THE EFFECT OF METHYLPHENIDATE ON BRAIN HEMODYNAMICS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEASURED BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

by

Nermin Topaloğlu

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, 2007

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Assistant Prof. Dr. Ata Akın, for his supports, patience, and helps at every step of my thesis work. He has always encouraged me with his warm welcome, motivation and tolerance.

I would also like to thank Ercan Kara, Burcu Erdoğan, Esin Karahan and Sinem Serap who helped me throughout this project with their knowledge, ideas and especially with their friendship.

Last, I would like to thank my family, especially my mother and my brother for their moral support and encouragement throughout my studies.

ABSTRACT

THE EFFECT OF METHYLPHENIDATE ON BRAIN HEMODYNAMICS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER MEASURED BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

Attention-deficit/hyperactivity disorder (ADHD) is a very common neurodevelopmental disorder. Approximately 30%– 60% of individuals diagnosed with ADHD in youth have symptoms that persist into adulthood. This neurobehavioral disorder results in significant functional impairment. It decreases the life quality of the patients. Therefore, the need for recognition and treatment of patients with ADHD is necessary. Methylphenidate (MPH) is known to reduce hyperactivity in individuals with ADHD. Yet little is known about how it alters neural activity and how this relates to its clinical effects.

Functional Near-Infrared Spectroscopy (fNIRS) is a portable, non-invasive brain imaging method measuring the changes in oxygenated hemoglobin [HbO2] and deoxyhemoglobin [HbH] levels particularly in prefrontal cortex.

In this study, 15 adult, right handed cases with DSM-IV diagnosis of Attention deficit hyperactivity disorder (ADHD) were evaluated with fNIRS during a cognitive task which is Stroop test. The goal of this study is to examine MPH-induced hemodynamic changes during a cognitive activity, and to examine how these changes correlate with measures of behavioral response to the drug during Stroop task.

It is found that MPH effectively decreased HbO levels. The reason of the decreased level of HbO after medication is vasoconstriction. MPH normalized the behavior during an executive function test. MPH has a great effect on the response time of the subjects to NS, CS, and IS. MPH always shortens the durations of the reaction times.

Keywords: Functional Near-Infrared Spectroscopy, Attention-Deficit/Hyperactivity Disorder (ADHD), Methylphenidate, Stroop task, adult.

ÖZET

DİKKAT-EKSİKLİĞİ/HİPERAKTİVİTE BOZUKLUĞUNDA METİLFENİDATIN KAN DİNAMİĞİ ÜZERİNDEKİ ETKİSİNİN İŞLEVSEL YAKIN KIZIL ÖTESİ SPEKTROSKOPİ İLE ÖLÇÜLMESİ

Dikkat eksikliği Hiperaktivite bozukluğu (DEHB) çocuklarda cok sık rastlanan sinirgelişimsel bir bozukluktur. DEHB teşhisi konulan çocukların yaklaşık %30-%60'ı yetişkinlikte de aynı semptomları sürdürürler. Bu bozukluk önemli işlevsel rahatsızlıklara sebep olur. Hastaların yaşam kalitesini düşürür. Bu yüzden DEHB teşhisi konulan kişilerin tedavisi önemlidir. Metilfenidat, DEHB hastalarında hiperaktiviteyi azaltan ilaçtır. Henüz sinirsel aktiviteyi nasıl degiştirdiği ve klinik sonuçları ile arasındaki bağlantı tam bilinmemektedir.

İşlevsel yakın kızıl ötesi spektroskopi, özellikle prefrontal korteksteki oksijenli hemoglobin ve oksijensiz hemoglobin miktarındaki değişiklikleri ölçmek için kullanılan taşınabilir, nonefraktif beyin görüntüleme metodudur.

Bu çalışmada, sağ elini kullanan 15 yetişkin DEHB hastası Stroop test olarak adlandırılan bilişsel bir test sırasında işlevsel yakın kızıl ötesi spektroskopi metodu ile değerlendirilmiştir. Bu çalışmanın amacı, bilişsel bir aktivite sırasında metilfenidatın kan dinamiğini nasıl etkilediğini bulmak ve kan dinamiğindeki değişimler ile davranışsal tepkiler arasında nasıl bir bağlantı kurulacağını araştırmaktır.

Bu çalışma sonunda, metilfenidatın oksijenli hemoglobin miktarını etkili olarak düşürdüğü bulunmuştur. Bu durum ilacın sebep oldugu vazokonstriksiyondan kaynaklanmaktadır. Ayrıca metilfenidat bilişsel test sırasında davranışları da normalize etmiştir, sorulara verilen cevap sürelerini düşürmüştür.

Anahtar Sözcükler: İşlevsel Yakın Kızıl Ötesi Spektroskopi, Dikkat-Eksikliği/Hiperaktivite Bozukluğu, Metilfenidat, Stroop Test, Yetişkin

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p	Significant number

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit/Hyperactivity Disorder
NIR	Near-infrared
NIRS	Near-infrared spectroscopy
fNIRS	Functional near-infrared spectroscopy
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
HbO_2 / Hb	Oxy/Deoxy-hemoglobin
[HbO_2] / [Hb]	Concentration of oxy/deoxy-hemoglobin
LED	Light emitting diodes
DSM	The Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
MPH	Methylphenidate
DA	Dopamine
DAT	Dopamine transporters
NE	Norepinephrine
DRD4	Dopamine receptor 4
DAT1	Dopamine transporter-1
DBH	Dopamine beta hydroxylase enzyme
DRD2/DRD5	Dopamine receptor genes
NET	Norepinephrine Transporter
rCBF	Regional Cerebral Blood Volume
SPECT	Single photon emission computed tomography
QEEG	Quantified computerized EEG
OT	**O**ptical topography
CT	Computerized tomography
PCB	Printed circuit board
NS	Neutral stimuli
CS	Congruent stimuli
IS	Incongruent stimuli

1. INTRODUCTION

1.1. Motivation and Objective

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders. Approximately 30%– 60% of individuals diagnosed with ADHD in youth have symptoms that persist into adulthood [1]. Adults with ADHD share similar clinical features, co-morbidities, neuropsychological deficits, and failures in major life domains with ADHD children [4]. Children and adults with ADHD perform more poorly on tasks requiring cessation of motor activity, organization of information, planning, and complex problem solving, and learning and recalling oral instructions. And these deficits cause problems at school, home and/ or work throughout their life. Therefore, diagnosis and treatment of ADHD is important, which is only possible by understanding its dynamics. This study aims to observe the cerebrovascular dynamics of ADHD patients and find out the differences between their off and on methylphenidate dynamics.

In this study, the hemodynamic response during Stroop task was evaluated in adult cases with attention-deficit hyperactivity disorder (ADHD) and the hemodynamic response to this task in ADHD cases on and off methylphenidate (MPH) was compared. Our specific hypothesis is that the patients on MPH will have an altered hemodynamic response to cognitive tasks, with the effect of the drug on the veins by vasoconstriction.

1.2. Problem Statement

Neuroimaging studies are commonly carried out by fMRI, PET and EEG which are either invasive, have high spatial resolution but low temporal resolution or vice versa or poses constraints in terms of bulky instrumentation on the subject`s performance. A rapid, easy to apply, non-disturbing and non-invasive system is required to monitor the cerebrovascular dynamics during cognitive tasks.

Functional near infrared spectroscopy proposes to respond to all these challenges. Continuos wave fNIRS has been successfully used in many neuroimaging studies and is a validated system that is proved to measure cortex vascular reactivity. Hence in this study we aimed to use the CW-fNIRS technology to image and quantify the differences between the medicated and unmedicated ADHD adult cases performing a cognitive task. To our knowledge, this is the first study to integrate a drug study with fNIRS and cognitive task.

1.3. Contribution of the thesis

There is an ongoing debate as to how exactly the methylphenidate acts to improve the cognitive performance of ADHD subjects. Our findings indicate that through molecular mechanisms, the MPH triggers the vasomotor center of the brain to selectively constrict certain vessels hence, decrease the supply to certain area of the prefrontal cortex. This reduction actually will lead to the suppression of the background cognitive noise of the subjects, leave them with only a couple of highly activated areas to carry out the desired executive functions. We have observed a diminished reactivity in oxygenated blood one medicated. We believed this phenomenon will lead to a better understanding of the pathophysiology of ADHD and its treatment.

2. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common cognitive and behavioral disorder and characterized by pervasive inattention and/or hyperactivity-impulsivity. This neurobehavioral disorder results in significant functional impairment. The need for recognition and treatment of patients with ADHD is necessary because of an increased risk of those with unrecognized ADHD for persistent patterns of functional problems at home, in school, and/or at work; and because there can be beneficial responses to medication, i.e., stimulants, which was first reported in 1937, but therapeutically neglected for decades.

ADHD is no longer considered only a school-age disorder. A variety of studies supports the validity of ADHD in adults [4, 11]. Research studies have shown that some people with ADHD may have observable differences in central nervous system metabolism, neuropsychological test results, and neuroanatomic structure [3, 4, 5, 9, 12].

Understanding the underlying neurological underpinnings of ADHD is important for the design of effective psychological and pharmacological interventions. The neurobiology of ADHD can be explored with three different approaches: neuropsychological, neurochemical, and neuroanatomical [47]. Evidence from all three disciplines has found structural and functional abnormalities in the basal ganglia of children with ADHD [48, 49].

At least 11 different neuroanatomical theories of ADHD were described. These theories can be categorized into two domains. The “bottom-up” theories propose disturbances in subcortical regions, such as the thalamus, and hypothalamus and reticular activating systems are responsible for ADHD symptomology. The “top-down” theories attribute the dysfunction to frontal and prefrontal and sagittal cortices [50]. Neuroimaging studies of children with ADHD have investigated and found evidence of abnormalities in the frontal cortex, basal ganglia, corpus callosum, and cerebellum. Preliminary evidence has not found differences in the thalamus in children with ADHD.

2.1. Classification and Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, is the standard classification of mental disorders used by mental health professionals in the United States. DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), published in 1994, was the last major revision of the DSM.

According to the DSM-IV criteria for diagnosing ADHD, at least 6 of 9 inattentive symptoms or at least 6 of any combination of 6 hyperactivity and 3 impulsivity symptoms must have persisted for six months, are maladaptive, and not due to developmental level. DSM-IV states that symptoms must persist for at least 6 months and that they must be present before age 7 years for the diagnosis to be made. In addition, the symptoms must be severe enough to be considered maladaptive, be inconsistent with the patient's level of development, and not be exclusively due to another condition. There must be some impairment present in at least 2 settings (e.g., school, work, and home) along with clear evidence of significant impairment in social, educational, or work-related functioning. Finally, these symptoms must not be caused exclusively by a pervasive developmental or other mental disorder (e.g., personality or anxiety disorder).

The diagnosis of ADHD is a clinical one that is primarily based on a detailed history. The features that a patient exhibits can help to support the diagnosis, but ADHD is primarily a clinical diagnosis. Teenagers and adults with ADHD are at increased risk for engaging in unsafe behaviors, including conflict with authority figures, smoking, substance abuse (in adulthood), speeding while driving, and delinquency. Substance abusers with ADHD tend to prefer other drugs over alcohol and may have greater persistence of substance abuse. Children with ADHD who are treated with stimulants (i.e., methylphenidate) are less likely to be substance abusers than children with ADHD not treated with stimulants.

Adults with ADHD often suffer from lack of organization, frustration, and feelings of failure. The frustration comes from awareness of a gap between their potential and repeated sub-optimal outcomes. Many adults with ADHD have been misdiagnosed, and/or treated with inappropriate medications and psychotherapies. Many are creative and visionary and have

found partners who have areas of strength and skills that compensate for their own areas of deficiency [6].

Family dynamics tend to reflect greater disorganization when at least one parent and child have ADHD. At least 25% of children with ADHD have a parent who also has ADHD. More than 50% of adults with ADHD have at least one child with ADHD. It is not unusual for the proper diagnosis in a child to lead to identification of ADHD (or another psychiatric diagnosis) in a parent and/or siblings [11].

Defective "executive function" or self-awareness and regulation are postulated by some clinicians to be of major significance in adults [4]. For example, a common problematic pattern in executive function involves poor organization, lack of planning, and boredom following a consistent routine. Poor self-regulation results in easy distractibility at work or responding without inhibition to internal or external stimuli rather than more resourceful use of internalized principles, plans, or prior commitments.

2.2. Epidemiology

ADHD is manifest in approximately 4-12% of children between the ages of 6 and 12 years. The variance is due to changing diagnostic criteria over time, variations of assessments in different settings, and geographical areas, and estimates based on referrals. Due to the lower rates of defiance in girls with ADHD than in boys, ADHD is more likely to be recognized in boys than in girls. [1, 12].

The most prevalent co-morbid conditions in children identified by Brown et al were oppositional defiant disorder, conduct disorder, and anxiety. Each co-morbidity occurred in approximately 25-33% of patients diagnosed with ADHD. Approximately 20% of patients had depressive or learning disorders. In community settings, males were diagnosed at least three times as often as females [2].

ADHD in girls is a more serious risk factor for substance abuse than in boys [1, 2]. Between 15% and 35% of affected children have one or more additional psychiatric disorders (e.g., anxiety, depression, oppositional defiance/conduct disorders, learning disabilities, tic

disorder, or substance abuse). The inattentive type of ADHD appears to be associated more often with anxiety, depression, and learning disabilities, but with fewer behavioral problems. The hyperactive-impulsive and combined subtypes are more often associated with antisocial personality disorder in adulthood, conduct disorders, and oppositional defiant disorders [1, 2, 12].

There are no definitive epidemiological studies to indicate prevalence of ADHD in adults or persistence from childhood. Two longitudinal studies have followed "hyperactive" children and adolescents diagnosed with ADHD based on older criteria. The findings on persistence were widely discrepant, 11% and 60% persistence, respectively.

Other diagnoses from these studies reported in adulthood included antisocial personality disorder and substance abuse. More recent studies indicate persistence of symptoms of childhood ADHD into adulthood may be as high as 66-75% and that between 1% and 6% of the general adult population has appreciable evidence of ADHD [11, 12].

A diagnosis of ADHD should be considered in adults who have lifelong problems with inattention, disorganization and executive function, cognitive restlessness, vocational and academic underachievement based on their intelligence and education, substance abuse, stability in relationships (e.g., multiple divorces), or who consistently engage in thrill-seeking and risky behaviors [4, 8, 12, 12].

2.3. Pathophysiology of ADHD

People with ADHD have problems with inattention, hyperactivity, and/or impulsivity. Children and adults with ADHD perform more poorly on tasks requiring cessation of motor activity, organization of information, planning, and complex problem solving, and learning and recalling oral instructions.

Studies of neurochemistry and metabolism, brain imaging, epidemiological risk factors, and genetics, support the concept that ADHD is a polymorphic genetic disorder involving central nervous system neurotransmitter and receptor regulation. No single gene, neurotransmitter, altered pathway, or mechanism has been found to account for the observed

patterns of dysfunction and co-morbidities. Many studies points towards involvement of multiple factors involving inheritance, amounts of neurotransmitters in specific brain areas, and deficits in specific neurocircuits. In addition to genetics, environmental and psychosocial factors also contribute to brain development. [13].

2.4. Pharmacologic Treatment of ADHD

Methylphenidate (MPH) is an effective treatment for attention-deficit/hyperactivity disorder (ADHD). It is a mild central nervous system stimulant. But it does not directly affect the central nervous system. It is believed that MPH acts on the dopamine mechanism. Methylphenidate blocks the dopamine transporters (DAT), the main mechanism for removing dopamine (DA) from the synapse, is believed to be involved in its therapeutic properties. By this way, it is supposed that MPH causes vasoconstriction [54]. The pharmacologic properties of MPH have been well characterized in several preclinical studies; however, its mechanism of action is not completely understood [40]. Research suggests that MPH works by increasing the level of extracellular dopamine (DA) in the brain [41, 42]. This theory has been supported, in part, by preclinical studies that found MP blockades of DA transporters (DATs) as well as norepinephrine transporters [43, 44]. Dysfunction of the dopaminergic as well as the noradrenergic systems, which have self-regulatory functions such as mediating selective attention (noradrenergic neurons) and motivation (dopaminergic neurons), are implicated in the pathogenesis of ADHD [43, 44].

