WORKING MEMORY PERFORMANCE ASSESSMENT WHILE MONITORING THE PREFRONTAL CORTEX HEMODYNAMICS BY MEANS OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY

by

Ceyhun Ekrem KIRIMLI

B.Sc., in Molecular Biology and Genetics, Boğaziçi University, 2005

Submitted to the Institute of Biomedical Engineering
in partial fulfillment of the requirements
for the degree of
Master of Science
in
Biomedical Engineering

Boğaziçi University
June, 2008

WORKING MEMORY PERFORMANCE ASSESSMENT WHILE MONITORING THE PREFRONTAL CORTEX HEMODYNAMICS BY MEANS OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY

APPROVED BY:

Assist. Prof. Dr. Ata Akın …….
(Thesis Supervisor)

Prof. Dr. Hale Saybaşılı ……..…

Assist.Prof. Dr. Ayşecan Boduroğlu ……..…....

DATE OF APPROVAL: 16.June.2008

ACKNOWLEDGEMENTS

I am greatly thankful to my advisor Ata AKIN for his guidance and support in every possible way and his critique on the written material of this thesis. His knowledge, ambition and passion for biomedical science opened new horizons for my career. He showed me the right door and encouraged me to pass through it.

I would also like to thank Ayşecan Boduroğlu for her kindness, understanding and open mindedness. She encouraged me to develop the model used in the thesis and methodology. Her contribution and knowledge deepened my curiosity in different aspects of scientific research.

I am also grateful to Hale Saybaşılı for her understanding and support during the preparation and presentation of this work

Finally I would like to thank to the love of my life, my wife, Elçim Elgün Kırımlı. I don't know where she gets all that patience! She's my perfect counterbalance. May GOD bless her in all her endeavours because without her unreserved support, not only completion of this study but also my graduation from would not have been possible. This thesis is dedicated to her.

ABSTRACT

WORKING MEMORY PERFORMANCE ASSESSMENT WHILE MONITORING THE PREFRONTAL CORTEX HEMODYNAMICS BY MEANS OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY

One of the most popular experimental paradigms for functional neuroimaging studies of working memory has been the n-back task, in which subjects were asked to monitor the identity or location of a series of verbal or nonverbal stimuli and to indicate when the currently presented stimulus is the same as the one presented n trials previously. It is well known that dorsoleateral and ventrolateral prefrontal cortex is especially active during cognitive task requiring working memory performance. Functional near-infrared spectroscopy (fNIRS) is an optical imaging method, which allows non-invasive in vivo measurements of changes in the concentration of oxygenated (HbO_2) and deoxygenated (DeoxyHb) haemoglobin in cortical tissue.

In this thesis functional near infrared spectroscopy was used to determine the activity on prefrontal cortex while 9 graduate student subjects were asked to take an n-back test involving increasing amounts of working memory load. A gamma function variate was used to model the hemodynamic response behavior during the task and statistical analysis on data was applied to determine important parameters from the near infrared spectroscopic signals that are in correlation with the working memory load.

According to the model applied, a significant correlation between the working memory load and hemodynamic response function parameters determined form the near infrared spectroscopic signal, was observed especially on left and right channels on the forehead probe of NIRS device. Model applied in this thesis enabled a quantification of the working memory load solely by using fNIRS as a neuroimaging device.

Keywords: Functional Near-Infrared Spectroscopy, Working Memory, n-back, Prefrontal Cortex, Gamma function, Hemodynamic Response Function

ÖZET

İŞLEVSEL HAFIZA PERFORMANSININ, FONKSİYONEL YAKIN KIZIL ÖTESİ SPEKTROSKOPİ İLE, PREFRONTAL CORTEX HEMODİNAMİĞİNİN GÖRÜNTÜLENMESİ SIRASINDA, ÖLÇÜLMESİ

İşlevsel hafızanın fonksiyonel nöro-görüntülenmesi çalışmalarında sıkça kullanılan deneysel paradigmalarından biri de *n*-öncesi testidir. Bu testte deneklerden sözlü yada sözlü olmayan bir seri uyaranın konum yada kimligini belirlemeleri ve o anda verilen uyaranın "n" önceki uyaranla aynı olup olmadığını tespit etmeleri beklenir. İşlevsel hafızanın işlemesini gerektiren bu tür bilişsel görevlerde dorsolateral ve ventrolateral prefrontal korteksin çalıştığı önceki bilimsel çalışmalarla sabittir. İnvazif olmayan fonksiyonel yakın kızıl ötesi spektroskopi (fNIRS) kortekse ilişkin oksijenli (HbO_2)ve oksijensiz (deoksiHb) hemoglobin konsantrasyon değişimlerinin ölçülmesine olanak verir.

Bu tezde dokuz yüksek lisans öğrencisinin prefrontal korteks aktivitesi, artan işlevsel hafıza yükü içeren n-öncesi testi yapılırken , fonksiyonel kızıl ötesi spektroskopi ile ölçülmüştür. Test esnasında oluşan hemodinamik tepki fonksiyonunu modellemek için gama fonksiyonu, fonksiyonun önemli parametrelerini belirlemek içinse istatistiksel analiz yöntemleri uygulanmıştır.

Uygulanan modele göre, yakın kızıl ötesi spektroskopik sinyalinden elde edilen hemodinamik tepki fonksiyonunun parametreleri, işlevsel hafıza yükü ile belirgin bir korelasyon göstermiştir. Bu korelasyon özellikle alna takılan probun sağ ve sol bölge kanallarında gözlenmiştir. Tezde uygulanan model işlevsel hafıza yükünün, bir nöro-görüntüleme yöntemi olan fonksiyonel kızıl ötesi spektroskopi ile ölçülmesine olanak vermiştir.

Anahtar Sözcükler: İşlevsel Yakın Kızıl Ötesi Spektroskopi, İşlevsel Hafıza, n-önceki, Prefrontal Korteks, Gama fonksiyonu, Hemodinamik Tepki Fonksiyonu

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

fNIRS	Functional Near Infrared Spectroscopy
HbO_2	Oxyhemoglobin
WM	Working Memory
LTM	Long Term Memory
SAS	Supervisory Activating System
PET	Positron Emission Tomography
fMRI	Functional Magnetic Resonance Imaging
PFC	Prefrontal Cortex
ACC	Anterior Cingulate Cortex
BA	Brodmann Area
p	Significance Number
LED	Light Emitting Diode
PCB	Printed Circuit Board
NIR	Near Infrared Spectroscopy
FWHM	Full Width at Half Maximum
3D	Three Dimensional
ANOVA	Analysis of Variation

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Motivation and Objective

Recent scientific research demonstrates that working memory is one of our most crucial cognitive capabilities, essential for countless daily tasks like following directions, remembering information momentarily, complex reasoning or staying focused on a project. More importantly, this broadened understanding of the importance of working memory can provide great hope to a range of people who suffer from working memory deficits, including children and adults with attention problems, people with learning disabilities, and stroke victims among others.

Though working memory has been studied for decades in both animals and humans, only recently proven to be a plastic function of the brain, able to be strengthened through rigorous training [1]. Dispelling the long held belief that working memory is a fixed property of the individual, this breakthrough research, has shed new light on the treatment of attention deficits.

Developing the best strategy to strengthen working memory requires a method to monitor the working memory performance. This study was done to develop such a monitoring method using functional near infrared spectroscopy.

1.2 Contribution of the thesis

A model of hemodynamic response involving a variate of gamma function is developed to analyze the functional near infrared spectroscopic signals and a correlation between the parameters of hemodynamic response and working memory load is observed. Lateral prefrontal cortex is shown to be the region activated and represented this correlation.

2. WORKING MEMORY, NEUROPSYCHOLOGICAL STUDIES AND fNIRS

2.1 The Working Memory Model

Working memory (WM) is a crucial concept in cognitive psychology and cognitive neuroscience. It refers to the "central" structures and processes that temporarily maintain, store and manipulate information for supporting human thought process. WM is a limited capacity system: it permits to keep "active" a limited amount of information for a brief period of time, and to operate on it. In particular, WM permits to temporarily maintain task-relevant information during performance of complex cognitive tasks that require willingness, awareness, and attention such as reasoning, planning, manipulation of linguistic information, and the executive control and coordination of perception and action in complex cognitive operations.

WM provides also an interface to long-term memory (LTM) [2] , that is instead responsible for the "passive" storage of information for longer periods of time: WM can "upload" and "download" information to and from LTM.

A parallel can be done between the concept of working memory and the supervisory activating system (SAS) for the willed control of action [3-5].

Baddeley and Hitch identified three components of working memory [6]. The central executive component is the most important. Its functions include the regulation of information from other memory systems such as long-term memory, and the processing and storage of information. The processing resources used by the central executive to perform these various functions are, however, limited in capacity. The efficiency with which the central executive fulfills a particular function therefore depends on whether other demands are simultaneously placed on it. The greater the competition for the limited resources of the executive, the more its efficiency at fulfilling particular functions will be reduced.

The central executive is supplemented by two components which are termed “slave systems”. Each slave system is specialized for the processing and temporary maintenance of material within a particular domain. The phonological loop maintains verbally coded information, whereas the visuo-spatial sketchpad is involved in the short-term processing and maintenance of material which has a strong visual or spatial component. Figure 2.1 provides a simple schematic representation of the working memory model.

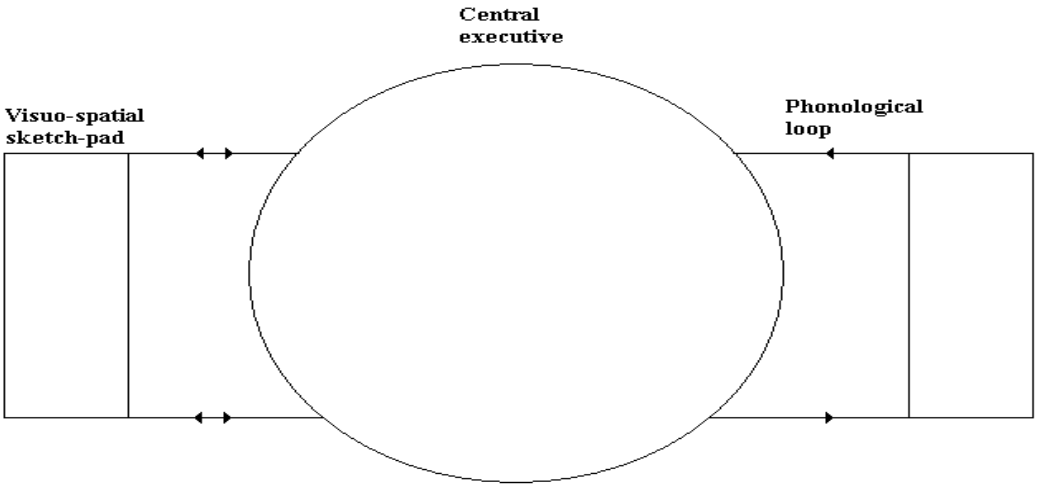

Figure 2.1 A simplified representation of the Baddeley and Hitch [6] working memory model.

The central executive fulfils many different functions. Some of its primary functions are regulatory in nature: It coordinates activity within working memory and controls the transmission of information between other parts of the cognitive system. In addition, the executive allocates inputs to the phonological loop and sketchpad slave systems, and also retrieves information from long-term memory. These activities are fuelled by processing resources within the central executive, but which have a finite capacity. Cognitive tasks that have been suggested to involve the central executive include mental arithmetic [7], recall of lengthy lists of digits [6], logical reasoning [6], random letter generation [8], semantic verification and the recollection of events from long-term memory [7].

The phonological loop is a slave system specialized for the storage of verbal material. It comprises two components, as shown in Figure 2.2 [10] The phonological store represents material in a phonological code which decays with time. A process of articulatory rehearsal serves to refresh the decaying representations in the phonological

store and so to maintain memory items. The rehearsal process is also used to recode nonphonological inputs such as printed words and pictures into their phonological form so that they can be held in the phonological store. In contrast, spoken speech information gains direct access to the phonological store without articulatory rehearsal.

