SIMILARITY AND CONSISTENCY ANALYSIS OF FUNCTIONAL CONNECTIVITY MAPS

by

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ABSTRACT

SIMILARITY AND CONSISTENCY ANALYSIS OF FUNCTIONAL CONNECTIVITY MAPS

Functional connectivity (FC) refers to statistical relations of activations of distinct neuronal populations without any reference to causal or anatomic connections. One of the problems in FC studies is, to interpret the resultant FC matrix and only few studies in the literature have focused on consistency and temporal variability of FC networks. In this study functional near infrared spectroscopy (fNIRS) signals were recorded from prefrontal cortex (PFC) of 12 healthy subjects during a stroop test. Mutual information was used as a metric to determine functional connectivity between PFC regions. 2D correlation based similarity measure was used as a method to analyze within-subject and inter-subject consistency of FC maps, and how they change in time. How functional integration changes during to stroop test session was also investigated, using a graph-theoretical metric "global efficiency". It was found that within-subject consistency (0.61 ± 0.09) is significantly higher ($p < 0.001$) than inter-subject consistency (0.28 ± 0.13). Within-subject consistency was not found to be task-specific. Results also revealed that there is a gradual change in FC patterns during stroop session for congruent and neutral tasks, where there is no such trend in the presence of an interference effect (incongruent task). Finally it was found that, the changes in global efficiency of the FC networks during the stroop test session exhibit a parallel trend. One of the results of these findings is that it is feasible to study consistency, inter-subject variability and temporal changes in functional connectivity during a cognitive task with fNIRS.

Keywords: Functional Connectivity, fNIRS, Stroop Task, Mutual Information, Interference, Graph Theory.

ÖZET

İŞLEVSEL BAĞLANTILILIK HARİTALARININ BENZERLİK VE TUTARLILIK ANALİZİ

İşlevsel baglantılılık (İB) nedensel veya anatomik baglantı olmaksızın sinir hücresi öbeklerinin aktiviteleri arasındaki istatistiksel ilişkiye gönderme yapar. İB çalışmalarındaki sorunlardan biri, elde edilen İB haritalarının analiz edilmesidir ve az sayıda çalışma bu haritaların tutarlılığını ve zamansal değişimini incelemiştir. Bu çalışmada sağlıklı 12 bireyden stroop testi sırasında prefrontal korteks (PFK) bölgesinden işlevsel yakın kızılaltı spektroskopi (IYKS) cihazı yolu ile ölçümler alındı. Her iki PFK bölgesi arasındaki işlevsel bağlantıyı ölçmek için "Karşılıklı Bilgi" hesaplaması kullanıldı. Bireylerin kendi içlerinde ve bireyler arası İB tutarlılığını ve İB'nin zamansal değişimini incelemek amacıyla 2D korelasyon kullanıldı. Ayrıca bir çizge teorisi yöntemi olan "küresel verimlilik" ölçümü kullanılarak, işlevsel entegrasyonun zaman içerisinde nasıl değiştiği incelendi. Bulgularımıza göre bireylerin kendi içlerindeki İB tutarlılıkları (0.61 ± 0.09), bireyler arası İB tutarlılığından (0.28 ± 0.13), istatistiksel olarak belirgin şekilde yüksek ($p < 0.001$). Bireylerin İB matrislerinin zamana bağlı olarak değiştiği, ancak karõ?ma (interferans) durumunda böyle bir durumun olmadığı görüldü. Küresel verimlilik ölçümünün de bu değişime paralel bir değişim gösterdiği tespit edildi. Bulgularımızın sonuçlarından biri, İB ağlarının tutarlılıklarının ve zamansal değişimlerinin iYKS teknolojisi ile incelenebileceğini göstermiş olmasıdır.

Anahtar Sözcükler: İşlevsel Bağlantılılık, iYKS, Stroop Testi, Karşılıklı Bilgi, İnterferans, Çizge Kuramı.

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LIST OF ABBREVIATIONS

fNIRS	functional Near Infrared Spectroscopy
PFC	Prefrontal Cortex
FC	Functional Connectivity
PET	Positron Emission Tomography
EEG	Electroencephalography
fMRI	functional Magnetic Resonance Imaging
BOLD	Blood Oxygen Level Dependent
CBF	Cerebral Blood Flow
ADHD	Attention Deficit Hyperactivity Disorder
MI	Mutual Information
CW	Continuous Wave
IC	Inter-Subject Consistency
C_p	Within-Subject Consistency of Subject p
sec	Seconds
N	Neutral
C	Congruent
IC	Incongruent

1. INTRODUCTION

Recent advances in neuroscience have discovered the presence and significance of large-scale neural networks in brain. It is considered that investigation of the dynamics and properties of these networks would lead to a better understanding of brain function [1]. These networks can be defined based on anatomical or functional connections. Functional connectivity (FC) refers to the statistical relations of activations of distinct neuronal populations without any reference to causal or anatomic connections [2]. The result of an FC analysis is an FC matrix, which represents pair-wise connectivity values of the distinct brain regions. FC is studied in different neuroimaging modalities such as fMRI (functional magnetic resonance imaging), PET (positron emission tomography), EEG (electroencephalography) and recently fNIRS (functional near infrared spectroscopy) [3, 4].

Besides cognitive studies of FC, substantial part of the FC studies in the literature has focused on resting state FC. Resting state FC is expected to reveal functional networks in the absence of a cognitive task, which is called the *default mode network* [5]. However, it is not clear what "resting state" is, and it has been shown that during a so-called resting state, there is significant cognitive activity [6, 7]. We decided to focus our study on cognitive FC and used the well-known stroop test as a cognitive task in this study.

Stroop interference is one of the most studied phenomena in cognitive psychology. The main principle of the stroop test is to present two different stimuli, color and text for a recognition task. When the two stimuli are incongruent with each other, interference effect occurs which mostly presents itself with increased reaction times [21]. Stroop effect is considered to be related to selective attention, inhibition and control of behavior, where attention is considered to be related to the activity of the prefrontal cortex (PFC) [8, 9, 10, 11].

Functional near infrared spectroscopy (fNIRS) was used in this study, which is a noninvasive neuroimaging tool. With fNIRS it is possible to monitor hemodynamic changes in cortex of the brain, similar to functional magnetic resonance imaging (fMRI). In contrast to fMRI, fNIRS is based on optical principles, rather than magnetic resonance. This brings about many advantages such as low cost, portability, high temporal resolution and comfort for the patients in monitoring duration. Previous studies has have shown that it is feasible to apply functional connectivity methods to fNIRS signals [12, 13, 14, 15, 16].

There is a lack of methods to investigate the dynamical properties of FC matrices. Conventionally, FC is computed by correlating a time series signal from one area (fMRI voxel or EEG electrode) with a signal from another area (fMRI voxel or EEG electrode). This choice of using the whole time series poses a limitation to investigate the dynamical properties of the FC matrices. Even when several task blocks are used, an average of signals corresponding to these tasks blocks are computed in order to increase the strength of the statistics [44]. Interestingly only several studies considered investigating the consistency of FC networks [28, 29]. Within-subject consistency investigation would require segmenting the data, which in practice is not advisable for fMRI BOLD signal due to low sampling rate. In this study, it was decided to explore the fNIRS data to elucidate the dynamical properties of the FC matrices derived from hemodynamical activity. I hypothesize that

> *The consistency and similarity of FC matrices throughout a recording session carry information about the dynamical behavior of the network under investigation and that this value can be used to quantify the neural correlates of a cognitive task.*

On the other hand, population analysis of FC maps of subjects based on fNIRS signals is also being studied in the literature, where inter-subject variation is often ignored and FC maps of different subjects are averaged or constructed in a common protocol [37, 43].

In this study, consistency and variations in patterns of FC maps were investigated. Although neuroscientists have long observed moment-to-moment variability of neuronal activity, this phenomenon is usually ignored [17]. Because of the complexity of neuroimaging data, researchers tend to extract meaningful information from these data by minimizing the variations, which are mostly considered to be noise [17]. Other than possible sources of noise in instrumentation, noise is considered to be a natural consequence of operation of brain [18]. But there is also a moment-to-moment variability in neuronal activity, which should be distinguished from noise [18]. This study focuses on consistency and variability of FC networks, both within-subjects and inter-subjects.

