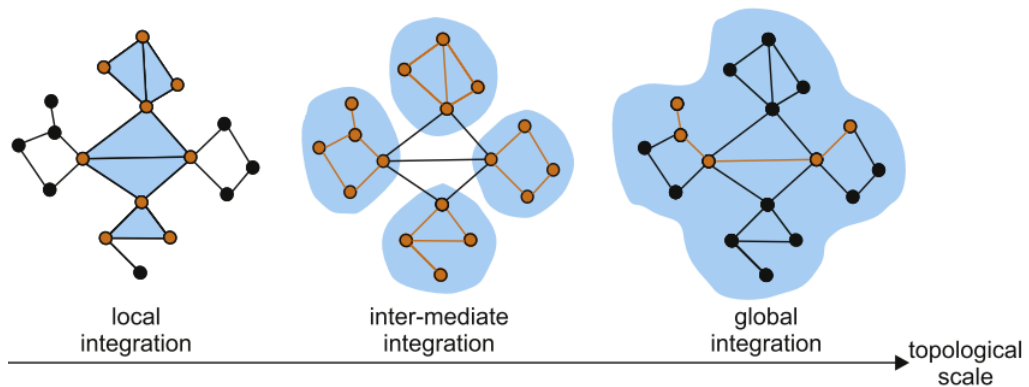


Figure 2.7: Different organization levels [5].

Clustering coefficient and local efficiency reflects the capacity of network for information transfer between the nearest neighbours of the node. Although they depend on different parameters, they are closely related.

Network analysis has proven to be particularly valuable for topological analysis of structural and functional connectivity data [7, 12]. The increase of network analysis can be explained by several motivations. First of all, complex networks represent not only the natural structure but also undergoing dynamic changes of topology [119]. Second, it promises a reliable [120] quantification of the networks with small number of easily computable metrics [64, 18, 15]. Third, it provides a chance to investigate structural-functional connectivity relationships defining them explicitly on the same map [121, 122, 123]. Finally, it is possible to see connectivity abnormalities in neurological and psychiatric disorders by comparing structural or functional network topologies [65, 60, 124]

**2.3.2.4 Graphs of Resting State.** Resting state is the period where the participants are instructed to relax. The participant is awake, but not actively involved in an effortful task. It is thought that spontaneous fluctuations originate from intrinsic neuronal activity. This intrinsic brain activity is not a random noise, it is correlated within widely distributed neuroanatomical systems [125].



Several studies have focused on topology of structural and functional resting state connectivity via graph theoretic approach. Using MEG measurements, Stam showed small-world networks in functional connectivity data of human for the first time [126]. Another study conducted by Basset et al. revealed that functional MEG networks were efficient small-world networks and the degree distribution was an exponentially truncated power law [124]. Some studies using resting state fMRI have shown that global network consists of cohesive modular structure and those modules mainly correspond to functionally or structurally related brain regions [127].

He et al. used the method of cortical thickness correlation to demonstrate a small-world architecture in human anatomical networks. This was the first structural based study identifying hubs and certain graph theoretical metrics. It is followed by diffusion tensor imaging (DTI) studies done by Hangmann et al. [128]. They observed high clustering and short path lengths compatible with the previous findings. It has been shown that the global network could be divided into six main modules. On the other hand, hubs could not be identified with this technique [129]. Gong et al. worked with a large sample of subject in a DTI study. They reported that network showed small world architecture and truncated power-law topological distribution. They detected major hub regions in association cortices [130]. As a result of another study done by Gong et al. we know that ageing is related to loss of connectivity strength [131].

There has also been increasing attention focused on brain diseases. By a structural MRI study He et al. showed that Alzheimer's disease patients had altered structural networks such as increased clustering and path length [132]. Abnormal resting state functional connectivity has been shown by different studies. Using a resting state fMRI, Supekar et al. indicated that patients with Alzheimer's disease had decreased clustering. A resting state MEG study conducted by Stam also reported that patients with this disease had abnormal small world organization and highly connected neural network hubs [133]. Decreased clustering, global efficiency and local efficiency have been reported by resting state fMRI study done with schizophrenia patients. Moreover, the reduction was negatively correlated with the illness duration [134]. Wang et al worked with a group of boys with attention deficit/hyperactivity disorder (ADHD) and

a control group. In both groups resting state functional connectivity networks revealed small-world topology. However, an altered functional connectivity was observed in the brain of ADHD compared to control group. Increased local efficiency and decreased global efficiency were interpreted as a sign of a disorder-related shift of the topology toward regular networks [135].

Recent studies have linked the resting state functional connectivity to the cognitive functions. Synchronized regions during rest form resting-state networks (RSNs) [136]. The consistent formation of RSNs is reported by different studies [137, 17]. One of the most studied RSNs is 'default mode network (DMN)' linking posterior cingulate cortex (PCC) with medial frontal regions and bilateral inferior parietal regions. Different RSNs are observed corresponding to functional networks such as motor network [125], visual network [138] and higher order cognitive networks. In contrast to the other resting-state networks, the neural activity of the DMN increase during rest and decrease during cognitive task [139, 136]. Decreased metabolic activity may be related to increased engagement of regions in the DMN.

DMN was linked to integration of cognitive and emotional processing [136]. Hampson et al. investigate the functional connectivity between regions in the DMN during resting state and the performance of a WM task [140]. They reported that they were functionally connected at rest and during a verbal WM task (2-back). Behavioral analysis revealed that working memory performance significantly correlated with connectivity at rest ( $p = 0.01$ ) and during WM task ( $p = 0.04$ ). In a graph theoretical study, Song et al. supported the idea that the functional integration of DMN may be associated with the individual differences in cognitive ability. They investigated the functional connectivity differences between the more intelligent group and the average group. It has been shown that there was significant differences in the global efficiency of the DMN [141]. Further studies have focused on the overall resting state topology of the brain related to cognitive performance.

### 2.3.3 Task-Related Changes of Functional Connectivity

A contemporary theory of information processing in the brain is the global workspace theory [142, 143]. According to this theory, spatially localized and topologically segregated brain regions are related to fast and automatic processes. On the other hand, for slow or consciously effortful tasks connectivity network exhibits topologically integrated and spatially distributed architecture. Based on this theory, Giessing et al. hypothesized that higher cognitive ability was related to higher efficiency of information processing and lower topological clustering [144]. In a resting state fMRI study, they used nicotine replacement and duration of sustained attention task to enhance or impair cognitive ability in healthy volunteers. Nicotine enhanced the task performance and these subjects showed a higher global efficiency and a lower clustering.

A previous study done by Kitzbichler et al. also had compatible results with predictions of global workspace theory [145]. Using MEG, they investigated differences in network topology during performance of n-back task at several levels of difficulty. They reported that greater cognitive effort was related to higher global efficiency, lower clustering and lower modularity.

Although several studies focused on task-related changes in functional connectivity [146, 147], the spatiotemporal associations between resting-state and task-related networks have rarely been investigated. It has been shown that these two states have similar network organization [148, 149] and resting state activity could be seen as a predictor of task-related activations [150]. On the other hand, other studies reported that task-related networks were the reorganization of resting state networks [146, 151].