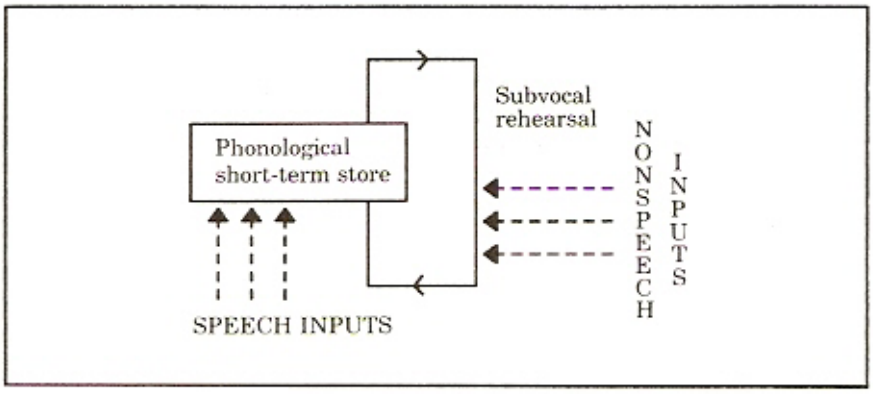

Figure 2.2 The phonological loop mode, based on Baddeley [10].

The two component architecture of the phonological loop is based on a large body of experimental evidence accumulated during the past 35 years. More recently, it has also been supported by studies of neuropsychological patients with deficits that appear to correspond to subcomponents of the loop.

The visuo-spatial sketchpad is a slave system specialized for the processing and storage of visual and spatial information, and of verbal material that is subsequently encoded on the form of imagery. Unsurprisingly, there is little indication that this component of working memory plays a significant role in language. Theoretical progress concerning the structure and functioning of the sketchpad has been less rapid than for its sister slave system, the phonological loop, but some important characteristics of visual working memory have been established. The first systematic investigation of the visuo-spatial sketchpad was reported by Baddeley, Grant, Wight and Thomson [11]

To sum up, according to the working memory approach, short-term memory plays an active role in processing and storing information in the course of complex cognitive tasks such as language processing. The specific model short-term memory that has emerged from research motivated by the working memory approach has three principal components. The central executive possesses limited-capacity processing resources, which

can be used for particular processing activities, and also for controlling action and the transmission of information between other components of the memory system. The central executive is supplemented by the operation of two specialized subsystems. The phonological loop is capable of processing and maintaining phonological information, and consists both of a phonological short-term store and a subvocal control process used both for rehearsal and recoding information into phonological form. The visuo-spatial sketchpad is involved in generating images and in retaining information with visual or spatial dimensions.

By the late 1990's, an attempt was done to specify more clearly the role of the central executive by proposing that its functions were entirely that of an attentionally-based control system, and abandoning the idea that it also had a capacity for storage [12]. This had the advantage of focusing attention on the fractionation of executive processes [13], but was then challenged by the identification of a range of phenomena that did not fit neatly into the Baddeley and Logie [12] model. These typically reflected two deficits within the model. The first was a need for a system that would allow visual and verbal codes to be combined and linked to multidimensional representations in LTM. The second comprised the need for the temporary storage of material in quantities that seemed clearly to exceed the capacity of either the verbal or visuospatial peripheral subsystems. With the need to provide an account of working memory span, and of fundamental features of STM as the capacity to chunk information [14], resulted in the proposal of a fourth component of the working memory system, namely the "episodic buffer" [15]. This is assumed to be a limited capacity system that depends heavily on executive processing, but which differs from the central executive in being principally concerned with the storage of information rather than with attentional control. It is capable of binding together information rather from a number of different sources into chunks or episodes, hence the term "episodic"; it is a buffer in the sense of providing a way of combining information from different modalities into a single multi-faceted code as shown on Figure 2.3. Finally it is assumed to underpin the capacity for conscious awareness (Baddeley, 2000).

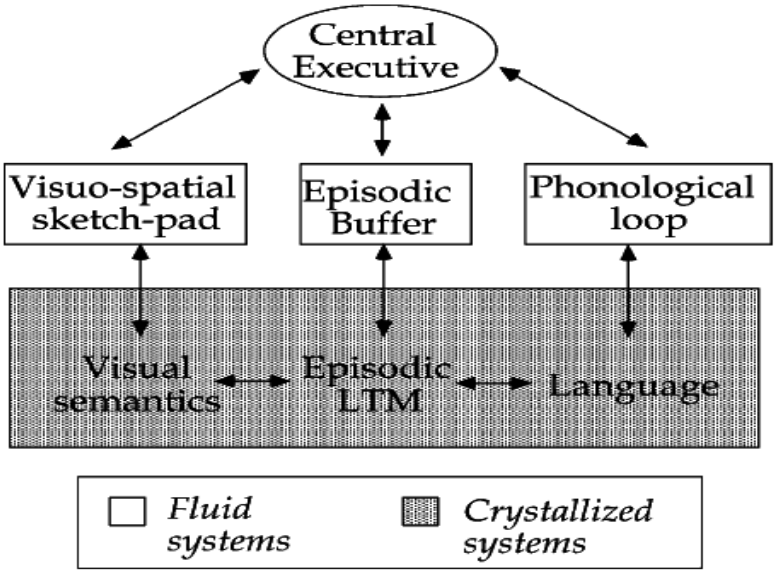

Figure 2.3 The current multi-component model of working memory. The episodic buffer is assumed to form a temporary storage system that allows information from the subsystems to be combined with that from long-term memory into integrated chunks. The system is assumed to form a basis for conscious awareness.

2.2 Working Memory and Localization

The first insights into the neuronal basis of working memory came from animal research. Fuster [16] recorded the electrical activity of neurons in the prefrontal cortex (PFC) of monkeys while they were doing a delayed matching task. In that task, the monkey sees how the experimenter places a bit of food under one of two identical looking cups. A shutter is then lowered for a variable delay period, screening off the cups from the monkey's view. After the delay, the shutter opens and the monkey is allowed to retrieve the food from under the cups. Successful retrieval in the first attempt – something the animal can achieve after some training on the task – requires holding the location of the food in memory over the delay period. Fuster found neurons in the PFC that fired mostly during the delay period, suggesting that they were involved in representing the food location while it was invisible. Later research has shown similar delay-active neurons also in the posterior parietal cortex, the thalamus, the caudate, and the globus pallidus [17].

Localization of brain functions in humans has become much easier with the advent of brain imaging methods (PET and fMRI). Research has confirmed that areas in the PFC are involved in working memory functions. During the 1990s much debate has centered on

the different functions of the ventrolateral (i.e., lower areas) and the dorsolateral (higher) areas of the PFC. One view was that the dorsolateral areas are responsible for spatial working memory and the ventrolateral areas for non-spatial working memory. Another view proposed a functional distinction, arguing that ventrolateral areas are mostly involved in pure maintenance of information, whereas dorsolateral areas are more involved in tasks requiring some processing of the memorized material. The debate is not entirely resolved but most of the evidence supports the functional distinction.

Brain imaging has also revealed that working memory functions are by far not limited to the PFC. A review of numerous studies shows areas of activation during working memory tasks scattered over a large part of the cortex. There is a tendency for spatial tasks to recruit more right-hemisphere areas, and for verbal and object working memory to recruit more left-hemisphere areas. The activation during verbal working memory tasks can be broken down into one component reflecting maintenance, in the left posterior parietal cortex, and a component reflecting subvocal rehearsal, in the left frontal cortex.

There is an emerging consensus that most working memory tasks recruit a network of PFC and parietal areas. One study has shown that during a working memory task the connectivity between these areas increases. Other studies have demonstrated that these areas are necessary for working memory, and not just accidentally activated during working memory tasks, by temporarily blocking them through transcranial magnetic stimulation (TMS), thereby producing an impairment in task performance [18].

A current debate concerns the function of these brain areas. The PFC has been found to be active in a variety of tasks that require executive functions [19]. This has led some researchers to argue that the role of PFC in working memory is in controlling attention, selecting strategies, and manipulating information in working memory, but not in maintenance of information. The maintenance function is attributed to more posterior areas of the brain, including the parietal cortex. Other authors interpret the activity in parietal cortex as reflecting executive functions, because the same area is also activated in other tasks requiring executive attention but no memory [20].

Most brain imaging studies of working memory have used recognition tasks such as delayed recognition of one or several stimuli, or the n-back task. Experimental research and research on individual differences in working memory, however, has used largely recall. It is not clear to what degree recognition and recall tasks reflect the same processes and the same capacity limitations.

A few brain imaging studies have been conducted with the reading span task or related tasks. Increased activation during these tasks was found in the PFC and, in several studies, also in the anterior cingulate cortex (ACC). People performing better on the task showed larger increase of activation in these areas, and their activation was correlated more over time, suggesting that their neural activity in these two areas was better coordinated, possibly due to stronger connectivity [21,22].

2.3 N-back test

In recent years, variants of the "n-back" procedure [23] have been employed in many human studies to investigate the neural basis of working memory processes. In the most typical variant of this task, the volunteer is required to monitor a series of stimuli and to respond whenever a stimulus is presented that is the same as the one presented n trials previously, where n is a prespecified integer, usually 1, 2, or 3. The task requires on-line monitoring, updating, and manipulation of remembered information and is therefore assumed to place great demands on a number of key processes within working memory. Across studies, many different types of stimuli have been used via various input modalities (visual, auditory, and olfactory) making demands on different processing systems. Load is often varied up to 3-back, although the validity of results have been questioned sometimes when the ability to successfully perform the task decreases [24]. Parametric designs, comparing $n = 1$, $n = 2$, and $n = 3$ trials are often employed, although in some studies a 0-back control condition, which requires participants to respond whenever a prespecified stimulus is presented, has been used. This condition does not require the manipulation of information within working memory.

The dorsolateral frontal cortex (approximate Brodmann areas [BA] 9/46) has been implicated in numerous cognitive functions that are relevant to the n-back task, including holding spatial information on-line [25-27], monitoring and manipulation within working memory [28,29], response selection [30], implementation of strategies to facilitate memory [31], organization of material before encoding [32], and verification and evaluation of representations that have been retrieved from long-term memory [33-34]. The mid-ventrolateral frontal cortex (BA 45,47), has been specifically implicated in a similarly diverse but distinct set of cognitive processes that may be relevant to the n-back task, including the "selection, comparison and judgment of stimuli held in short-term and long-term memory" [35], holding nonspatial information on-line [36,37], stimulus selection [38], the specification of retrieval cues [39], and the "elaboration encoding" of information into episodic memory [40,41]. The parietal cortex has been shown to be involved in a wide variety of cognitive tasks and in the context of these experiments it is often difficult to untangle its precise function from that of the prefrontal cortex. Typically, this region has been thought of as involved in the implementation of stimulus response mapping [42-47], although it has also been described as a "buffer for perceptual attributes" [24] and is thought to be involved in storage of working memory contents. Activity in the anterior cingulate cortex is often described in relation to increased effort, complexity, or attention [24] and this region also seems to play a role in error detection and response correction.

3. METHOD

3.1 Subjects

Six female and three male voluntary healthy subjects participated in the study. All subjects were thoroughly informed about the experiment protocol and informed consent was obtained before the experiments begin.

3.2 *N*-Back Test

The cognitive paradigm employed in this thesis consisted of three versions of a letter *n*-back task. For the 1-back condition (low WM load), participants were introduced to press a response button (match button), whenever a letter that appeared on a computer screen in front of them was identical to the preceding letter, if not they were asked to press another button (mismatch button). For the 2-back condition (medium WM load) they had to press the match button whenever the presented letter was identical to the one two trials before that, if nonidentical they had to press the mismatch button. For the 3-back condition (high WM load), they had to press the match and mismatch buttons whenever the presented letter was identical and nonidentical to the one three trials before that respectively as shown in Figure 3.1. Each test consisted of 3 sequences with rest periods of 60 seconds in between each sequence. The baseline hemodynamic response was recorded during the rest period before the first sequence begin. Each sequence consisted of 20 letters, each letter appearing on computer screen for 500 milliseconds and 2700 millisecond interval is present until the next letter appears. Thus each 20 trial sequence lasts for 64 seconds and together with 3 rest periods of 60 seconds one test lasts for 372 seconds which is 6,2 minutes. The whole procedure consisted of totally 5 tests as first 2 tests were done as practice.

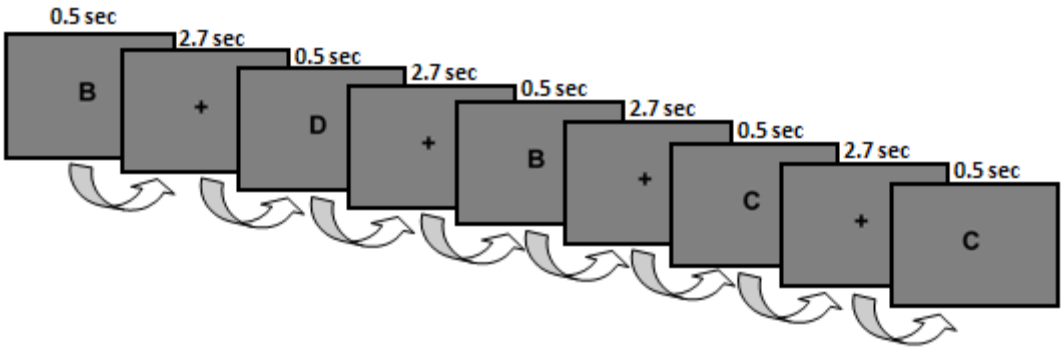

Figure 3.1 Representing the general n-back paradigm used during the experiment. Between each letter a "+" sign is displayed, the time values on each frame above represents the display time in seconds.