A method based on correlation-based similarity of networks was used in this study, as a way of investigating variations and consistency of functional connectivity networks. Instead of using the time-series data as a whole to construct a single FC matrix, time series data was segmented and several FC matrices were constructed from each segment. A coherence based mutual information metric was used to compute functional connectivity between fNIRS nodes. Then, similarities of the FC matrices were used to investigate inter-subject consistency, within-subject consistency and time-dependant variation of the FC matrices. 2D correlation was used to compute similarity between two FC matrices. In order to detect presence of changes in FC patterns during the mental task, the relation between FC map similarity and their proximity in time of record was investigated. Finally the changes in functional integration in the FC maps were investigated based on a graph theoretical measure "global efficiency".

2. BACKGROUND

This study includes methods from a broad range of fields such as neuroimaging, signal analysis, information theory, graph theory and statistics. This section is dedicated to the explanations of the methods and concepts used from these fields.

2.1 Functional Near Infrared Spectroscopy (fNIRS)

Some of the functional brain imaging methods rely on monitoring hemodynamic changes in cerebral blood flow (CBF), since CBF to the neuronal units in brain is considered to be correlated to the demand of those certain neuronal units [33]. fMRI is one of those methods, which allows us to monitor these hemodynamic changes. A recently emerging brain imaging technology, fNIRS is also able to monitor hemodynamic changes non-invasively similar to fMRI, but it is based on optical principles, rather than magnetic resonance. fNIRS has certain advantages over fMRI such as higher temporal resolution, low cost, portability and the comfort that it offers for patients during monitoring. These advantages make fNIRS potentially an ideal tool for monitoring hemodynamics of the cortex of the brain.

The basic principle of fNIRS relies on the fact that, there is a difference between the amount of light reflected from oxygenated blood and deoxygenated blood (Fig. 2.1). This means that an activated brain region will reflect different amount of light than it reflects when it is not activated. fNIRS is able to detect these optical changes which is associated with the functional activity of the brain [34].

Light in the range of 650-950 nm wavelength (near-inrared region) is known to pass through the skull and it can reach the cerebral cortex up to a depth of 2.5 cm from the skin surface [34]. A typical fNIRS probe is seen in Fig. 2.2(a) and the corresponding brain regions that are monitored in terms of hemodynamic changes is seen in Fig. 2.2(b). As seen in the images, only pre-frontal cortex (PFC) is monitored using this type of

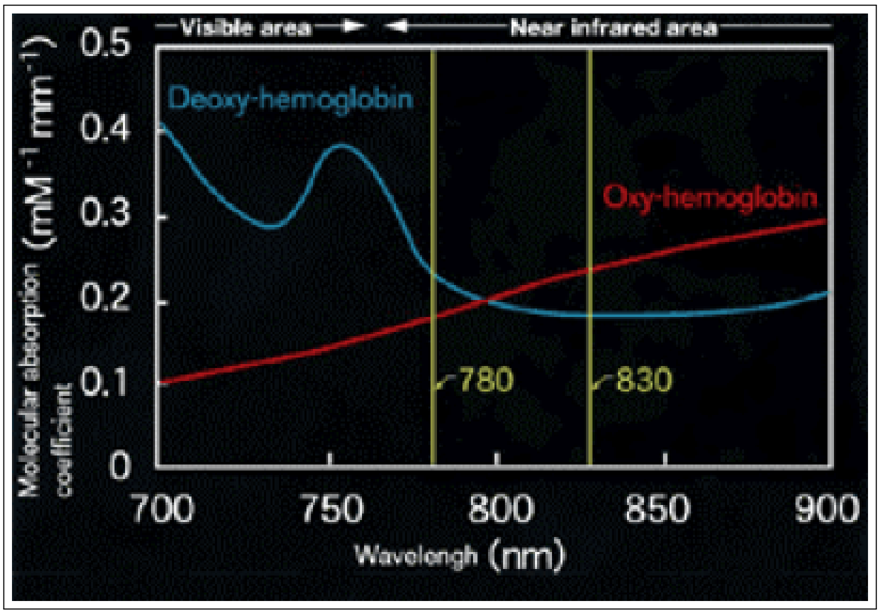


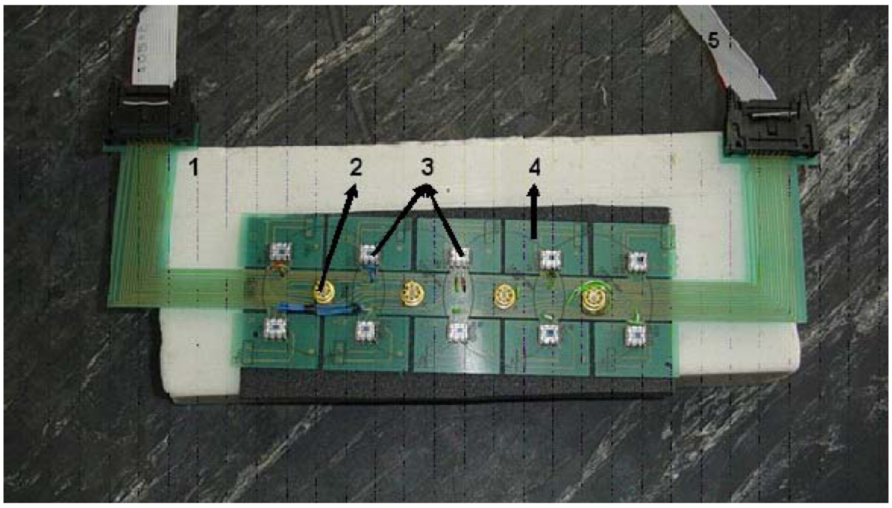
Figure 2.1 Different optical characteristics of oxygenated and deoxygenated hemoglobins in near-infrared range.

probe. Although full-head fNIRS devices are also present, we preferred this geometry since we were interested in PFC activity [35].

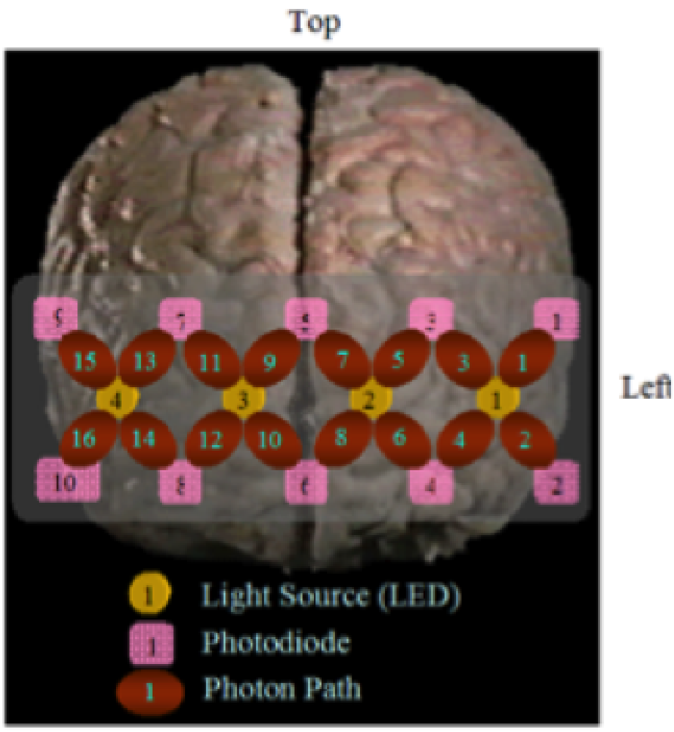
2.2 Functional Connectivity

Modern views of neuroscience and neurology focus on dynamics of large scale neural networks in brain for explaining its functions [1]. These networks can be based on anatomical or functional connections. Functional connectivity (FC) refers to the statistical relations of activations of distinct neuronal populations without any reference to causal or anatomic connections [2], while anatomical connectivity refers to physiological and structural connections between neurone populations, as its name suggests. Combination of these two types of connectivity is called as effective connectivity which refers to causal relations between connected neuronal populations [4].