Rzucidlo et al. performed fMRI scans while at rest and while performing 2-back task [152]. They reported that network topology is fairly stable within the same state for both rest and working memory. However, network topology varied significantly between rest and task. They indicated that there was higher local efficiency in rest significantly. On the other hand, global efficiency and degree was not significantly different for these states.

Using graph theoretical approach, De Salvo et al. investigated the relation between resting-state and task-related networks [153]. They used fMRI data taken during resting state and visual semantic decision making. They observed three main highly intra-connected modules in the resting state, and a language-related module during task. Greater number of within-module connections and fewer between-module connections were reported for task-related networks.

Breckel et al. analysed the topological changes of functional brain network during a designed experiment [154]. Experiment consisted of a sustained attention task and two resting state before and after the task. When they compared the pre-task and task-related networks, topology showed an increase in global efficiency and a decrease in clustering. They also investigated the ongoing task and post-task and reported the changes as a result of mental fatigue. It has been shown that network clustering and efficiency decreased over time.

Wang et al. used similar experimental design with an active semantic-matching task period [155]. A decrease in global efficiency and an increase in local efficiency were reported.

#### **2.3.4 Relation Between Resting State Functional Connectivity and Cognitive Performance**

Recent studies in healthy controls emphasized the association between efficiently organized brain network and intellectual performance. By using fMRI, it has been shown that there was a correlation between intelligence and functional connectivity of regions distributed in the frontal, parietal, occipital and limbic lobes [156]. Using graph theoretical approach on DTI data Li et al. introduced the link between structural connectivity and cognitive performance. Participants were divided into general and high intelligence groups according to their IQ test scores. High intelligence group showed a higher global efficiency and a shorter characteristic path length which can be interpreted as a more efficient parallel information processing [157]. This study

supports the importance of an increase in information transfer capacity for intelligence [158]. Another study done by van den Huevel et al. using resting state fMRI supported the neural efficiency hypothesis of intellectual performance [159]. They investigated the correlation between IQ test scores and graph theoretical metrics obtained from resting state functional connectivity matrices. Negative correlation between clustering coefficient and IQ was found. It has also been reported that this correlation was mainly observed in frontal and parietal regions. Another important result was the relation between higher global efficiency and higher IQ.

In a MEG study done by Douw et al, subjects were evaluated by test scores in eight different cognitive tasks distributed in six cognitive domain [160]. Their total cognitive performances were compared to their resting state overall topologies. Results linked better cognitive performance with higher local connectivity in theta band, higher clustering coefficient in delta and theta bands and higher small-worldness in theta and lower gamma bands. Langer et al. conducted an EEG study focusing on the relation between resting state connectivity and performance in well-known intelligence test Ravens Advanced Progressive Matrices (RAPM) [161]. It has been shown that higher clustering coefficient and lower characteristic path length were strongly related with intelligence. They concluded that connectivity networks of brighter subjects revealed higher small-worldness.

Stevens et al. used resting state fMRI and a visual-spatial working memory task to investigate the relation between modular structure of the network and task performance in two different sessions 3 week apart [162]. They linked more modular resting state network with higher cognitive ability. This result was valid for not only inter-individual variations but also intra-individual variations.

Using resting state fMRI, relationship between network organization and cognitive performance was investigated by Alavash et al. [114]. They used two working memory tasks with different contents. Visual-spatial and numerical contents correspond to two slave systems of Baddeley's working memory model. In this study, it has been shown that resting state topology selectively effected the performance in two

working memory tasks. The results revealed that global efficiency and modularity were associated with performance in visual-spatial working memory, and clustering coefficient was correlated with performance in numerical working memory.

## 3. METHODOLOGY

### 3.1 Participants

The EEG data were recorded by Prof. Metehan Irak at Bahçeşehir University from healthy volunteers. Fifteen healthy right-handed participants (mean age:  $22.7 \pm 3.0$ ; 12 females, 3 males) signed a written consent approved by Bahçeşehir University Committee for Scientific Research and Publication Ethics prior to the study. These participants were screened carefully with a medical history and excluded if they reported any vision problem, past major head injuries, psychiatric or neurological disorders, and intake of any psychoactive medications. EEG scans were performed while at rest and while performing the n-back working memory task. Participants were sitting in a comfortable chair in a dimly illuminated, sound-shielded Faraday recording cage. They were seated approximately 70 cm from the 19 inch screen to avoid unnecessary eye movements.

### 3.2 Experimental Procedure

Before data collection, the study protocol was explained to each participant. Two different experimental set ups were performed: (1) Spontaneous EEG of the subject were recorded for 2 min for eyes closed condition. (2) EEG signals were recorded during n-back working memory task.

During resting state EEG recordings, subjects were instructed to close their eyes, relax, minimize eye and body movement, but stay awake and not to engage in any particular mental activity for two minutes. During performance of n-back test, the participants were instructed to respond as fast and as accurately as possible to matching stimulus by pressing one button. There was a short training session prior to experiment. Total registration time was about 50 minutes.

### 3.2.1 N-Back Task

The n-back task has been commonly used to investigate working memory processing since the task requires online monitoring, updating, and manipulation of remembered information [163]. Recently, variants of the n-back procedure have been used in order to investigate the neural mechanism underlying working memory . In this study, participants underwent verbal n-back working memory tasks.

The participants were presented with a sequence of letters, each 2 seconds apart. They are asked to decide whether a letter currently presented on the screen is the same as the one presented n letters earlier. The memory demands increase as n increases. In order to minimize the possible effect of the presentation sequence, the order of letters was randomly assigned for each participants. When the letter was the same as the one n letters ago, the participants had to press the button. In all other cases, the participants were instructed to wait for the next stimulus without any response. The participants' responses were monitored (reaction times and outcomes).

The stimuli were presented in a block-design in which each block consisted of 18 trials . Participant's brain activity was recorded through 8 alternating blocks of 2-back and 3-back conditions, with a rest period (5 s) between blocks. Valid instruction was given visually at the beginning of each block. In every trial a stimulus presentation time was 240 ms and an inter-stimulus interval was 1760 ms.

## 3.3 Data acquisition and preprocessing

Continuous EEG was recorded with 32-channel Neuroscan equipment (Neuroscan 4.51) using electro-cap (QuickCap). 30 Ag-AgCl surface electrodes were placed over the scalp according to the 10-20 international electrode placement system (30 EEG channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz and O2; 2 channels for eye movements: HEOG and VEOG). Vertical and horizontal eye movements were



measured with two electrodes.

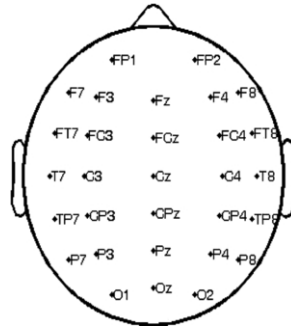


Figure 3.1: 10-20 international system.