Each sequence during the tests was randomly generated by the computer. Number of matches and mismatches could be adjusted by the sequence generating computer software. Five test were performed and the details are described in Table 3.1 below.

Table 3.1 Table represents the number of mismatch and match trials in each sequence applied during the experiment

	N	Match	Mismatch
Test 1	1	2	18
Test 2	2	2	18
Test 3	1	4	16
Test 4	2	4	16
Test 5	3	4	16

3.3 Data Acquisition and Analysis

Data acquisition was held in a dark room. Subjects were given information about the task they were about to handle and forehead probe of the functional near infrared device shown in Figure 3.2 was attached to the foreheads of subjects by an elastic bandage. FNIRS device was attached to the forehead probe by 16 pin cables. Two computers were used in the experiment; one recorded the data while other was used to run the *n*-back tests.

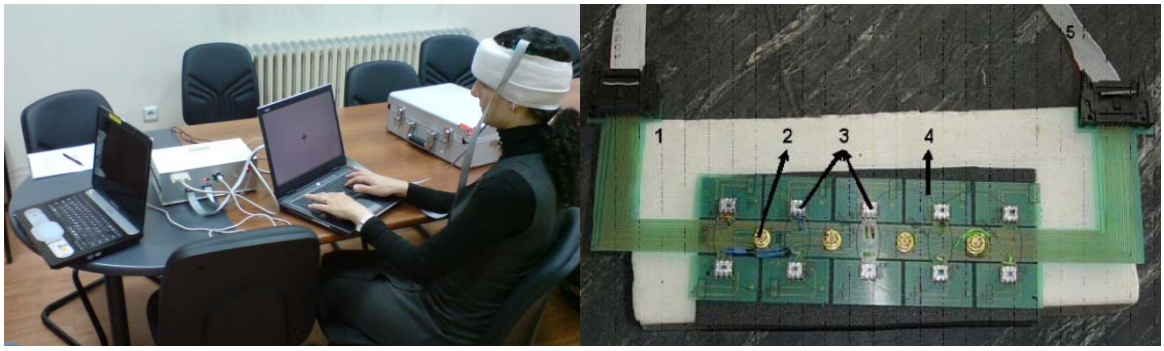

Figure 3.2 (Left) Represents the experimental setup, computer on the left records the data from the fNIRS device standing in between the two computers. Computer on the right runs the n-back task and records the performance data of the subjects. This computer is also connected to the fNIRS device by a parallel port to automatically send the markers whenever a new letter appears on the screen. The head probe attached to the forehead of the subject is shown on right. (Right) A 4-LED (2) probe with 10 photodetectors (3) placed in a PCB (4) on a grey phantom (1), and connected to the FNIRS device via 16 pin cables (5).

N-back test routines were written by MATLAB software. Markers were embedded in the data by this computer whenever each letter appeared on the screen. -1 value appeared as marker in the voltage data. During the test subjects were asked to hit two buttons on the keyboard one is the match key and the other one was mismatch key which were “s” and “l” keys. These keys were chosen as they are far away from each other considering their position on keyboard. Thus subjects were obliged to use left and right hands for match and mismatch cases.

3.3.1 Calculation of HbO2 concentration from the near infrared signal

Experiments were performed using a continuous wave near-infrared spectroscopy device (NIROXCOPE 301) built in Biophotonics Laboratory of Bogazici University [48,49]. The device consists of four light emitting diodes working in the near infrared spectrum as light sources and ten photodetectors which are sensitive in the NIR spectrum. The lights sources have multiple wavelengths including 730nm for Hb and 850nm for HbO2. Calculation of concentration changes of oxy-Hb and deoxy-Hb in blood is based on a modified version of Beer-Lambert law. Four nonoverlapping quadruples of photodetectors are obtained when time and wavelength are multiplexed. Detectors are placed equidistantly away from the source at the center within each quadrant with a source-detector distance of 2.5 cm. This guarantees a probing depth of approximately 2.0 cm from the scalp and This amount of separation has been shown to reliably probe the cortical

activity [49-52] Detector layout is shown in Figure 3.3. Sampling rate of the system used is 1.77Hz.

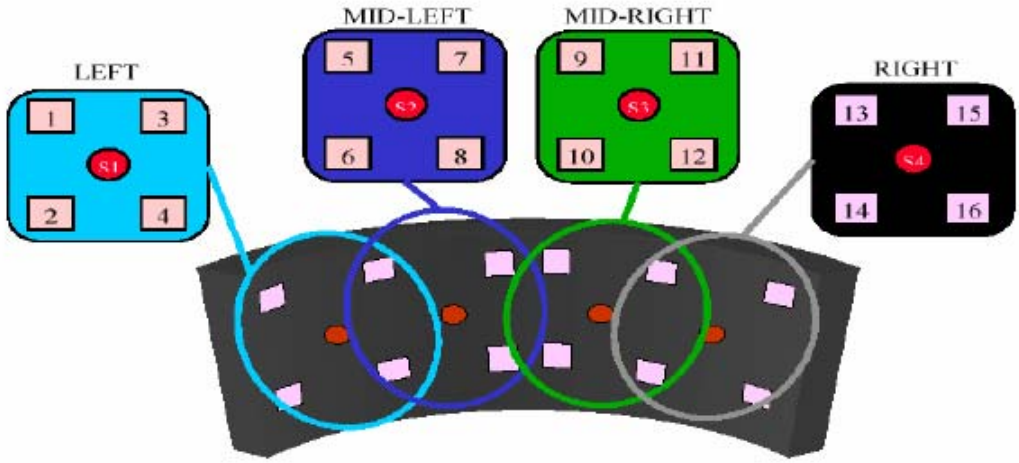

Figure 3.3 Source-detector configurations on the brain probe and nomenclature of photodetectors [50].

3.3.2 Single Trial Hemodynamic Response Detection

The following variate of the gamma function , Equation. 3.1, was chosen in this study to model the single trial hemodynamic responses within an event related paradigm;

$$hf(A, B, \alpha, \beta) = A.t^{\alpha}.e^{\beta.t} + B \quad (3.1)$$

where A is the amplitude, B represents the DC level of the gamma function, the parameters α and β represents changes in the rise time and fall time of the gamma function. A typical gamma function is presented in Figure 3.4.

Once each hemodynamic response was obtained for each single trial, the selective features (amplitude, full width half maximum and time to peak) were extracted for classification purposes for this particular trial.

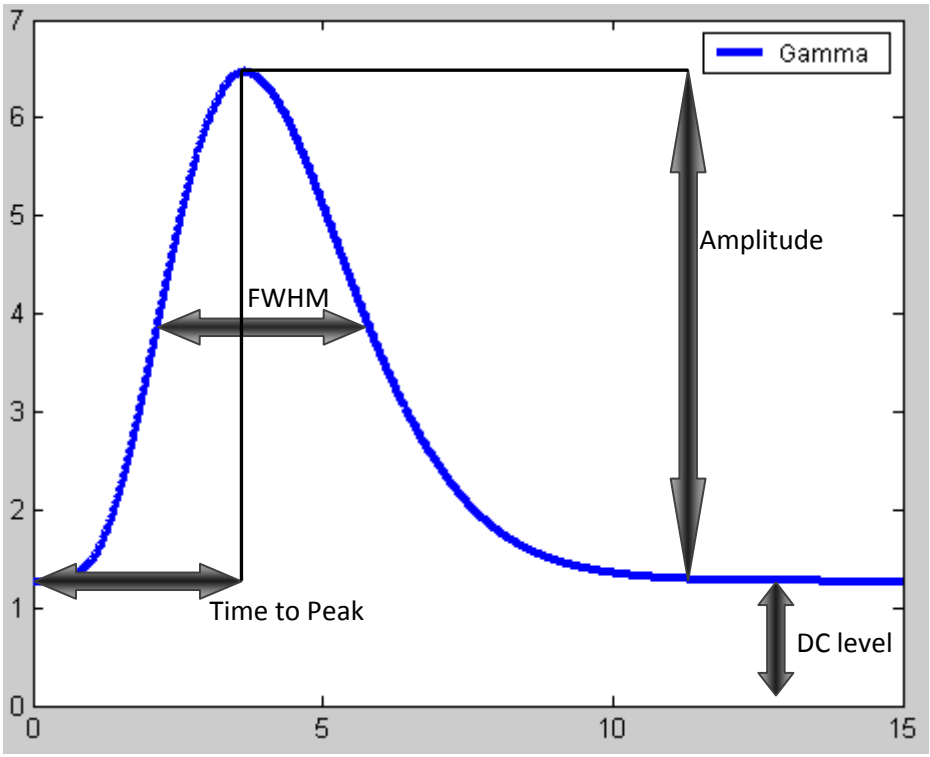

Figure 3.4 A typical gamma function and its parameters.

3.3.3 Model Fitting for Single Trial Detection

The oxyhemoglobin data measured by fNIRS was fitted to a linear model, where each hemodynamic response to N single trials or stimuli were summed to form the total oxyhemoglobin data HbO_2. Although the stimuli are rapid and the resulting hemodynamic response function predictions overlap summation was applied. Below, Equation. 3.2, explains the linear model used;

$$HbO_2 = \sum_{i=1}^{N} hf_i \tag{3.2}$$

where hf_i is the evoked response for the ith stimulus presented at time t, respresented by a gamma function with unknown parameters expressed as in Equation. 3.3 :

$$hf_i = A_i t_i^{\alpha_i} e^{\beta_i t_i} \tag{3.3}$$

For each sequence with 20 trials 20 gamma functions with four parameters should have been estimated such that the following error Equation. 3.4 between the actual oxyhemoglobin data and the linear summation of the 20 estimated gamma functions would be minimum.

$$\varepsilon = \min\,(HbO_2 - \sum_{i=1}^{N} h\, f_i)^2 \tag{3.4}$$

The following Figure 3.5 shows the procedure and regression done minimize the error above.

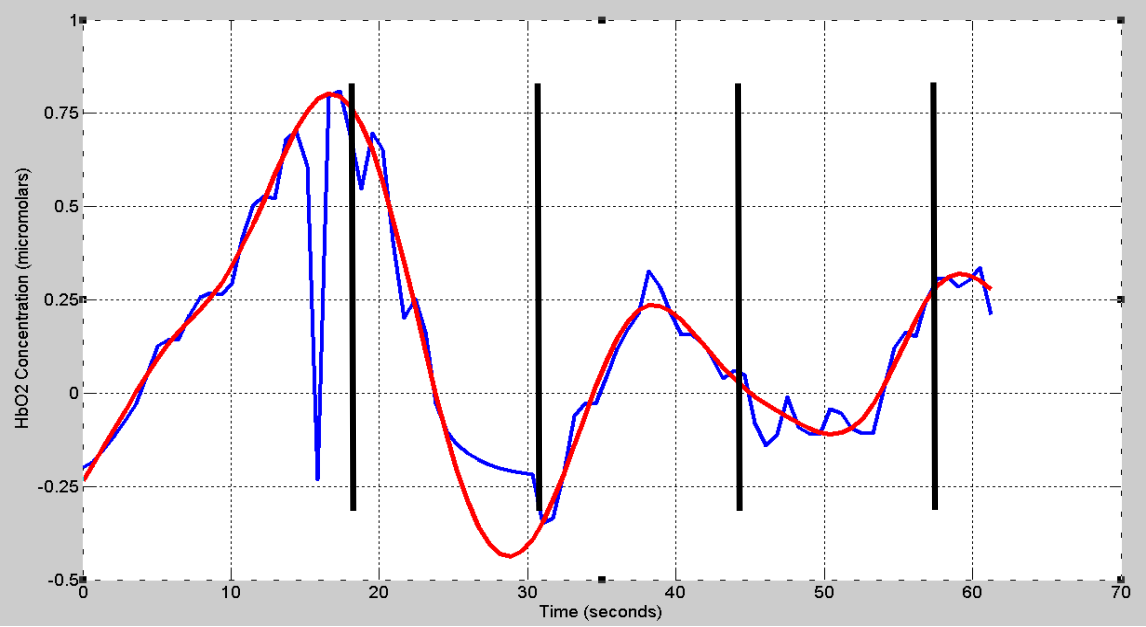

Figure 3.5 Red curve respresents a typical n-back test data from only one channel of the fNIRS device. The blue line represents the fitted curve on the data calculated from the linear model described above. 20 gamma functions with time delay of 3.2 second between any adjacent function is added and the error between the curves were minimized by nonlinear constrained regression. Black vertical lines represents the points chosen on data to make the regression easier by dividing into four parts for each *n*-back sequence.