The scope of this thesis is functional connectivity in PFC of human brain. Neurological or cognitive disorders such as Alzheimer's disease, epilepsy, schizophrenia, attention deficit and hyperactivity disorder (ADHD) and migraine are considered to



(a)



(b)

Figure 2.2 (a) The rectangular probe used in the study (b) Approximate probing locations on the PFC of the rectangular probe seen in (a).

be related to the loss or impairment of the communication between several neuronal regions while functioning [4, 39, 40]. Therefore studies in functional connectivity can reveal valuable knowledge for diagnosis and assessment of these disorders.

2.3 Connectivity Measures and Mutual Information

Functional connectivity between brain regions can be evaluated using various different measures including, correlation, partial correlation, coherence, mutual information and autoregressive models. Mutual information was used in this study to compute the functional connectivity. Mutual information has an advantage compared to correlation since it can detect nonlinear dependencies of neural signals [25, 26]. In correlation computation, two signals need to have the same phase in order to determine their statistical relationship accurately, where a phase lock condition is not required in mutual information metric.

Mutual information has been used in the literature as a metric to estimate connectivity between brain regions, with EEG and fMRI [22, 23, 24]. Zhou et al. proposed a method for computing mutual information of two signals based on their coherence in the frequency domain [25], which was used in this study. The mutual information of i^{th} and j^{th} time-series in frequency domain is given in Eq. 2.1.

$$\phi(i,j) = [1 - exp(-2\delta_{ij})]^{\frac{1}{2}} \tag{2.1}$$

where

$$\delta_{ij} = \frac{1}{2\pi}\int_{\lambda 1}^{\lambda 2} \log(1 - coh_{ij}(\lambda))\,\mathrm{d}\lambda \tag{2.2}$$

and the cross coherence function $coh_{ij}(\lambda)$ is given as

$$coh_{ij}(\lambda) = |R_{ij}(\lambda)|^2 = \frac{|f_{ij}(\lambda)|^2}{f_{ii}(\lambda)f_{jj}(\lambda)} \tag{2.3}$$

where $f_{ij}(\lambda)$ is the cross spectral density between i^{th} and j^{th} time-series; $f_{ii}(\lambda)$ and $f_{jj}(\lambda)$ are spectral densities of i^{th} and j^{th} time-series respectively.

In Eq. 2.2, mutual information is computed as a sum of coherence values in a frequency band. In Eq. 2.1, this value is normalised into the range of (0,1).

2.4 Graph Theory

Mathematical study of networks is known as graph theory [20]. Graph theory is an old topic in mathematics, but recently it is being used to analyze complex networks that arise from analysis of biological organisms. Brain is also a large and complex network as mentioned in functional connectivity section. Graph theory is used as a way to analyze both anatomical and functional networks in brain, and to extract futures from these networks.

A graph consists of nodes and edges. Each region in PFC measured by fNIRS (the red regions in Fig. 2.2(b)) is represented by a node in the graph. Each functional connection between these regions are represented by an edge.

There are many different network measures in graph theory, which measure various characteristics of networks. Some of the characteristics measured by these measures are functional segregation, functional integration, small world characteristics, centrality, network resilience [20]. For example functional segregation defines "the ability for specialized processing to occur within densely interconnected groups of brain regions" [20], while functional integration indicates how much integrated the processing occurs.

Such characteristics can be measured with different metrics and can be applied to binary, weighted, directed or undirected networks. Binary networks are networks in which each connection is identical, where weighted networks consist of connections of different strengths. In directed networks, each connection has a direction (plus or minus), where in undirected networks there is no such direction. The functional networks created by mutual information connectivity are undirected and weighted networks. Each weighted network can be converted to binary network by applying threshold to the connectivity values.

Global efficiency is a graph theoretical measure, which is a measure of the functional integration of a network and it can even be computed in networks that are not fully connected [20]. Mathematically, global efficiency is computed as given in Eq. 2.4.

$$E = \frac{1}{n}\sum_{i\in N} E_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} d_{ij}^{-1}}{n-1} \tag{2.4}$$

Where E_i is the efficiency of node i, d_{ij} is the shortest path length (distance) between nodes i and j (Eq. 2.5), and N is the set of all nodes in the network.

$$d_{ij} = \sum_{a_{uv}\in g_{i\leftrightarrow j}} a_{uv} \text{ , where } g_{i\leftrightarrow j} \text{ is the shortest path between nodes } i \text{ and } j \tag{2.5}$$

Since the inverse of the shortest paths are taken into account, it is possible to use this measure for the networks which are not fully connected and the result value is mainly affected by the short connections.

2.5 Stroop Effect

Strop test is a cognitive test, which is commonly used in psychology. The main principle of the stroop test is to present two different stimuli, color and text for a recognition task. When the two stimuli are incongruent with each other, interference effect occurs which mostly presents itself with increased reaction times [21].

There are typically three types of questions in a stroop test: neutral, congruent and incongruent questions (Fig. 3.1). In neutral questions, letters without a meaning (such as "XXXX" string) is presented in a certain colour and its colour is written below the string. The subject is expected to determine whether if the word below defines the colour of the string above correctly or not. In congruent questions, the upper string is replaced by the word of the colour, congruent with the real colour of the upper word.

In incongruent questions, the color and meaning of the upper word are conflicting.

The increased reaction time is considered to be caused by the need for resolving two conflicting stimulus separately and suppressing one of the results. This is named as stroop interference effect, named after John Ridley Stroop, who first published this effect in 1935. Other than interference, there is also "facilitation effect" that can be observed in a stroop test, when the two stimulus are congruent. It is considered that when color and word stimuli are congruent, they facilitate each other, resulting in faster reaction times [50]. But facilitation effect is not as significant as interference effect and it is not always observed [50].

Interference effect seen in stroop test is a widely studied phenomenon in the literature and it is considered to be related to the activity of PFC [8, 9, 10, 11, 52]. Previous studies suggest that PFC is involved when a conflict has been experienced, which is the situation in incongruent questions of the stroop test [53]. The fNIRS device used in this study monitors hemodynamic changes in PFC region of the brain.

3. METHODS

3.1 Data Collection

3.1.1 Subjects

12 healthy subjects recruited from college graduate students volunteered for this study. The study was approved by the Ethics Board of Boğaziçi University and informed consent forms were signed and collected from the participants.

3.1.2 Protocol

Subjects were asked to reply the stroop test questions of three different types: neutral, congruent and incongruent (Fig. 3.1). The subjects were asked to detect if the word below defines the color of the word above correctly or not. In the neutral case, a nonverbal stimulus was introduced in the upper word, as a series of X's. Subjects made a left mouse click with their forefinger of the right hand to indicate a match case, and a right mouse click with their middle finger for non-matching cases.

Each type of stimulus was applied in 5 different blocks (Fig. 3.2). Each block consisted of 6 questions of the same task type, each of these 6 questions are 4 seconds apart. Maximum allowed response time was 2.5 seconds. Between each task block, there was a short resting period of 20 seconds.

Performance of the subjects in neutral, congruent and incongruent tasks were compared. The performance measure includes reaction time and accuracy of the answers.