Imaging studies of the human brain have shown that MPH dose dependently blocks the DAT in striatum. These studies showed that for intravenous administration, the MPH required to block 50% of DAT (median effective dose [ED50]) was estimated to be .075 mg/kg, and for oral administration, the ED50 was estimated to be .25 mg/kg [45]. Thus, a standard therapeutic dose of .5 mg/kg is expected to block more than 60% of DAT. Although MPH has been considered a weak psychostimulant due to the rapid metabolism of oral doses into ritalinic acid, which has a weak affinity for DAT, these results indicate that at the doses used, therapeutic MPH blocks a large percentage of the DAT [45].

2.5. Genetics

Both genetic and environmental factors contribute to ADHD. Twin studies confirm a genetic link as monozygotic twins show a 55% to 90% concordance rate for ADHD. Recent studies describe ADHD as a polygenic disorder that involves multiple genes that determine the severity of symptoms. ADHD may be best viewed as the extreme of a behavior that varies genetically throughout the entire population on a continuum [14, 16]. There is no brain scan or blood test which confirms ADHD, however, the right prefrontal cortex, caudate nucleus, and globus pallidus are typically smaller, which suggests lack of connectivity of key brain regions that modulate attention, stimulus processing, and impulsivity [17].

The neurotransmitters dopamine (DA) and norepinephrine (NE) are implicated in the pathophysiology of ADHD. Dopamine is a neurotransmitter involved in reward, risk taking, impulsivity, and mood. Norepinephrine modulates attention, arousal and mood. Brain studies on individuals with ADHD suggest a defect in the dopamine receptor D4 (DRD4) gene and overexpression of dopamine transporter-1 (DAT1). The DRD4 receptor uses DA and NE to modulate attention to and responses to one's environment. The DAT1 or dopamine transporter protein takes DA/NE into the presynaptic nerve terminal so it may not have sufficient interaction with the postsynaptic receptor. The implications of these limited receptor findings require further study; however, it seems clear that dopamine and norepinephrine are involved in the pathophysiology of ADHD.

Family environment adversity factors (eg. high degree of psychosocial stress, maternal mental disorder, paternal criminality, low socioeconomic status, foster care) have been linked to increased rates of ADHD as well [18].

ADHD has characteristics of a polygenic inheritance rather than being an autosomal dominant, recessive, or mixed disorder. The exact number of genes involved and their overall relative contributions are not known. The genetic basis of ADHD and its relationship to other disorders with genetic components are the subject of ongoing research studies. There is probably a combined effect from several different genes, each of which makes a small contribution [19]. In families with a child with ADHD, there is about 15-25% likelihood that a sibling also has ADHD. Approximately 15-40% of children with ADHD have a parent with ADHD.

Conclusions from studies of families, adopted children, and fraternal vs. identical twins, indicate that about 70-95% of the variance in symptoms of ADHD is genetic. In identical twins with ADHD, there is about a 70-80% concordance compared with a co-occurrence of 30-40% in fraternal twins. Several distinct neuropsychiatric disorders that run in families, probably genetically related to ADHD and with relatively high co-morbidities with ADHD, are indicative of some shared genes. More research needs to be done, however, to conclusively prove these shared gene associations. These neuropsychiatric disorders include depression, anxiety, tic disorders, learning disorders, substance abuse, and conduct disorders [3, 12, 13].

Evidence from molecular genetic studies and response to drugs that affect brain dopaminergic and noradrenergic activity, including changes in cerebral blood flow, suggests that there are multiple genes involved in ADHD which involve the neurotransmitters, receptors, and/or transporters for dopamine and norepinephrine. Some of the specific dopaminergic genes implicated by some researchers include, but are not limited to, the dopamine receptor genes DRD2 and DRD5, the dopamine transport gene DAT1, and defective alleles of the dopamine beta hydroxylase enzyme (DBH) responsible for conversion of dopamine to norepinephrine [3].

Some of the involved adrenergic genes include the receptors ADRA2A, ADRA2C, and the norepinephrine transporter (NET) [3]. Conflicting results have been seen in defective gene identification studies including the DRD4 dopamine receptor gene; it can bind both dopamine and norepinephrine. Researchers generally agree that serotonin, glycine, and GABA do not play a major role in ADHD. Researchers differ on the emphasis of the relative importance of dopaminergic vs. noradrenergic factors [3, 8, 19, 26].

There are measurable clinical benefits from stimulants on inattentive, hyperactive, and impulsive behaviors. These results, seen in numerous short-term, placebo-controlled, double-blinded clinical studies for approval of stimulants to treat ADHD in children and adolescents, as well as other studies, have paved the way for a more scientific understanding of ADHD [27, 28, 29]. The precise mechanisms of action of stimulants are still unknown. Pharmacokinetic and pharmacodynamic studies with some stimulants indicate that tachyphylaxis or acute tolerance may develop and dissipate rapidly during a single dose.

Stimulants may facilitate dopaminergic activity in cognitive centers but reduce dopaminergic stimulation in areas responsible for hyperactivity and impulsivity. People with ADHD generally have increased dopamine transporter density and activity.

There is some evidence that there are different pathophysiological mechanisms involved in the different subtypes of ADHD. The hyperactive-motor vs. the emotional/cognitive-impulsive/inattentive features of ADHD may have different underlying mediators, pathways, and familial patterns. Intriguingly, there are differences in the time effects and dose-response relationships to stimulants. In general, hyperactive symptoms, which may be considered more primitive than cognitive dysfunctions, respond more favorably to lower doses of stimulants and/or less frequent dosing than do cognitive symptoms.

ADHD in adults is more associated with cognitive dysfunction than motor hyperactivity. Various data, including animal models and PET scans suggest that hyperactivity may result from excess dopaminergic activity in the striatum and/or nucleus accumbens [8].

2.6. Neuroimaging Studies

Results of neuroimaging studies on large numbers of people with ADHD have yet to be presented and published. Neuroimaging studies are expensive to conduct and the results have not always been consistent. They are currently considered tools for basic brain research including studying the effects of drugs. Magnetic Resonance Imaging (MRI) studies have found slight decreases in total cerebral volume, smaller anterior regions in the corpus callosum, smaller areas of the right prefrontal cortex, caudate nucleus, globus pallidus region of the basal ganglia, cerebellar hemispheres, and vermis, particularly the posterior-inferior lobules.

Positron Emission Tomography (PET) scans show people with ADHD often have reduced perfusion to the bilateral frontal areas (adults more so than adolescents), the caudate nuclei, and the basal ganglia. Administration of stimulants may increase cerebral perfusion to these areas [4, 5].

According to another study with PET, Measures of regional cerebral blood flow (rCBF) were acquired at rest adult subjects with ADHD during both an unmedicated state and after a 3-week period of chronic dosing with a clinically optimal dose of MPH. Compared with the on-MPH condition, the off-MPH condition was associated with relative increases in rCBF bilaterally in the precentral gyri, left caudate nucleus, and right claustrum. The on-MPH condition was associated with relative increases in rCBF in the cerebellar vermis [33].

Another PET study showed that adults with ADHD had prefrontal cortical deactivation in response to an intellectual challenge, as opposed to increased prefrontal cortical activity that was seen in normal adults [37].

In a SPECT analysis, it is reported that hypoperfusion in the regions of the prefrontal cortex and the basal ganglia which normalized with stimulant medication [34, 35]. Sieg *et a* reported SPECT findings in 10 patients with the diagnosis of attention deficit hyperactivity disorder (ADHD), showing uptake asymmetries with less activity in the left frontal and left parietal regions in comparison to control patients [36].

Lubar, who has performed spectral analysis of quantified computerized EEG (QEEG) on children and adolescent patients with ADHD, found that when these patients performed a concentration task, such as reading or copying figures, there was an increase in frontal lobe theta activity (slow brain wave activity) rather than the expected decrease in frontal lobe slow wave activity that is found in normal controls [38, 39].

Functional MRI revealed differences between children with ADHD and healty controls in their frontal-striatal function and its modulation by methylphenidate during response inhibition. ADHD children had greater frontal activation on one task and reduced striatal activation on another task. The drug improved response inhibition in both groups. It increased frontal activation to an equal extent in both groups. In contrast, it increased striatal activation in ADHD children but reduced it in healthy children [51].

