EVALUATION OF THE EFFECT OF AGING ON BRAIN ASYMMETRY WITH FUNCTIONAL NEAR INFRARED SPECTROSCOPY

by

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ABSTRACT

EVALUATION OF THE EFFECT OF AGING ON BRAIN ASYMMETRY WITH FUNCTIONAL NEAR INFRARED SPECTROSCOPY

Cognitive aging is a natural and lifelong process which may lead to the neurological diseases as dementia and Alzheimer's. Investigation of the aging process on the cerebral hemodynamics of subjects would lead to the prevention of neurological diseases which are the last stages of cognitive aging process. The aim of this study was to investigate the prefrontal cortex (PFC) oxygenation increase as working memory load was increased, to determine the effect of cognitive aging on PFC hemoglobin oxygenation and to analyze the lateralization index of young and middle aged adults. The study included measurement of hemodynamic changes with Functional Near-Infrared Spectroscopy (fNIRS) during a mental arithmetic task. The study demonstrated that during the mental arithmetic study, prefrontal cortex (PFC) hemoglobin oxygenation increased with the increasing working memory load for both groups; there was no significant hemoglobin oxygenation difference between both groups; young subjects used right PFC regions, while the middle aged subjects used left PFC regions during the mental arithmetic task and lastly the lateralization index of two groups increased with the increasing memory load.

Keywords: Functional Near-Infrared Spectroscopy (fNIRS), local oxygen consumption, working memory, prefrontal cortex (PFC), mental arithmetic task (MA), lateralization index (LI).

ÖZET

YAŞLANMADA BEYİN ASİMETRİSİNİN İŞLEVSEL YAKIN KIZIL ALTI SPEKTROSKOPİ İLE ÖLÇÜMÜ

Bilişsel yaşlanma, ileri evrelerinde demans ve Alzheimer gibi nörolojik hastalıkları da beraberinde getiren doğal ve yaşam boyu süren bir süreçtir. Bu sürecin beyin hemodinamiği üzerinde olan etkisinin incelenmesi ve farklılıkların tespiti, yaşlanmanın ileri aşamalarında da ortaya çıkabilecek hastalıkların önlenmesinde önemli rol oynayacaktır. Bu çalışmanın amacı, hafıza yükü arttıkça hemoglobin oksijenlenmesinin değişiminin incelenmesi, yaşlanmanın beynin prefrontal korteks (PFK) kısmında hemoglobin oksijenlenmesi üzerine olan etkisinin belirlenmesi ve lateralizasyon indeksinin (LI) ilerleyen yaşla olan değişikliğinin tespitidir. Çalışma sırasında noninvazif bir beyin görüntüleme tekniği olan işlevsel yakın kızıl altı spektroskopi (iYKAS) ve zihinsel aritmetik testi (MA) kullanılmıştır. Çalışma sonunda, zihinsel aritmetik testi esnasında bilişsel hafıza yükü arttıkça hemoglobin oksijenlenmesinin arttığı, iki grup arasında hemoglobin oksijenlenmesi arasında fark olmadığı, bilişsel hafıza testi sırasında gençlerde beynin prefrontal korteksinin sağ lobunun, orta yaşlılarda ise sol lobunun daha aktif olduğu ve her iki grubun da lateralizasyonunun hafıza yükü artıkça arttığı tespit edilmiştir.

Anahtar Sözcükler: Kognitif yaşlanma, nörolojik hastalık, yakın kızılötesi spektroskopi yöntemi, bilişsel hafıza, bölgesel oksijen tüketimi, prefrontal korteks, zihinsel aritmetik testi (MA), lateralizasyon indeksi (LI).

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p	Significant Number

LIST OF ABBREVIATIONS

NIR	Near-infrared
NIRS	Near-infrared spectroscopy
fNIRS	Functional near-infrared spectroscopy
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
HbO_2	Oxyhemoglobin
Hb	Deoxy-hemoglobin
[HbO_2]	Concentration of Oxyhemoglobin
[Hb]	Concentration of Deoxy-hemoglobin
LED	Light emitting diodes
rCBF	Regional cerebral blood volume
PFC	Prefrontal cortex
LI	Lateralization index
MA	Mental Arithmetic

1. INTRODUCTION

1.1 Motivation and Objective

Working memory (WM) is a brain system to store and manipulate information for a short period of time in order to carry out complex cognitive tasks such as learning, reasoning and language comprehension. It requires storage and processing of the information simultaneously [1].

Cognitive aging is a natural and life persisting process which can lead to the neurological diseases such as dementia and Alzheimer's disease. Investigation of the aging process on the cerebral hemodynamics of subjects would lead to the prevention of neurological diseases which are the last stages of cognitive aging process.

A more systematic analysis of working memory could prove that the working memory concept provides a useful tool in understanding a range of neuropsychological deficits related to aging , such as Alzheimer's, Parkinson's disease and dementia which in turn would open the gate of understanding the exact normal cognitive aging process.

In this study, the hemodynamic response during a mental arithmetic task (MA) was evaluated among both young and middle aged adults and the responses among these two groups were compared. Our specific hypothesis was that the hemodynamic response would increase as working memory load increased in all subjects and this response would be lower in middle aged subjects. Also, there would be a functional change of prefrontal cortex (PFC) region of human brain because of the aging effect on brain physiology.

The goal of this study was to investigate the effect of aging on prefrontal cortex oxygenation during the activation of brain and to improve understanding of the neurovascular coupling physiology during cognitive tasks with respect to aging by using

functional near infrared spectroscopy.

1.2 Problem Statement

Aging is a process of natural life and it brings about many cognitive diseases such as dementia, Alzheimer's and Parkinson's disease. Although there are neuroimaging studies focusing on aging mostly carried out by fMRI and PET, these methods have some disadvantages as being invasive, being cumbersome and immobile. Also, these techniques provide high spatial resolution but low temporal resolution.

An easy-to-use, noninvasive, mobile and rapid system is required to monitor and compare the cerebrovascular dynamics during cognitive tasks for early detection and treatment of the cognitive problems of aging. Similar to the scientists who are putting an effort to detect cancer prone cells before the onset of the disease, an easy to apply neuroimaging technique could be used to detect the cognitive problems related to aging before the symptoms.

Functional near infrared spectroscopy is a key solution to all these handicaps. It is a noninvasive, mobile and easy-to-use method. Also, it has high temporal resolution and it can be used on aged people during their everyday life. Improved tasks used with functional near infrared spectroscopy could give the start points (age, area) of the human brain morphology change with senescence and lead scientists to treat the aging related cognitive diseases before the symptoms.

1.3 Contribution of the Thesis

Although there are many aging related cognitive studies, to our knowledge, no fNIRS study could come across to compare the spatio-temporal oxygenation profiles of young and middle aged subjects with mental arithmetic task. Mental arithmetic

task is an advantageous task compared to the others because observation of all 3 components of working memory, namely central executive, visuospatial sketchpad (VSSP) and phonological loop is possible with its usage in psychological studies. Also, this task is easy to apply and the participants do not have difficuly in adapting this task because it is used in daily life. To our knowledge, this study will be the first in literature to apply MA task between two different aging groups with functional near infrared spectroscopy. This easy to apply technique could be used on aged people to detect the cognitive differences from the young people, even the breakpoint ages of the changes in the human brain in order to investigate the possibility of precautions for the cognitive diseases.

2. BACKGROUND

2.1 Working Memory

Working memory provides humans to store information that has limited amount for a short period of time and to use that information. The limited amount of information could be 1-10 items and the short period can be between 1-60 seconds. The use of information would be both maintenance and manipulation as in the case of mental mapping of an address while the directions are given or it would be just maintenance as in the case of remembering the phone number while trying to dial it. The former case takes the interest of the psychologists because this case is claimed to be the gate to more complicated mental processes like decision making, language understanding, learning and problem solving [1].

Working memory requires storage and processing of information simultaneously and a more analytic approach could prove that the working memory concept provides a useful tool in understanding a range of neuropsychological deficits, which in turn would lead to understanding normal cognitive functioning. Neural basis of working memory is determined via either lesion experiments in animals or imaging experiments in humans. Before the 1960s, the term working memory was referred as short-term memory. Today, most scientists replaced the concept of working memory to the concept of short-term memory, having a stronger emphasis on the manipulation of information instead of passive maintenance [2].

2.2 Models of Working Memory

Any working memory model must specify;

1. How information enters to the working memory system

2. How such information is kept active

3. How such information is used [3].

There are several models about working memory in literature [4] and these models can be classified according to different dimensions. However, one of the most crucial classifications is whether the working memory is a unitary system involved in attentional control [5, 6] or whether it is a multicomponent system composed of several subsystems [7, 8].

Among the unitary system models, Cowan and his colleagues [4 and 5] proposed that working memory is a part of long term memory and is organized in two embedded levels namely, activated long term memory representations and focus of attention. The difference between them is that there is no limit to activation of long term representations of working memory whereas the focus of attention is capacity limited and can hold up to 4 activated representations (chunks, units). Oberauer et al. [9] included one element focus to this model and proposed his ideas by the example that although a person can hold four digits (chunks, units) at the same time in mind, he can add the number three to each digit one by one. He claimed that attentional component selects one digit, processes it and then shifts to the other digit. In addition to the Cowan model, Ericsson and Walter Kintsch [10] proposed long term working memory concept as the set of processes which includes holding of a few concepts in working memory and using them as cues to retrieve everything connected to them by the retrieval structures [3].

The multicomponent model of working memory includes three independent systems: the phonological loop, the visuospatial sketchpad (VSSP) and the central executive. The phonological loop delineates and stores speech based information and it is crucial for the acquisition of both native and second language vocabulary. The visuospatial sketch pad plays a role for providing visual and spatial information and central executive is assumed to be an attentional controlling system [7].

According to the Baddeley's multicomponent model, working memory consists of separate storage buffers for verbal and visuospatial information. The results of psychological and neuroimaging experiments claim that there are two different WM systems for the verbal and spatial information and each WM system uses 3 components as;

1. Storage component: Stores information for a short period of time and decays it quickly,
2. Rehearsal component: Recalls the decaying contents,
3. Executive component: Processes the information [1].

The frontal cortex which includes the third of total human brain is the important structure that provides human beings to engage in working memory processes [11]. There is evidence that although the short term storage and executive processes which operate on the contents of short term storage are related to each other, there are also some neurological patients having intact executive processes but defective short term storage or vice versa [12]. The involvement of the PFC in the working memory has been investigated in numerous neuroimaging studies. These studies are mainly from both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies using a wide range of working memory tasks [13-19].

Among these studies, the ones with a parametric working memory task, such as n back task and mental arithmetic task, are ideally suited to examine the dynamic changes of the working memory task while the memory load is increased substantially during the same experiment [1, 12, and 13]. As a result of the studies about the relationship of working memory load and prefrontal cortex activation, it is claimed that PFC contributes to both active maintenance and executive control process components of working memory and the activation of PFC increases with the increasing working memory load [20].

2.3 Mental Arithmetic (MA) Task

Among working memory studies, mental arithmetic has been widely used in the past 25 years [20]. There are several reasons for its frequent usage. Firstly, people use mental arithmetic in their daily lives. Secondly, mental arithmetic is used with common facts, thus decreasing individual differences which could be seen with other cognitive tasks and lastly, this easy to apply task uses the same mental structures as other cognitive tasks [3].