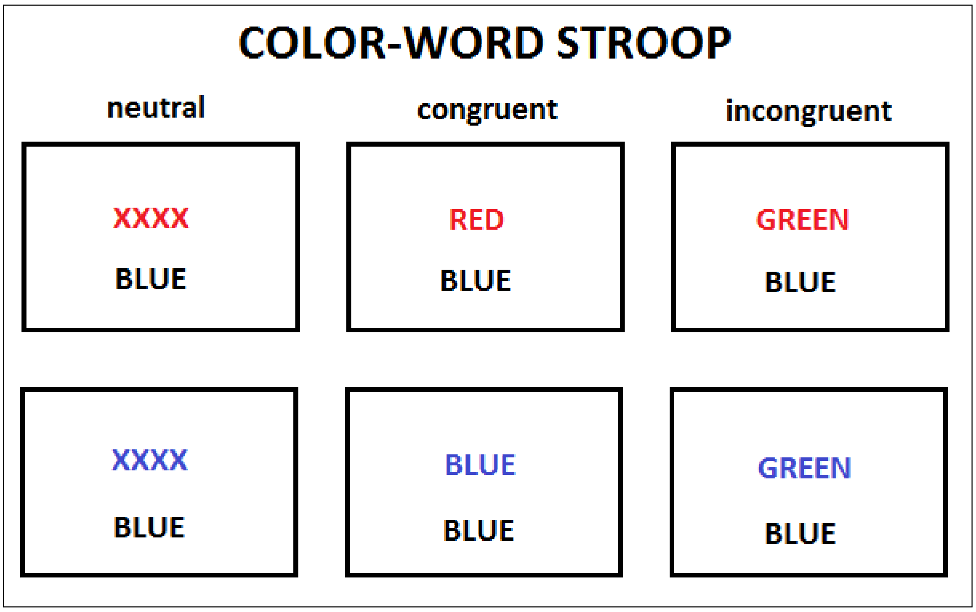


Figure 3.1 Three different stimuli in stroop task: neutral, congruent, and incongruent. The upper questions are the cases where the word below wrongly defines the colour of the word above. The other three questions given at the bottom represent the opposite case; the word below correctly defines the colour of the word above.

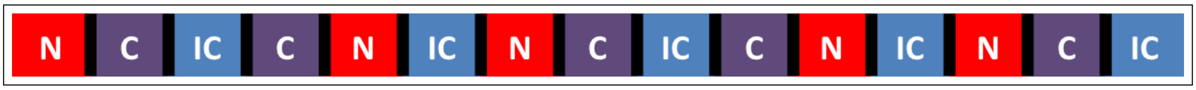


Figure 3.2 Three different stimuli in stroop task: neutral, congruent, and incongruent

3.1.3 fNIRS Data Collection

In this study, a 16 channel CW-fNIRS device (NIROXCOPE 301 now ARGES Cerebro, Hemosoft Inc., Ankara Turkey) was used, which was developed in Biophotonics Laboratory (now Neuro-Optical Imaging Laboratory) of Boğaziçi University [36, 37, 38]. This device has 4 sources of light, surrounded with 10 optical sensors. At a given time only one of these light sources and surrounding 4 detectors are active. Therefore 16 time series data was collected from each subject corresponding to 16 regions in PFC region, given in Fig. 2.2(b). The data were previously recorded and published in another study [38].

3.1.4 Data Preprocessing

During test sessions, time series signals from 16 regions of PFC defined in Fig. 2.2(b) were recorded. The raw data collected was firstly used to generate the time series of relative oxygenation change in CBF, by using a modified version of Beer Lambert Law [34]. Normally it is possible to measure oxyhemoglobin, deoxyhemoglobin and total hemoglobin concentrations. A previous study suggested that oxyhemoglobin has the strongest correlation with the BOLD (blood oxygenation level dependant) signal measured by fMRI [54]. Therefore, oxyhemoglobin concentrations were computed and signals corresponding to the changes in oxyhemoglobin concentrations in 16 regions in PFC were generated. Then, these 16 time series signals were filtered by the bandpass filter at the range of 0.03-0.25 Hz to eliminate slow drifts and physiological noise. Mutual information between each signal pair was computed by using the Eq. 2.1 - 2.3. The result of mutual information computation is a number between 0 and 1. Zero mutual information represents no connectivity between regions, while a value of one means that two regions include exactly the same information content.

3.1.5 Functional Connectivity Matrices

The result of computing connectivity with MI for each signal pair is a symmetric FC matrix with diagonal entries equal to 1. Ignoring the diagonal and lower triangle parts, the FC network is represented by the upper triangle as given in Fig. 3.3. This is a 16 by 16 matrix, where each pixel in the figure represents the strength of connectivity between pairs of regions. Darker pixels represent lower connectivity (close to 0) where lighter pixels represent high connectivity (close to 1). Diagonal entries are ignored since they are equal to 1. Lower triangle is also ignored, since this is a symmetrical matrix as a result of mutual information's being a non-directional connectivity measure.

FC matrices were computed from signals corresponding to the time range of each task. Since there are 15 tasks in total (5 neutral, 5 congruent, 5 incongruent) with rest periods in between, 15 FC matrices were generated per subject corresponding to 15

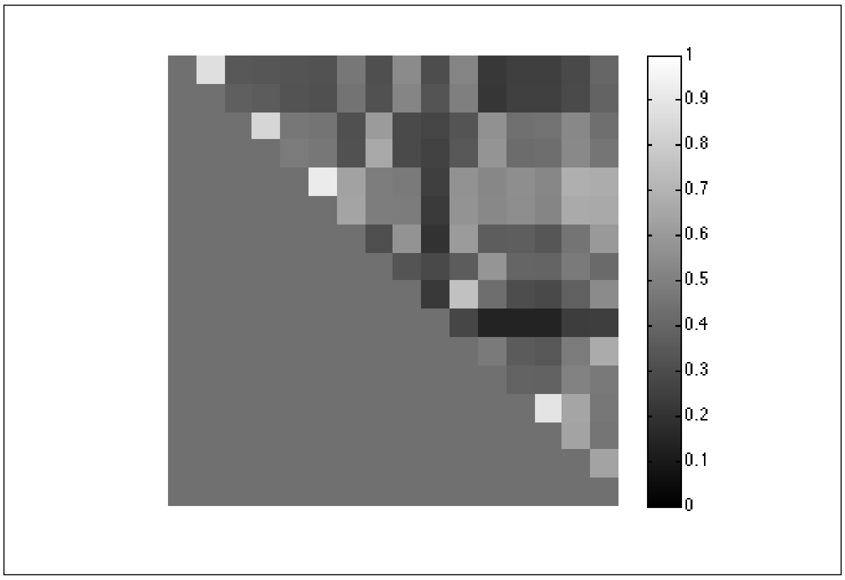


Figure 3.3 FC matrix computed for a subject based on fNIRS signals recorded during stroop task. Diagonal and lower triangles entries are removed since the matrix is symmetric and diagonal entries are equal to 1.

task periods.

3.2 Similarity and Consistency Analysis

2D correlation is a method commonly used to compute similarity of two images or patterns, especially for registration purposes [27]. Similarity of two FC networks can be computed by 2D correlation [28]. In this study, this was computed as in Eq. 3.1.

$$r = \frac{\sum_m \sum_n (A_{mn} - \overline{A})(B_{mn} - \overline{B})}{\sqrt{(\sum_m \sum_n (A_{mn} - \overline{A})^2)(\sum_m \sum_n (B_{mn} - \overline{B})^2)}} \tag{3.1}$$

Where A and B are two different FC matrices and $\overline{A}$ and $\overline{B}$ are the means of them; respectively. Since lower triangle and diagonal entries hold no additional information, in order to avoid the additional correlation bias caused by the same symmetrical properties of any two maps, lower triangle and diagonal entries were replaced by the mean of the upper triangle values. As a result, they did not contribute into correlation computation [28].

2D correlation was used as a way to measure similarity of two FC maps. Similarity of maps can be used to investigate the consistency of FC maps for subjects. Instead of computing connectivity values over the whole time series during the Stroop test, I divided the time series into subsequent intervals, where each time interval corresponds to a block of Stroop test questions of the same type.

In order to investigate within-subject consistency of FC networks, similarities between FC matrices of the same subject were computed and averaged [28, 29], as in Eq. 3.2.

$$C_p = \frac{2}{M^2 - M} \sum_{i}^{M} \sum_{j>i}^{M} \texttt{Corr2}(\mathcal{F}_p(i), \mathcal{F}_p(j)) \tag{3.2}$$

Where Corr2 is 2D correlation function as given in Eq. 3.1, $\mathcal{F}_p(i)$ is the i^{th} functional connectivity matrix corresponding to subject p, C_p is the consistency of FC matrices of subject p and M is the number of FC matrices that each subject has (in our case $M = 15$).