According to another functional MRI analysis, the neuroactivation pattern observed in the hyperactive adolescents differed quantitatively and qualitatively from that of the comparison subjects during performance of two tasks testing high-level executive control. The hyperactive adolescents showed less brain activity, predominantly in the right hemisphere

mesial frontal cortex during both tasks and in the right inferior prefrontal cortex and left caudate nucleus during the stop task. The brain region that was activated in the comparison but not in the hyperactive subjects during performance of both tasks was the right mesial frontal gyrus. The activation of this area in both tasks suggests that it subserves higher-order motor control functions, such as motor attention and response selection, common to both tasks. In subjects with ADHD, the structural development of this area has been related to performance on selective attention and subnormal cerebral glucose metabolism has been observed during performance on sustained attention. The underfunctioning of a structure responsible for motor attention may underlie the deficits in different executive functions in ADHD. Less activation in the posterior cingulate during the delay task suggests that not only prefrontal but also posterior parts of the midline attentional system are affected in ADHD [52].

2.7. The Neurovascular Coupling Hypothesis

Some nerve fibers innervate several blood vessels in the brain, for example the ones in the meninges, and the extracranial arteries. These fibers provide a pathway for signal transmission from blood vessels into the brain [24]. Some chemicals play an important role in this pathway. They are neurotransmitters. They can cause vasodilation or vasoconstriction. The British neurophysiologist C. Sherrington showed, in experimental animals, increases in blood flow localized to the parietal cortex in response to sensory stimulation (Roy and Sherrington, 1890). He postulated that “the brain possesses intrinsic mechanisms by which its vascular supply can be varied locally in correspondence with local variations of functional activity.” He also proposed that “chemical products of cerebral metabolism” produced in the course of neuronal activation could provide the mechanism to couple activity with increased blood flow. Therefore, the brain activity can be monitored by measuring the concentration of the oxyhaemoglobin and deoxyhaemoglobin in the cerebral blood flow. The figure below represents the neurovascular coupling.

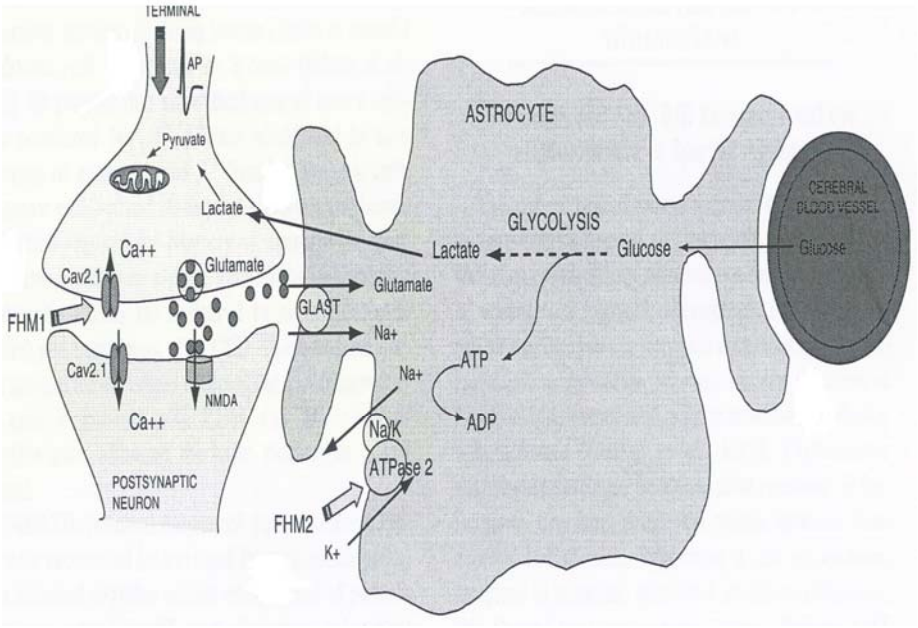

Figure 2.1 Astrocytes couple synaptic activity to glucose utilization in the brain [53]

3. Functional Near-Infrared Spectroscopy (fNIRS)

3.1. NIRS – The Theory

Near-infrared radiation can be used to monitor the degree of oxygenation of certain metabolites. This led to the development and increasingly widespread use of clinical near-infrared spectroscopy (NIRS). Cerebral function can be monitored by NIRS system. It is a safe and non-invasive means of monitoring cerebral function. There is a window of wavelengths in the near infrared region between 600 and 1000 nm in which photons are able to penetrate tissues far enough to illuminate deeper structures such as cerebral cortex. [22] In addition, there are compounds in tissue such as oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (Hb) whose absorption of light changes with tissue oxygenation. The concentrations of HbO_2 and Hb vary rapidly during alterations in cerebral perfusion and oxygenation. Since absorption of the activated region varies by changes in the blood volume and oxygenation, brain activation can be measured by detecting the intensity change of near-infrared light that passes through the brain [23]. Typical applications of NIRS include pharmaceutical, medical diagnostics (including blood sugar and oximetry), food and agrochemical quality control, as well as combustion research.

3.2. The use of fNIRS in Neuroimaging

This optical method can be used in a number of fields of science including physics, physiology, or medicine. It was only in the last few decades that NIRS began to be used as a medical tool for monitoring patients. For medical research, NIRS can be accompanied by other modalities such as magnetic resonance imaging (MRI) or computerized tomography (CT). For example, NIRS can be used for non-invasive assessment of the brain function through an intact skull in human subjects by detecting changes in blood hemoglobin concentrations associated with neural activity. This application is sometimes called optical topography (OT) in which NIRS is used for functional mapping of the human cortex. The term optical tomography is used when NIR is applied to obtain slices of sectional images of tissue or structure. The terms NIRS and OT are often used interchangeably, but they have

some distinctions. The most important difference between NIRS and OT is that OT is mainly used to detect spectroscopic reflection and scattering simultaneously from multiple measurement points and display the results in the form of map, whereas NIRS provides similar data using fewer measurement points.

The primary application of NIRS to the human body uses the fact that the transmission and absorption of NIR light in human body tissues contains information about hemoglobin concentration changes. When a specific area of the brain is activated, the localized blood volume in that area changes quickly. Optical imaging can measure the location and activity of specific regions of the brain by continuously monitoring blood hemoglobin levels through the determination of optical absorption coefficients.

NIRS can be accompanied by other modalities such as magnetic resonance imaging (MRI) or computerized tomography (CT). For example, NIRS can be used for non-invasive assessment of the brain function through an intact skull in human subjects, by detecting changes in blood hemoglobin concentrations associated with neural activity. This is known as fNIRS (functional near-infrared imaging).

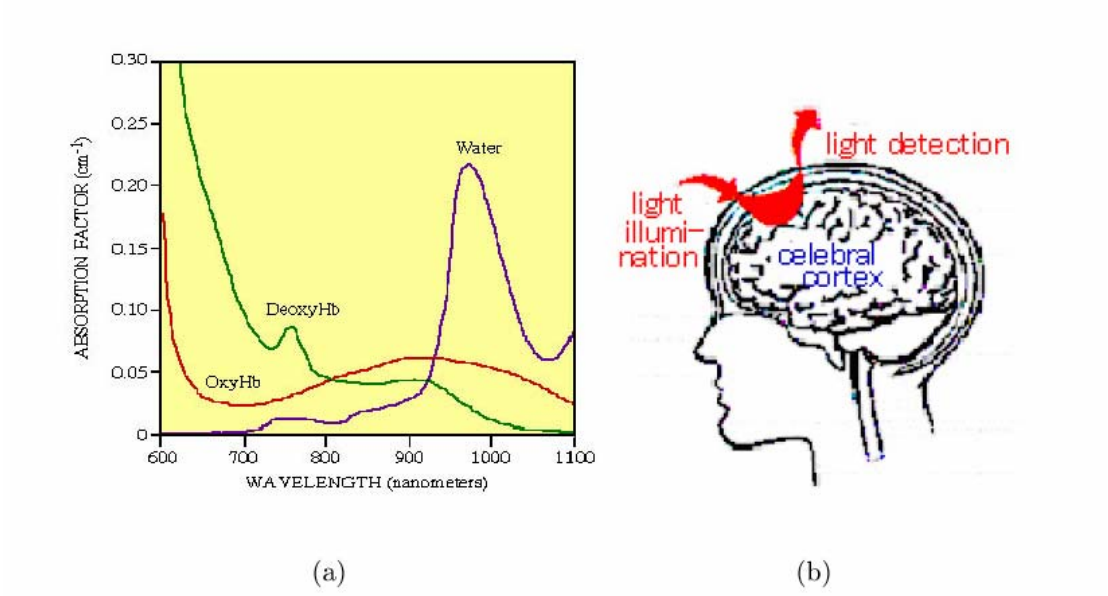

Figure 3.1 a) The absorption spectrum of chromophores (b) the model of optical neuroimaging [20]

3.3. Niroxcope 301

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

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

The current version of this device is named Niroxcope 301. The probe of this device has light sources, photodetectors and special backing and band material as in Figure 3.3. It consists of four LEDs and ten detectors that require external control for their operation. Light sources used in this thesis are multi-wavelength light-emitting diodes.