How the single digit arithmetic is processed has been of interest to many researchers. However, little research on the role of working memory in mental arithmetic has been done before. The stages of mental arithmetic can be classified as encoding (visually or phonologically), calculation (visualizing on a mental blackboard, rehearsal as phonological items) and response. Multicomponent model of working memory suits well to explain these 3 stages. According to this model, mental arithmetic seems to involve all three components of the working memory system but the involvement of each component would depend on the type of the task [3].

Some of these mental arithmetic studies are about correlations between working memory and arithmetic in humans [21-25]. These studies demonstrate the general idea that 3 components of working memory are involved in mental arithmetic tasks.

In the fNIRS study done by Tanida et al. [22], the mental arithmetic task was used to investigate the relation between asymmetry of prefrontal cortex activities and autonomous nervous system. The results of this study indicated that mental arithmetic task had an important role in the cerebral regulation of heart rate by decreasing the parasympathetic effects or increasing the sympathetic effects. Also, right hemisphere is more activated than left hemisphere in greater HR increases. They concluded that right prefrontal cortex activity predominantly adjusts sympathetic effects during the mental arithmetic task.

Sato and his colleagues performed a mental arithmetic task [25] to compare men-

tal task performance and subjective workload among young and middle aged woman who were not regular computer users. They found lower correct rate and response time performance of middle aged women than those of young women and they concluded that mental task performance in middle-aged women was worse than those of young women.

2.4 Neural Changes in the Aging Brain and Cognitive Aging

It is known that neural mechanisms are more vulnerable to the aging process as a result of the alterations in plasticity of neurons and cells. It is also suggested that profound loss of neurons does not mainly lead to the cognitive impairments in aging which is a result of alterations in plasticity [26]. The main reason of plasticity change is suggested to be the alterations of neural morphology, cell to cell interactions and gene expression. Concerning brain morphology, alterations are very area specific, and small region specific changes in dendrite branching and spine density are more characteristic of cognitive aging [27, 28]. Further studies show that the most associated behavioral impairments result from region specific changes in dendrite morphology, $Ca^{(}+2)$ deregulation, gene expression or the factors which ultimately alter the neural network dynamics that support cognition [26].

Variation and change in the former studies provide evidence that some regional volume reductions occur in several brain areas including prefrontal cortex. These regional brain reductions can be: cell body shrinkage, regional white-grey matter loss or decline of small diameter fibers [26]. Also, the morphology of PFC seems to be more effected by the aging process than the morphology of most of the other brain regions [29]. Figure 2.1 shows the longitudinal changes in adjusted volumes of PFC.

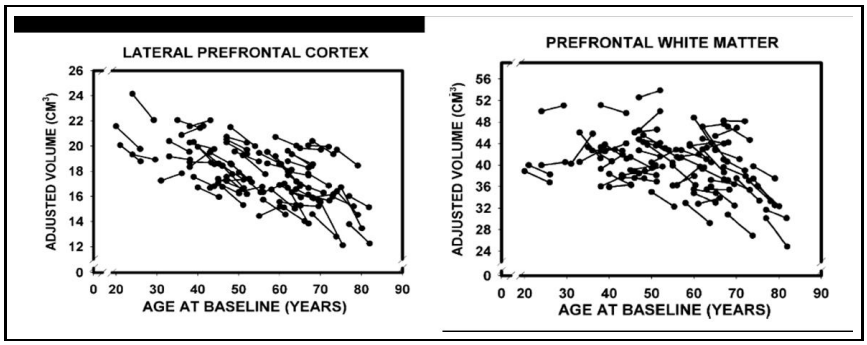

Figure 2.1 Longitudinal changes in adjusted volumes at the prefrontal cortex as a function of age [62]

2.5 Neuroimaging Studies of Cognitive Aging

Neuroanatomical, neuropsychological, neuroimaging and behavioral research support the fact that the two brain hemispheres are asymmetric although molecular and a genetic base of this asymmetry is not clear [30]. The change of this asymmetry with the age has been analyzed by Cabeza et al. and according to the studies of hemispheric asymmetry and aging [31-34]; two main theories are common as:

1. Right hemi-aging model

This model states that right hemisphere is effected to a greater degree than left hemisphere and the validity of this model has been investigated with various functional domains such as verbal or spatial functions [30].

Goldstein and his colleagues studied this model with 1,247 subjects [35], divided into six age groups (20's-70s) with a modified Halstead-Reitan Battery that consisted of 6 different cognitive tasks. When the test scores were analyzed, they found a significant increase in the right hemisphere points with age, with a significant, but less pronounced, effect for the left hemisphere points. The results indicate that right hemisphere ages in a deeper manner than does left hemisphere.

Diana M. Orbelo and her colleagues [36] studied emotional and attitudinal infor-

mation during speech which is known to be a dominant function of the right hemisphere function. In their study, the researchers used sixty-nine healthy subjects, ages 22 to 83 years, and the subjects who had right or left-brain damage. According to the results, production of melody of speech, measured by variation in fundamental frequency, was unimpaired in older subjects, whereas comprehension of melody of speech was impaired. The pattern of performance across affective comprehension tasks in older subjects resembled the pattern found after right-brain damage. The results demonstrated age-related loss in the comprehension of melody of speech that is most likely due to a processing deficit involving right hemisphere. This study indirectly demonstrated that the age related cognitive decline is more apparent in the right hemisphere than in the left hemisphere.

2. Hemispheric asymmetry reduction in older adults model (HAROLD) model

This model is generally theorized with functional neuroimaging studies and more popular than the right hemi aging model. The HAROLD model states that prefrontal cortex (PFC) activity tends to be less lateralized in older adults than in younger adults. This model is supported by functional neuroimaging evidence with various functional domains such as episodic memory encoding and retrieval, semantic memory retrieval, working memory, perception, and inhibitory control. According to the Harold model, age related asymmetry reductions could be found when PFC activity is right lateralized in young adults as in the case of episodic retrieval as well as when PFC activity is left lateralized in young adults as in the case of episodic encoding and semantic retrieval.The results of studies indicate that this theory can be applied not only to the process related hemisphere asymmetries such as episodic encoding, semantic retrieval, but also to the stimuli related hemispheric asymmetries as verbal and spatial working memory [32]. Some of the studies supporting HAROLD model including working memory are in table 2.1.

Figure 2.2 is a neuroimaging configuration of HAROLD model studied by Cabeza et al. [39]. (In this table, DR is delayed response task; the plus signs show activity,

Table 2.1
Neuroimaging working memory studies supporting HAROLD Model [32]

Cognitive domain imaging technique:materials/task (reference)	Younger		Older	
	left	right	left	right
working memory				
PET:letter DR[50]	+	-	+	+
PET:location DR[50]	-	+	+	+
PET:number N-back[51]	+	+++	++	++

whereas the minus signs indicate no activity. The increase in the number of plus signs gives a comparative increase in that study. It does not give comparisons between studies.)

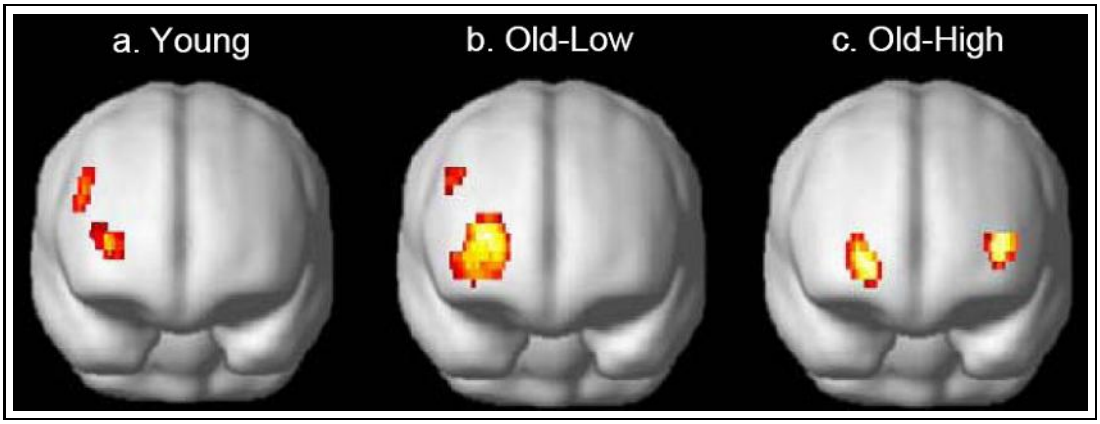

Figure 2.2 Neuroimaging configuration of HAROLD model [39]

Reuter-Lorenz et al. [37] found that younger adults had PFC activity during a delayed response task significantly in the left hemisphere for verbal stimuli but in the right hemisphere for spatial stimuli. In contrast, PFC activity was seen bilaterally for both types of stimuli in older adults.

In addition, Dixit et al. [38] supported supported the HAROLD model evidence by using an N-back task on 40 volunteers at an age range of 18-48 and found greater neural activity of right PFC than of left PFC for younger adults, whereas middle-aged subjects exhibited bilateral activity. This study suggests that the HAROLD model may be observed before the age of 50.

2.6 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is a novel technology to monitor the changes in biological tissues using non-ionizing electromagnetic radiation with wavelengths between 600-900 nm. The availability to noninvasive monitor cortical tissue was first studied about 30 years ago by F. F. Jobsis in the study of 'Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameter' [40]. He was the first to use infrared light to penetrate the skull. Some of the primary studies of monitoring brain activity were performed by Chance et al. [41] and Hoshi et al. [42]. The research into NIR based brain activity monitoring have become popular in the past 20 years with various number of applications such as neonatal care, education and training, and cognitive studies [43].

In the beginning of 1990s, Villringer et al. [44] introduced fNIRS as a new tool for monitoring cognitive activity. They found a pattern of increases in oxy-Hb and decreases in deoxy-Hb associated with cognitive activity with visual stimulation and picture observation tasks applied on healthy adult subjects. They also proved that these alterations were not due to changes in skin blood flow, but rather due to hemodynamic changes in the brain. They claimed that this new method could be developed into a noninvasive method for collecting data regarding cerebral hemodynamics related to brain activity. These initial studies served to prove the potential usages offered by fNIRS [45].

The research into NIR based brain activity studies has its motivation from the fact that this method is an advantageous alternative to other neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Firstly, NIR method provides information which is not available with other techniques such as oxygenation information which is an indicator of brain activation [45]. Secondly, temporal resolution is higher in NIR equipment in comparison to fMRI and PET [46]. Higher temporal resolution is one of the factors in modeling fast oscillatory noise related to normal physiological functions [47]. Thirdly, NIR is generally safer than PET because it does not rely on ionizing radiation and the energy

accumulated by the brain is not harmful to the tissue. Fourthly, some equipment of fNIRS type is portable and easier to use. Lastly, fNIRS is a noninvasive technique and can be used safely with individuals who have plates, pins and other metallic implants that might cause problems with other magnetic imaging techniques such as fMRI [45].

2.7 The Physical Theory of NIRS

Functional optical imaging is monitoring the physical changes related with brain activity by optical methods and optical imaging lies behind three properties as [48]:

1. Optical parameters related to the the interactions of light with brain tissue:

When a light passes through a solution of a chromophore (colored compound), it is absorbed by the compound or scattered at an unchanged frequency. This two phenomenon leads to the attenuation of light through the tissue. To measure the interactions of light with brain tissue, a typical optical apparatus consists of a light source by which the tissue is irradiated, and a light detector that receives light after it has been reflected from or transmitted through the tissue. The attenuation of light can be described with modified Beer Lambert law as in figure 2.3. (In this figure, the Modified Lambert-Beer Law: A= excxdxB+G, (A=log Io/I, e=specific extinction coefficient, c=substance concentration, d=with of the cuvette, B=differential path length factor, G=signal loss due to light scattering).