Inter-subject consistency was also investigated to understand how consistent the FC matrices of different subjects are. I did this computation as given in Eq. 3.3.

$$IC = \frac{2}{(N^2 - N)M^2} \sum_{p}^{N} \sum_{r>p}^{N} \sum_{i}^{M} \sum_{j}^{M} \texttt{Corr2}(\mathcal{F}_p(i), \mathcal{F}_r(j)) \tag{3.3}$$

Where N is the number of subjects, $\mathcal{F}_p(i)$ is the i^{th} functional connectivity matrix corresponding to subject p and $\mathcal{F}_r(j)$ is the j^{th} functional connectivity matrix corresponding to subject r. This is simply to compute average similarity of FC matrices of a pair of 2 subjects, and computing an average of all resultant values. The resultant IC is the inter-subject consistency value.

Finally I computed within task and inter-task consistency of FC matrices for each subject. If within task consistency is significantly higher than inter-task consistency, this means that FC patterns differ for different cognitive tasks. To measure within task consistency, I computed average similarity of FC matrices of the same task (neutral, congruent or incongruent) for each subject. Then I computed average and standard deviation of all subjects for each task. To measure inter-task consistency, I computed average similarity of FC matrices corresponding to different tasks for each subject. I computed average neutral-congruent FC map similarity, and repeated it for neutral-incongruent and congruent-incongruent.

3.3 Investigating Time Varying Changes in FC Matrices

In many studies of functional imaging, connectivity values are computed over the whole time series to find the FC map, which assumes that FC map characteristics do not change during the recording session. In order to understand whether if the variations in the patterns of FC matrices (inconsistencies) of a subject are just random fluctuations or caused by a progression during the recording session, I investigated the relationship between the time lag between the FC matrices and their similarities. In other words, whether if the similarity between two FC matrices of the same subject increases when their presentation times are closer to each other was subject to question. If there is a progressive change in the patterns of FC maps of subjects, then test block pairs that are distant in time should show less similarity in their FC maps, compared to the test block pairs that are closer in time.

The time difference of stroop blocks versus their similarity in FC matrices were plotted. Since there are 15 task blocks in our stroop test protocol with the same duration, the time difference between these task blocks can have 14 different values for a subject. These values do not differ significantly across subjects, since task block and rest durations are fixed in our protocol. Therefore there can be at most 14 different values for difference of task block presentation times, for all subjects. Since the order of congruent, neutral and incongruent questions were arranged randomly, there are variable number of block pairs that have certain differences in their times of record. I averaged FC similarity values of all task block pairs that have the same time distance in all subjects. I did this computation for neutral, congruent and incongruent task types independently. I computed correlation between time difference and FC map similarity variables. I also plotted these points on a graph and I fitted a linear line to see the rate of change in patterns of FC matrices, if there is any. I used MATLAB's `polyfit` function for line fitting. I investigated this relation for 3 task types (Neutral, Congruent, Incongruent) and compared their results.

3.4 Investigating the Change in Global Efficiency

Global efficiency is considered to reflect the overall capacity of the network for integrated processing [46]. Some studies suggested that it is a superior measure of functional integration [45]. Global efficiency is found to be lower in attention deficit and hyperactivity disorder (ADHD) patients [47, 48]. As a result I considered global efficiency to be be a good measure to understand changes in attention level and habituation. I investigated how global efficiency changes during stroop session.

Firstly the weighted FC matrices were reduced into binary graphs by applying a threshold to the connections. Previously Skidmore et al. suggested to use 10% threshold for functional connectivity matrices [49]. This means to take the connection with highest strength as reference and accepting the other connections within 90%-100% range of this value. I tried using threshold values from 8% to 12%. I preferred 8% since it resulted in highest strength in statistics. I computed the time-global efficiency correlation to see if there is any consistent and meaningful change.

I firstly plotted global efficiency value measurements and corresponding time instants of all subjects in a common plot, for different task types to visualise the general tendency of global efficiency for each task type. I computed correlation of time and global efficiency in this common data. Secondly I repeated these separately for each subject and for each task type to see individual trends.

I used Brain Connectivity Toolbox for computing graph theoretical metrics [20].

4. RESULTS

4.1 Stroop Task Results

The comparison of reaction times for 3 different tasks Neutral (N), Congruent (C) and Incongruent (I) are given in Fig. 4.1 and their values are 0.98 *sec*, 1.05 *sec*, 1.17 *sec*, respectively. The incongruent questions resulted in significantly higher reaction times, while difference between reaction times for congruent and neutral questions are marginally significant. The one-way anova test produced the results given in Table 4.1.

Table 4.1
Summary of the anova results for reaction time for different task types (N, C, IC).

Source of Variation	**df**	**Mean Square**	**F**	**p**
Task	2	0.11762	3.15	0.056
Error	33	0.03735		
Total	35			

Comparison of correct answers between neutral, congruent and incongruent tasks are given in Fig. 4.2 below. Average number of correct answers was 29.5 for neutral tasks, 29.2 for congruent tasks and 27.8 for incongruent tasks out of 30 questions. A `ttest` showed that the numbers of correct answers that subjects gave to the congruent and neutral questions are not significantly different. On the other hand it is seen that number of correct answers decrease significantly for incongruent questions. The one-way anova result for comparison of the task types is summarised in Table 4.2.

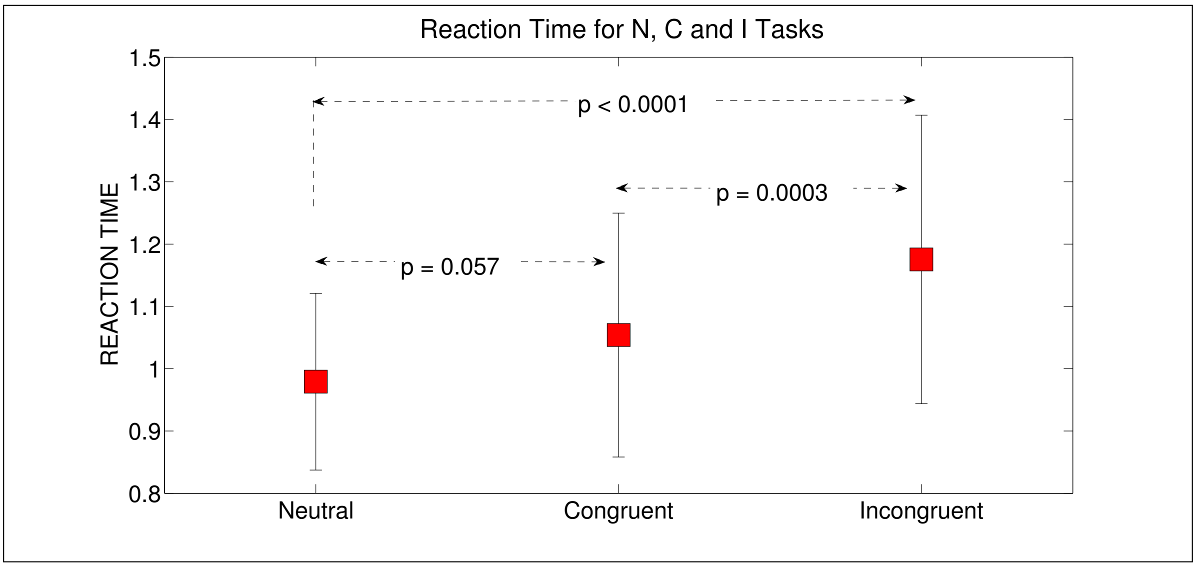


Figure 4.1 The comparison results for reaction time in 3 different tasks Neutral (N), Congruent (C) and Incongruent (I) tasks.