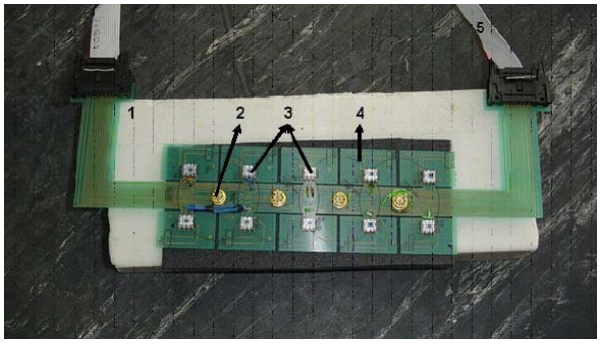

Figure 3.2 A 4-LED (2) probe with 10 photodetectors (3) placed in a PCB (4) on a grey phantom (1)

In NIROXCOPE 301, the distance between light sources (LEDs) and detectors is 2.5 cm, which enables nearly 2 cm penetration depth in the tissue as in Figure 3.3.

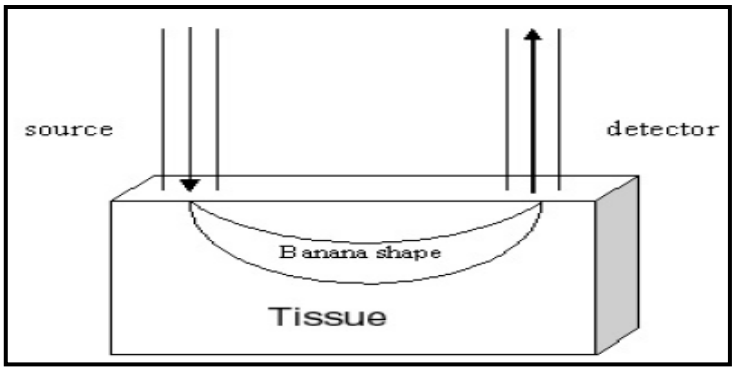

Figure 3.3 The banana-shaped travel of light in tissues

4. METHOD

4.1. Subjects

15 Adult subjects diagnosed with ADHD were included in this study. Adult ADHD subjects were ascertained from outpatient clinics of two university hospitals. Diagnoses were made by DSM-IV ADHD criteria. ADHD subjects underwent two fNIRS evaluations with an interval of 24 hours. They were evaluated with fNIRS during Stroop test performance. Half of the subjects were scanned first off MPH and then on MPH, and the other half vice versa. For the on MPH recordings, a fixed dose of 10 mg of MPH was applied 45 minutes before the test.

4.2. Experimental Protocol

In this study, 15 adult, right handed cases with DSM-IV diagnosis of Attention deficit hyperactivity disorder (ADHD) were evaluated with fNIRS during Stroop test performance. Stroop task is a color-word matching task. They were presented with two words one written over the other. The top one was written in ink-color whereas the below one was in white (over a black background). If a word is displayed in a color different from the color it actually names the color in which it is displayed must be named. Subjects were asked to judge whether the word written below correctly denotes the display color of the upper word. If so, subjects have to press the left mouse button and if not to the right mouse button.

Stroop task consists of neutral, congruent and incongruent stimuli (NS, CS, IS; respectively). In the neutral condition upper word consisted of four X's (XXXX) in ink-color. In the congruent condition ink-color of the upper word and the word itself were the same. In incongruent condition, ink-color of the upper word and the word itself were different. The stimuli were presented in a semi-blocked manner. Each block consisted of 6 trials. Inter stimulus interval within the blocks was 4 seconds and blocks were placed 20 seconds apart in time. The stimulus type within a block was homogeneous (but the arrangement of correct and

false stimuli might change), i.e. a block consisted only of, for instance, congruent trials, which may be correct or false. There were 5 blocks of each stimulus type.

Experiments were performed in a silent and dark room to prevent any other stimuli. Stimuli were presented via a computer screen. The subjects performed the task only with their right hands.

4.3. Data Collection

Experiments were performed using a continuous wave near-infrared spectroscopy device (NIROXCOPE 301) built in Biophotonics Laboratory of Bogazici University [22]. The system has four light emitting diodes that are 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 805nm for HbO_2. Four non-overlapping 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. Detector layout is shown in Figure 4.1.

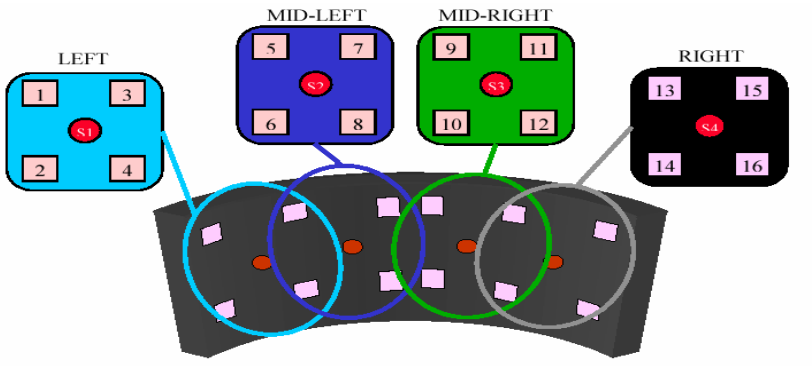

Figure 4.1 Source-detector configurations on the brain probe and nomenclature of photodetectors [46].

The source detector distance is designed to be 2.5 cm, corresponding to 2 cm of average adult cortex depth making it possible to observe the first millimeters of the gray matter. For measurement, probe is placed on the forehead of the subjects aligning the base with the eyebrows.

The data gathered from the experiment is used to calculate the relative changes in [Hb] and [HbO_2] signals according to the Beer Lambert Law. The sampling rate is 1.77 Hz.

Figure 4.2 A photograph of the functional optical imager, NIROXCOPE 301 [20]

4.4. Data Analysis

fNIRS provides [HbH] and [HbO2] data from 16 regions over the forehead. The program developed in the MATLAB® environment is utilized for the analysis of the data. First of all, all the data was divided into three frequency bands: high, low and very low frequency. To eliminate the spikes, outlier elimination and filtering was performed in all of these frequency bands. And data analysis was performed by examining the data in the very low frequency band. Finally, all of the responses to neutral (NS), congruent (CS) and incongruent stimuli (IS) obtained from 16 detectors were plotted to determine the maximum and minimum values of the responses in each drug-off and on cases. To select the maximum and minimum values, GINPUT which is the MATLAB library function with which numerical

data was extracted from the plots, was used. It enables the user to select points from the figure using the mouse for cursor positioning. Two points per plot were selected to obtain the parameters as marked with colored marks in Figure 4.3.