However this cannot achieved due to limitations of the regression time required to minimize a function with 80 parameters, since every 4 parameter of each 20 gamma function should have to be determined. Thus each test data is divided into four sets of smaller data including only 5 trials of letters. Regression took much less time since 5 trials required in total of 20 free variables to be determined so that the error between the actual data and model is minimized.

3.3.4 Statistical Analysis

Selective features of each gamma function determined after regression generated still a big enough data requiring statistical analysis. Each subject passed through three *n*-back (*n*=1, *n*=2 and *n*=3) tests with each test composed of 3 sequences of 20 trial tasks. Thus for each channel 180 gamma functions were determined. Especially the selective features of these gamma functions (DC level, Time to peak, FWHM and Amplitude) were used in ANOVA tests to determine whether there is a statistical difference between three major tests performed by the subjects. This data was used first to determine which channels displayed a statistically meaningful change in hemodynamic response with increasing working memory load.

3.3.5 Design of Hemodynamic Response Mapping and Performance Data

Hemodynamic response was measured and quantified by the selected parameters of the gamma functions. For each channel these parameters were averaged among all the subjects. For instance FWHM average for each channel was determined and these average values were interpolated on the 3D surface structure of the forehead. This surface is chosen constant and did not vary for each subject. 16 points on this constant surface is determined from the data as the averaged gamma function properties. The rest of the points on the surface mesh were interpolated. The following Figure 3.6 represents one such sample interpolation.

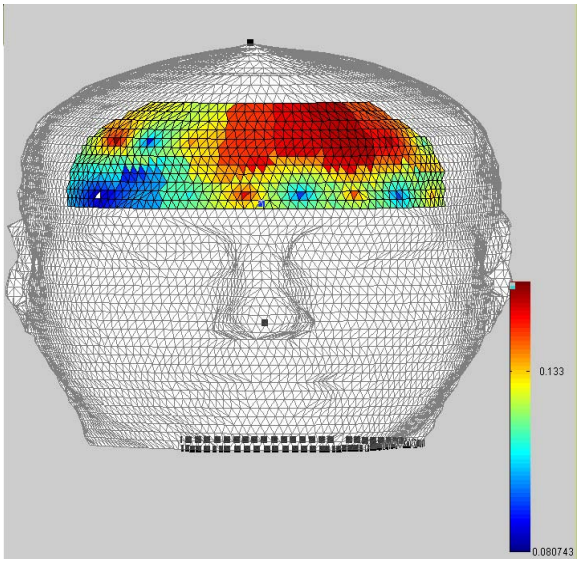

Figure 3.6 Interpolation of DC level average of all subjects and all channels when *n*=2. Colorful small cells in the graph represents the 3D forehead surface which are used to interpolate 16 known values on.

Performance data consisted of five possible cases. There were matches and mismatches in each sequences and subjects were asked to press two keys or no key at all in case they were unsure of whether the letter appeared is a match or mismatch. The five cases are represented on Table 3.2 below. However in this study only matching trials with correct answers are taken into consideration.

Table 3.2 Table represents the performance data assessment applied in the analysis of the experiments

	Match	Mismatch
Correct	Number of match key presses when a match appeared on the screen	Number of mismatch key presses when a mismatch appeared on the screen
Incorrect	Number of mismatch key presses when a match appeared on the screen	Number of match key presses when a mismatch appeared on the screen
Blank	Number of no presses when a letter appeared on the screen	

4. RESULTS AND DISCUSSION

4.1 Hemodynamic Response Function Parameters in Different *N*-back Tests

Hemodynamic response function chosen as a model in this thesis is a variate of gamma function with four parameters basically as shown below Equation. 4.1.,

$$hf(A,B,\alpha,\beta) = At^{\alpha}e^{\beta t} + B \tag{4.1}$$

Selective features of this function includes, amplitude, time to peak, full width at half maximum and DC level. These features give a better understanding on the characteristics of the hemodynamic function deduced from the data. Each subject took three n-back tests and the device composed of 16 channels, making it possible to record data from 16 different locations on forehead. The following results shows the gamma function features fitted on the data during different n-back tests (n=1, 2 and 3). Three sequences composed of 20 letters each has been shown to the subjects. Minor differences between successive sequences were also shown.

Device used in this study composed of 16 channels as previously shown on Figure 3.3. Channels are grouped according to the their positions on the forehead.

After determination of hemodynamic response function parameters for each subject, the average of data is estimated by calculating the mean by excluding the highest and lowest 5 percent of the data for each parameter and ANOVA tests were performed for each channel to see difference in various *n*-back tests for each channel.

4.1.1 DC level

Analysis of variation tests indicated a statistically significant ($p < 0.05$) increase in DC level by increasing working memory load in channels 1, 2, 3, 15 and 16. Channel 1's DC level data is shown on Table 4.1 below.

Table 4.1 Trimmed mean of DC level data for each subject during each *n*-back test is calculated for channel one and anova test resulted in a p value below 0.05.

		Channel 1	
Subject	n1	n2	n3
1	0.32	0.57	1.28
2	-0.19	0.70	1.33
3	-0.32	0.15	0.30
4	-0.12	1.25	0.57
5	0.86	0.67	0.41
6	0.13	0.27	0.88
7	0.30	0.05	0.41
8	0.21	0.55	0.30
9	0.16	0.32	0.74
Average	0.15	0.50	0.69
Variance	0.12	0.13	0.16
p		0.02	

Average DC levels for channels 1, 2, 3, 15 and 16 were interpolated on the forehead model in Figure 4.1 below to illustrate the hemodynamic response during different *n*-back tests.

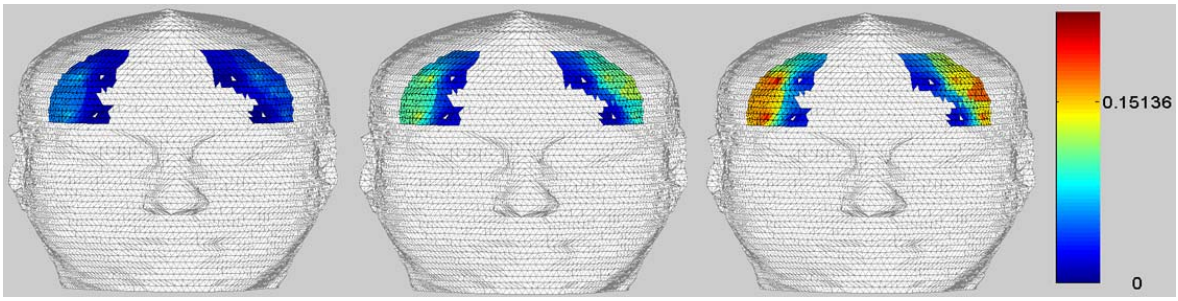

Figure 4.1 DC level average values for channels 1, 2, 3, 15 and 16 were interpolated on a forehead model. Working memory load and DC level is directly proportional for these channels.

According to the data above it is clearly seen that DC level of hemodynamic response increases with increasing working memory load, especially on the bilateral prefrontal cortex.

4.1.2 Time to Peak

Average time passed to peak of hemodynamic response is calculated for each subject by excluding the highest and lowest 5 percent of data. These trimmed average values were analyzed by using ANOVA test to see which channels illustrated statistical significance ($p<0.05$). Channels 1, 2, 4, 14 and 16 had statistical significance as only channel 2 data is shown on Table 4.2 below.

Table 4.2 Trimmed mean time to peak data for each subject during each *n*-back test is calculated for channel one and anova test resulted in a p value below 0.05.

		Channel 2	
Subject	n1	n2	n3
1	1.47	1.80	
2	1.05	2.42	3.02
3	2.08	1.62	
4	1.30	2.70	2.09
5	1.22	3.45	3.13
6	2.32	2.89	1.74
7	2.41	3.08	5.73
8	0.88	1.39	1.95
9	2.71	1.67	5.30
Average	1.72	2.33	3.28
Variance	0.45	0.55	2.63
p		0.02	

Average time to peak values for channels 1, 2, 4, 14 and 16 were interpolated on the forehead model in Figure 4.2 below to illustrate the hemodynamic response during different *n*-back tests.

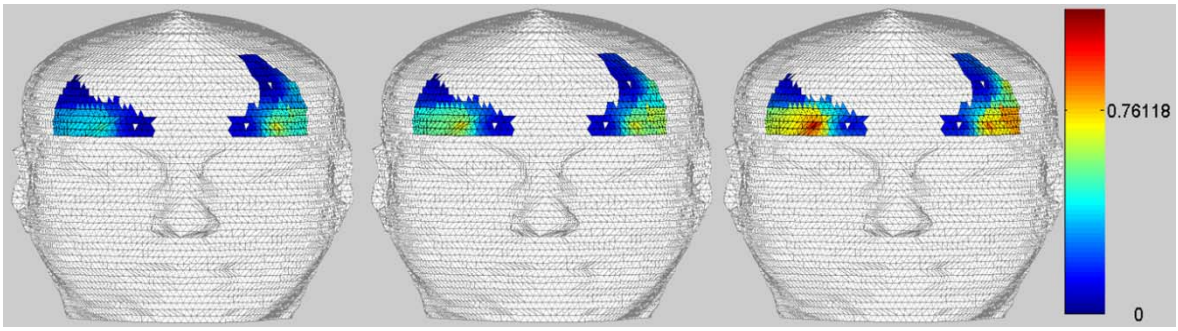

Figure 4.2 Time to peak average values for channels 1, 2, 4, 14 and 16 were interpolated on a forehead model. Working memory load and time to peak is directly proportional for these channels.

4.1.3 Amplitude

Amplitude of hemodynamic response is calculated for each subject by excluding the highest and lowest 5 percent of data. These trimmed average values were analyzed by using ANOVA test to see which channels illustrated statistical significance ($p<0.05$). Channels 1, 3, 14, 15, 16 had statistical significance as only channel 14 data is shown on Table 4.3 below.

Table 4.3 Trimmed mean of amplitude data for each subject during each *n*-back test is calculated for channel one and anova test resulted in a p value below 0.05.

		Channel 14	
Subject	n1	n2	n3
1	0.74	1.58	0.97
2	0.16	0.01	0.21
3	0.12	0.84	1.29
4	0.16	0.15	1.00
5	0.36	1.82	1.13
6	0.62	0.80	1.75
7	0.25	0.46	0.66
8	0.49		1.31
9	0.29	0.18	0.88
Average	0.35	0.73	1.02
Variance	0.05	0.45	0.19
p		0.02	

Average time to peak values of channels 1, 3, 14, 15 and 16 were interpolated on in Figure 4.3 below to illustrate the hemodynamic response during different *n*-back tests.

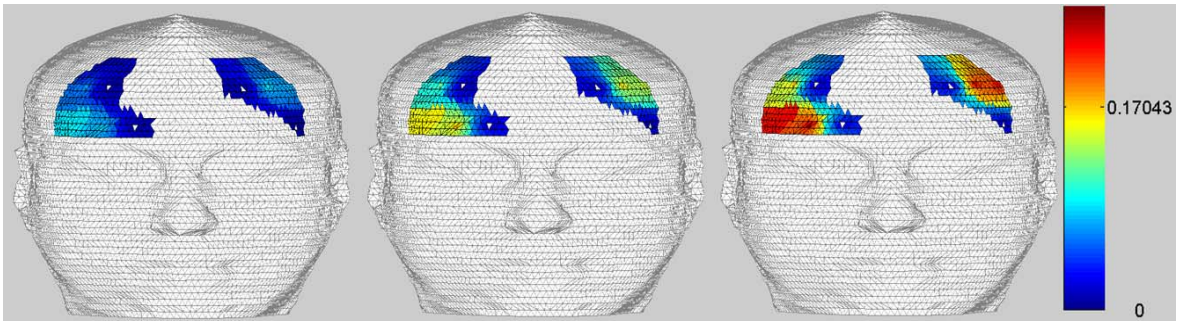

Figure 4.3 Amplitude average values for channels 1, 3, 14, 15 and 16 were interpolated on a forehead model. Working memory load and amplitude is directly proportional for these channels.