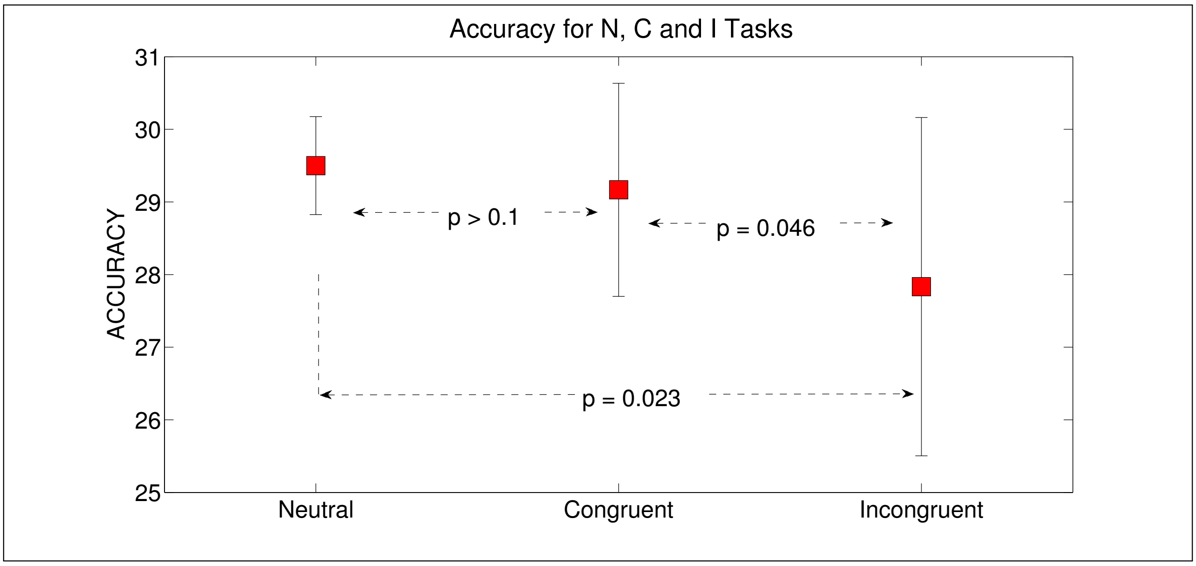


Figure 4.2 The comparison results for number of correct answers (accuracy) in 3 different tasks Neutral (N), Congruent (C) and Incongruent (I) tasks.

Table 4.2
Summary of the anova results for accuracy of answers for different task types (N, C, IC).

Source of Variation	df	Mean Square	F	p
Task	2	9.33333	3.49	0.0423
Error	33	2.67677		
Total	35			

4.2 Consistency Results

The average within-subject consistency of the FC matrices was computed as 0.61 ± 0.09 for 12 healthy control subjects. The result of inter-subject consistency was found as 0.28 ± 0.13, which is significantly lower than within subject consistency. The comparison of within subject consistency and inter-subject consistency is given in Fig. 4.3.

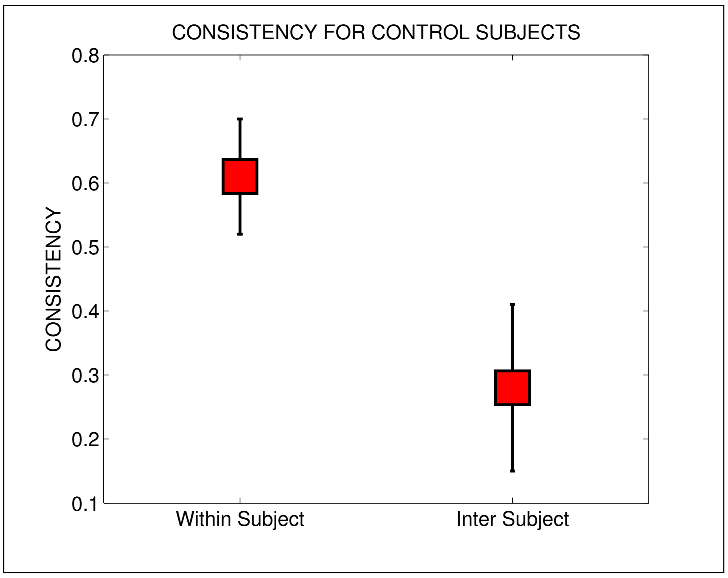


Figure 4.3 Within-subject versus inter-subject consistency.

It was found that within-subject consistency does not change with task type. Within task and inter-task consistency results are given in Fig. 4.4. Both within task and inter-task consistency values are in the range between $0.605 - 0.615$ and `ttest` confirmed that there is no significant difference between them.

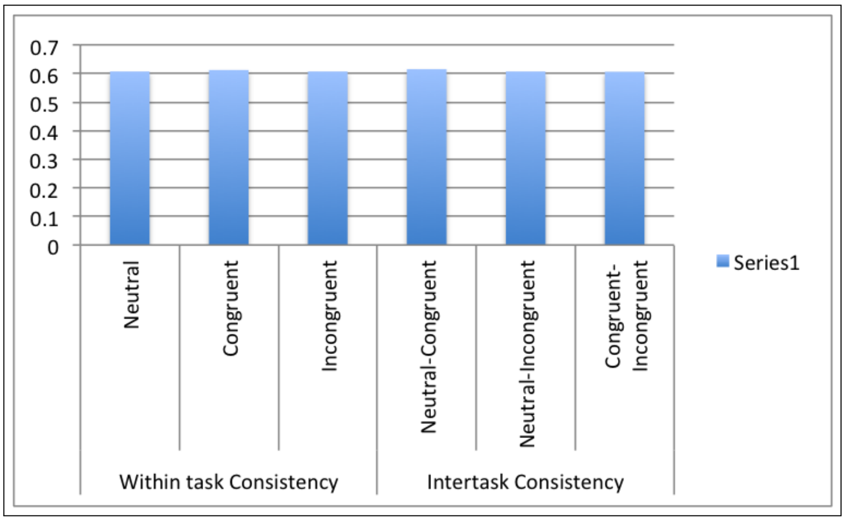


Figure 4.4 Within-task and inter-task consistency values.

4.3 Time Varying Changes in FC Matrices

Relation between similarities of FC matrixes and their distance in time is given in Fig. 4.5. The correlation between time-difference and FC matrix similarity is -0.83 for neutral tasks and -0.67 for congruent tasks. It is seen that there is a progressive change in patterns in FC maps for neutral and congruent questions, while no such trend is seen for incongruent questions.

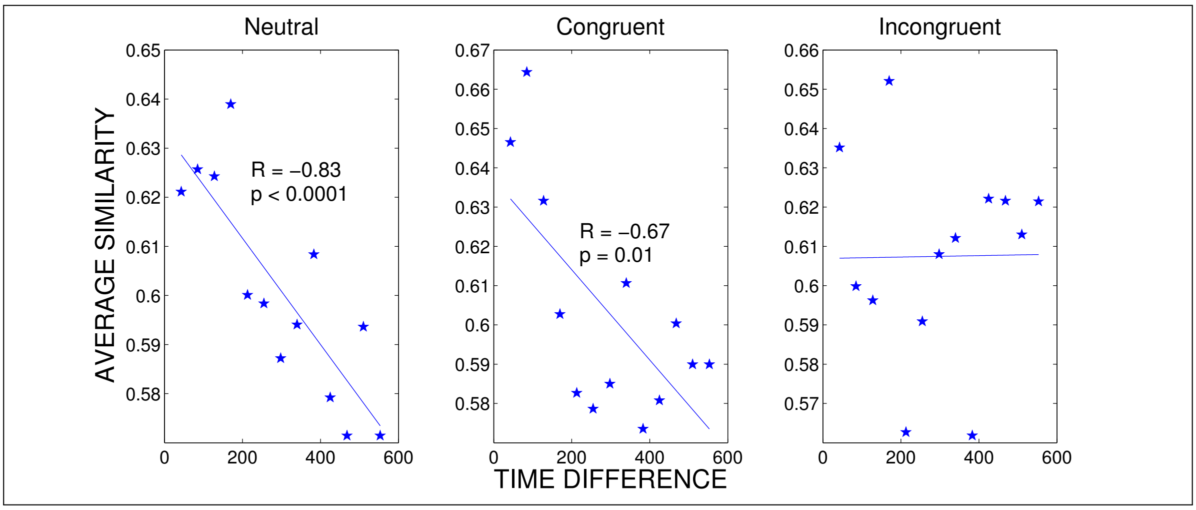


Figure 4.5 Correlation of FC Matrix pairs versus their corresponding distance in time.

Slope values for the fitted lines in 4.5 is given in Fig. 4.6. We see that slopes computed for rate of change in patterns of FC maps for neutral questions (1.08×10^{-4})

and congruent questions (1.15×10^{-4}) are close to each other.