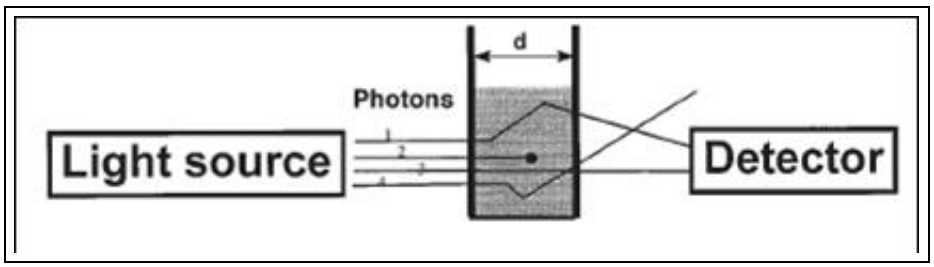

Figure 2.3 Light absorption and scattering on optical measurement: Modified Beer-Lambert Law [48]

2. The physiological parameters, physiological events associated with brain

activity:

These events can be subdivided into two as the cellular physiological events and intravascular events. Anion and water fluxes making a change in membrane potential across neuron membrane; increase of the oxidized redox state of intracellular NADH, flavoproteins and cytochrome-c oxidase (CO), increase of the glucose consumption and oxygen consumption can be given as cellular physiological events. In addition to the cellular physiological events, local brain activity induces a local arteriolar vasodilation and consequently an increase in local cerebral blood volume (rCBV) and blood flow (rCBF), known as neurovascular coupling. At the capillaries, the increase in rCBF is because of higher blood flow per capillary, achieved with higher blood flow velocity rather than with opening and closing of previously unused capillaries. The increase in rCBF and oxygen delivery exceeds the increase in local oxygen consumption. Therefore, cerebral blood oxygenation which is also known as HBO_2 level increases locally [48].

3. The relations between physiological and optical parameters:

Optical measurements can be in two ways as with or without exogenous contrast agents. Brain activity is accompanied by certain physiological properties such as increase in concentration. These events increase the amount of some physiological properties such as concentration of molecules. The change in physiological events is measured by its influence on the optical parameters such as light absorption and light scattering [48].

Considering specially fNIRS as a neuroimaging tool, near-infrared light, especially between 700 and 900 nm can easily pass through biological tissue because light in this region is less scattered and is absorbed by only a few biological chromophores such as hemoglobin, myoglobin and cytochrome oxidase. Therefore, this wavelength range is considered to be ideal for the noninvasive measurement of biological tissues. Spectra of hemoglobin vary with its oxygenation state. The transmitted light through the tissue one can obtain information about the oxygenation-deoxygenation state of hemoglobin [48].

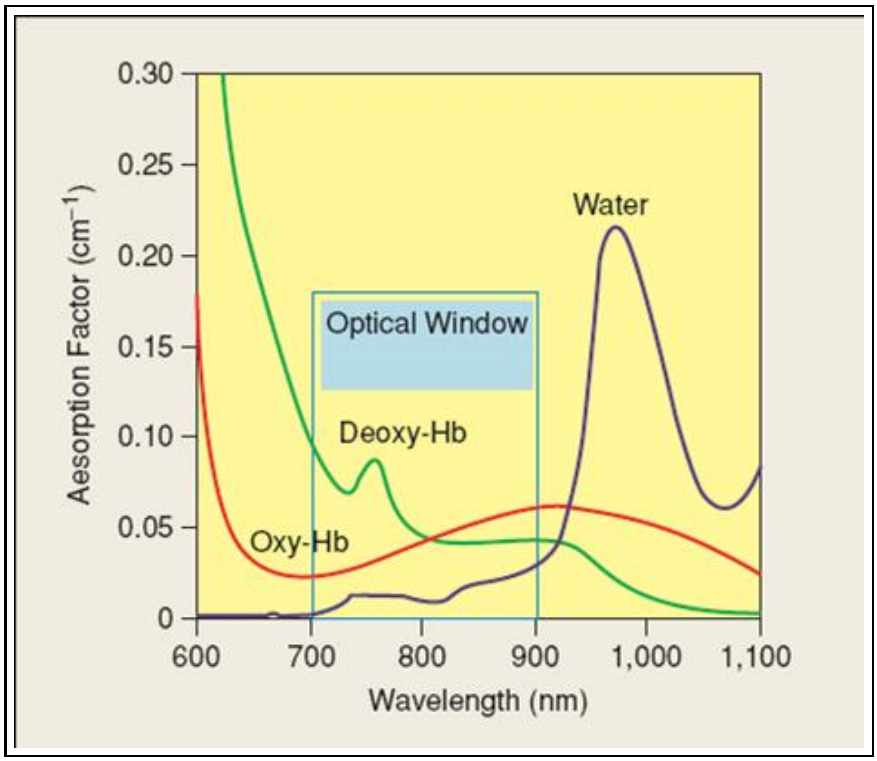

Figure 2.4 Absorption spectrum in near hemoglobin infrared window [59]

Based on the optical parameters of the biological tissue as absorption and scattering, three types of activity-related signals have been recorded non-invasively [48]:

1. Changes in hemoglobin oxygenation,
2. Changes in CO oxidation,
3. Fast optical signals presumably related to changes in light scattering.

Among these 3 measurements, the hemoglobin oxygenation change is the most prominent phenomenon. Brain activity is associated with an early decrease in hemoglobin oxygenation followed by accompanying slower increase in hemoglobin oxygenation. Near infrared studies would cover the increase in hemoglobin oxygenation that occurs within several seconds after the onset of increased brain activity. These signals are based on the fact that the blood flow response to functional activation exceeds the increase in oxygen consumption. Therefore, when the NIRS measuring site is located

over an area in which cerebral blood flow increases during brain activity, for example, the prefrontal cortex during a working memory task, a localized increase in [oxy-Hb] and a decrease in [deoxy-Hb] could be measured [48].

In a typical fNIRS tool, the light source is coupled to the participant's skull with fibre-optical bundles (optode). As the light enters to the tissue, a second optode can collect light after it has passed through the tissue beneath the optodes. The light-receiving optode is connected to a light detecting system such as a photomultiplier or a CCD camera [48].

2.8 The Use of fNIRS in Cognitive Studies

Various studies demonstrate that fNIRS is a sensitive instrument for the measurement of cerebral hemoglobin changes related to working memory [22, 23, 42, 44, 46, 49 and 50], verbal fluency [51, 52] and various cognitive functions [53, 54].

2.9 Niroxcope 301

NIROXCOPE was developed at the Biophotonics Laboratory of the Institute of Biomedical Engineering in Boğaziçi University. This device is composed of:

1. Transmitter/receiver circuits which control the LEDs, light sources with the software and LED currents,
2. A software to control the device and store the data on the computer for offline analysis,
3. A probe which consists of detectors and light sources on a flexible printed circuit board (PCB).

The current version of this device is called as Niroxcope 301. The probe of this device has 4 light sources (LEDS), 10 photodetectors as in Figure 2.5. In this figure, the spatial sensitivity profile of photons traveling in a four layer model of the adult human head is illustrated with the layers: (1) surface (scalp and skull); (2) cerebrospinal fluid; (3) grey matter and (4) white matter.

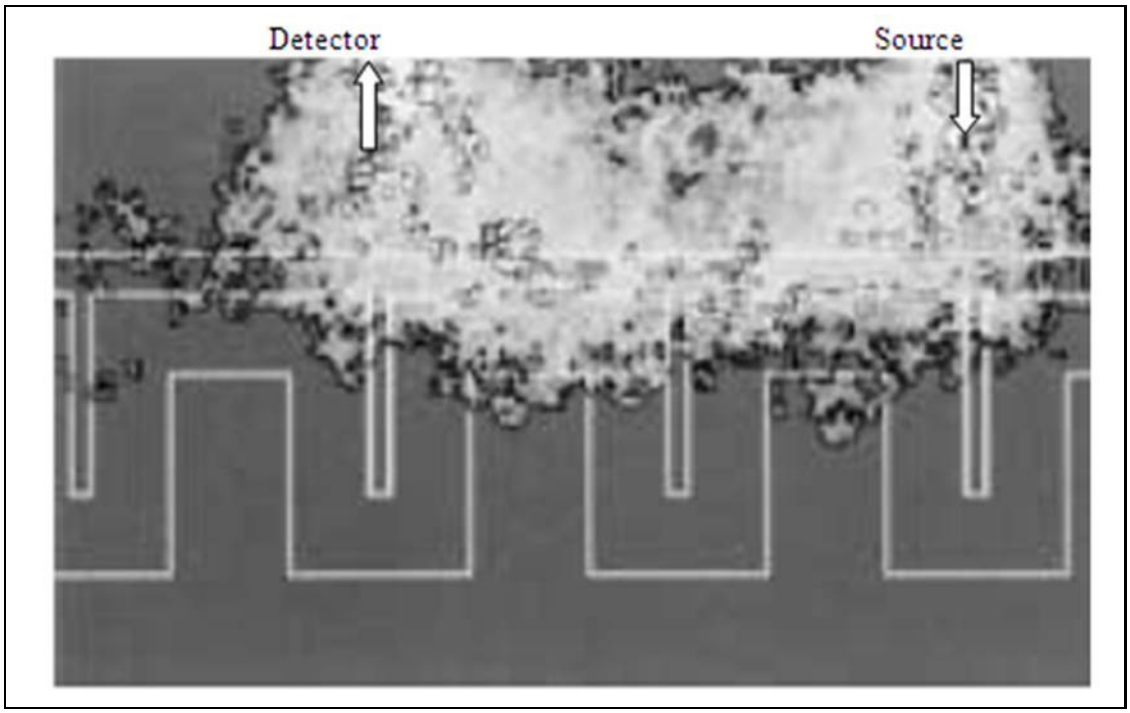

Figure 2.5 Near-infrared spectroscopy and imaging [48]

In NIROXCOPE 301, light sources (LEDs) are 2.5 cm distant from the detectors and 2 cm banana-shape penetration depth in the tissue can be maintained as in figure 2.6 (In this figure (4) is the probe, (3) is the photodetector.). Figures 2.7 and 2.8 also illustrate the measurement princible of NIROXCOPE 301. (In these figures (2) is the light source, (2) is the photodetector.)