4.1.4 Full Width at Half Maximum

FWHM value for each curve was averaged for each subject for every channel by excluding the highest and lowest 5 percent of data. Trimmed average values were analyzed by ANOVA to see which channels had statistical significance ($p < 0.05$). Channels 1, 2, 4, 13, 15 and 16 had p values below 0.05. Only channel 16's data is shown in Table 4.4.

Table 4.4 Trimmed mean of FWHM data for each subject during each *n*-back test calculated for channel 1 ($p < 0.04$).

		Channel 16	
Subject	n1	n2	n3
1		7.25	4.33
2	3.67	13.13	8.43
3	1.30	7.24	3.33
4	4.07	2.31	2.32
5	3.08	2.59	27.47
6	1.84	2.16	
7	1.61	2.96	5.60
8	8.90	11.13	
9	4.40	1.71	3.56
Average	3.61	5.61	7.86
Variance	5.19	16.27	9.10
P		0.04	

Average full width at half maximum values for channels 1, 2, 4, 13, 15 and 16 were interpolated on the forehead model in Figure 4.4 below to illustrate the hemodynamic response during different *n*-back tests.

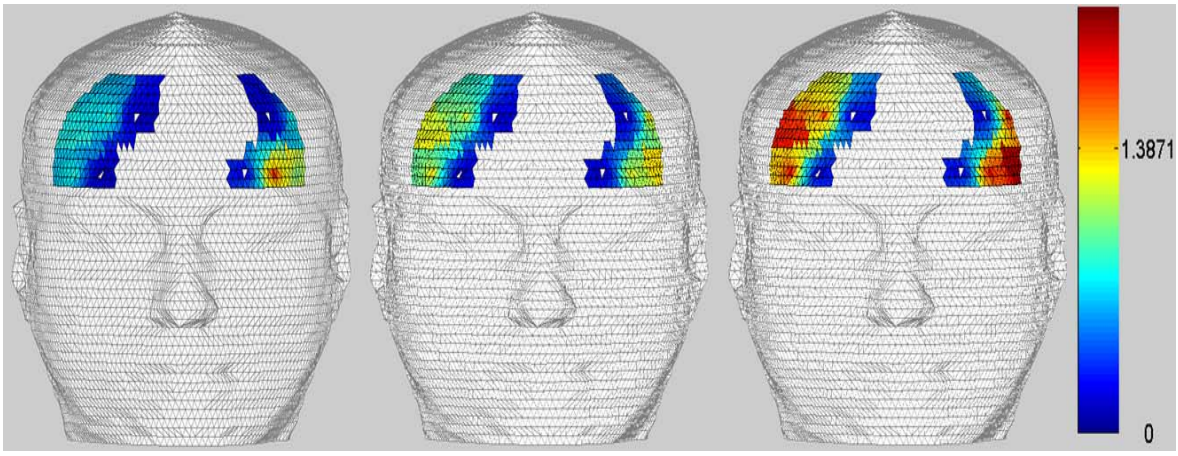

Figure 4.4 Full width at half maximum average values for channels 1, 2, 4, 13, 15 and 16 were interpolated on a forehead model. Working memory load and FWHM is directly proportional for these channels.

4.2 Correlation between Performance and Hemodynamic Response.

Response times of subjects to every trial are recorded during the *n*-back tests applied in this study. Average response times of each subjects to trials where a match appeared on the screen and a match button is pressed is shown in Table 4.5 below for different *n*-back tests. Trimmed mean is determined to calculate the average for each subject. The lowest and the highest 5 percent response time data were excluded. Anova test resulted in a statistically significant difference and a direct proportion between response time and *n* value

Table 4.5 Trimmed mean of response time data showed an increase in response time with increasing *n* value.

	Response Time in seconds		
Subject	*N*=1	*N*=2	*N*=3
1	0.61	0.91	1.08
2	0.89	0.74	1.23
3	0.60	0.76	1.06
4	0.88	1.12	0.87
5	0.41	1.37	1.33
6	0.52	0.94	1.76
7	0.83	1.10	1.35
8	1.01	0.84	0.83
9	0.71	0.40	0.33
Average	0.72	0.91	1.09
Variance	0.04	0.08	0.16
p		0.05	

ANOVA test result of the data above clearly showed, as in Figure 4.5 that response time increases with increasing *n* value. Thus working memory load is directly proportional to *n*.

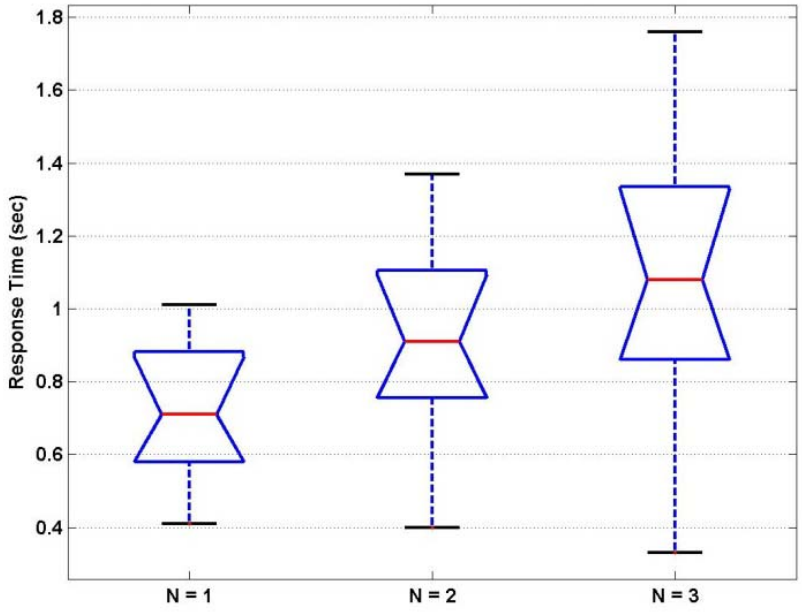

Figure 4.5 ANOVA results of average response times of subjects to matching trials with a correct answer.

4.2.1 Correlation of Behavioral Data with Neuroimaging Data

Interaction between *n* value and working memory load is an important factor which can be used to analyze the interaction between working memory load and fNIRS signal since results up to here already clearly showed an interaction between fNIRS signal and different *n* values. The following figures for DC level, time to peak, amplitude and full width at half maximum indicates the relationship between these parameters calculated from the fNIRS signal and working memory load.

Relationship between DC level averages and response time is calculated from the channels which represented statistically significant data among different *n*-back tests is shown in Figure 4.6 below. Channels 1, 2, and 3 located on the left region of forehead and channels 15 and 16 located on the right gave statistically reliable data, thus average DC level data from these channels were used to see whether a lateralization exists.

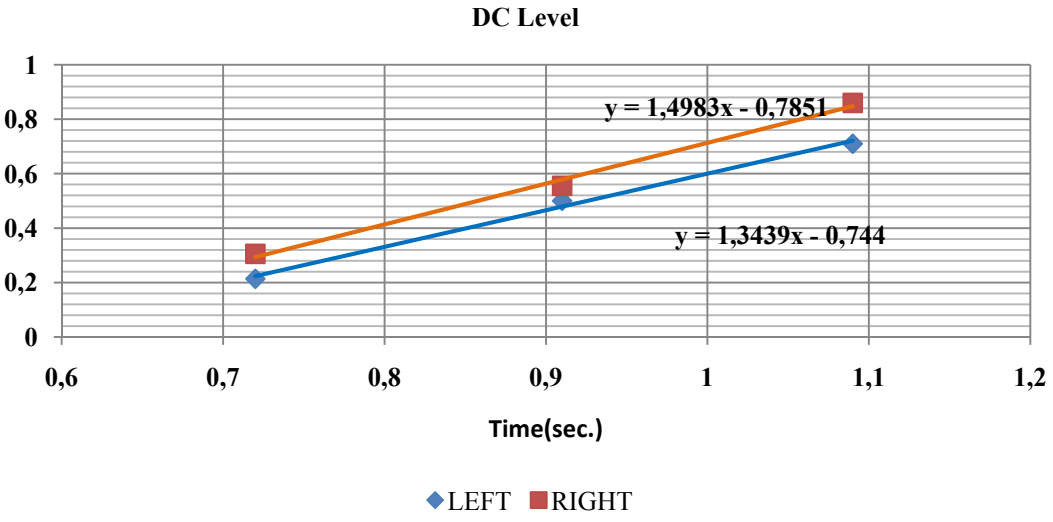

Figure 4.6 Graphics above represent the average DC values of all subjects, calculated from the fNIRS device's channels 1, 2, 3, 15 and 16, which represented a statistical significance in different *n* back tests.

According to this although there is some difference between DC level concentrations of left and right lateral prefrontal cortex, right side having a slightly more HbO_2 concentration, slopes of the lines fitted on the data indicates that working memory load affected the hemodynamic response in both sides almost equally.

Relationship between time to peak averages and response time is calculated from the channels which represented statistically significant data among different *n*-back tests is shown in Figure 4.7 below. Channels 1, 2, and 4 located on the left region of forehead and channels 14 and 16 located on the right gave statistically reliable data , thus average time to peak data from these channels were used to see whether a lateralization exists.

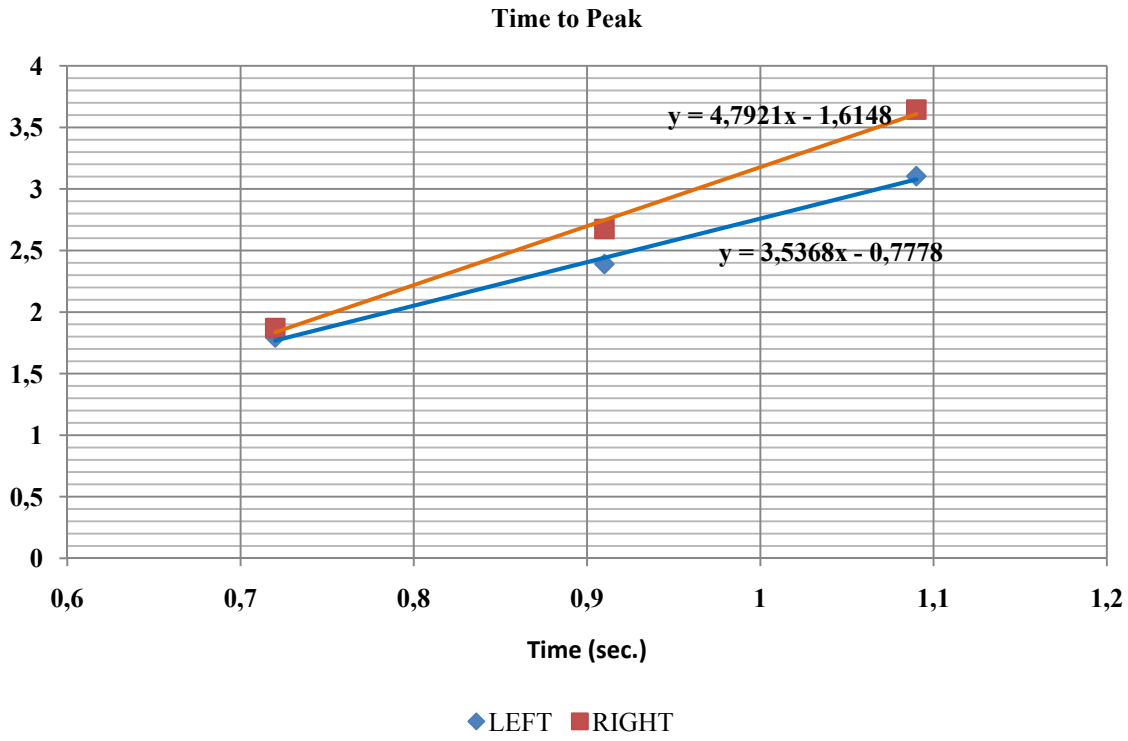

Figure 4.7 Graphics above represent the average time to peak values of all subjects, calculated from the fNIRS device's channels 1, 2, 4, 14 and 16, which represented a statistical significance in different *n* back tests.

According to this, there is some difference between time passed till the hemodynamic response peaks for left and right lateral prefrontal cortex, right side taking slightly more time and slopes of the lines fitted on the data indicates that working memory load affected the hemodynamic response on right side slightly more with respect to the left side.

Relationship between amplitude averages and response time is calculated from the channels which represented statistically significant data among different *n*-back tests is shown in Figure 4.8 below. Channels 1 and 3 located on the left region of forehead and channels 14, 15 and 16 located on the right gave statistically reliable data, thus average amplitude data from these channels were used to see whether a lateralization exists.