Preprocessing of EEG data were done using NeuroScan software (NeuroScan Inc.). Bioelectrical signals were amplified by a Synamps 32-channel amplifier (Neuroscan Inc.) with a sampling rate of 1000 Hz. The impedance of each electrode had to be less than 10 k $\Omega$ . Artifact rejection was performed. The digital EEG data were band-pass filtered to remove signals outside the range of 0.16-100 Hz and in the frequency bands of interest: 8-16 Hz (alpha), 16.1-32 Hz (beta) and 32.1-64 Hz (gamma) [145].

The n-back EEG data were epoched according to outcomes of the task. Four types of epochs were obtained for each experimental conditions (2-back and 3-back): (1) Hit (when there was matching and the subject reported it), (2) Rejection (when there was no matching and the subject did not press the button), (3) Omission (when there was matching but the subject did not press the button), and (4) False Alarm (when there was no matching, but the subject answered that there was).

Hits and rejections were regarded as correct responses. Only trials in which participants responded correctly were concatenated and analyzed.

Further processing for network statistics was done on a MATLAB 12a environment (MathWorks Inc.) using modification of the Brain Connectivity Toolbox ([www.brain-connectivity-toolbox.net](http://www.brain-connectivity-toolbox.net)) scripts [5].

### 3.4 Analysis

The approach to compute the graph theoretical metrics follows a certain algorithm. Details of this algorithm is given below and summarised in Algorithm 1.

1. Every EEG electrode on the scalp corresponds to a node in the functional connectivity network. In order to measure the association between each pair of nodes, we employed the Pearsons correlation as the connectivity weight,  $w_{ij}^{f,c}$ . We obtained 30x30 weighted symmetric connectivity matrices for different frequency bands ( $f : \alpha, \beta, \gamma$ ) and different experimental conditions ( $c$ : rest, 2back, 3back). Rows and columns in these matrices represent nodes, while matrix entries denote correlations between the node pairs.  $w_{ij}^{f,c} = \text{corr}(v_i, v_j)$ ,  $\forall v_i, v_j \in N$  where  $f = \{\alpha, \beta, \gamma\}$  and  $c = \{r, 2b, 3b\}$ .
2. Self-correlations were discarded :  $w_{ij} = 0$ , if  $i = j$
3. According to Erdos-Renyi model, a graph having  $n$  nodes is predicted to be fully connected if the connection density  $\kappa \geq \frac{2 \ln n}{n}$  [145]. So we fixed connection density at 23% according to number of nodes that we had,  $n = 30$ .
4. For each correlation matrix  $W$ , a threshold  $T$  is adjusted. The threshold was determined according to predefined connectivity density  $\kappa$  to fix the number of edges in the network.

$$\kappa = \sum \frac{[W > T]}{n(n-1)} \quad (3.1)$$

This application allowed us to compare network properties at different times, frequency bands and experimental conditions , while controlling the connection density.

5. The computed threshold was applied to the correlation matrix  $W$ .

$$w_{ij}^T = \begin{cases} w_{ij} - T & w_{ij} > 0 \\ 0 & otherwise \end{cases} \quad (3.2)$$

6. Graph theoretical metrics detailed below were computed to investigate network integration on different levels of network organization. We worked with undirected weighted graphs so all the parameters will be given in this content.
7. We generated 100 surrogate data by randomizing every connectivity matrix for every participant. Edges were reassigned while preserving the weight, degree, and strength distributions of the network. The randomized matrices were analysed through the same process with the experimental connectivity matrix.
8. Metrics obtained by experimental data were normalized by using surrogate data.
9. Statistical analysis.

### 3.4.1 Characteristic Path Length

Since the link between two nodes were derived from Pearson' correlation, we used the path length formula defined for communication networks  $d_{ij} = \min \sum_{i,j \in N} \frac{1}{w_{ij}}$ . The characteristic path length  $L$  of a graph is the average of the path lengths between all pairs of nodes [13]. It is an indicator of overall connectedness of the network.

$$L = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} d_{ij} \quad (3.3)$$

### 3.4.2 Global Efficiency

The average over all pairwise efficiencies is the global efficiency of the graph. High global efficiency reflects the highly integrated organization.

$$E_{glob} = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} \frac{1}{d_{ij}} \quad (3.4)$$

### 3.4.3 Local Efficiency

The Local efficiency is the mean of the global efficiencies of all subgraphs containing the node computed for every node in the graph neighbours of each of the vertices of the graph [62].

$$E_{loc} = \frac{1}{n} \sum_{i,j \in N} E_{glob}(G_i) \quad (3.5)$$

### 3.4.4 Clustering Coefficient

For weighted graphs, there are at least six proposals for the definitions of the weighted clustering coefficient. We used the definition based on the 'intensity' of triangles [164].

$$C_i = \frac{\sum_{j,k \in N} \sqrt[3]{(w_{ij}w_{ik}w_{jk})}}{k_i(k_i - 1)} \quad (3.6)$$

### 3.4.5 Modularity

Modularity was estimated using optimization algorithm of Newman [165]. While 0 means the community structure is equivalent to a random one, its upper bound is 1. 1 means a network formed by disconnected modules.  $\delta_{m_i, m_j}$  is equal to 1 if nodes  $v_i$  and  $v_j$  belong to the same module, and 0 otherwise.  $l$  is the sum of all weights in the network and  $m_i$  is the module containing node  $i$ .  $\frac{k_i k_j}{l}$  corresponds to the connectivity of a given null model where  $k_i = \sum_j W'_{ij}$ .

$$Q = \frac{1}{l} \sum_{i,j \in N} [W_{ij} - \frac{k_i k_j}{l}] \delta_{m_i, m_j} \quad (3.7)$$

where

$$l = \sum_{i,j \in N} w_{ij} \quad (3.8)$$

---

**Algorithm 1** Graph Theoretical Approach to EEG
 

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**Compute Correlations:**  $w_{ij}^{f,c} = \text{corr}(v_i, v_j)$ ,  $\forall v_i, v_j \in N$  where  $f = \{\alpha, \beta, \gamma\}$ , and  $c = \{r, 2b, 3b\}$ .

**Discard self correlations:**  $w_{ij} = 0$ , if  $i = j$ ,

**Compute threshold  $T$**  based on  $\kappa = 0.23$ ,

**Compute thresholded  $W$  matrix:**

$$w_{ij}^T = \begin{cases} w_{ij} - T & w_{ij} > 0 \\ 0 & \text{otherwise} \end{cases} \quad (3.9)$$

**Compute graph theoretical metrics:**

$$L = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} d_{ij} \quad (3.10)$$

$$E_{glob} = \frac{1}{n(n-1)} \sum_{i,j \in N, i \neq j} \frac{1}{d_{ij}} \quad (3.11)$$

$$E_{loc} = \frac{1}{n} \sum_{i,j \in N} E_{glob}(G_i) \quad (3.12)$$

$$C_i = \frac{\sum_{j,k \in N} \sqrt[3]{(w_{ij} w_{ik} w_{jk})}}{k_i(k_i - 1)} \quad (3.13)$$

$$Q = \frac{1}{l} \sum_{i,j \in N} [W_{ij} - \frac{k_i k_j}{l}] \delta_{m_i, m_j}$$

where

$$l = \sum_{i,j \in N} w_{ij} \quad (3.14)$$

**Generate surrogate data**

**Normalize metrics**

**Perform statistical analysis**

---

## 4. RESULTS

Since global and local efficiency are essentially well-defined versions of the classical metrics characteristic path length and clustering coefficient, we gave the results in these metrics.