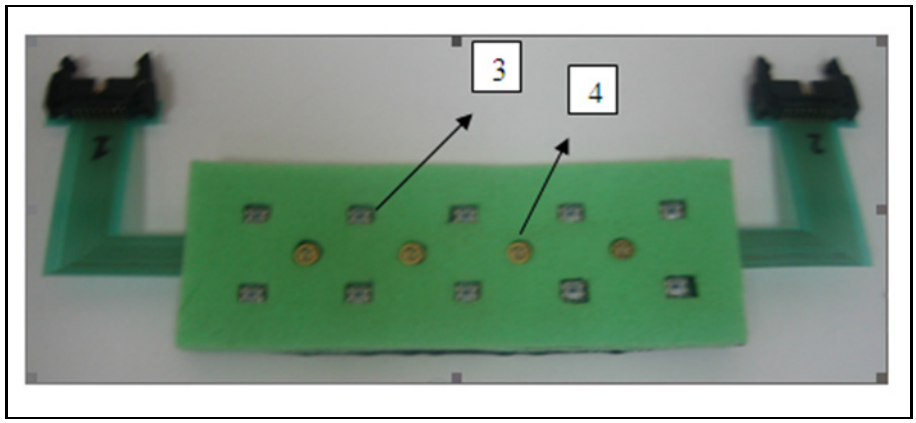

Figure 2.6 A 4-LED probe with 10 photo detectors

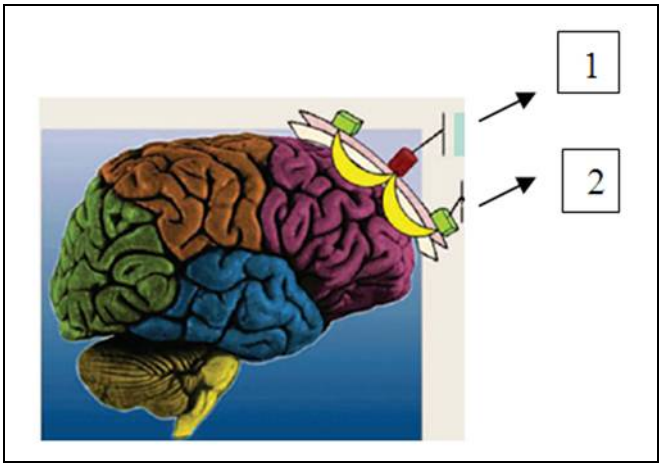

Figure 2.7 The photon path inside the human head [59]

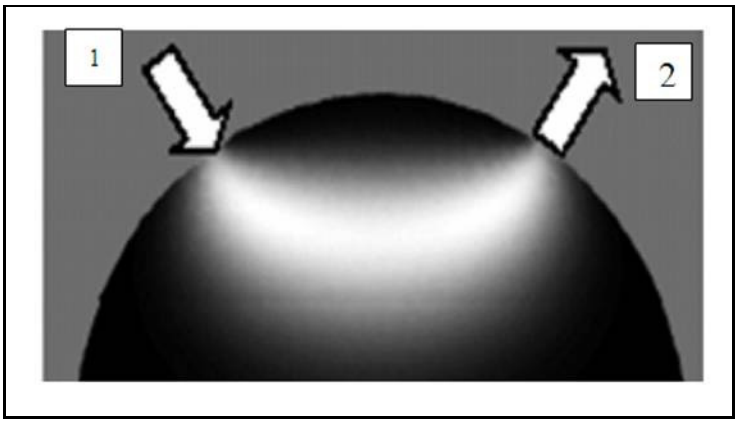

Figure 2.8 The banana-shaped travel of light in tissues [43]

3. METHOD

3.1 Subjects

13 right handed young subjects (9 woman, 4 men, aged (19-25) years; mean (23.00) years, std. dev. (1.58)) and 11 right handed middle aged subjects (9 men, 2 women, aged (53-62) years, mean (55.36 years, std. dev. (3.07)) participated in the present study. The young group included college students. The middle aged group was selected from a company's white collar actively working people. The study was approved by Boğaziçi University Ethics Committee. All subjects were informed about the study before the experiment. The participants didn't have any psychiatric or neurological diseases in their background.

3.2 Experimental Protocol

13 right handed young subjects (group Y) and 11 right handed middle aged subjects (group O) were evaluated with fNIRS during MA task performance.

The data of group Y were collected in Boğaziçi University Biophotonics Laboratory, whereas group O participants were evaluated in a company. During the experiment, the subjects were seated in a comfortable chair in a silent dark room in order to eliminate environmental noise and all other distracters.

Data were obtained during a mental arithmetic (MA) task in order to activate the prefrontal cortex, since MA task has been performed in recent neuroimaging studies to analyze the activation of prefrontal cortex by working memory load [31, 32, 33, 44 and 45]. MA task used in the study included only subtraction and included three steps as easy, moderate and hard complication step. In the first complication step, the participants were asked to subtract serially a 2-digit number from a 2-digit number

(e.g. 43-25), in the second complication step, they were asked to perform a 2-digit number subtraction from a 3-digit number (e.g. 457-69) and in the third complication step, they were asked to subtract a 2-digit number from a 4-digit number (e.g. 1406-18) as quickly as possible. The duration of the task protocol was; 1^{st} rest (baseline period): 60s, 1^{st} complication step: 60s, 2^{nd} rest: 60s, 2^{nd} complication step: 60s, 3^{rd} rest: 60s, 3^{rd}complication step: 60s, 4^{th} rest (recovery period): 60s. No time limit was implemented on the participants to do the mental subtractions in each complication step and the subjects were let to conceive the answer to each question as much as they needed. The 1^{st} complication step included 20 questions, whereas the 2^{nd} and the 3^{rd} steps 15 question each.

3.3 Data Collection

The experiments were performed with a continuous wave near infrared spectroscopy device (NIROXCOPE 301) which was built in Biophotonics Laboratory of Boğaziçi University. The NIROXCOPE 301 includes diodes that are emitting light in the near infrared spectrum as light sources and ten photo detectors which are sensitive in the NIR spectrum system. The lights sources emit light in three wavelengths including 850, 730 and 805 nm. Photo detectors are placed equidistantly away from the light source at the center. When time and wavelengths are multiplexed, four non-overlapping quadruples of photo detectors are obtained. Detector layout is shown in figure 3.1.

The sampling rate of the system was 1.77 Hz, and Beer Lambert Law was used to calculate the relative changes in [HbO_2] and [Hb] signals in the obtained data.

In the experiment system, brain probe was placed on the forehead of the subjects and the detector source distance was designed to be 2.5 cm which corresponds about 2 cm of average adult prefrontal cortex depth and makes it to observe the first millimeters of the grey matter.

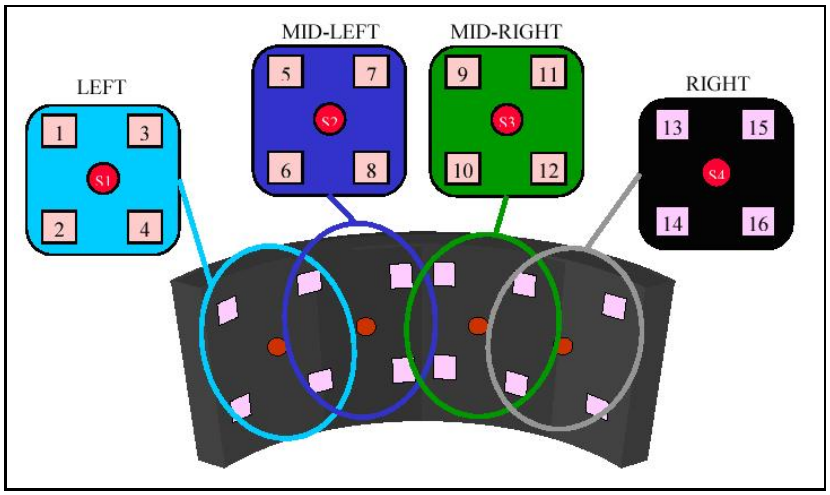

Figure 3.1 Source-detector configurations on the brain probe and nomenclature of photodetectors [58]

3.4 Performance Analysis

The performance was considered to be the wrong answer percentage in the study. Firstly, for group Y, at the first complication step, individual wrong answer percentage was obtained by taking the ratio of number of wrong answers to the total number of answered questions for each subject. Secondly, the individual performances were averaged to obtain a mean performance value. For the averaging step, the performance values from those of the subjects who had wrong answer percentage $>75\%$ were discarded. Thirdly, the same procedure was done for each complication step. Standard deviations were also calculated for each complication step. Fourthly, the individual performances of all 3 complication steps were one way ANOVA analyzed to see the performance differences between the steps. Fifthly, because the number of men and women were different among group Y, the performances for men and women were one way ANOVA tested to see if there is a gender difference among the subjects and it was confirmed that the data had no significant sex difference in the group Y ($p>0.05$).

The same five analysis steps were repeated for also the group O, and it was again confirmed that there were no significant sex difference in the group O ($p>0.05$).

As the last stage of performance analysis, the performances for each complication

Figure 3.2 MA task data taking with functional optical imager, NIROXCOPE 301

step of group O and group Y were one way ANOVA tested to compare these two different groups.

3.5 Response Time Analysis

As the subjects were not forced to answer a definite number of questions and they were let to conceive the answer of the questions as much as they require, the mean number of the questions answered were different in each complication step. Because the duration of each complication step was 60 seconds, this period was divided to the mean number of answered questions at that step to find out the response time for that level of difficulty. Firstly, the individual response times at each step were averaged to obtain a mean response time value. Secondly, the same procedure was done for each complication step. Thirdly, the individual response times of all 3 complication steps were one way ANOVA analyzed to see the response time differences between the steps.

The same three analysis steps were repeated for also group O and as the last

stage of response time analysis, the response times for each complication step of group O and group Y were one way ANOVA tested to compare these two different groups.

3.6 Statistical Analysis

The [HbH] and [HbO_2] data from 16 regions over the forehead of all subjects were obtained with fNIRS. The analysis of the data was done with a program in the MATLAB environment.

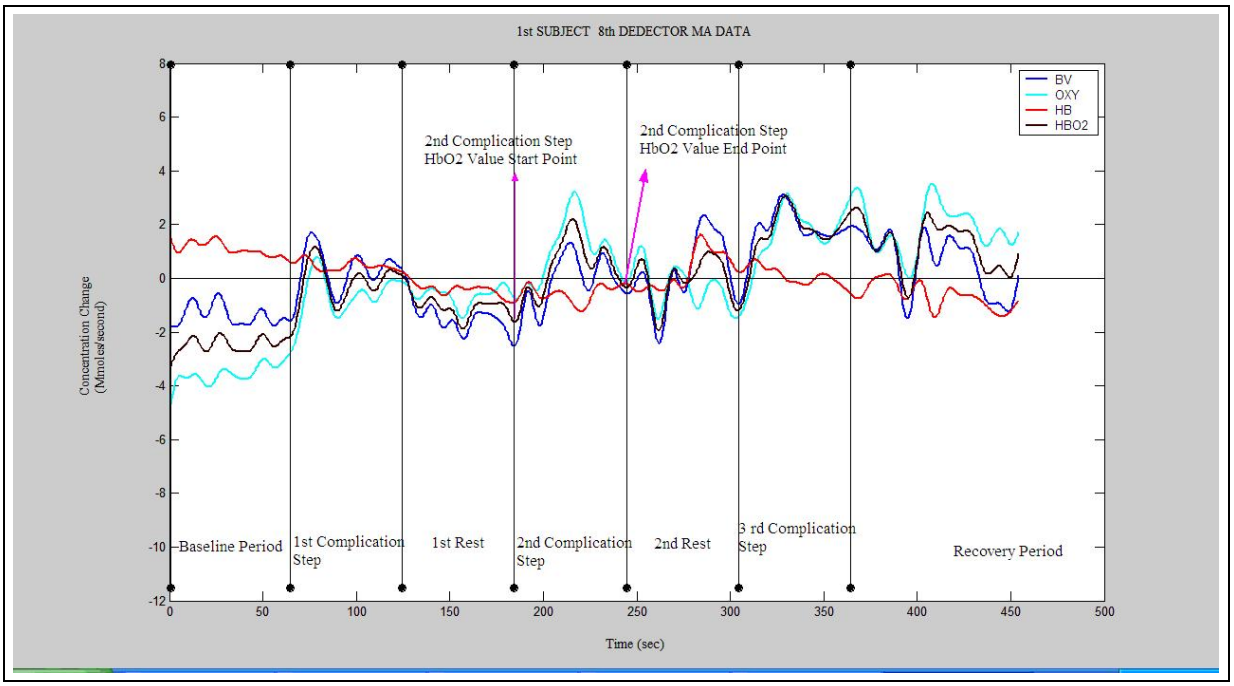

Figure 3.3 An example of fNIRS data from a single detector of a subject during MA task