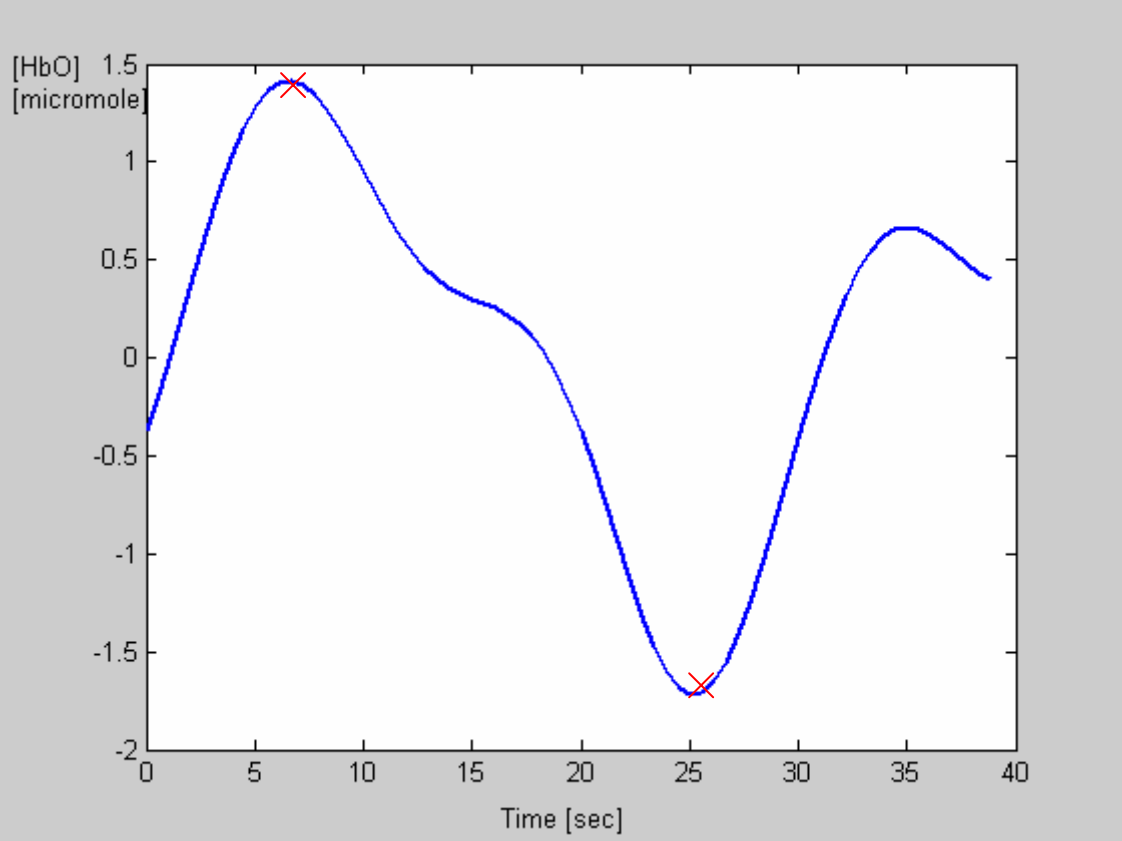

Figure 4.3 Two input points to determine parameters of the maximum and minimum values.

4.5. Statistical Analysis

In order to compare the hemodynamic responses of drug-off and on cases, the differences between the maximum and minimum values of the responses to all three types of stimuli were compared. Statistical significance between groups was tested by the t-test. The statistically significant level of difference was considered to be at $p < 0.05$. The region between $0.1 < p < 0.05$ was considered as marginal significant. Finally, the mean values of the groups which are statistically significant and marginal siginificant, were calculated to plot their bar graphics.

To find the interference between the different types of stimuli (IS-CS, IS-NS, CS-NS) the minimum or maximum values of these stimuli were subtracted from each other. And then again statistical significance between groups was tested by the t-test.

After all of these analyses, behavorial performances of the subjects were analysed. Reaction time is the duration in which the subjects answered the questions and they were directly related with behavorial performances. By using a MATLAB code, reaction times of the subjects for each type questions were calculated. After calculating the mean reaction times, they were compared with the HbH and HbO data.

5. RESULTS AND DISCUSSION

The data gathered from measurement is shown in figures 5.1 and 5.2. They are raw data. They were analysed in MATLAB environment. The figure 5.1 shows the oxyhaemoglobin and deoxyhaemoglobin data obtained from the detector 9 before medication. The figure 5.2 shows the oxyhaemoglobin and deoxyhaemoglobin data obtained from the detector 9 after medication. It is a data from one of the subjects. These data can be varied from one subject to another subject. HbH and HbO values can be either positive or negative. In some cases, there can be seen many oscillations. Sometimes, more simple data were gathered fromt he measurements.

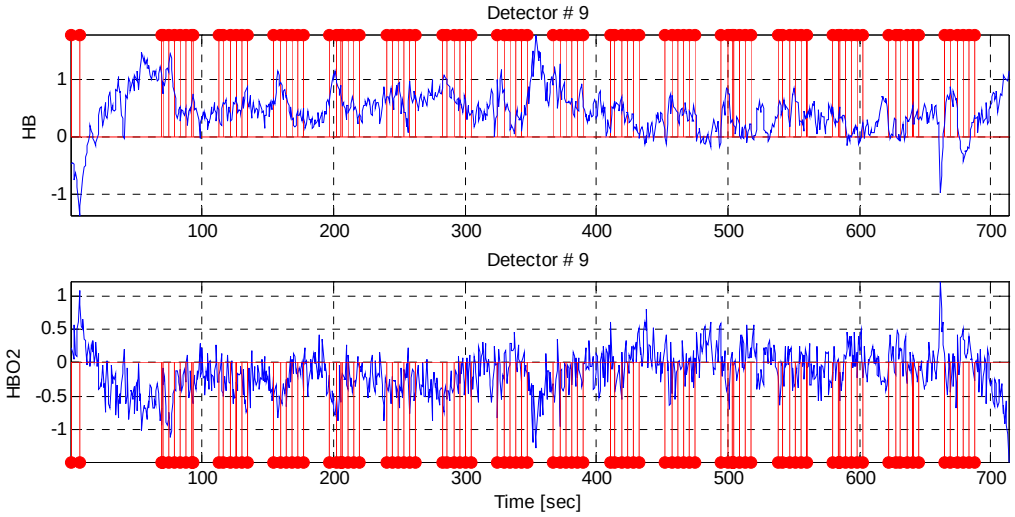

Figure 5.1 HbH and HbO data gathered from the 9th detector before medication.

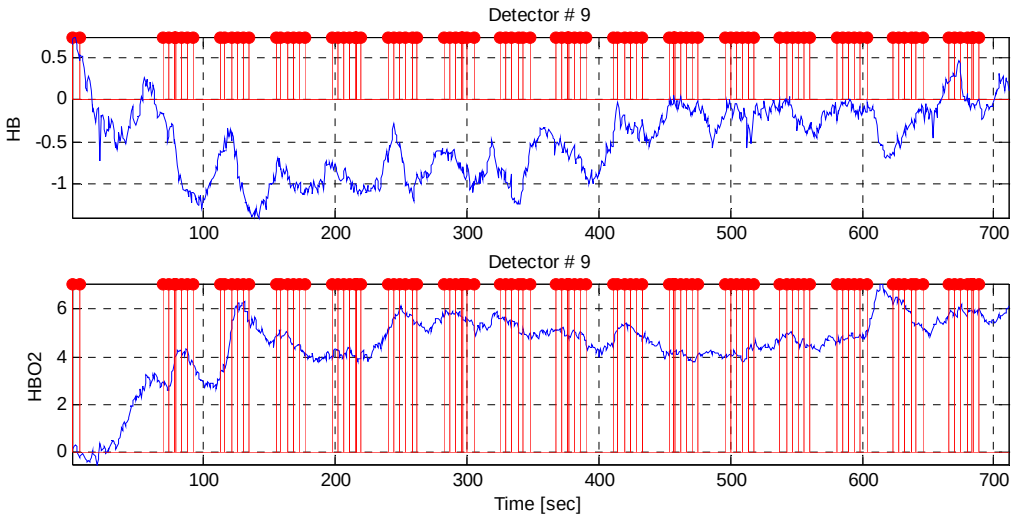

Figure 5.2 HbH and HbO data gathered from the 9th detector after medication**.**

Table 5.1 shows the data obtained from 15 ADHD patients off and on MPH. These are the minimum values of deoxyhaemoglobin signals obtained from the 2nd, 10th and 12th detectors. They give significant results in the t-test. Only the responses to incongruent and congruent stimuli have siginificant results in this category. It can be seen that MPH-on values are generally greater than the MPH-off values. The decrease is only seen in the responses to congruent stimuli obtained from 12th detector.