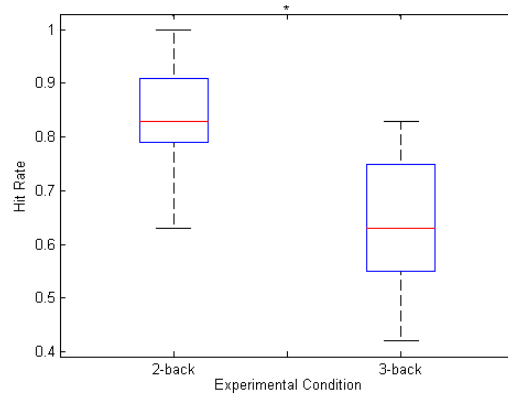
### 4.1 Behavioral Results

In order to verify the participants' attendance to the task, we checked their performance on the most challenging experimental condition [166]. All participants had responded correctly to more than 75% of the items in the 3-back condition.

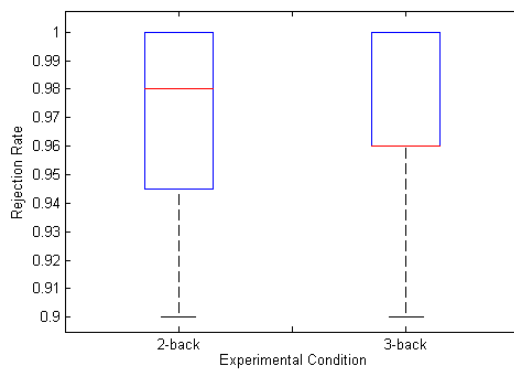
Table 4.1: Behavioral Data

		2-back	3-back	Significance
Hit Rate	mean	0.843	0.650	p<0.01
	std	0.100	0.125	
Rejection Rate (ms)	mean	0.969	0.968	0.91
	std	0.033	0.35	
Response Time	mean	742	773	0.21
	std	147	161	

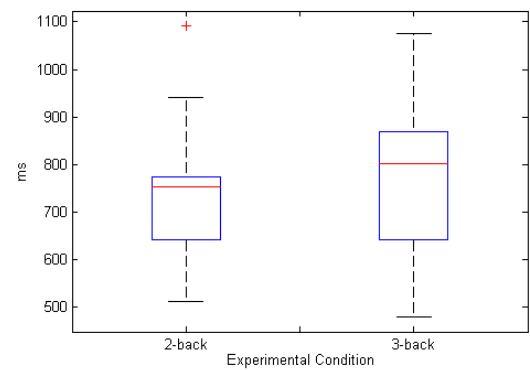
Variable difficulty of the task was inferred from the mean accuracy of performance. Hit rate was defined as the ratio between the number of hits and possible number of hits, and similar for rejection rate. When we consider the correct responses, there was no significant difference in the rejection rates for 2-back ( $0.969 \pm 0.033$ ) and 3-back ( $0.968 \pm 0.034$ ) conditions ( $p=0.908$ ). On the other hand, the hit rates for 2-back ( $0.843 \pm 0.100$ ) condition was significantly higher than 3-back ( $0.650 \pm 0.125$ ) condition ( $p<0.001$ ). The mean response time for 2-back condition was  $741 \pm 147$  and  $773 \pm 161$  for 3-back condition. There was no significant difference in response time for two level of task difficulty ( $p=0.206$ ). Therefore, hit rates were considered when comparing participants' performances.



(a) Hit rate



(b) Rejection rate



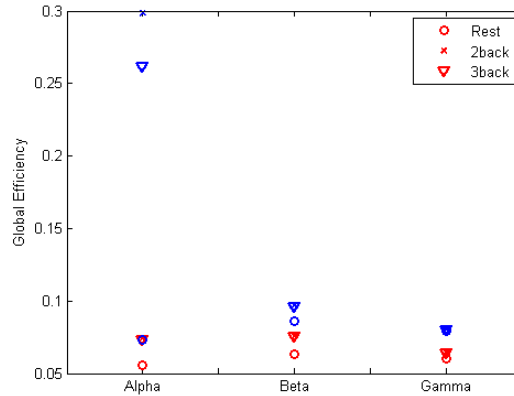
(c) Response time

Figure 4.1: Behavioral analysis.

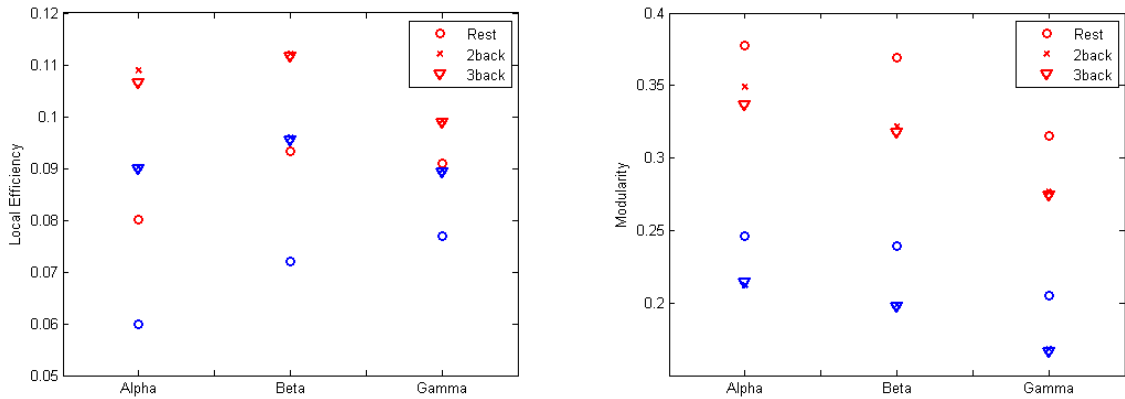
## 4.2 Graph Theoretical Results

To be sure that the EEG data was not completely randomized or dominated by random noise, we used null model. Results were averaged and evaluated statistically. We performed 2-tailed paired t-test.

There were significant differences between surrogate data and EEG data in metrics. Global efficiency was significantly higher in the surrogate data compared to the EEG data reflecting the activity during rest in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band ( $p < 0.001$ ); during performance of 2-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band; and 3-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band. Local efficiency was significantly higher in EEG data during rest in  $\alpha$ -band



(a) Global efficiency of the network obtained from EEG data (red) and surrogate data (blue).



(b) Local efficiency of the network obtained from EEG data (red) and surrogate data (blue) (c) Modularity of the network obtained from EEG data (red) and surrogate data (blue).

Figure 4.2: Comparisons of metrics obtained from EEG data and surrogate data.

( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band ( $p < 0.001$ ); during performance of 2-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band; and 3-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band. Modularity was significantly higher in EEG data during rest in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band ( $p < 0.001$ ); during performance of 2-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band; and 3-back task in  $\alpha$ -band ( $p < 0.001$ ),  $\beta$ -band ( $p < 0.001$ ) and  $\gamma$ -band.

We evaluated the Pearson's correlation between metrics. Global and local efficiency revealed negative correlations during different task conditions. These correlations were salient in  $\beta$ -band with  $r = -0.62$  for 2-back ( $p = 0.014$ ) and  $r = -0.51$  for 3-back



condition ( $p=0.049$ ). There was correlation between local efficiency and modularity during rest in  $\alpha$ -band ( $r=0.47$ ,  $p=0.077$ ), in  $\beta$ -band ( $r=0.54$ ,  $p=0.038$ ) and in  $\gamma$ -band ( $r=0.55$ ,  $p=0.034$ ). The correlation between modularity and global efficiency was not significant during rest and task.

#### 4.2.1 Task-Related Network Reorganization

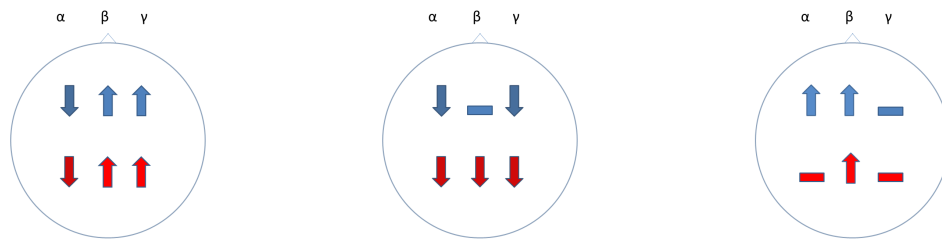
Table 4.2: Effects of experimental conditions (rest, 2-back, 3-back).

	df	Alpha		Beta		Gamma	
		F	p	F	p	F	p
<b>Global Efficiency</b>							
Experimental condition	14	1.960	0.062	4.770	0.000	3.560**	0.002**
<b>Local Efficiency</b>							
Experimental condition	14	3.650	0.002**	3.010	0.006**	2.930	0.008**
<b>Modularity</b>							
Experimental condition	14	2.430	0.022*	4.320	0.001**	2.310	0.029*

The results of the two-way ANOVA. \* $p<0.05$  and \*\* $p<0.01$ .

In order to understand the task-related changes we focused on the network reorganization. When we considered the whole brain, task related functional connectivity networks had higher global efficiency than resting state in  $\beta$ -band and  $\gamma$ -band but lower global efficiency in  $\alpha$ -band. Local efficiency values were lower during task according to resting state in every frequency band. Task-related network organization was more modular especially in  $\beta$ -band compared to resting state. Hence, the network reorganization contains greater number of within-module connections and fewer between-module connections than during rest.

To see the changes in nodal scale, we evaluated the changes in local efficiency. Task-related connectivity networks revealed lower local efficiency especially in frontal, then occipital and parietal lobes compared to rest.



(a) Changes in global efficiency. (b) Changes in local efficiency. (c) Changes in modularity.

Figure 4.3: Task related network reorganization.

Arrows indicate significant increase or decrease of the metric in a certain frequency band according to the rest. Blue for 2-back vs rest, Red for 3-back vs rest.

Table 4.3: Paired t-test results for comparing metrics during rest and task

		Alpha		Beta		Gamma	
		Rest	Task	Rest	Task	Rest	Task
Global Efficiency	Rest vs 2-back	0.76	0.25**	0.76	0.81*	0.73	0.79*
	Rest vs 3-back	0.76	0.28*	0.76	0.81**	0.73	0.79*
Local Efficiency	Rest vs 2-back	1.36	1.20*	1.20	1.10	1.31	1.16**
	Rest vs 3-back	1.36	1.18**	1.20	1.10*	1.31	1.16*
Modularity	Rest vs 2-back	1.53	1.65*	1.53	1.67*	1.54	1.63
	Rest vs 3-back	1.53	1.58	1.53	1.66*	1.54	1.61

\* $p < 0.05$  and \*\* $p < 0.01$ .

## 4.2.2 Correlation Between Cognitive Performance and Graph Theoretical Metrics

Correlation between graph theoretical metrics and participants' performance have been evaluated. Hit rate was used as an indicator of cognitive performance. When we considered the resting state connectivity network, the correlation coefficient of global efficiency and cognitive performance was  $r=0.48$  in  $\alpha$ -band ( $p=0.071$ ),  $r=0.52$  in  $\beta$ -band ( $p=0.045$ ) and  $r=0.58$  in  $\gamma$ -band ( $p=0.022$ ).

Table 4.4: Correlation between cognitive performance and resting state metrics.

		Global efficiency			Local efficiency			Modularity		
		$\alpha$	$\beta$	$\gamma$	$\alpha$	$\beta$	$\gamma$	$\alpha$	$\beta$	$\gamma$
Cognitive performance	r	0.48	0.52	0.58	0.3	0.44	0.41	0.49	0.55	0.39
	p	0.071	0.045*	0.023*	0.277	0.103	0.131	0.064	0.033*	0.149

\* $p < 0.05$  and \*\* $p < 0.01$ .

We found correlation between local efficiency and cognitive performance in  $\alpha$ -band ( $r=0.30$ ,  $p=0.277$ ),  $\beta$ -band ( $r=0.43$ ,  $p=0.103$ ) and  $\gamma$ -band ( $r=0.41$ ,  $p=0.131$ ).

In addition, the correlation coefficient of modularity and cognitive performance was  $r=0.49$  in  $\alpha$ -band ( $p=0.064$ ) and  $r=0.55$  in  $\beta$ -band ( $p=0.033$ ) and  $\gamma$ -band ( $r=0.39$ ,  $p=0.149$ ).

#### 4.2.3 Correlation with Cognitive Performance at the Nodal Scale

In addition to global scale, we evaluated correlation between local efficiency during resting state and cognitive performance in nodal scale. We observed that cognitive performance is negatively correlated with local efficiency of the channels O1 ( $r=-0.58$ ,  $p=0.024$ ) and OZ ( $r=-0.47$ ,  $p=0.081$ ), and positively correlated with the local efficiency of the channels F3 ( $r=0.55$ ,  $p=0.035$ ), F4 ( $r=0.57$ ,  $p=0.027$ ) and FZ ( $r=0.56$ ,  $p=0.031$ ) in  $\alpha$ -band. In  $\beta$ -band performance was positively correlated with local efficiency of the channels F3 ( $r=0.54$ ,  $p=0.037$ ), FZ ( $r=0.50$ ,  $p=0.056$ ), F4 ( $r=0.46$ ,  $p=0.083$ ), FC3 ( $r=0.58$ ,  $p=0.024$ ), FC4 ( $r=0.60$ ,  $p=0.019$ ) and P8 ( $r=0.49$ ,  $p=0.062$ ). In  $\gamma$ -band a positive correlation was observed between performance and local efficiency of the channels F3 ( $r=0.44$ ,  $p=0.098$ ) and F4 ( $r=0.49$ ,  $p=0.062$ ).