The analysis of the [HbO_2] data from group Y was done in five steps. Firstly, because the number of women and men were unequal in the young group, the [HbO_2] data of each complication from men and women in this group were one way ANOVA tested and, it was confirmed that the data had no significant sex difference in the young group ($p>0.05$). Secondly, the [HbO_2] data of all complication steps provided from each young subject were one way ANOVA tested for each detector in order to find out the meaningful detectors which have one way ANOVA p values lesser than

0.05. Thirdly, for each young subject, 1^{st}-8^{th} detectors were grouped to represent left hemisphere of the PFC whereas 9^{th}-16^{th} detectors were grouped to represent right hemisphere of the PFC. Fourthly, mean value of the meaningful detectors from all group Y among 1^{st}-8^{th} detectors that have the $p < 0.05$ for each complication step were considered to determine the average [HbO_2] value for that complication step in the left hemisphere. Likewise, mean value of the meaningful detectors from all group Y among 9^{th}-16^{th} detectors that have the $p < 0.05$ for each complication step were considered to determine the average [HbO_2] value for that complication step in the right hemisphere. Fifthly, the individual mean values of left and right hemispheres were of each complication step were one way ANOVA tested to see the differences of Hb oxygenation between complication steps. Sixthly, the mean values of the meaningful detectors among 1^{st}-8^{th} (left hemisphere) detectors of each young subject for each complication step were subtracted from the mean values of the meaningful detectors among 9^{th}-16^{th} detectors (right hemisphere) of each young subject for each complication step to determine the individual lateralization indexes (LI_i=$Right_i$-$Left_i$/$Right_i$+$Left_i$) for each subject. Lastly, the individual lateralization indexes were averaged to calculate the young average lateralization index (LI_y). In the young average lateralization index (LI_y) determination step, the [HbO_2] values from those of the subjects who had wrong answer percentage >75 % were discarded.

Because the number of women and men were unequal in the group O, the data from men and women in this group were one way ANOVA tested and it was confirmed that the data had no significant sex difference in the group O ($p>0.05$).The similar steps were followed for the group O. First of all, the data that was provided from group O one way ANOVA tested ($p>0.05$) in each detector in order to find out the meaningful detectors. Then, the average HbO_2 values in the right and left hemispheres of each group O subject for each complication step were provided and one way ANOVA tested to see the Hb oxygenation differences among 3 steps. Next, the Individual Lateralization Indexes (LI_i=$Right_i$-$Left_i$/$Right_i$+$Left_i$) for each subject was calculated with the average HbO_2 values in the right and left hemispheres. In the last step, the lateralization indexes for each subject were used to calculate the middle aged average lateralization index (LI_o). Again in the lateralization index (LI_o) determination step,

the [HbO_2] values from those of the subjects who had wrong answer percentage >75 % were discarded.

To eliminate the spikes, outlier elimination and detrend filtering was performed in all of these frequency bands.

4. RESULTS AND DISCUSSION

Table 4.1 indicates the mean performances (wrong answer percentage) obtained from young subjects (group Y) and middle aged (group O) subjects. In this table, the performance for each complication step indicates the wrong answer percentage (number of wrong answers/number of total answers) of that step. It is seen in the table that the mean performances of the two groups increase as the complication of the task increases significantly (for group Y, p_{1-2} =0.01, p_{1-2-3}=0.00, p_{2-3}=0.01; for group O, p_{1-2} =0.04, p_{1-2-3}=0.00, p_{2-3}=0.04). In the following table ,STD is the standard deviation.

Table 4.1
Performance (wrong answer percentages) of group Y and group O

Performance	Group Y	Group 0
2digit-2digit	0.11 STD:0.10	0.18 STD:0.13
3digit-2digit	0.25 STD:0.12	0.34 STD:0.12
4digit-2digit	0.44 STD:0.18	0.49 STD:0.11

Figure 4.1 is the mean performance (wrong answer percentage) comparison obtained from group Y and group O. The increase of performance with working memory load and complication of the task can be seen easily. When the individual performances of the both groups were 1 way ANOVA tested for each complication task, no significant difference between these two groups was seen for all complication steps ($p>0.05$). In the following table ,STD is the standard deviation.

Table 4.2 represents the mean response time values obtained from group Y and group O subjects. When the individual response times of group O were one way ANOVA tested for each complication task, significant difference between complication

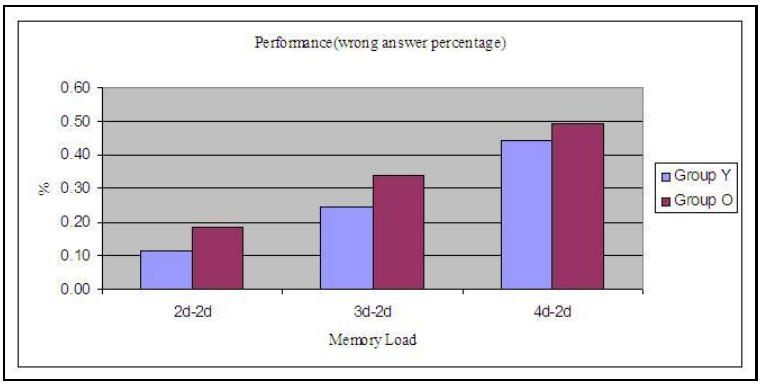

Figure 4.1 Performance (wrong answer percentages) comparisons of group Y and group O

task 1 and 2 was seen. No significant difference between complication tasks 2 and 3 was observed. (p_{1-2}=0.00, p_{1-2-3}=0.00, p_{2-3}=0.32). Similarly, when the individual response times of group Y were 1 way ANOVA tested for each complication task, significant difference between complication task 1 and 2 was seen. No significant difference between complication tasks 2 and 3 was observed (p_{1-2}=0.00, p_{1-2-3}=0.00, p_{2-3}=0.54). In the following table ,STD is the standard deviation.

Table 4.2
Response times of group Y and group O

Response time	Group Y	Group 0
2digit-2digit	5.07 STD:1.91	5.81 STD:2.46
3digit-2digit	12.69 SSTD:6.35	18.41 TD:8.08
4digit-2digit	14.20 STD:0.18	22.45 STD:7.89

Figure 4.2 demonstrates the comparison of mean response time values obtained from group Y and group O subjects. When the mean response time of group Y and group O were one way ANOVA tested for each complication task, no significant difference between these two groups was seen for the 1^{st} and 2^{nd} complications steps (p>0.05). However a significant difference was seen between 2^{nd} and 3^{rd} steps.

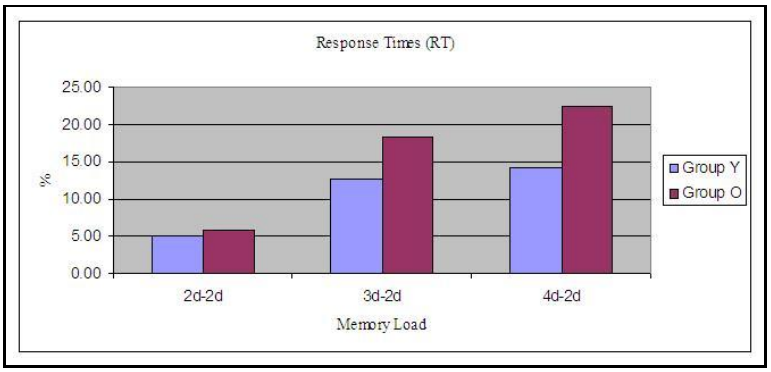

Figure 4.2 Response time comparisons of group Y and group O

Table 4.3 is the one way ANOVA comparisons of individual response times and performances of group Y and group O subjects at each step.

Table 4.3
Performance and response time one way ANOVA results of group Y and group O

Performance	Group Y	Group 0
2digit-2digit	0.16	0.41
3digit-2digit	0.15	0.06
4digit-2digit	0.48	0.01

Concerning the Hb oxygenation data, detectors d5, d6, d7, d8, d9, d10, d11, d12, d13, d14 and d16 were meaningful detectors ($p<0.05$) for group O, whereas detectors d2, d6, d10, d12, d6 were meaningful for group Y. Figure 4.3 is the figure of mean Hb oxygenation data obtained from the meaningful detectors of group O.

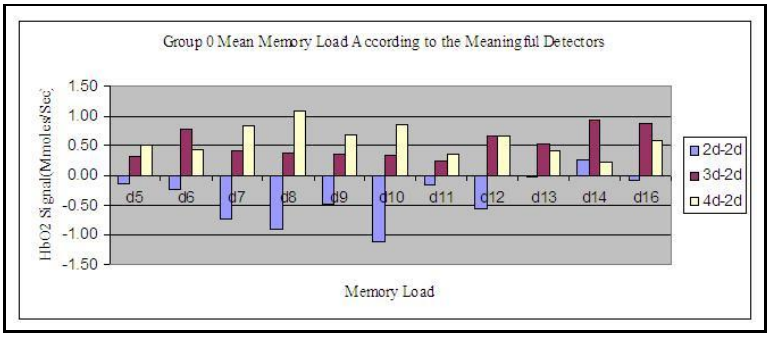

Figure 4.3 Meaningful detectors of group O according to HB oxygenation

Figure 4.4 is the figure of mean HB oxygenation data obtained from the meaningful detectors of group Y subjects. Table 4.4 is the mean Hb oxygenation data

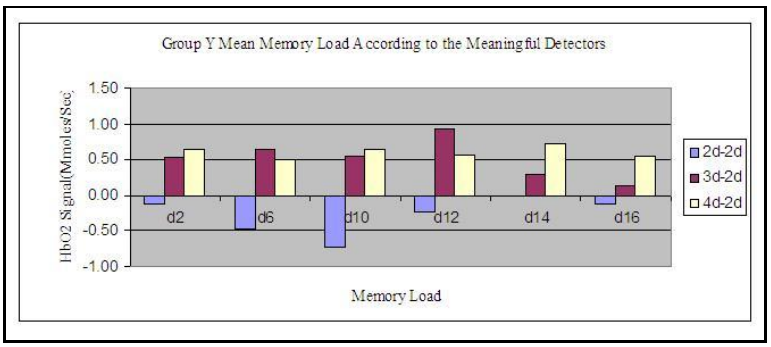

Figure 4.4 Meaningful detectors of group Y according to HB oxygenation

obtained from group Y. In this table, mean of the HB oxygenation data from the 1^{st}-8^{th} detectors represent HB oxygenation at the left hemisphere whereas mean of the HB oxygenation data from the 9^{st}-16^{th} detectors represent HB oxygenation at the right hemisphere of the PFC.

Table 4.4
Mean HB oxygenation at the two hemispheres of group Y according to the meaningful detectors

Group Y mean HB oxygenation signal(Mmoles/sec)	left hemisphere	right hemisphere
2digit-2digit	-0,30	-0,27
3digit-2digit	0,59	0,48
4digit-2digit	0,57	0,62

Table 4.5 is the mean HB oxygenation data obtained from group O subjects. In these tables, mean of the HBO2 data from the 1^{st}-8^{th} detector represent HB oxygenation at the left hemisphere whereas mean of the HB oxygenation data from the 9^{st}-16^{th} detectors represent HB oxygenation at the right hemisphere of the PFC.