Table 5.1 Mean values of the significant deoxyhaemoglobin data (minimum values)

HB	**off**	**on**
minimum	**mean**	**mean**
is-10	-0.4281	-1.4016
cs-2	-0.5279	-1.6641
cs-12	-1.5285	-0.6018

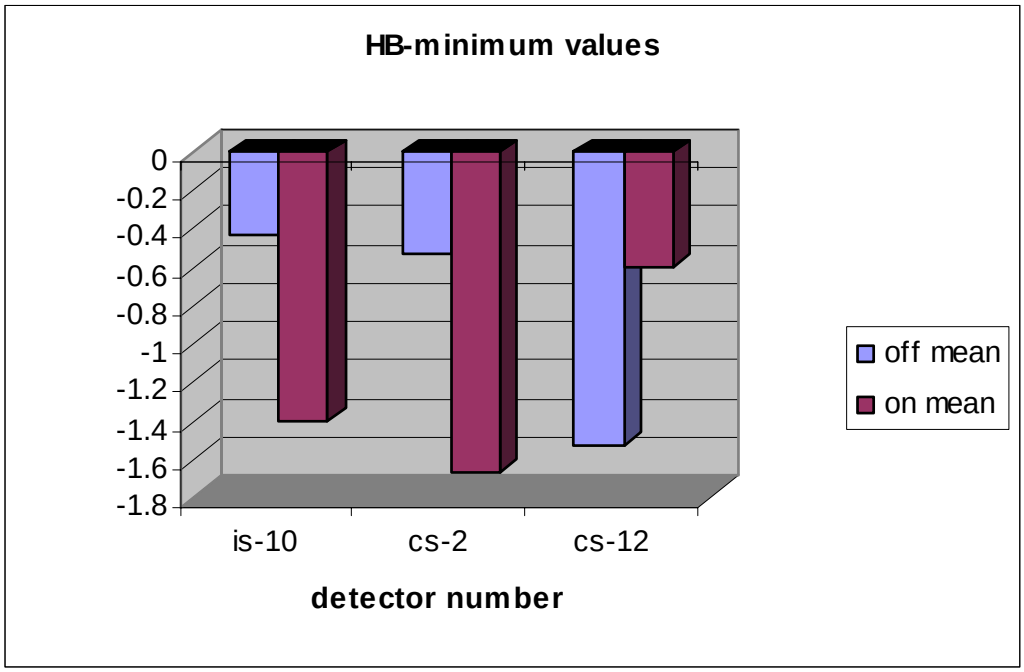

Figure 5.3 Mean values of the significant deoxyhaemoglobin data (minimum values)

Figure 5.3 is the bar graphic of the mean values shown in Table 5.1. In this graphic, the results can be seen more clearly. There is increase in the signals obtained by 2nd (for incongruent stimuli) and 10th detectors (congruent stimuli) and decrease in the signal obtained from 12th detector (congruent stimuli).

Table 5.2 shows maximum values of deoxyhaemoglobin signals obtained from the 6th and 16th detectors. They give significant results in the t-test. Only the responses to congruent stimuli have significant results in this category. Here, we see that MPH-off values are greater than MPH-on values for the 6th detector. But MPH-on values are greater than MPH-off at the 16th detector.

Table 5.2 Mean values of the significant deoxyhaemoglobin data (maximum values)

HB	off	on
maximum	mean	mean
cs-6	1.146	0.116
cs-16	0.288	0.761

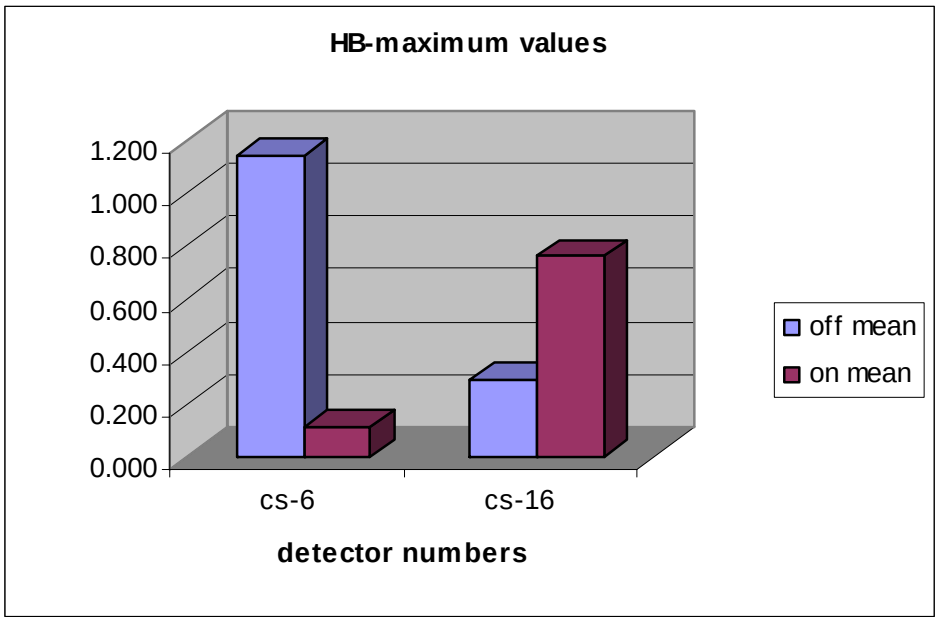

Figure 5.4 Mean values of the significant deoxyhaemoglobin data (maximum values)

Figure 5.4 is bar graphic of the mean values shown in table 5.2. The decrease at the detector 6 and the increase at the detector 16 can be seen more precisely.

Table 5.3 shows minimum values of oxyhaemoglobin signals obtained from the detectors 2, 7, 8, 11, 12, 13, 15. They give significant results in the t-test. The responses to congruent and neutral stimuli have significant results in this category. Here, we see that MPH-off values are always greater than MPH-on values except the detector 2 for the congruent stimuli.

Table 5.3 Mean values of the significant oxyhaemoglobin data (minimum values)

HBO	**off**	**on**
minimum	**mean**	**mean**
cs-2	-0.4923	-1.424
cs-8	-1.2939	-0.4879
cs-12	-1.243	-0.5871
ns-7	-1.2308	-0.461
ns-11	-1.1927	-0.552
ns-13	-0.9445	-0.237
ns-15	-1.3139	-0.4177

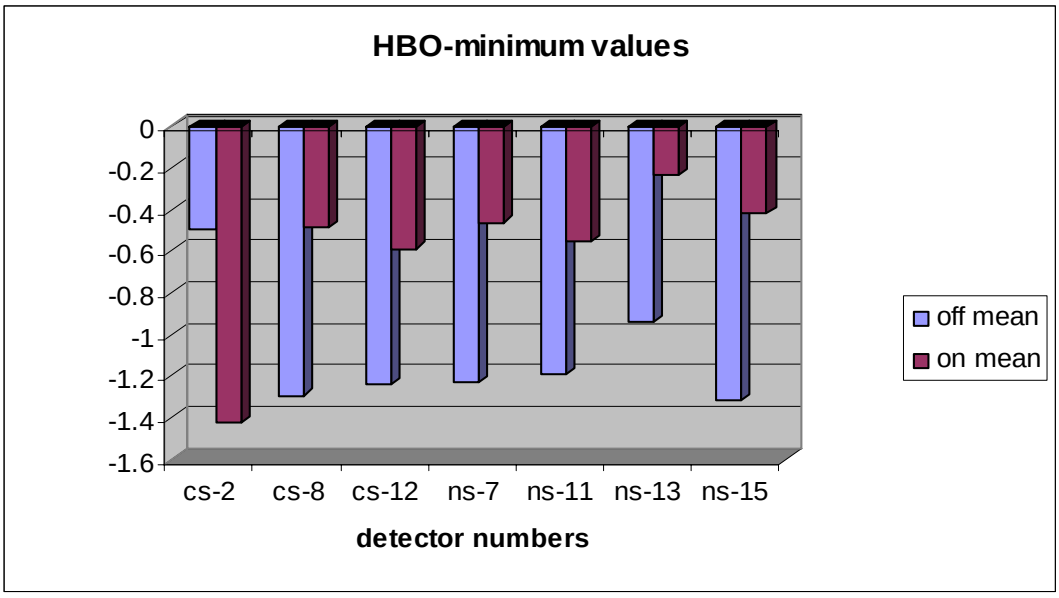

Figure 5.5 Mean values of the significant oxyhaemoglobin data (minimum values)

Bar graphic in Figure 5.5 shows the mean values in table 5.3. We can see here, the large decrease mentioned above.

Table 5.4 shows maximum values of oxyhaemoglobin signals obtained from the detectors 5, 8, 11. They give significant results in the t-test. They are mostly the responses to congruent stimuli and also incongruent stimuli. Here, again MPH-off values are always greater than MPH-on values.