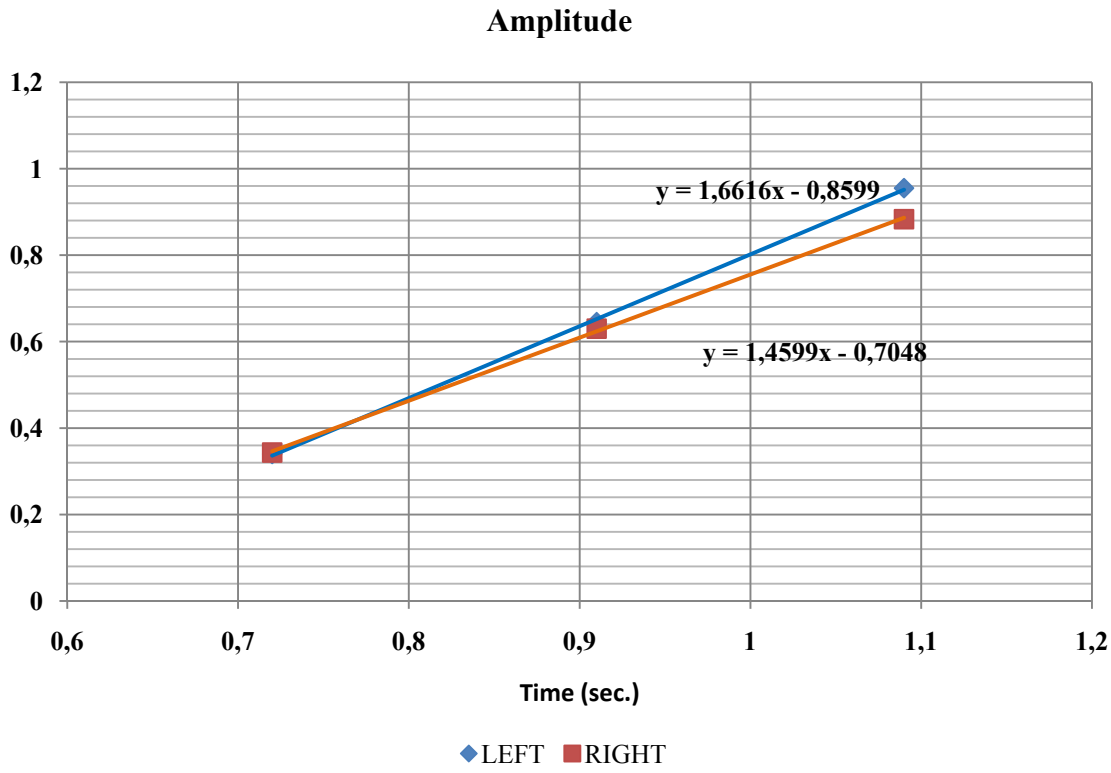

Figure 4.8 Graphics above represent the average time to peak values of all subjects, calculated from the fNIRS device's channels 1, 3, 14, 15 and 16, which represented a statistical significance in different *n* back tests

According to this, although there is no difference between amplitudes of the hemodynamic response of left and right lateral prefrontal cortex, slopes of the lines fitted on the data indicates that working memory load affected the hemodynamic response in left side slightly more than the right side of the prefrontal cortex.

Relationship between full width at half maximum averages and response time is calculated from the channels which represented statistically significant data among different *n*-back tests is shown in Figure 4.9 below. Channels 1, 2 and 4 located on the left region of forehead and channels 13, 15 and 16 located on the right gave statistically reliable data , thus average full width at half maximum from these channels were used to see whether a lateralization exists.

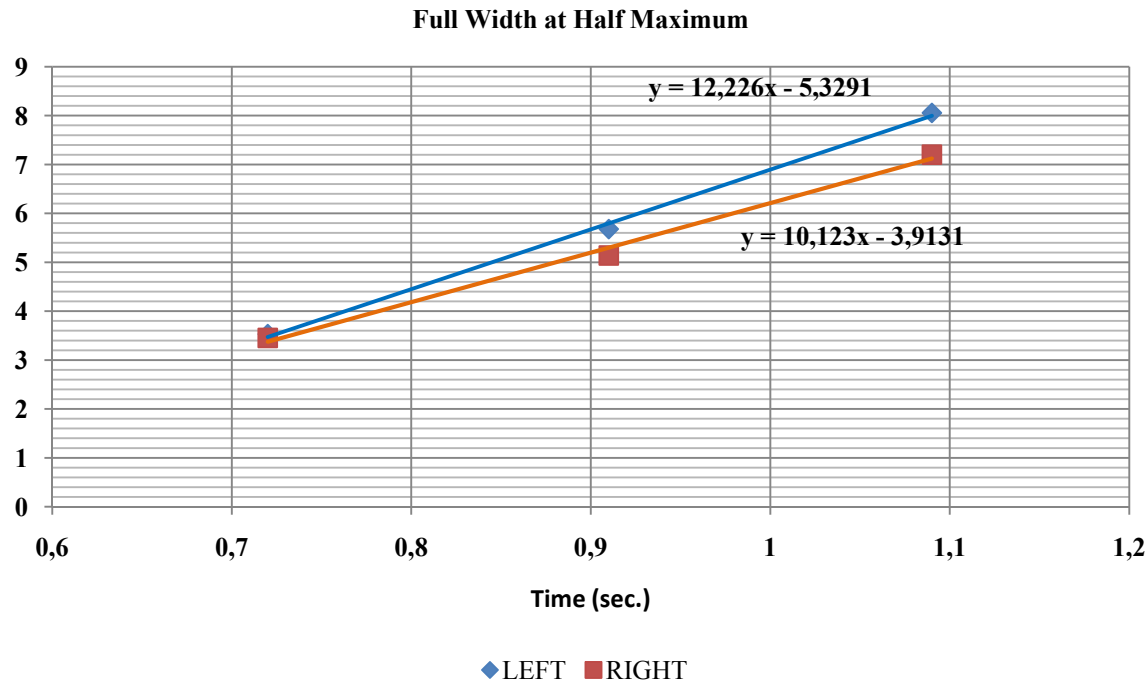

Figure 4.9 Graphics above represent the average full width at half maximum values of all subjects, calculated from the fNIRS device's channels 1, 2, 4, 13, 15 and 16, which represented a statistical significance in different *n* back tests.

According to this, although there is no significant difference in between full width at half maximum of the hemodynamic response of left and right lateral prefrontal cortex, slopes of the lines fitted on the data indicates that working memory load affected the hemodynamic response in left side slightly more than the right side.

4.3 Limitations

Hemodynamic response function model used in this study is a variation of gamma function with four parameters. However hemodynamic response has a more complicated form since there are lots of factors that might affect the behavior of the response. Model fitted on the data was eliminated according to the r-square values calculated for each fit. Approximately 20 percent of the fits were discarded from further analysis as a result of having r-square values below 0.8. It is important to underline that model used in this study is a very simplistic representative of the real hemodynamic response. In other words hypothesis of this thesis relies on a simple model of real hemodynamic response.

N-back tests in this study were practiced by the subjects before the fNIRS signal is recorded. However this practice period might not be adequate for all subjects owing to the complicated nature of the tests itself. The software used to develop *N*-back tests required 3 conditions from the subject, since they were asked to press two buttons or none. fNIRS signal analysis depends on the hypothesis that blood flow to the forehead is constant. Major error source during the whole study was due to movement of the fNIRS probe on forehead. This movement artifact occurred mostly during the indispensible resting periods.

Data collected from the subjects were analyzed in such a way that only one possible outcome among five possible answers to each trial is taken into account. Only the case in which subjects pressed the match button when a match occurred is chosen in this study for analysis. This represents less than 20 percent of all trials in the experiments.

During the experiment subjects' moods also may have affected the data. The level of anxiety, for instance is such an important factor. Pulse oximeter measurement might have been used to compensate for increase in hemodynamic response due to anxiety.

4.4 Future Work

This study represents the relationship between working memory load and hemodynamic response as determined by means of functional near infrared spectroscopic signals and application of an assumed hemodynamic response function model. However, only one of the five possible and existing answers to the trials of *n*-back tests was analyzed. Other cases also may be analyzed with the same model applied in this thesis to have an idea about the behavior of the hemodynamic response in incorrect answers and correct mismatch answers.

Sequences of letters appeared on the screen were randomly generated, thus they include deceptive 1-back matches in 2-back tests or 1-back and/or 2-back matches in 3-back tests. These misleading trials may also be analyzed for future work and differential examination of these cases may be important in terms of relation between working memory load and fNIRS signals detected.

5. CONCLUSION

Functional near infrared spectroscopy has shown to be a reliable neuroimaging tool to monitor the hemodynamic response while a working memory task is being held. Moreover the model applied in this study not only clearly represented the activated areas during the task but also illustrated an obvious correlation between working memory load and hemodynamic response as determined by the fNIRS device. This promising approach may be developed to quantify the working memory load of any practice.