The Hb oxygenation data of group Y from the meaningful detectors were one way ANOVA tested for the left hemisphere and right hemisphere separately, significant differences between complication step 1 and 2 were observed (left: p_{1-2}=0.00, p_{1-2-3}=0.00; right: p_{1-2}=0.01, p_{1-2-3}=0.01). No significant differences were seen between complication step 2 and 3 (p>0.05). Similarly, the Hb oxygenation data of group

Table 4.5
Performance and response time one way ANOVA results of group Y and group O

Group O mean HBO2 signal(Mmoles/sec)	left hemisphere	right hemisphere
2digit-2digit	-0,51	-0,31
3digit-2digit	0,49	0,56
4digit-2digit	0,72	0,55

O from the meaningful detectors were one way ANOVA tested for the left hemisphere and the right hemisphere separately, significant difference between complication steps 1 and 2 was observed (left: p_{1-2}=0.01, p_{1-2-3}=0.00; right: p_{1-2}=0.01, p_{1-2-3}=0.01). No significant difference was seen between complication steps 2 and 3 (p>0.05). Figure 4.5 indicates the comparisons of the left and right hemisphere mean HB oxygenation data obtained from group Y and group O.

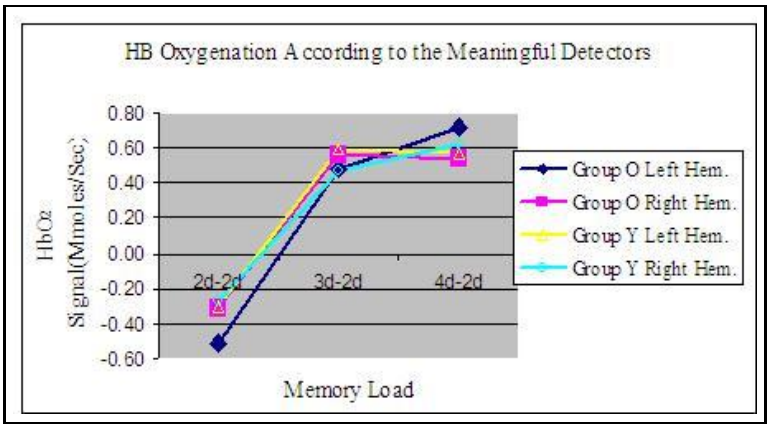

Figure 4.5 The comparison of mean HB oxygenation at the two hemispheres of both groups according to the meaningful detectors

Table 4.6 demonstrates the mean lateralization indexes of group Y and group O subjects. For the lateralization indexes, mean Hb oxygenation data from the meaningful detectors of the right hemisphere has been subtracted from the mean Hb oxygenation data from the meaningful detectors of the left hemisphere (LI_i=$Right_i$-$Left_i$/$Right_i$+$Left_i$). In this table, lateralization indexes are found to be right lateralized for the group Y whereas it is left lateralized for the group O subjects and the lateralization shifts more as the task gets harder.

Table 4.6
Lateralization indexes of both groups

LI	LIy	LIo
2digit-2digit	0.10	-0.18
3digit-2digit	0.15	-0.12
4digit-2digit	0.58	-0.52

Figure 4.6 is the comparisons of lateralization indexes of group Y and group O subjects. In this figure, lateralization indexes of group Y and group O subjects are found opposite to each other and also the lateralization indexes increase as the working load (performance) increases with an exception of small amount of descent at the 2^{nd} complication step of the group O.

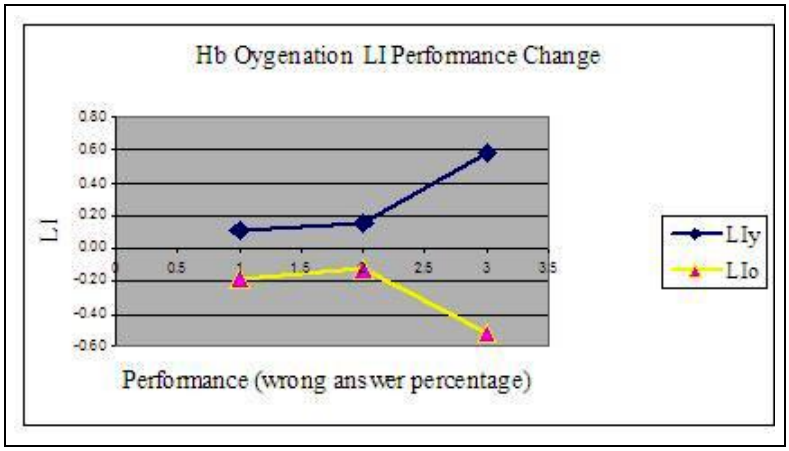

Figure 4.6 Lateralization indexes of both groups at the complication steps

This study was a pioneering work that uses a mental arithmetic task to compare two different aging groups with fNIRS. Comparison of young and middle aged subjects instead of young and old subjects was an additional innovation of this work. According to the review paper of Destefano et al. [3], among the three components of working memory, central executive is involved and attentional resources are needed for arithmetic problem solving. However, central executive is not needed for simple digit or more difficult problems when the subjects retrieve the answers from the memory. The phonological loop is only involved when participants used counting to solve the problems for the single digit problems; however it is also used for the derivation of interim

results. As the third working memory component, the role of visuospatial sketchpad (VSSP) in arithmetic studies needs further study. It could be a point of view that VSSP is only involved when the problems are visualized on a mental blackboard. They also suggest that it may be very difficult for the participant to use mental blackboard when the problem is very complex and no conclusion could be done with the existing literature. Although the mental arithmetic problems in the study, done by Destefano and his colleagues [3] were mainly covering addition problems of single digit or multidigit with the value of the carry from one column to the next is one, because in our study we also used the subtraction problems with similar properties, the parallel intuitive claims can be done. If the study contained only single digit operations, we could have concluded that the problems would be solved with only memory retrieval processes of working memory. However, our study contained 3 complication steps starting from the subtraction of 2 digit number from 2 digit number as the 1^{st} step, then subtraction of 2 digit number from 3 digit number as the 2^{nd} step, and subtraction of 2 digit number from 4 digit number as the last step. Concerning the 3 components of the working memory, the central executive resources might be involved not only for the retrieval process but also in increase as the number of the digits in operands would increase as it is said so in the study done by Noël et al. [55] because the usage of the executive resources would increase as the number of the digits in operands would increase. The design of our study aimed to increase the memory load with the increased complication steps which were similar as in some other working memory studies. It could be claimed that the executive functions were mostly used in the 3^{rd} complication step which included the retrieval of 4 digit numbers, then the 2^{nd} complication step, which included the retrieval of 3 digit numbers and lastly the 1^{st} complication step which included the retrieval of just 2 digit numbers. Similarly, as the complication step number increased, the usage of the phonological loop to maintain interim results and the usage of visuospatial sketchpad to visualize the information on mental blackboard would increase concurrently.

In this study, first of all, the mental arithmetic performances (wrong answer percentages) increased as the task got harder. This result indicated that as complication of the task increased, the working memory load increased along with constrain of

the brain and the subjects gave more wrong answers in both groups which were also seen in the previous study done by Mattay and colleagues [56]. Also, when the mean performances of two age groups were compared, no significant difference between these two groups was observed and this result was inconsistent with the studies in literature. However, previous studies including the one done by Mattay et al., usually covered either the higher aged subjects usually over 55 to a range of 75 and these subjects performed worse in the working memory tasks [55]. In contrast, group O of this study had an age average of 55.36 and they were all white collar actively working people, so, the similar performances between group Y and group O group were not surprising. These similar results between performances were important for the other steps of the study because they implicated that the subjects belonging to the two groups had performed their best and the HB oxygenation values obtained were comparable.

Second, the response times of the two groups increased as the task got harder until the hardest task. No significant differences were seen among the response times of step 2 and 3 for both groups. It was reasonable that as complication of the task increased, the working memory load increased along with constrain of the brain and the subjects had to spend more time more to answer the question correctly. This result was consistent with the study again done by Mattay et al. [56]. The unchanged response time values of the step 2 and step 3 with the concurrent decrease in the performances for both groups might be an indicator that the subjects got overwhelmed and started to answer the questions with less concentration. Also, the response times of the two groups were not significantly different from each other except the complication task 3 which was the most difficult complication task. In this task, group O had significantly higher response times, thus answered less questions than the group Y. This result was inconsistent with the results of the previous studies [56] in which the older group had higher response times than the younger in all steps .The similar response times until the last step was reasonable because we had not found a significant difference between the performances of both groups and this indicated that the subjects in both groups had spent the similar effort and time to answer the less harder the questions. However, the significant difference of the response time of group O at the most complicated task can be because of an indicator of the effort of the older subjects to compensate the

hardest questions.

Concerning hemoglobin oxygenation data obtained form the meaningful detectors of group Y and group O, the oxygenation of hemoglobin increases associated with the increase of the difficulty of the task. This result is again consistent with the previous fNIRS working memory study performed by Izzetoğlu and her colleagues with n back working memory test [57]. This test contained 0, 1, 2 and 3 back conditions, 0 back being the simplest stage, whereas the 3 back hardest one, an analogy to our mental arithmetic task with 3 complication steps. They found that the 0 back condition differed from 1 back and 2 back conditions and Hb oxygenation at 1 back condition was more than 0 back, the Hb oxygenation was more at 2 back than 1 back. In contrast, there was a slight decrease between 2 and 3 back conditions. In our study, we found obvious Hb oxygenation increase between 1^{st} and 2^{nd} complication steps so, a positive correlation between increasing workload and the oxygenation could be claimed in the prefrontal cortex, again in agreement with fMRI studies [12] although we could not find significant Hb oxygenation differences between 2^{nd} and 3^{rd} tasks. Also, in the study done by Izzetoğlu et al., a decrease of Hb oxygenation was observed at the most difficult 3 back condition which was much harder than our 3^{rd} complication step. The researchers claimed this result was because of concentration loss of the participants. Regarding our study, although no increase of Hb oxygenation was observed between 3^{rd} and 2^{nd} complication tasks, no significant drops have been seen between them too. It could be a point indicating the highly participation of the subjects in both groups. Another interesting point at the study of Izzetoğlu et al., was that when different types of working memory tasks were completed by the participants, different areas of PFC were activated (n back: 4^{th} detector, a video game: the whole PFC, a block anagram task: 5^{th} detector). In our study, we found significant activation at different detectors, weighing at the right hemisphere of the group Y, whereas at the left hemisphere of the group O. In their experiment they found a positive correlation between performance and Hb oxygenation. As the subjects started to make more mistakes, the Hb oxygenation decreased. This might seem inconsistent with our study. However it must again be mentioned the fact that their participants lost their concentration at some point which was consistent with the performance decrease and the decrease of the performance was

not because of the task difficulty but because of the concentration loss. The case in our study was different. Because there was not any Hb oxygenation level decrease with the wrong answer percentage increase, the increase of wrong answer percentage could be correlated to the memory load increase and difficulty of the task, not to the concentration loss of the participants. The indifferent Hb oxygenation and performance decrease of complication task with indifferent response times at task 2 and task 3 could be also another indicator that the end of the task 2 was the climax of the participant regarding Hb oxygenation level. After that point, the participants started making more mistakes and giving less effort to end the task as soon as possible. We claim that if we had a 4^{th} or even a 5^{th} complication task, we would have caught the worst performance with less response times and Hb oxygenation results at those tasks. So, we claim that higher wrong answer rates do not give an idea of brain activation by themselves. If the Hb oxygenation levels are decreasing concurrently, and response times are same or decreasing, it must be an indicator of concentration loss. However, if the oxygenation levels increase or stay at the same point, it should be an indicator of the difficulty of the task and capacity limit of the working memory.