Table 4.5: Correlation between cognitive performance and local efficiency at nodal scale.

		$\alpha$ -band					
		O1	OZ	F3	FZ	F4	
Cognitive performance	r	-0.58	-0.47	0.55	0.56	0.57	
	p	0.024*	0.081	0.035*	0.031*	0.027*	
		$\beta$ -band					
		F3	FZ	F4	FC3	FC4	P8
Cognitive performance	r	0.54	0.50	0.46	0.58	0.60	0.49
	p	0.037*	0.056	0.083	0.024*	0.019*	0.062
		$\gamma$ -band					
		F3	F4				
Cognitive performance	r	0.44	0.49				
	p	0.098	0.062				

\* $p < 0.05$  and \*\* $p < 0.01$ .

## 5. DISCUSSION

Watts and Strogatz's model explains the relation between regular, small-world and random graphs [13]. On one hand, there is a regular graph with low global and high local efficiency. On the other hand, there is a random graph with high global and low local efficiency. A network with small-world architecture lies between regular and random graph. It is highly clustered like a regular graph and globally efficient like a random graph. When we compared the network with the average of 100 randomized form of that network, results revealed that the network obtained from the EEG data was significantly different from surrogate data with lower global efficiency and higher local efficiency.

By definition of the modularity a network which is not random is expected to have higher modularity than the randomized network [165]. Our results are compatible with this expectation.

Alavash et al. showed that there was a negative correlation between global and local efficiency during rest [114]. Our results revealed negative correlation between global and local efficiency during 2-back and 3-back condition in  $\beta$ -band; however, they were not correlated during rest. Task related negative correlation may give information on requirements of the dynamical organization of the brain during n-back task. A positive correlation between local efficiency and modularity during rest indicates an association between local and intermediate level of information processing. On the other hand, we did not encounter a similar association between intermediate and global level of organization.

## 5.1 Task-Related Changes

Initially, we aimed to follow the methodology in the Kitzbichler’s MEG study by using correlation instead of wavelet synchronization [145]. Their results supported predictions based on global workspace theory: greater cognitive effort is associated with more integrated organization. They showed an increase in global efficiency, and a decrease in clustering and modularity in  $\beta$ -, and  $\gamma$ -bands as task difficulty increased. In contrast, our method did not reveal any difference between these two network organizations for different levels of difficulty.

Table 5.1: Summary of studies on task-related changes in resting state metrics (fMRI studies).

References	Task	Changes in global efficiency	Changes in local efficiency	Changes in modularity
[152]	N-back	no sig. change	increasing $\times$	no sig. change
[154]	Sustained attention task	increasing $\checkmark$	decreasing $\checkmark$	
[153]	Visual semantic decision making			increasing $\checkmark$
[155]	Active semantic-matching	decreasing $\times$	increasing $\times$	

Tick and cross indicate the comparison between our results and previous findings.

There are only a few graph theoretical studies focusing on rest-task related changes, and their results are contradictory. We showed that the global efficiency was higher during n-back task than rest in  $\beta$ -, and  $\gamma$ -bands. According to prior studies,  $\alpha$ -,  $\beta$ -, and  $\gamma$ -bands synchronization are related to communication between anatomically distributed neuronal groups [167, 168]. In addition, task related changes in graph theoretic metrics were more salient in  $\beta$ -, and  $\gamma$ -bands [145, 169]. On the other hand, we reported a lower global efficiency during task than rest in  $\alpha$ -band. It may be the result of the dominance of  $\alpha$ -band activity during awake resting state with eyes closed.

Using fMRI, Breckel et al. indicated a higher global efficiency during sustained attention task compared to rest [154]. In contrast, Wang et al. reported a lower global efficiency during active semantic-matching task [155], and Rzucidlo et al. claimed that there is no significant difference in global efficiency between these two states in n-back task [152].

Rzucidlo et al. reported a higher local efficiency [152] and Breckel et al. showed higher clustering coefficient at rest compared to task-related connectivity network [154]. Similarly, we observed a higher local efficiency during rest than task. On the other hand, Wang et al. reported higher local efficiency during active semantic-matching task [155]. When we consider these results, higher integration on the global level seems to weaken the organization on the local level. Tasks which require an integration of local networks may reveal higher local efficiency during task. The choice of the task might lead to a dynamic change in the network organization of the brain which might account for the contradictory findings in the literature.

Evolutionary biology studies link higher network modularity with enhanced robustness [117]. deSalvo et al. reported higher modularity during visual semantic decision making task than rest [153]. Our results showing higher modularity in task-related network organization compared to rest was compatible with previous findings.

The variability of findings may be the result of different cognitive processes underlying different cognitive tasks. For example, when we compared result of studies using sustained attention and active semantic-matching task, network efficiency shifts from local to global for sustained attention task. On the other hand, local processing might be more important for active semantic-matching task. As a result, we can claim that n-back task requires a shift of network architecture to a more integrated configuration. The choice of the imaging modality might also be responsible for the contradictory results.

Our results indicating higher global efficiency and modularity, and lower local efficiency during working memory task are compatible with neuropsychological theories

[170]. According to global workspace theory, conscious mental states are associated with integrated activity of distributed elements of the brain [142]. There are several studies reporting the neurophysiological changes related to conscious or effortful states [143].

## 5.2 Resting State Metrics as a Predictor of Cognitive Performance

Several studies have investigated the relation between individual difference in cognitive ability and resting state functional network integration on various organization levels. Most studies indicated that global efficiency and modularity are the predictors of cognitive performance regardless of the cognitive task domain. Meanwhile, there are conflicting results on the correlation between local efficiency (or clustering coefficient) and individual differences in cognitive ability.

Li et al. worked on structural connectivity and demonstrated that there was a correlation between global efficiency and IQ scores [157]. Heuvel et al. also showed a positive correlation between global efficiency of functional resting state network and better cognitive performance in IQ tests [159]. In addition, studies using characteristic path length reported a negative correlation with the performance in various cognitive tasks [160, 161]. Furthermore, Basset et al. reported a positive correlation between working memory performance and global efficiency in healthy young adults and patients with schizophrenia [124]. In agreement with prior studies our current results revealed that higher global efficiency is correlated with a better cognitive performance in  $\alpha$ -,  $\beta$ -, and  $\gamma$ -bands.

It has been shown that the structural and functional connections of the brain network are organized in a small-world architecture. Small-worldness requires efficient information transfer in global and local level. Douw et al. reported that there was a correlation between local efficiency and test scores for different cognitive tasks [160].



Table 5.2: Summary of studies on correlation between cognitive performance and resting state metrics.