APPENDIX A. *N*-BACK TEST CODE IN MATLAB PSYCHTOOLBOX

```
clear all; clc; HideCursor;
global distance
yuzde = 20;
N=2;
n='2';
a = 'A';
cont = 0;
ret = 0;
iti = 2.5; %display time
NumTrials = 20;
distance = 200;
hit = 0;
jj=1;
%-----------------------------
DIOout = digitalio('parallel','lpt1');
DIOin = digitalio('parallel', 'lpt1');
outparportlines = addline(DIOout,0:7,'out');
inparportlines = addline(DIOin,0:7,'in');
putvalue(DIOout, 0);
% 1
% putvalue(DIOout, ones(1,8));
% pause(0.6);
% putvalue(DIOout, zeros(1,8));
%-----------------------------
% Set up the window for drawing stimuli
%window = Screen('OpenWindow', 0, 1);
[window,MainRect] = Screen(0,'OpenWindow',[0 0 0]);

% Remove the blue screen flash and minimize extraneous warnings.
```

```
%Screen('Preference', 'VisualDebugLevel', 3);
%Screen('Preference', 'SuppressAllWarnings', 1);
%Screen('Flip', window);
% Disable text entry into script or command window during trial
%
%ListenChar(2);
% Initialise keyboard input
KbName('UnifyKeyNames');
Nomatch = KbName('s');
Match = KbName('l');
Enter = KbName('Return');
escapeKey = KbName('ESCAPE');
%rect = Screen(window,'rect');
% [X,Y] = RectSize(rect);
% X0 = X/2
% Y0 = Y/2
X0 = (MainRect(1)+MainRect(3))/2 - 100;
Y0 = (MainRect(2)+MainRect(4))/2 +30;
StimulusRect = CenterRectOnPoint([0,0,2*distance*cos(45*pi/180),
2*distance*cos(45*pi/180)],X0,Y0);
FixationPt = CenterRectOnPoint([0,0,10,10], X0, Y0);
% Text Properties and Colours
Screen(window,'TextFont', 'Arial');
Screen(window, 'TextSize', 40);
white = WhiteIndex(window);
black  = BlackIndex(window);
gray =(black + white)/2;
purple = [147, 112, 219];
Screen('FillRect',window,gray);
Screen(window,'TextSize',40);
Screen(window,'DrawText', 'Welcome to the n-Back Test', 380, 180, white);
Screen(window,'DrawText', 'If you see the same letter appeared',220,330, white);
Screen(window,'DrawText', n , 140, 380, black);
```

```
Screen(window,'DrawText', 'letters before, press the "L" key,',180,380, white);
Screen(window,'DrawText', ' otherwise press the "S" key', 200,430, white);
Screen(window, 'DrawText', 'Press Enter to continue...', 410, 530, white);
Screen(window,'Flip');
%%%%% set up angles %%%%%
angles = ['A' 'B' 'C' 'D' 'E' 'F'];
%%%%%%%%%Sequence Generator%%%%%%%%%
for ii=1:3
k=0;
for n=1:NumTrials
   sequence(ii,n)='Z';
   sequence2(ii,n)='Z';
end
while k < ((yuzde*NumTrials)/100)
   counter=ceil(rand(1)*(NumTrials-N));
   sayi = ceil(rand(1)*6);
   if counter<=N
      if ((sequence(ii,counter)=='Z' && sequence(ii,counter+N)=='Z')) %||
(sequence(counter)=='Z' && sequence(counter+N)~='Z' &&
sequence(counter+N)==angle(sayi))) && k+1 <= (yuzde*NumTrials)/100
         if sequence(ii,counter+2*N)==angle(sayi) && k+2 <= ((yuzde*NumTrials)/100)
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+2;
         elseif sequence(ii,counter+2*N)~=angles(sayi) && k+1 <=
((yuzde*NumTrials)/100)
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+1;
```

```
            end
        end
        if (sequence(ii,counter)=='Z' && sequence(ii,counter+N)==angles(sayi)) && k+1 <=
(yuzde*NumTrials)/100
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+1;
        end
    end
    if counter > N && counter <=NumTrials-2*N
        if (sequence(ii,counter)=='Z' && sequence(ii,counter+N)=='Z') %||
(sequence(counter)=='Z' && sequence(counter+N)~='Z' &&
sequence(counter+N)==angle(sayi))
            if sequence(ii,counter-N)==angles(sayi)&&
sequence(ii,counter+2*N)==angles(sayi) && k+3 <= ((yuzde*NumTrials)/100)
                sequence(ii,counter)=angles(sayi);
                sequence(ii,counter+N)= angles(sayi);
                sequence2(ii,counter)=angles(sayi);
                sequence2(ii,counter+N)= angles(sayi);
                k=k+3;
            elseif ((sequence(ii,counter-
N)==angles(sayi)&&sequence(ii,counter+2*N)~=angles(sayi))||(sequence(ii,counter-
N)~=angles(sayi) && sequence(ii,counter+2*N)==angles(sayi))) && (k+2 <=
((yuzde*NumTrials)/100))
                sequence(ii,counter)=angles(sayi);
                sequence(ii,counter+N)= angles(sayi);
                sequence2(ii,counter)=angles(sayi);
                sequence2(ii,counter+N)= angles(sayi);
                k=k+2;
            elseif sequence(ii,counter-N)~=angles(sayi) &&
sequence(ii,counter+2*N)~=angles(sayi) && k+1 <= ((yuzde*NumTrials)/100)
```

```
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+1;
        end
    end
    if sequence(ii,counter)=='Z' && sequence(ii,counter+N)==angles(sayi)
        if sequence(ii,counter-N)==angles(sayi) && k+2 <= ((yuzde*NumTrials)/100)
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+2;
        elseif sequence(ii,counter-N)~=angles(sayi) && k+1 <= ((yuzde*NumTrials)/100)
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+1;
        end
    end
end
if counter > NumTrials-2*N
    if (sequence(ii,counter)=='Z' && sequence(ii,counter+N)=='Z') ||
(sequence(ii,counter)=='Z' && sequence(ii,counter+N)==angles(sayi))
        if sequence(ii,counter-N)==angles(sayi)&& k+2 <= ((yuzde*NumTrials)/100)
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+2;
        elseif sequence(ii,counter-N)~=angles(sayi) && k+1 <= ((yuzde*NumTrials)/100)
```

```
            sequence(ii,counter)=angles(sayi);
            sequence(ii,counter+N)= angles(sayi);
            sequence2(ii,counter)=angles(sayi);
            sequence2(ii,counter+N)= angles(sayi);
            k=k+1;
        end
    end
  end
end
%-------------------------------------------------------------
%fill the gaps in the sequence without changing the total number of matches
for w2=1:NumTrials
  if sequence(ii,w2)=='Z'
    if w2 <= N
      sayi = ceil(rand(1)*6);
      while sequence(ii,w2+N)==angles(sayi)
      sayi = ceil(rand(1)*6);
      end
      sequence(ii,w2)=angles(sayi);
    end
    if w2 > N && w2 <= NumTrials-N
      sayi = ceil(rand(1)*6);
      while sequence(ii,w2+N)==angle(sayi)||sequence(ii,w2-N)==angles(sayi)
        sayi = ceil(rand(1)*6);
      end
      sequence(ii,w2)=angles(sayi);
    end
    if w2 > NumTrials-N
      sayi = ceil(rand(1)*6);
      while sequence(ii,w2-N)==angles(sayi)
        sayi = ceil(rand(1)*6);
      end
      sequence(ii,w2)=angles(sayi);
```

```
        end
    end
end
end
% Start Trial Counter
trial = 1;
numcorrect = 0;
numincorrect = 0;
numcorrectmatches = 0;
numincorrectmatches = 0;
numcorrectnomatches = 0;
numincorrectnomatches = 0;
unhit=0;
while cont == 0
    [ keyDown, seconds, keyCode ] = KbCheck;
    if keyDown
        if (keyCode(escapeKey))
            trial = 100;
            cont = 1;
            break
        end
        if (keyCode(Enter))
            %           Screen('Flip', window);
            WaitSecs(0.2);
            Screen(window,'FillRect',gray);
            cont = 1;
        end
    end
end
%-------------------------------------------------------
%%%%%%%% Trial Loop %%%%%%%%%%%%%
while jj<=3 && trial~=100
trial = 1;
```

```
numcorrect = 0;
numincorrect = 0;
numcorrectmatches = 0;
numincorrectmatches = 0;
numcorrectnomatches = 0;
numincorrectnomatches = 0;
unhit=0;
while trial <= NumTrials && ret < 1
%    Num = ceil(rand(1)*4);
%   angle = angles(Num);
   angle = sequence(jj,trial);
   % [x,y] = position(window, angle);
   putvalue(DIOout, ones(1,8));
   pause(0.71);
   putvalue(DIOout, zeros(1,8));
   anglelist(trial) = angle;
   secs = GetSecs;
   while GetSecs - secs < iti
      %        Screen('FrameOval', window ,white ,StimulusRect, 1);
      [ keyDown, seconds, keyCode ] = KbCheck;
     if GetSecs-secs < 0.5
         if trial==3 Screen('SaveAsEps'); end
         %Screen(window,'FillOval',purple, FixationPt);
         %CenterText(window, 'A', white, x, y);
         Screen(window, 'TextSize', 160);
         Screen(window,'DrawText',angle,560,320,black);
         %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials), 10, 10,
white);
         %Screen('Flip', window);
      else
         Screen(window, 'DrawText','+',560,320,black);
      end
      %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730, white);
```

```
Screen('Flip',window);
if keyDown && (keyCode(escapeKey) || keyCode(Match)|| keyCode(Nomatch))
   if (keyCode(escapeKey))
      ret = 1;
      secs = GetSecs - 10;
      break
   end
   if trial > N
      if ((anglelist(trial) == anglelist(trial-N)) && keyCode(Match))
         responsetime_answer(jj,trial, 1)= seconds-secs;
         responsetime_answer(jj,trial,2)= Match-38;
         numcorrect = numcorrect+1;
         numcorrectmatches = numcorrectmatches + 1;
         correct = 1;
         hit = 1;
         %                  Screen('FrameOval', window ,white ,StimulusRect, 1);
         %Screen(window,'FillOval', purple, FixationPt);
         %CenterText(window, angle, white, 620, 410);
         %Screen('Flip',window);
         %Screen(window,'DrawText','A',x,y,white);
         %Screen(window,'TextSize',40);
         Screen(window,'DrawText', 'CORRECT!' , 150, 20, white);
         %Screen(window,'TextSize',160);
         %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials),
10, 10, white);
         %Screen('Flip', window);
         if GetSecs-secs < 0.5
            Screen(window,'DrawText',angle,560,320,black);
            %Screen('Flip', window);
         else
            Screen(window, 'DrawText','+',560,320,black);
         end
```

```
            %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
            Screen('Flip', window);
            break
        elseif ((anglelist(trial) ~= anglelist(trial-N)) && keyCode(Match))
            responsetime_answer(jj,trial, 1)= seconds-secs;
            responsetime_answer(jj,trial,2)= Match-37;
            numincorrect = numincorrect + 1;
            numincorrectmatches = numincorrectmatches + 1;
            correct = 0;
            hit = 1;
            %                   Screen('FrameOval', window ,white ,StimulusRect, 1);
            %Screen(window,'FillOval', purple, FixationPt);
            %CenterText(window, angle, white, 620, 370);
            %Screen('Flip',window);
            %Screen(window,'DrawText', 'A',x,y,white);
            %Screen(window,'TextSize',40);
            Screen(window,'DrawText', 'INCORRECT!' , 100, 20, white);
            %Screen(window,'TextSize',160);
            %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials),
10, 10, white);
            %Screen('Flip', window);
            if GetSecs-secs < 0.5
               Screen(window,'DrawText',angle,560,320,black);
               %Screen('Flip', window);
            else
               Screen(window, 'DrawText','+',560,320,black);
            end
            %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
            Screen('Flip', window);
            break
        elseif ((anglelist(trial) ~= anglelist(trial-N)) && keyCode(Nomatch))
```

```
            responsetime_answer(jj,trial, 1)= seconds-secs;
            responsetime_answer(jj,trial,2)= Nomatch-34;
            numcorrect = numcorrect+1;
            numcorrectnomatches = numcorrectnomatches + 1;
            correct = 1;
            hit = 1;
            %                   Screen('FrameOval', window ,white ,StimulusRect, 1);
            %Screen(window,'FillOval', purple, FixationPt);
            %CenterText(window, angle, white, 620, 370);
            %Screen('Flip',window);
            %Screen(window,'DrawText','A',x,y,white);
            %Screen(window,'TextSize',40);
            Screen(window,'DrawText', 'CORRECT!' , 150, 20, white);
            %Screen(window,'TextSize',160);
            %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials),
10, 10, white);
            %Screen('Flip', window);
            if GetSecs-secs < 0.5
               Screen(window,'DrawText',angle,560,320,black);
               %Screen('Flip', window);
            else
               Screen(window, 'DrawText','+',560,320,black);
            end
            %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
            Screen('Flip', window);
            break
         elseif ((anglelist(trial) == anglelist(trial-N)) && keyCode(Nomatch))
            responsetime_answer(jj,trial, 1)= seconds-secs;
            responsetime_answer(jj,trial,2)= Nomatch-33;
            numincorrect = numincorrect + 1;
            numincorrectnomatches = numincorrectnomatches + 1;
            correct = 0;
```

```
            hit = 1;
            %                   Screen('FrameOval', window ,white ,StimulusRect, 1);
            %Screen(window,'FillOval', purple, FixationPt);
            %CenterText(window, angle, white, 620, 370);
            %Screen('Flip',window);
            %Screen(window,'DrawText', 'A',x,y,white);
            %Screen(window,'TextSize',40);
            Screen(window,'DrawText', 'INCORRECT!' , 100, 20, white);
            %Screen(window,'TextSize',160);
            %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials),
10, 10, white);
            %Screen('Flip', window);
            if GetSecs-secs < 0.5
               Screen(window,'DrawText',angle,560,320,black);
               %Screen('Flip', window);
            else
               Screen(window, 'DrawText','+',560,320,black);
            end
            %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
            Screen('Flip', window);
            break
         end
      end
   end
   while GetSecs - secs < iti
      [ keyDown, seconds, keyCode ] = KbCheck;
      if correct==1
         %Screen(window,'TextSize',40);
         Screen(window,'DrawText', 'CORRECT!' , 100, 20, white);
         %Screen(window,'TextSize',160);
```

```
        %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials), 10, 10,
white);
        %Screen('Flip', window);
        if GetSecs - secs < 0.5
           Screen(window,'DrawText',angle,560,320,black);
           %Screen('Flip', window);
        else
           Screen(window, 'DrawText','+',560,320,black);
        end
        %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
        Screen('Flip', window);
      elseif correct==0
        %Screen(window,'TextSize',40);
        Screen(window,'DrawText', 'INCORRECT!' , 100, 20, white);
        %Screen(window,'TextSize',160);
        %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials), 10, 10,
white);
        %Screen('Flip', window);
        if GetSecs - secs < 0.5
           Screen(window,'DrawText',angle,560,320,black);
           %Screen('Flip', window);
        else
           Screen(window, 'DrawText','+',560,320,black);
        end
        %Screen(window,'DrawText', sprintf('%.2f seconds', seconds-secs), 40, 730,
white);
        Screen('Flip', window);
      end
   end;
%    if hit == 0
%       if trial == 1 || trial == 2
%          numcorrect = numcorrect + 1;
```

```
%            correct = 1;
%        elseif trial > 2 && anglelist(trial) ~= anglelist(trial-2)
%            numcorrect = numcorrect + 1;
%            correct = 1;
%                     %Screen('DrawText', window, 'CORRECT' , 540, 620, white);
%        elseif trial > 2 && anglelist(trial) == anglelist(trial-2)
%            numincorrect = numincorrect + 1;
%            correct = 0;
%                    %Screen('DrawText', window, 'INCORRECT' , 540, 620, white);
%        end
%    end
   if hit == 0
      unhit=unhit + 1;
      responsetime_answer(jj,trial, 1)= iti;
      responsetime_answer(jj,trial,2)= 0;
   end
   hit = 0;
   %Screen(window,'DrawText', sprintf('TRIAL: %d of %d', trial, NumTrials), 10, 10,
white);
   %Screen(window,'FillOval', purple, FixationPt);
   if GetSecs-secs < 0.5
      Screen(window,'DrawText',angle,560,320,black);
      %Screen('Flip', window);
   else
     Screen(window, 'DrawText','+',560,320,black);
   end
   Screen('Flip', window);
   testlist(:,trial) = [angle; 720; 450];
   trial = trial + 1;
   %WaitSecs(0.5);
   while keyDown; [ keyDown, seconds, keyCode ] = KbCheck; end
end
if ret == 0 && trial~=100
```

```
   Screen(window, 'TextSize', 40);
   Screen(window,'DrawText', sprintf('Total Correct: %d', numcorrect), 50, 20, white);
   Screen(window,'DrawText', sprintf('Total Incorrect: %d', numincorrect), 50, 120, white);
   Screen(window,'DrawText', sprintf('Total Unhit: %d', unhit-N), 50, 220, white);
   Screen(window,'DrawText', sprintf('Total Correct Matches: %d', numcorrectmatches),
50, 320, white);
   Screen(window,'DrawText', sprintf('Total Correct No-matches: %d',
numcorrectnomatches), 50, 420, white);
   Screen(window,'DrawText', sprintf('Total Incorrect Matches: %d',
numincorrectmatches), 50, 520, white);
   Screen(window,'DrawText', sprintf('Total Incorrect No-matches: %d',
numincorrectnomatches), 50, 620, white);
   Screen(window,'DrawText', 'Press Any Key to end...', 50, 720, purple);
   Screen('Flip', window);
end
if ret ==0 && trial~=100 waitsecs(62);end
jj=jj+1;
end
%ListenChar(0);
if ret ==0 && trial~=100 && jj~=4
   keyDown = KbCheck;
   while keyDown == 0; keyDown = KbCheck; end;
end
sca;
```