Concerning the lateralization indexes, in a previous study done by Tanida et al. [22] the mental arithmetic task was found to be right lateralized which was consistent to our study. However, Tanida had used pulse-oximeter to measure the heart rates of the subjects which was an indicator of sympathetic and parasympathic and found right lateralization for the high HR, whereas left lateralization for the low HR. In our study, we had not used a pulse-oximeter and this would be a limitation for the experiment. A further study used with pulse-oximeter would give better results including the sympathetic effects of MA.

In our study, the number of the women and men were unequal in both groups. One way ANOVA analysis between men and women were taken at each step of the data analysis, to question if these was a gender difference between men and women, and no significant differences were obtained between two genders among both groups. It must be mentioned that there were some studies in literature about gender differences on aging [59], indicating age-related reductions in the frontal and temporal lobes to be

greater in men than in women. There were also studies claiming no gender difference on aging [60]. For example, in the MR study done by Coffrey and his colleagues [60] with 330 older people with the ages between 66-96 years, they observed main effects of age in the frontal region area but these effects were not different for men and women. However, because the studies in the literature are inconsistent studies, another study with the same procedure would be done on more subjects gender separated in order to find the gender effect on aging process.

If the performances and response times of the two groups are not significantly different from each other, 'why a hemispheric asymmetry change was observed' could be a question in mind. The answer lies behind the physiological changes in the human brain with age, and an compensation approach used for the aged people to win the game or at least be at the same level with youth: This strategy was supported by Cabeza and his colleagues [31-34] and they claimed that the people at older age recruit new areas of brain in order to compensate the performance of the young. Concerning the insignificant performance differences between our two groups, this hypothesis might be a possible explanation of the asymmetry change. Area specific alterations of brain morphology and brain shrinkage might cause new neurons and new brain areas are being recruited to compensate the neuronal loss of the brain [26, 62]. It can be also claimed that as the task gets harder, the elder people recruit new neurons and brain areas to compensate the loss of their right hemisphere according to the results of our study.

To our knowledge, there is no cognitive aging study using MA task to investigate the memory load and hemispheric differences in literature. However, HAROLD model is more supported with the studies that were mentioned before than the right hemi aging model that is consistent with our results. Although there are some studies especially done by Cabeza et al. [31-34] supporting the notion that functions attributed to one hemisphere is distributed to both hemispheres with aging, it must again be mentioned that the overall pattern of results is not clear according to some other studies [35,36]. The inconsistency of our study with the HAROLD model can be explained by the difference in methodology. In other words, by the task we used, for instance,

according to Dolcos and his colleagues [32], the cerebral hemispheres could be assumed to cooperate to perform complex, but not simple tasks. So, a change in hemispheric asymmetry would be more likely to be observed with more complex tasks. Considering our study, subjects of group O were educated the similar levels as group Y and they were actively working people, so the MA arithmetic task might not be very complex for group O to associate both of the two hemispheres tin order o compensate the task. Another possible explanation of the inconsistent findings is that differential age-related decline applies only to some regions within the right hemisphere. If the right hemi-aging hypothesis is task dependent, another methodology that might be used in our research would change the results a lot and a differential effect of aging on the right hemisphere could be found in another task differently depending on the particular brain regions involved. It should be mentioned that regardless of which one of the two hypotheses can be engaged according to the complexity and type of the task, further research on the right hemi-aging hypothesis is required.

The research about the recruitment of different areas of human brain with the aging parameter would lead to understanding the mechanisms underlying many aging related cognitive diseases and pave the way to prevent them. Although there are neuroimaging studies with cognitive tasks [61] comparing cognitive function of young, healthy aged or cognitively diseased brain, further research is needed to understand the exact mechanisms and differences between these 3 different groups.

5. CONCLUSION

The effect of aging on brain hemodynamics with mental arithmetic task containing 3 working memory load steps was evaluated with the participation of 13 young and 11 right handed middle aged subjects in the present study. Data obtained from 16 detectors from both group subjects were statistically analyzed and compared. Also, the performances and response times of two different age groups were evaluated. The lateralization indexes (LI_i=$Right_i$-$Left_i$/$Right_i$+$Left_i$) of each groups were calculated according to the hemoglobin oxygenation at the left and right prefrontal cortex of both groups. Increase of response times, performances and hemoglobin oxygenation were seen concurrent with the memory load increase to a certain level for both groups. The mean performances were parallel for each group and response times were different only for the most difficult step containing the most memory load. As a result of the lateralization index analysis, mental arithmetic task was found to be activating right hemisphere more than left hemisphere for the young group, whereas activating left hemisphere more than right hemisphere for the middle aged group. Also, it was found that this lateralization shifts to the edges as the memory load increases. The results of this study could be a neuroimaging study demonstrating the right hemi-aging model which is an alternative to the more accepted HAROLD model in the cognitive aging literature.

APPENDIX A. HB OXYGENATION VALUES OBTAINED FROM ALL THE DETECTORS FROM GROUP Y

In Appendix A and B, the unequal number of data in each detector is because of working of some detectors for some subjects.

	detector 1		
Group Y	1st task	2nd task	3rd task
sb.1	0.37	0.50	-0.10
sb.2	-0.46	0.64	0.59
sb.3	0.93	1.34	0.03
sb.4	0.29	0.83	0.93
sb.5	-0.08	0.16	0.02
sb.6	-0.48	1.42	1.72
sb.7	-0.50	0.20	0.16
sb.8	0.51	0.64	-0.66
sb.9	2.25	1.24	-1.08
sb.10	0.38	0.07	0.24
sb.11			
sb.12			
sb.13			

	detector 2		
Group Y	1st task	2nd task	3rd task
sb.1	0.22	0.99	2.52
sb.2	-0.27	0.55	-0.04
sb.3	-0.18	0.55	0.27
sb.4	0.10	0.67	0.23
sb.5	0.68	0.77	0.64
sb.6	0.77	-0.09	1.03
sb.7	-1.51	-0.26	-0.37
sb.8	-0.15	1.49	0.98
sb.9	0.14	0.36	0.15
sb.10	-0.96	1.94	1.48
sb.11	0.73	0.86	0.96
sb.12	-0.32	-0.30	-0.07
sb.13	-0.80	-0.29	0.81

	detector 3		
Group Y	1st task	2nd task	3rd task
sb.1	0.42	0.85	3.06
sb.2	0.43	0.06	0.36
sb.3	0.19	0.59	0.22
sb.4	0.66	-0.38	-0.64
sb.5	-1.04	0.65	0.95
sb.6	0.87	-0.11	1.71
sb.7	-0.26	0.07	0.06
sb.8	-0.20	1.02	0.76
sb.9	-0.01	0.85	0.50
sb.10	-0.96	1.08	0.41
sb.11	1.08	0.34	0.71
sb.12	-0.18	-0.52	0.02
sb.13	-0.85	-0.48	0.53

	detector 4		
Group Y	1st task	2nd task	3rd task
sb.1	0.97	0.41	2.54
sb.2	0.03	0.11	-0.23
sb.3	0.34	0.76	0.07
sb.4	0.10	0.66	-0.20
sb.5	0.01	1.04	0.99
sb.6	-1.08	0.20	-0.42
sb.7	-0.09	1.22	1.06
sb.8	0.02	0.06	-0.56
sb.9	-0.25	-0.21	-0.21
sb.10	-1.11	-0.38	0.42
sb.11			
sb.12			
sb.13			

Group Y	detector 5		
	1st task	2nd task	3rd task
sb.1	-0.54	1.67	1.93
sb.2	-0.07	0.38	0.21
sb.3	0.54	0.44	0.11
sb.4	0.76	0.77	-1.66
sb.5	-1.35	1.43	0.43
sb.6	0.29	0.00	2.63
sb.7	-1.22	-0.41	0.41
sb.8	-1.01	0.32	1.51
sb.9	0.27	0.92	0.68
sb.10	4.26	0.97	-3.86
sb.11	0.52	0.82	0.61
sb.12	-0.37	-0.39	0.29
sb.13	-0.83	-0.48	0.65

Group Y	detector 6		
	1st task	2nd task	3rd task
sb.1	0.06	1.20	2.50
sb.2	-0.49	0.56	-0.27
sb.3	0.75	0.57	-0.13
sb.4	-2.57	2.09	1.62
sb.5	-1.75	1.02	0.90
sb.6	0.10	0.16	-0.40
sb.7	-0.15	0.38	0.29
sb.8	-0.14	-0.22	-0.08
sb.9	-0.15	-0.06	0.09
sb.10			
sb.11			
sb.12			
sb.13			

Group Y	detector 7		
	1st task	2nd task	3rd task
sb.1	-0.93	1.29	1.86
sb.2	0.49	0.93	0.16
sb.3	0.48	0.35	0.25
sb.4	2.99	-0.75	-4.42
sb.5	-0.72	0.96	0.08
sb.6	1.60	1.22	0.05
sb.7	-0.72	0.34	0.53
sb.8	-1.58	0.38	1.47
sb.9	-1.02	-1.12	-1.14
sb.10	2.35	-0.01	-1.58
sb.11	-1.67	-0.87	3.56
sb.12	-0.49	-0.13	0.30
sb.13	-1.07	-0.56	0.60

Group Y	detector 8		
	1st task	2nd task	3rd task
sb.1	-0.93	1.01	2.55
sb.2	-0.62	0.24	0.00
sb.3	0.57	0.60	0.22
sb.4	-4.52	1.33	2.93
sb.5	-1.53	0.79	0.36
sb.6	1.37	0.87	1.43
sb.7	-1.06	0.13	0.27
sb.8	-1.50	0.60	2.71
sb.9	-3.51	-3.81	-3.37
sb.10	1.30	0.55	-1.17
sb.11	0.72	0.87	-1.45
sb.12	-0.45	-0.39	0.14
sb.13	-0.97	-0.71	0.38

Group Y	detector 9		
	1st task	2nd task	3rd task
sb.1	-1.77	1.02	1.18
sb.2	0.06	0.48	0.54
sb.3	0.18	0.51	0.55
sb.4	3.35	-1.58	-4.66
sb.5	-1.46	0.87	0.98
sb.6	1.39	1.23	0.02
sb.7	-0.35	1.26	1.91
sb.8	-1.08	1.54	1.50
sb.9	-0.68	-0.59	-0.23
sb.10	-2.45	1.73	1.50
sb.11	-2.31	-2.54	4.58
sb.12	-0.55	-0.27	0.26
sb.13	-1.68	-0.23	1.29

Group Y	detector 10		
	1st task	2nd task	3rd task
sb.1	0.10	2.19	1.32
sb.2	-0.75	0.09	-0.41
sb.3	0.53	0.54	0.15
sb.4	-1.05	1.47	-0.49
sb.5	-1.37	0.55	0.63
sb.6	0.95	0.71	0.46
sb.7	-1.01	0.53	0.95
sb.8	-2.09	2.74	3.55
sb.9	-1.51	-1.50	-1.43
sb.10	-0.49	1.31	1.10
sb.11	-0.99	-0.27	1.57
sb.12	-0.79	-0.57	0.38
sb.13	-1.10	-0.58	0.58