References	Imaging method	Task	Global eff. and perf.	Local eff. and perf.	Modularity and perf.
[157]	DTI	IQ	Pos. corr. ✓		
[159]	fMRI	IQ	Pos. corr. ✓	Neg. corr. ✗	
[160]	MEG	Eight different cognitive tasks	Pos. corr. ✓	Pos. corr. ✓	
[161]	EEG	Intelligence test	Pos. corr. ✓	Pos. corr. ✓	
[162]	fMRI	Visuo-spatial working memory			Pos. corr. ✓
[114]	fMRI	Computational span		Pos. corr.	✓
[114]	fMRI	Spatial working memory	Pos. corr. ✓		Pos. corr. ✓

Tick and cross indicate the comparison between our results and previous findings.

They also linked better cognitive performance with higher small-worldness. Langer et al. showed that clustering coefficient and small-worldness were strongly related with intelligence. Giessing et al. demonstrated that nicotine replacement enhanced the cognitive performance and these participants revealed increased global efficiency and decreased clustering coefficient [144]. Our results supported the idea that higher cognitive performance requires higher local efficiency observed at rest.

On the other hand, Heuvel et al. reported negative correlation between clustering coefficient and IQ test scores [159]. Studies investigating cognitive impairment also gave contradictory results. Positive correlation was supported by a study performed with schizophrenia patients [171]. However, it has been shown that children with frontal lobe epilepsy had higher clustering coefficient compared to healthy controls

[172].

There are studies evaluating the relation between modularity and cognitive ability. Steven et al. reported higher modularity as a predictor of higher performance in a working memory task [162]. It has been indicated that modular networks facilitate adaptation to new tasks [173].

Study conducted by Alavash leads widened perspective on task differences [114]. They predicted that resting state network topology might selectively influence a specific cognitive process. They focused on two tasks measuring different aspects of working memory to evaluate storage and transformation of information. While the computational span (CS) task assessed numerical working memory, the spatial working memory (SWM) task assessed to visual-spatial working memory. Results revealed that visual-spatial working memory requires globally integrated processing. On the other hand, numerical working memory requires denser networks on the local level integration.

Two different categories have been distinguished according to previous working memory studies presenting visual materials: numerical or verbal span tasks and spatial-figural working memory tasks [174]. This separation is compatible with slave systems of Baddeley's multi-component working memory model [101]. According to his model, phonologically coded visual stimuli (words or numbers) are stored and rehearsed in an articulatory loop. On the other hand, spatial and figural materials processed and memorized in visuo-spatial sketch pad [175].

Even though maintaining numerical and verbal information depends on articulatory loop, our results are not fully compatible with Alavash's findings. While we found that resting state global, local efficiency, and modularity correlated with working memory performance, they reported a correlation only with the clustering coefficient [114]. This dissimilarity might be due to the cognitive protocols used between the studies. On the other hand, it may actually point out to the difference of the brain organization for numerical and verbal span tasks. There are studies confirming such a difference between these two tasks [176]

### 5.3 Limitations

There are several factors that limit this study. First, the preprocessing is insufficient. It has been known that without appropriate preprocessing, data reveals high correlation due to the volume conduction [177]. Second, untreated volume conduction might cause a regular-like structure with high local efficiency. This may confound the analysis of network properties. Third, the correlation coefficient is the most primitive way to analyze the connectivity. It captures only linear interactions between time series and ignore the nonlinear interactions. There are some other measures sensitive to both linear and non linear interactions such as mutual information and phase synchronization [111]. Finally, unfortunately there are a few studies utilising EEG data that are similar to our study. Hence, we compared our results with studies that used mainly fMRI and different cognitive tasks.

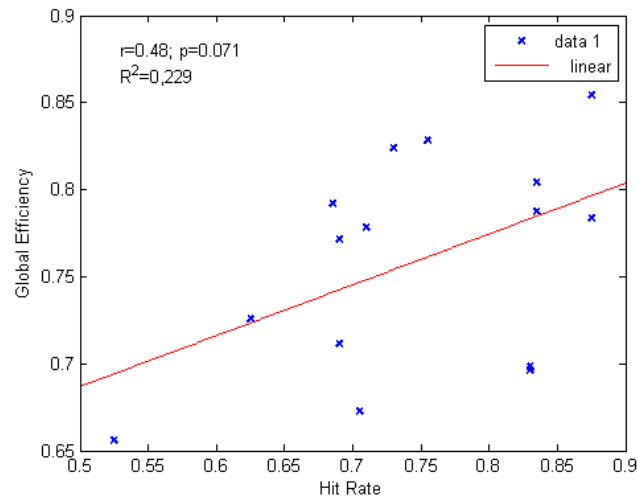
## 6. CONCLUSION AND FUTURE WORK

We showed that performing n-back task requires a reorganization of resting state network with higher global efficiency and modularity, and lower local efficiency. Therefore, more integrated network might be associated with the cognitive effort. In addition, we found a relation between resting state network organization and cognitive performance. Resting state metrics may be seen as predictor of individual differences in cognitive ability.

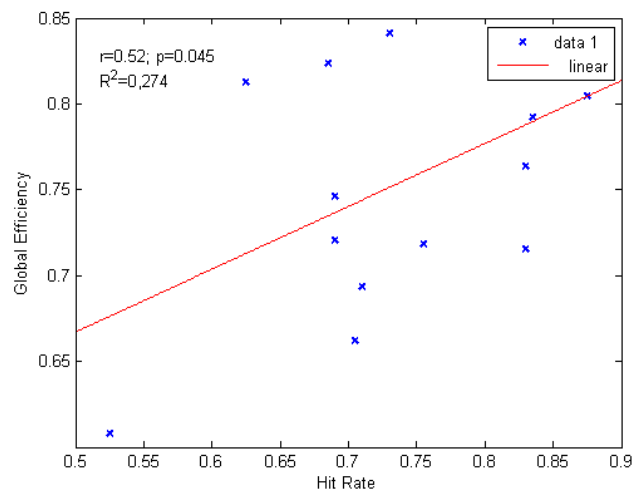
When we consider the lack of graph theoretical EEG studies related to task-related changes and differences in cognitive ability, the first step for the future work can be to replicate this study with improved methodology. Eliminating the volume conduction effect and using a method sensitive to both linear and nonlinear interactions may give more reliable results. Also various tasks can be used to understand the dynamics of cognitive functions. Furthermore, to investigate the temporal and spatial change in terms of network organization simultaneous EEG-fMRI studies may be helpful.