REFERENCES

1. Edin F., J. Macoveanu, P. Olesen, J. Tegnér, T. Klingberg, "Stronger synaptic connectivity as a mechanism behind development of working memory-related brain activity during childhood," *Journal of Cognitive Neuroscience,* Vol. 19(5), pp. 750-760, May 2007.

2. Atkinson R. and R. Shiffrin, "Human memory: A proposed system and its control processes," In *The psychology of learning and motivation: Advances in research and theory*, Vol. 2, pp. 742–775, Academic Press, New York, 1968.

3. Norman D. A. and T. Shallice, "Attention to action: Willed and automatic control of behavior," In *Consciousness and Self-Regulation: Advances in Research and Theory*, Plenum Press, 1986.

4. Cooper R., T. Shallice, and J. Farringdon, "Symbolic and continuous processes in the automatic selection of actions," In *Hybrid Problems, Hybrid Solutions, Frontiers in Artificial Intelligence and Applications*, pp. 27–37, IOS Press, Amsterdam, 1995.

5. Shallice T., "Specific impairments of planning," *Royal Society of London Philosophical Transactions Series B*, Vol. 298, pp. 199–209, 1982.

6. Baddeley A.D., G.J. Hitch, "Working memory," In *The psychology of learning and motivation*, Vol. 8, pp. 47-90, New York: Academic Pres, 1974.

7. Hitch G.J., "Developing the concept of working memory," In *Cognitive psychology: New directions,* pp. 156-196, London: Routledge and Kegan Paul, 1980.

8. Baddeley A.D., "The capacity for generating information by randomization," *Quarterly Journal of Experimental Psychology*, Vol. 18, pp. 119-129, 1966.

9. Baddeley A. D., V. J. Lewis, M. Eldridge, and N. Thomson, "Attention and retrieval from long-term memory," *Journal of Experimental Psychology: General*, Vol. 113, pp. 518-530, 1984a.

10. Baddeley A. D., "Working memory," *Oxford: Oxford University Press*, 1986.

11. Baddeley A.D., S. Grant, E. Wight, and N. Thomson, "Imagery and visual working memory," In *Attention and performance*, pp. 205-217, New York: Academic Press, 1975.

12. Baddeley A.D., R. H. Logie, "Working memory: The multiple-component model," In *Models of working memory,* pp. 28-61, New York: Cambridge University Press, 1999.

13. Baddeley A.D., "Exploring the central executive," *Quarterly Journal of Experimental Psychology*, Vol. 49A, pp.5-28,

14. Miller G.A., "The magical number seven, plus or minus two: Some limits on our capacity for processing information," *Psychological Review*, Vol. 63, pp. 81-97, 1956.

15. Baddeley A.D., "The episodic buffer: A new component of working memory? ", *Trends in Cognitive Sciences*, Vol. 4, pp. 417-423, 2000.

16. Fuster J. M., "Unit-activity in prefrontal cortex during delayed-response performance - neuronal correlates of transient memory," *Journal of Neurophysiology*, Vol. 36, pp. 61-78, 1973.

17. Ashby F.G., S.W. Ell, V.V. Valentin and M.B. Casale, "FROST: A distributed neurocomputational model of working memory maintenance," *Journal of Cognitive Neuroscience*, Vol. 17, pp. 1728-1743, 2005.

18. Mottaghy F. M., "Interfering with working memory in humans," *Neuroscience*, Vol. 139, pp. 85-90, 2006.

19. Kane M. J., and R. W. Engle, "The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective," *Psychonomic Bulletin and Review*, Vol. 9, pp. 637-671, 2002.

20. Collette F., M. Hogge, E. Salmon, & M. Van der Linden, "Exploration of the neural subtrates of executive functioning by functional neuroimaging," *Neuroscience*, Vol. 139, pp. 209-221, 2006.

21. Kondo H., N. Osaka, & M. Osaka, "Cooperation of the anterior cinculate cortex and dorsolateral prefrontal cortex for attention shifting," *NeuroImage*, Vol. 23, pp. 670-679, 2004.

22. Osaka N., M. Osaka, H. Kondo, M. Morishita, H. Fukuyama, and H. Shibasaki, "The neural basis of executive function in working memory: an fMRI study based on individual differences," *NeuroImage*, Vol. 21, pp. 623-631, 2003.

23. Gevins A.S., B.C. Cutillo, "Neuroelectric evidence for distributed processing in human working memory," *Electroencephalogr. Clin. Neurophysiol.*, Vol. 87, pp. 128-143, 1993.

24. Callicott J.H., V.S. Mattay, A. Bertolino, K. Finn, R. Coppola, J.A. Frank, T.E. Goldberg, D.R. Weinberger, "Physiological characteristics of capacity constraints in working memory as revealed by functional MRI," *Cereb. Cortex,* Vol. 9, pp. 20 –26, 1999.

25. Courtney S.M., L. Petit, J.V. Haxby, L.G. Ungerleider, "The role of prefrontal cortex in working memory: examining the contents of consciousness," *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, Vol. 353, pp. 1819 –1828, 1998.

26. Goldman-Rakic P.S., "Working memory dysfunction in schizophrenia," *J.Neuropsychiatry Clin. Neurosci., Vol.* 6, pp.348 –357, 1994.

27. Jonides J., E.E. Smith, R.A. Koeppe, E. Awh, S. Minoshima, M.A. Mintun, "Spatial working memory in humans as revealed by PET," *Nature*, Vol. 363, pp. 623– 625, 1993.

28. Owen A.M., "The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging," *Eur. J. Neuroscience,* Vol. 9, pp. 1329 –1339, 1997.

29. Petrides M., "Frontal lobes and behavior," *Curr. Opin. Neurobiol.,* Vol. 4, pp. 207–211, 1994.

30. Rowe J.B., I. Toni, O. Josephs, R.S. Frackowiak, R.E. Passingham, "The prefrontal cortex: response selection or maintenance within working memory?", *Science,* Vol. 288, pp. 1656 –1660, 2000.

31. Bor D., J. Duncan, R.J. Wiseman, A.M. Owen, "Encoding strategies dissociate prefrontal activity from working memory demand," *Neuron,* Vol. 37, pp. 361–367, 2003.

32. Fletcher P.C., T. Shallice, R.J. Dolan, "The functional roles of prefrontal cortex in episodic memory," *I. Encoding. Brain*, Vol. 121, pp. 1239–1248, 1998.

33. Dobbins I.G., H. Foley, D.L. Schacter, A.D. Wagner, "Executive control during episodic retrieval: multiple prefrontal processes subserve source memory," *Neuron*, Vol. 35, pp. 989 –996, 2002.

34. Rugg M.D., P.C. Fletcher, K. Allan, C.D. Frith, R.S. Frackowiak, R.J. Dolan, "Neural correlates of memory retrieval during recognition memory and cued recall.", *Neuroimage*, 8:262–273., 1998.

35. Petrides M., "Frontal lobes and behavior," *Curr. Opin. Neurobiology,* Vol. 4, pp. 207–211, 1994.

36. Courtney S.M., L.G. Ungerleider, K. Keil, J.V. Haxby, "Transient and sustained activity in a distributed neural system for human working memory," *Nature*, Vol. 386, pp. 608–611, 1997.

37. Goldman-Rakic P.S., "Working memory dysfunction in schizophrenia," *J. Neuropsychiatry Clin. Neuroscience,* Vol. 6, pp. 348 –357, 1994.

38. Rushworth M.F., P.D. Nixon, M.J. Eacott, R.E. Passingham, "Ventral prefrontal cortex is not essential for working memory," *J. Neuroscience*, Vol. 17, pp. 4829–4838, 1997.

39. Dobbins I.G., H. Foley, D.L. Schacter, A.D. Wagner, "Executive control during episodic retrieval: multiple prefrontal processes subserve source memory," *Neuron*, Vol. 35, pp. 989 –996, 2002.

40. Henson R.N., T. Shallice, R.J. Dolan, "Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis," *Brain*, Vol. 122, pp. 1367–1381, 1999.

41. Wagner A.D., D.L. Schacter, M. Rotte, W. Koutstaal, A. Maril, A.M. Dale, B.R. Rosen, R.L. Buckner, "Building memories: remembering and forgetting of verbal experiences as predicted by brain activity," *Science*, Vol. 281, pp. 1188 –1191, 1998.

42. Andersen R.A., C.A. Buneo, "Sensorimotor integration in posterior parietal cortex," *Adv. Neurol.*, Vol. 93, pp. 159 –177, 2003.

43. Corbetta M., G.L. Shulman, "Control of goal-directed and stimulus-driven attention in the brain," *Nat. Rev. Neurosci.*, Vol. 3, pp. 215–229, 2002.

44. Dreher J.C., J. Grafman, "Dissociating the roles of the rostral anterior cingulate and the lateral prefrontal cortices in performing two tasks simultaneously or successively," *Cereb. Cortex,* Vol. 13, pp. 329–339, 2003.

45. Kimberg D.Y., G.K Aguirre., M. D'Esposito, "Modulation of task-related neural activity in task-switching: an fMRI study," *Brain Res. Cogn. Brain. Res.*, Vol. 10, pp. 189 –196, 2000.

46. Miller E.K., J.D. Cohen, "An integrative theory of prefrontal cortex function," *Annu. Rev. Neurosci.*, Vol. 24, pp. 167–202, 2001.

47. Rushworth M.F., T. Paus, P.K. Sipila, "Attention systems and the organization of the human parietal cortex," *J. Neurosci.*, Vol. 21, pp. 5262–5271, 2001.

48. Akın A., D. Bilensoy, U.E. Emir, M. Gülsoy, Candansayar S., and Bolay H., "Cerebrovascular dynamics in patients with migraine: Nearinfrared spectroscopy study," *Neuroscience Letters*, Vol. 400, pp. 86-91, 2006.

49. Akgül C.B., A. Akin, and B. Sankur, "Extraction of cognitive activityrelated waveforms from functional near-infrared spectroscopy signals," *Med.&Biol.Eng.&Comput*., Vol. 44, pp. 945-958, 2006.

50. Akgül C.B., B. Sankur, and A. Akin, "Spectral analysis of event-related hemodynamic responses in functional near infrared spectroscopy," *J. Comput. Neurosci.*, Vol. 18, pp. 67-83, 2005.

51. Boas D.A., K. Chen, D. Grebert, and M.A. Franceschini, "Improving the diffuse optical imaging spatial resolution of the cerebral hemodynamic response to brain activation in humans," *Opt. Lett.*, Vol. 29, pp. 1506-1508, 2004.

52. Fabbri F., A. Sassaroli, M.E. Henry, and S. Fantini, "Optical measurements of absorption changes in two-layered diffusive media," *Phys. Med. Biol*., Vol. 49, pp. 1183-1201, 2004.