Group Y	detector 11		
	1st task	2nd task	3rd task
sb.1	-0.60	1.43	1.55
sb.2	-0.14	0.24	0.25
sb.3	0.20	0.46	0.49
sb.4	2.23	-2.32	-2.90
sb.5	-1.35	0.30	0.92
sb.6	1.02	0.67	0.75
sb.7	1.07	2.33	3.77
sb.8	-0.86	0.94	1.43
sb.9	0.24	0.16	0.39
sb.10	-0.61	1.90	-0.25
sb.11	-0.80	-0.12	0.68
sb.12	-0.06	-0.06	0.04
sb.13			

Group Y	detector 12		
	1st task	2nd task	3rd task
sb.1	0.83	2.31	1.10
sb.2	-0.65	0.36	-0.57
sb.3	0.41	0.55	0.38
sb.4	-1.06	0.99	-0.04
sb.5	-0.90	0.87	0.78
sb.6	2.23	1.48	-1.41
sb.7	-0.35	1.05	1.32
sb.8	-1.47	1.62	2.57
sb.9	0.11	0.42	0.49
sb.10	-0.54	1.62	0.39
sb.11	0.02	0.77	1.05
sb.12	-0.86	0.21	0.70
sb.13	-0.97	-0.30	0.56

Group Y	detector 13		
	1st task	2nd task	3rd task
sb.1	-0.25	0.40	2.20
sb.2	-0.15	0.40	0.12
sb.3	0.46	0.84	0.63
sb.4	1.44	-1.95	-0.59
sb.5	-0.45	0.00	0.94
sb.6	0.50	0.34	1.57
sb.7	-0.83	-0.10	0.43
sb.8	-0.63	1.13	0.97
sb.9	0.80	0.65	0.23
sb.10	-0.37	0.88	-0.10
sb.11	-0.65	-0.45	0.20
sb.12	-1.01	-0.64	0.51
sb.13			

Group Y	detector 14		
	1st task	2nd task	3rd task
sb.1	0.39	0.22	2.12
sb.2	-0.41	-0.07	-0.37
sb.3	0.51	0.86	0.58
sb.4	-0.34	-0.15	0.72
sb.5	0.54	0.23	1.29
sb.6	1.21	0.87	0.63
sb.7	-0.12	0.75	0.67
sb.8	-0.70	0.80	1.38
sb.9	-0.15	-0.20	-0.16
sb.10	-0.23	0.87	0.67
sb.11	0.85	0.21	1.14
sb.12	-0.48	0.03	0.15
sb.13	-1.04	-0.41	0.62

Group Y	detector 15		
	1st task	2nd task	3rd task
sb.1	-0.04	0.34	2.76
sb.2	0.05	0.01	-0.31
sb.3	0.29	0.47	0.27
sb.4	0.52	-0.06	0.11
sb.5	0.96	0.49	-0.45
sb.6	-0.53	-0.26	0.37
sb.7	0.91	1.12	1.07
sb.8	-0.74	-0.35	0.22
sb.9	0.80	0.45	0.24
sb.10	-0.26	0.16	0.22
sb.11	-0.94	-0.74	0.33
sb.12			
sb.13			

Group Y	detector 16		
	1st task	2nd task	3rd task
sb.1	-0.17	0.52	1.96
sb.2	-0.50	0.05	-0.23
sb.3	0.43	0.38	0.22
sb.4	0.79	0.12	-0.72
sb.5	0.92	-0.13	1.44
sb.6	0.43	0.24	0.89
sb.7	-0.54	0.31	0.24
sb.8	-0.51	1.21	1.20
sb.9	-0.28	-0.08	-0.36
sb.10	-1.27	-0.67	1.55
sb.11	0.47	0.39	0.68
sb.12	-0.32	-0.30	-0.07
sb.13	-1.00	-0.42	0.39

APPENDIX B. HB OXYGENATION VALUES OBTAINED FROM ALL THE DETECTORS FROM GROUP O

	detector 1		
Group O	1st task	2nd task	3rd task
sb.1	0.37	0.50	-0.10
sb.2	-0.46	0.64	0.59
sb.3	0.93	1.34	0.03
sb.4	0.29	0.83	0.93
sb.5	-0.08	0.16	0.02
sb.6	-0.48	1.42	1.72
sb.7	-0.50	0.20	0.16
sb.8	0.51	0.64	-0.66
sb.9	2.25	1.24	-1.08
sb.10	0.38	0.07	0.24
sb.11			

	detector 2		
Group O	1st task	2nd task	3rd task
sb.1	0.14	0.43	0.10
sb.2	0.31	0.95	0.08
sb.3	0.48	0.99	1.42
sb.4	-0.05	0.31	0.18
sb.5	-0.69	1.30	1.57
sb.6	0.62	0.54	-1.30
sb.7	0.12	0.65	-0.44
sb.8	-0.46	2.28	1.08
sb.9	2.73	0.57	-0.86
sb.10	-0.01	0.23	0.22
sb.11			

	detector 3		
Group O	1st task	2nd task	3rd task
sb.1	0.03	0.51	0.25
sb.2	0.58	0.58	0.12
sb.3	0.24	0.61	0.26
sb.4	-0.35	-0.05	0.37
sb.5	-0.06	0.64	1.00
sb.6	0.32	0.57	-0.25
sb.7	1.36	0.27	-1.16
sb.8	0.12	0.15	-0.15
sb.9			
sb.10			
sb.11			

	detector 4		
Group O	1st task	2nd task	3rd task
sb.1	0.18	0.60	0.27
sb.2	0.23	0.36	-0.10
sb.3	0.12	1.13	0.14
sb.4	0.19	0.72	1.85
sb.5	-0.03	0.55	0.56
sb.6	-0.26	1.06	0.60
sb.7	0.21	0.63	-0.33
sb.8	3.50	1.78	0.50
sb.9			
sb.10			
sb.11			

Group O	detector 5		
	1st task	2nd task	3rd task
sb.1	-0.45	0.43	0.69
sb.2	0.34	0.62	0.68
sb.3	-0.68	0.29	0.44
sb.4	0.10	-0.08	-0.06
sb.5	-0.46	0.33	1.10
sb.6	-0.24	0.32	0.35
sb.7	0.17	0.47	0.32
sb.8	0.01	0.28	0.60
sb.9			
sb.10			
sb.11			

Group O	detector 6		
	1st task	2nd task	3rd task
sb.1	0.14	0.36	0.00
sb.2	-1.44	1.15	1.07
sb.3	-0.31	0.93	-0.63
sb.4	-0.81	0.87	-0.29
sb.5	0.10	0.50	0.52
sb.6	-0.58	0.85	0.45
sb.7	-0.44	0.44	0.40
sb.8	1.34	1.20	2.06
sb.9			
sb.10			
sb.11			

Group O	detector 7		
	1st task	2nd task	3rd task
sb.1	-0.41	0.15	0.47
sb.2	-2.21	1.75	1.26
sb.3	-1.63	-0.43	1.62
sb.4	-0.98	0.34	0.65
sb.5	-0.32	0.54	-0.21
sb.6	-0.25	0.36	0.83
sb.7	-1.30	-0.33	0.91
sb.8	-0.61	0.37	0.41
sb.9	0.46	1.14	1.82
sb.10	0.03	0.44	0.54
sb.11			

Group O	detector 8		
	1st task	2nd task	3rd task
sb.1	-0.63	0.22	0.52
sb.2	-3.65	1.61	1.95
sb.3	-1.39	-0.86	0.01
sb.4	-0.15	-0.14	2.01
sb.5	-0.35	0.61	0.23
sb.6	-0.72	0.18	0.70
sb.7	-1.45	-0.98	1.74
sb.8	-2.51	0.29	2.01
sb.9	0.12	1.57	0.99
sb.10	0.64	1.39	1.46
sb.11	-0.04	0.44	0.39

Group O	detector 9		
	1st task	2nd task	3rd task
sb.1	-1.19	0.16	1.36
sb.2	-1.90	1.52	0.74
sb.3	-0.92	-0.05	1.32
sb.4	-0.36	0.34	0.97
sb.5	-0.02	0.05	-0.41
sb.6	0.05	0.41	0.32
sb.7	-0.95	-0.24	1.17
sb.8	-0.26	0.29	-0.22
sb.9	0.84	0.70	1.33
sb.10	-0.16	0.36	0.35
sb.11			

Group O	detector 10		
	1st task	2nd task	3rd task
sb.1	-0.64	0.10	0.42
sb.2	-3.25	1.98	1.33
sb.3	-1.83	-1.32	1.52
sb.4	-1.38	0.56	-0.38
sb.5	-0.34	0.30	0.06
sb.6	-0.27	0.49	-0.09
sb.7	-1.98	-1.51	2.42
sb.8	-1.91	0.69	1.30
sb.9	-1.69	2.00	1.58
sb.10	1.64	0.22	0.72
sb.11	-0.69	0.26	0.43

Group O	detector 11		
	1st task	2nd task	3rd task
sb.1	-0.53	0.09	0.27
sb.2	-0.05	0.14	0.59
sb.3	0.14	0.37	0.75
sb.4	0.25	0.00	-0.09
sb.5	0.05	0.38	0.41
sb.6	-0.73	0.53	0.41
sb.7	-0.28	0.25	0.29
sb.8			
sb.9			
sb.10			
sb.11			

Group O	detector 12		
	1st task	2nd task	3rd task
sb.1	-0.32	0.20	0.12
sb.2	-0.97	1.07	0.62
sb.3	-0.78	0.12	1.13
sb.4	-0.93	0.67	1.61
sb.5	0.15	0.42	0.04
sb.6	0.18	0.84	-0.38
sb.7	-0.58	0.02	1.14
sb.8	-0.62	0.65	0.32
sb.9	-2.11	2.68	1.33
sb.10	0.27	0.29	0.97
sb.11	-0.48	0.29	0.37

Group O	detector 13		
	1st task	2nd task	3rd task
sb.1	-0.22	0.25	0.15
sb.2	0.47	1.20	0.45
sb.3	-0.18	1.01	1.36
sb.4	-0.03	0.13	0.00
sb.5	0.28	0.15	0.25
sb.6	-0.47	0.73	0.41
sb.7	0.04	0.29	0.40
sb.8			
sb.9			
sb.10			
sb.11			

Group O	detector 14		
	1st task	2nd task	3rd task
sb.1	0.04	0.58	0.12
sb.2	-0.04	1.46	0.69
sb.3	0.26	1.08	0.19
sb.4	-0.27	0.77	1.07
sb.5	0.06	0.27	0.05
sb.6	0.44	0.31	-0.16
sb.7	0.10	0.76	0.66
sb.8	-0.21	0.77	0.06
sb.9	-0.20	2.01	0.57
sb.10	2.58	2.13	-0.73
sb.11	0.10	0.23	0.03

Group O	detector 15		
	1st task	2nd task	3rd task
sb.1	-0.03	0.32	0.06
sb.2	0.14	0.31	-0.51
sb.3	0.54	0.33	0.17
sb.4	0.00	0.62	-0.11
sb.5			
sb.6			
sb.7			
sb.8			
sb.9			
sb.10			
sb.11			

Group O	detector 16		
	1st task	2nd task	3rd task
sb.1	0.02	0.47	0.18
sb.2	-0.30	1.97	0.94
sb.3	0.08	0.76	0.03
sb.4	0.31	0.36	0.30
sb.5	-0.06	0.36	-0.02
sb.6	0.65	0.21	0.00
sb.7	-0.75	0.89	2.51
sb.8	-0.01	0.53	-0.14
sb.9	-1.76	2.66	2.54
sb.10	0.85	1.18	-0.19
sb.11	0.09	0.12	0.31

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