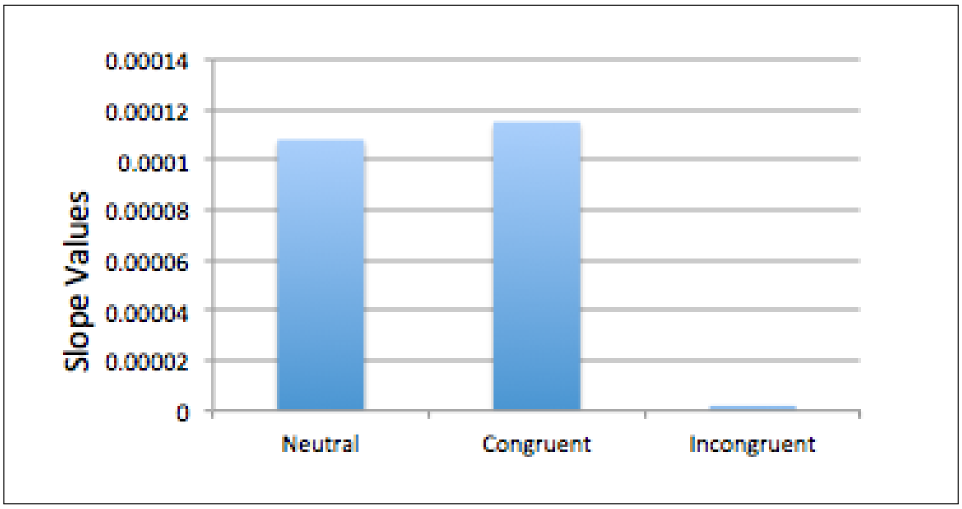


Figure 4.6 Slope values corresponding to rate of change in FC patterns for neutral, congruent and incongruent tasks.

4.4 Global Efficiency Changes During Stroop Session

Global efficiency values versus time plots for different task types are given in Fig. 4.7. All subjects are included in these plots. The only significant correlation between time and global efficiency was found for neutral tasks (p=0.03, r=-0.28). For the other tasks r values were close to zero (-0.08 and 0.08 for congruent and incongruent, respectively) where p value of the correlations were over 0.5.

Changes in global efficiency in FC networks for each subject are given in Fig. 4.8. As seen in the figure, global efficiency values for neutral tasks are more in decreasing trend, while global efficiency values for incongruent tasks are mostly in a stationary or increasing trend.

I compared time-global efficiency correlations for neutral, congruent and incongruent tasks. Average time-global efficiency correlation for neutral tasks was computed as -0.3, which is significantly higher than that for incongruent tasks 0.14 ($p = 0.04$). Average time-global efficiency correlation for congruent tasks was found to be -0.15,

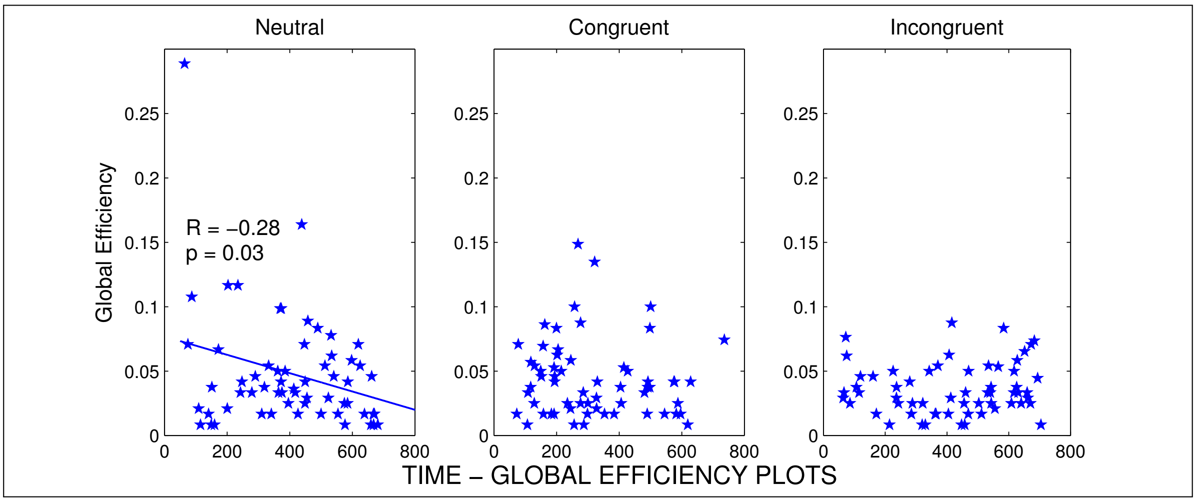


Figure 4.7 Global efficiency versus time of record. The only significant relation was found for neutral tasks, where correlation value equals to -0.28 and p value is 0.03.

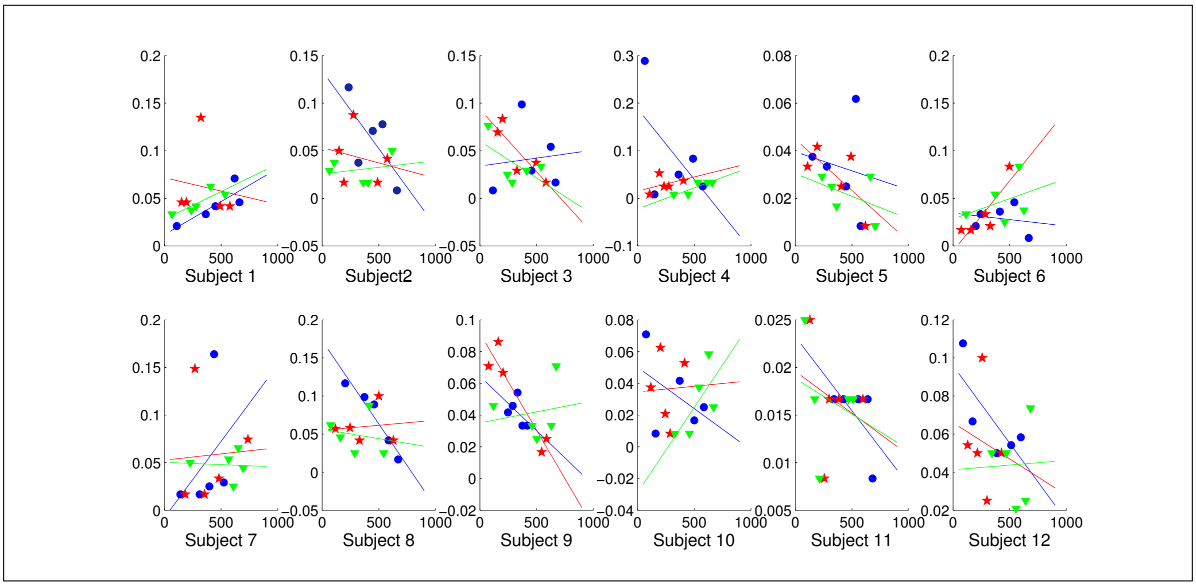


Figure 4.8 Global efficiency versus time during stroop session. Each Y axis represents global efficiency values and each X axis represents corresponding presentation times in the stroop test session. Each plot corresponds to one subject. Blue marks and lines correspond to neutral tasks, red marks and lines correspond to congruent tasks and green ones correspond to incongruent tasks.

which is larger than incongruent tasks at a marginally significant level ($p = 0.06$). `ttest` showed no difference between neutral and congruent tasks ($p > 0.5$).

The most clear trend was observed in subject 8. I included the thresholded binary FC matrices of subject 8 corresponding to neutral tasks, as an example in Fig. 4.9.

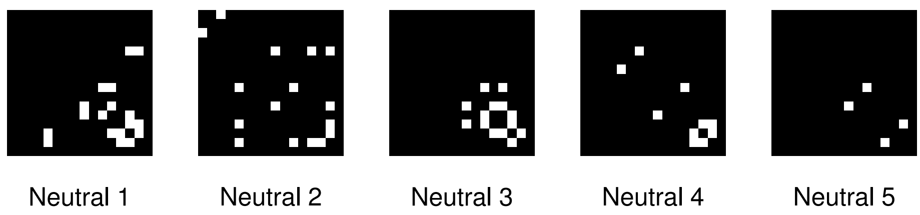


Figure 4.9 Thresholded binary FC matrices of subject 8 corresponding to neutral tasks. We see how it changes during the stroop task session, from left to right.