## APPENDIX A. GRAPHS

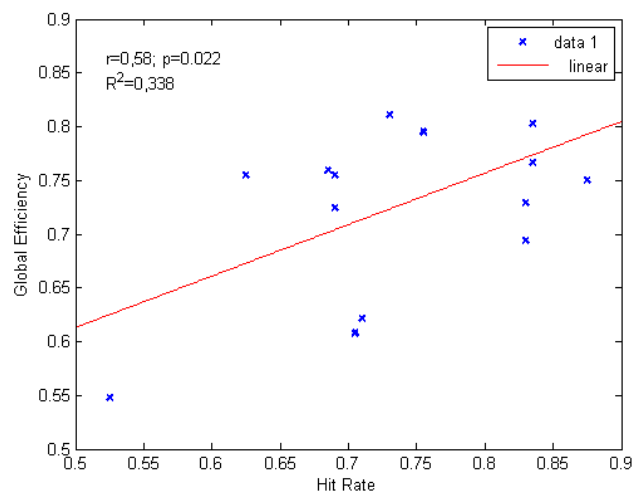
### A.1 Correlation Between Cognitive Performance and Graph Theoretical Metrics



(a) Alpha band

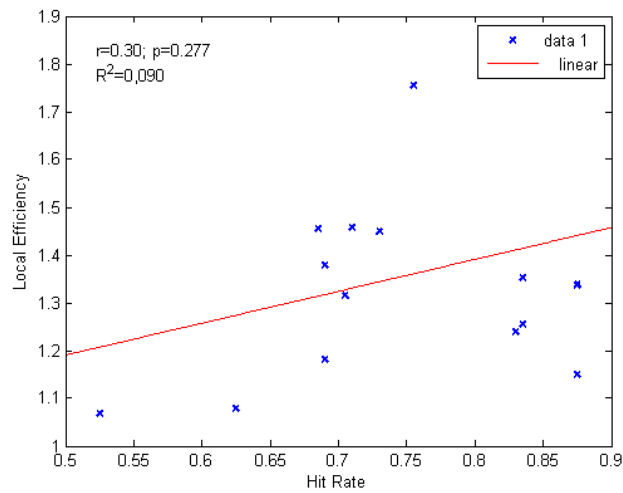


(b) Beta band

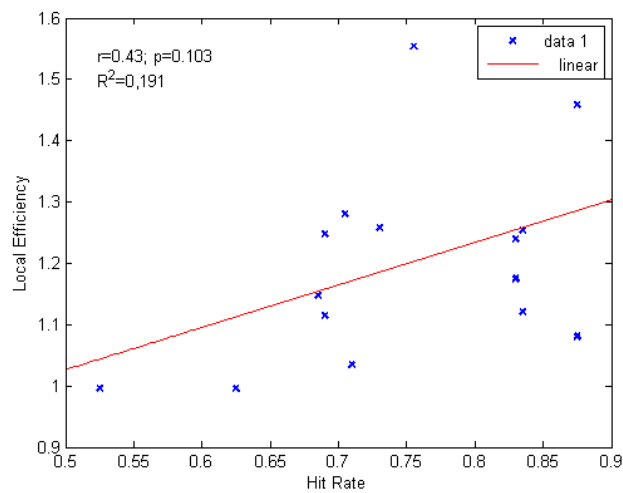


(c) Gamma band

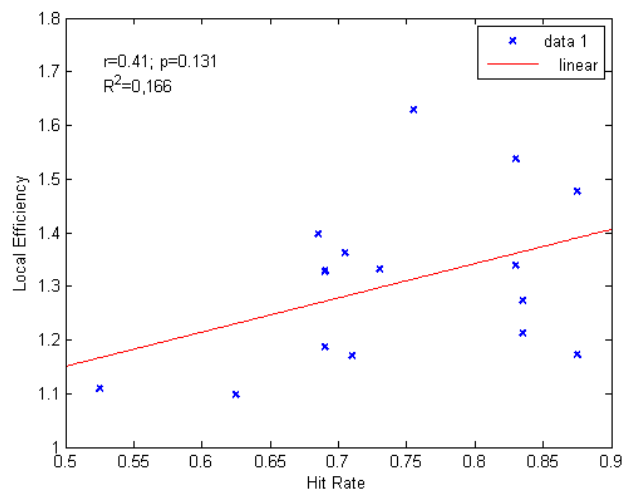
Figure A.1: Correlation between cognitive performance and resting state global efficiency in different frequency bands.



(a) Alpha band

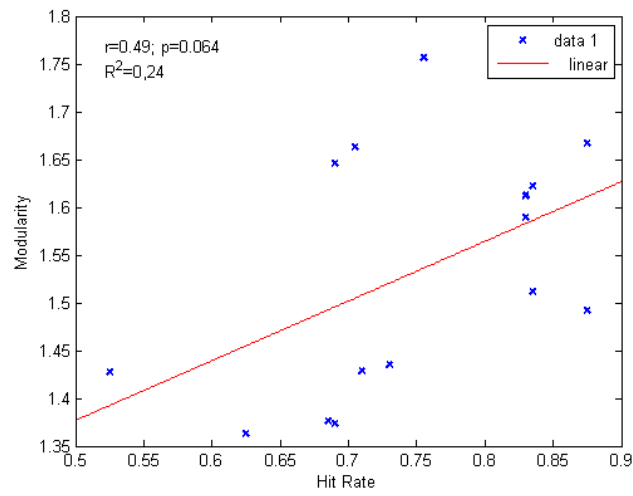


(b) Beta band

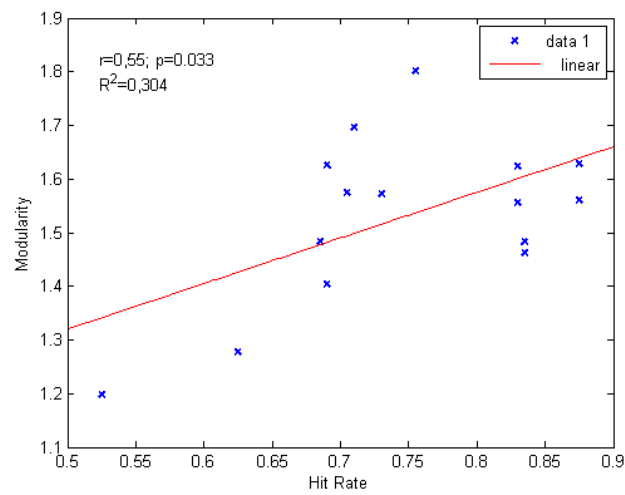


(c) Gamma band

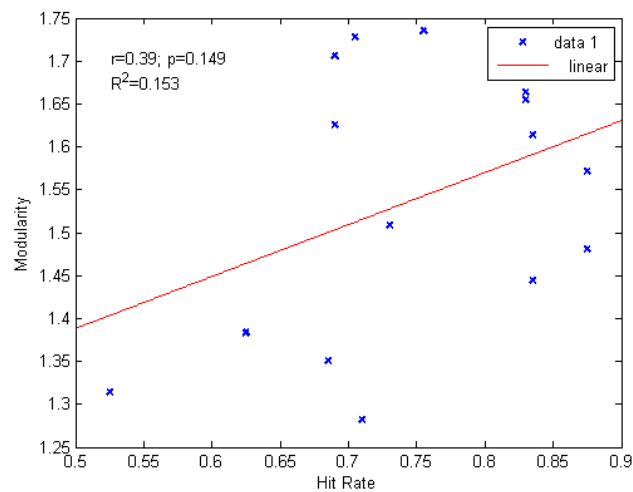
Figure A.2: Correlation between cognitive performance and resting state local efficiency in different frequency bands.



(a) Alpha band



(b) Beta band



(c) Gamma band

Figure A.3: Correlation between cognitive performance and resting state modularity in different frequency bands.



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