5. DISCUSSION

Stroop test was used in this study as a cognitive task for evoking a measurable PFC activity. It was observed that incongruent type questions of stroop test resulted in significantly higher reaction times compared to congruent and neutral type questions. This was an expected result from the stroop test, since there is a well known "interference effect" in the incongruent type questions [31]. When the verbal and color inputs conflict with each other, which is the case in incongruent type questions, subjects need to process them both, and suppress one of them to decide. This is called the interference effect, which results in higher reaction times, as our results also confirm. When reaction times for congruent and neutral tasks are compared, it can be seen that congruent tasks resulted in higher reaction times, where the difference was marginally significant. This means that the facilitation effect was not observed, which is an effect when two different stimuli are congruent and they facilitate each other, resulting in lower reaction times. But facilitation effect is not considered as significant as interference effect and it is not always observed in stroop tests[50]. It was suggested that congruent tasks can result in even higher reaction times, due to the conflict that arises in deciding which dimension (color or word) should be attended for responding [32].

Previous studies suggest that stroop interference effect is related to the activity of PFC [8, 9, 10, 11, 21]. Functional connectivity during stroop task has also been studied in the literature. A study by Kadosh et al. [19] revealed functional networks that are active during stroop task and have found that these networks include PFC region. A study by Harrison et al. revealed increased connectivity (measured with canonical variants) in interference condition. Several previous studies have shown that it is possible to study functional connectivity with fNIRS [12, 13, 14, 15, 16]. Aydore et al. studied functional connectivity with fNIRS using stroop test and their study revealed increased "information transfer" in interference condition [37]. However most of these studies have ignored temporal and/or inter-individual variability of functional connectivity. Consistency and temporal variability of FC matrices were investigated in this study.

Functional connectivity can be measured with different metrics, including correlation, coherence, autoregressive methods or mutual information. Previously mutual information was used successfully in some FC studies [?, 26]. Mutual information was preferred in this study for computing functional connectivity between pairs of signals, because mutual information has an advantage compared to correlation since it can detect nonlinear dependencies of neural signals [25, 26]. In correlation computation, two signals need to have the same phase in order to determine their statistical relationship accurately, while a phase synchronization is not required in mutual information metric.

It was found that there is a high consistency in patterns of FC networks computed for healthy control subjects. But no difference between inter-task and within-task consistency could be detected. On the other hand, inter-subject consistency is found to be significantly lower than within-subject consistency. Similar results were found in a previous similar study done with EEG, where within-subject consistency in the same recording session was found to be 0.84 and intersubject consistency was found to be 0.42 [28]. An other previous study done with fMRI had investigated consistency of FC networks within different sessions (not during the same recording session) and they had found that inter-subject consistency is lower than within-subject consistency [30]. Results found in the present study are consistent with these previous studies in the literature.

The low inter-subject similarity among the maps might be due to a mere different wiring patterns among subjects or systemic error since there is a lack of co-registration algorithm of probe placement on each subject. Population analysis of FC maps of subjects based on fNIRS signals is being studied in the literature, where FC maps of different subjects are averaged or constructed in a common procedure [37, 43]. The low inter-subject consistency found in this study implies that making a populations analysis of FC matrices of different subjects might be risky, due to differences in patterns of FC matrices corresponding to different subjects. Although there are some studies for developing registration protocols for fNIRS [42], there is no standard method in the literature yet. The results of this study shows the necessity of such methods in order to do population analysis of functional connectivity based on fNIRS signals. After registration is applied to fNIRS data, it would be possible to determine whether if there is a difference in FC characteristics between subjects.

A high within-subject consistency was found, which implies that a consistent FC pattern exists in PFC for the stroop task for subjects. But there is also a variability of FC matrices of the same subject. Some part of this variation could be related to noise, but not necessarily noise of the measurement system. Noise is also present in the brain and it is considered to be a natural consequence of operation of the brain [18]. In several studies such noise has been termed as task related spontaneous fluctuations, physiological in origin. Other than noise, this variability could also be related to moment-to-moment variation of the brain activity, which should be distinguished from noise [18]. In order to understand this, I investigated the time lag-similarity relationship of FC matrices.

It was found that, for congruent and neutral type questions, FC map patterns of pairs of stroop question blocks are more similar, if they are closer in time. I interpret this result as a consequence of a progressive change in FC patterns during the stroop task, for neutral and congruent tasks. It is interesting that no such trend was detected for incongruent tasks. I interpret this finding as a consequence of the challenge of the interference effect present in incongruence tasks. Due to interference effect, subjects need to preserve their attention span for incongruent questions throughout the recording session, while in neutral and congruent tasks the subjects learn and get used to the questions and therefore the attention and hence the resources allocated required for these tasks decrease in time. This is called habituation affect and this is one of the concerns about averaging signals or FC matrices corresponding to subsequent task blocks [44]. The results of the present study shows that, this effect should be considered especially for some mental tasks such as neutral and congruent questions of the stroop test. The slopes computed for different task types is given in Fig. 4.6, which can be considered as rate of change in FC patterns. Slope for congruent and neutral tasks were observed to be close to each other. The interpretation of the progressive changes in FC patterns as loss of attention is in consistence with the previous studies that have shown the relation between the activity in PFC and attention [8, 9, 10, 11].

In order to understand the time varying changes found in neutral and congruent tasks, I investigated how functional integration of the FC network changes in time. It was found that, during the stroop test session, the changes in global efficiency values for neutral tasks and incongruent tasks are significantly different. When overall tendency of the global efficiency was investigated for all subjects, it was seen that it significantly decreases during the test session only for neutral tasks (Fig. 4.7). This is in consistence with the result that most significant time-lag versus FC similarity relation was observed for neutral tasks (4.5). When global efficiency changes were investigated individually, the tendency of decrease in global efficiency for neutral tasks is significantly higher than that of incongruent tasks (although it is not seen for all subjects). This general tendency might indicate that, the progressive change trend detected for congruent and especially for neutral tasks might be a result of graph-property changes, in particular global efficiency of the FC networks in PFC. I used global efficiency metric, since it is usable for disconnected networks and it is suggested to be a superior measure of functional integration [45]. As it is considered to measure integral information processing capacity, I assume that it can reflect the attention and habituation effect. The results in the literature, which indicate that ADHD patients have lower global efficiency in their FC networks, are consistent with this assumption. The 8^{th} subject had one of the most clear decrease in global efficiency in FC matrices for neutral maps. When we observe the thresholded binary graph (Fig. 4.9) of this subject, we see that the number of connections decline during the stroop session, which result in a decrease in global efficiency.

An other significant result of this study is the feasibility of studying the temporal variability of functional connectivity by using fNIRS.

6. CONCLUSIONS AND FUTURE WORK

In this study temporal characteristics, within subject and inter-subject consistency of functional connectivity networks were investigated during a strop task, which includes three different mental tasks: neutral, congruent and incongruent. Mutual information was used for computing functional connectivity maps, and 2D correlation was used to compute similarity of two functional connectivity networks.

It was found that FC patterns are different across subjects, where we get consistently similar FC patterns from the same subject. The difference across subjects can be due to inter-subject differences in functional connectivity in their PFC, or due to lack of registration algorithm for fNIRS. A future work here would be application of registration methods to fNIRS signals in order to determine inter-subject differences in FC map patterns.

It was also found that during a stroop test session, FC patterns exhibit a gradual change in time, for congruent and neutral questions, which was interpreted as subjects are getting used to the questions and probably need less attention in the later periods of the stroop test for these question types. But for incongruent questions, we do not see a gradual change in FC patterns, which might be caused by the interference effect involved in incongruent type questions. As a result, this study have shown interference effect in functional connectivity of PFC, by investigating the temporal characteristics of FC maps and it is shown that it is possible to investigate temporal variability and consistency of FC networks by fNIRS.

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