Table 5.4 Mean values of the significant oxyhaemoglobin data (maximum values)

HBO maximum	**off mean**	**on mean**
is-11	1.8412	1.1662
cs-5	1.4516	0.675
cs-8	1.7053	0.7948
cs-11	1.6432	0.3479

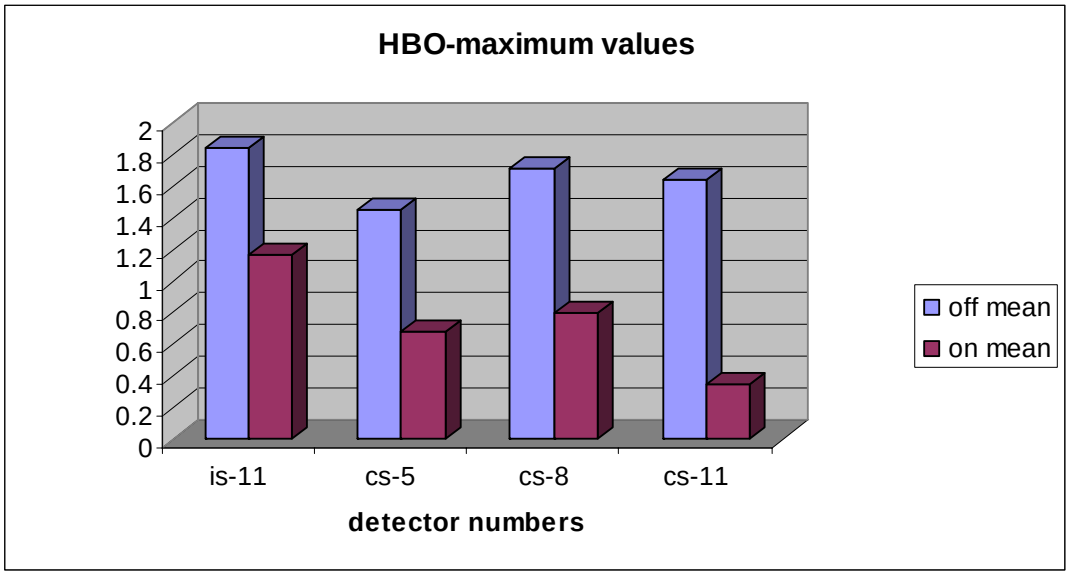

Figure 5.6 Mean values of the significant oxyhaemoglobin data (maximum values)

The data shown in table 5.4 is bar-graphed in figure 5.6. The decrease between the MPH-off and on values can be seen here mora clearly.

To find the differences of the resposes to different stimuli, the minimum and maximum values of deoxy- and oxyhaemoglobin data of these stimuli were subtracted from each other. For example, minimum values of congruent and neutral stimuli were subtracted from the minimum values of incongruent stimuli (IS-CS). Also, the data of neutral stimuli were subtracted from congruent stimuli (CS-NS). These process was applied to maximum values, too. These results are called interference.

Table 5.5 shows the interference results of minimum deoxyhaemoglobin data. These are the significant mean values for the detectors 2, 10, 11, 12, 13. Here we see great difference between the incongruent stimuli with other types. Interference for the MPH-off data is positive. After treatment with methylphenidate, the interference is calculated as negative. These results can be seen more easily in figure 5.57.

Table 5.5 Mean values of the significant interference results of the deoxyhaemoglobin data (minimum values)

HB	off	on
minimum	mean	mean
is-ns 10	1.2833	-2.9946
is-cs 11	0.9093	-2.0462
is-cs 12	0.2268	-1.7555
is-cs 13	0.6383	-1.3879
cs-ns 2	-0.0122	-0.5031

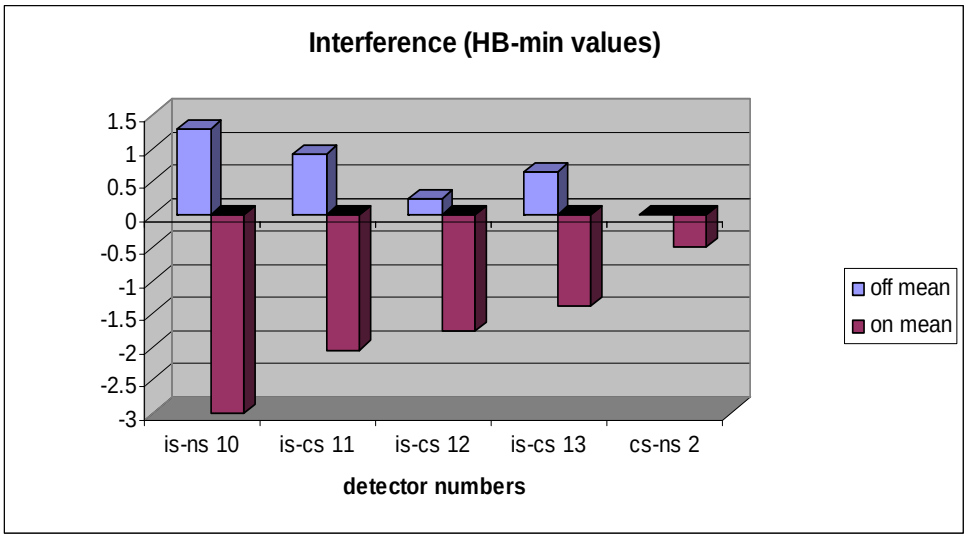

Figure 5.7 Mean values of the significant interference results of the deoxyhaemoglobin data (minimum values)

Table 5.6 shows the interference results of maximum deoxyhaemoglobin data. These are the significant mean values for the detectors 15 and 16. Here the only significant difference is between the congruent and neutral stimuli. These results are different from the previous results. Because interference for the MPH-off data is negative now. After treatment with methylphenidate, the interference is calculated as positive. These results can be seen more easily in figure 5.8.

Table 5.6 Mean values of the significant interference results of the deoxyhaemoglobin data (maximum values)

HB	off	on
maximum	mean	mean
cs-ns 15	-0.433	-0.0027
cs-ns 16	-0.8097	0.2385

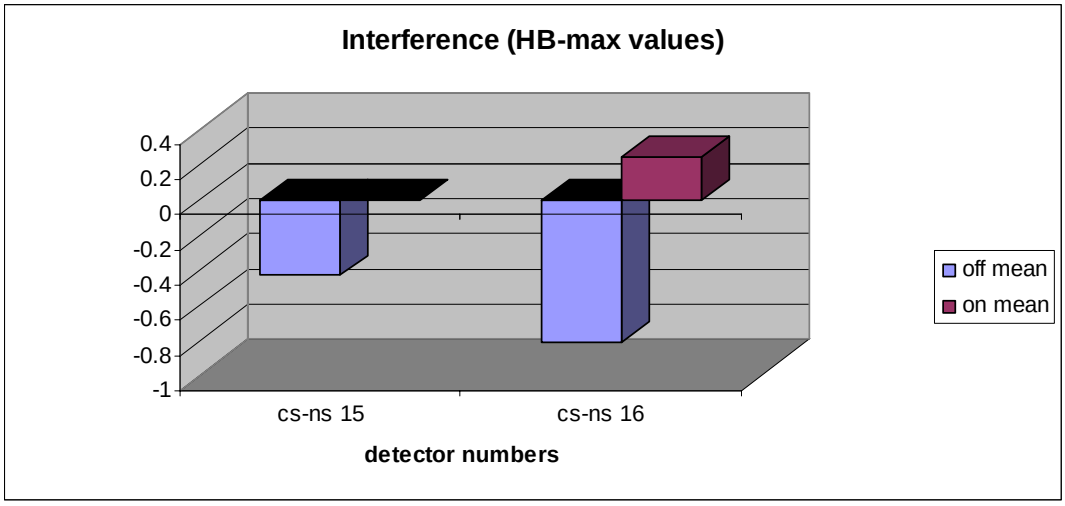

Figure 5.8 Mean values of the significant interference results of the deoxyhaemoglobin data (maximum values)

Table 5.7 shows the interference results of minimum oxyhaemoglobin data. These are the significant mean values for the detectors 2, 8, 13, 15. These significant results obtained from this category are like the minimum deoxyhaemoglobin data. The responses to incongruent stimuli gives more difference than others do. Figure 5.9 shows the results in bar-graphic.

Table 5.7 Mean values of the significant interference results of the oxyhaemoglobin data (minimum values)

HBO	**off**	**on**
minimum	**mean**	**mean**
is-cs 2	-0.3409	0.8633
is-ns 8	1.2409	0.0303
is-ns 13	0.6369	-0.2016
is-ns 15	1.1377	0.1103
cs-ns 15	0.717	-0.3389

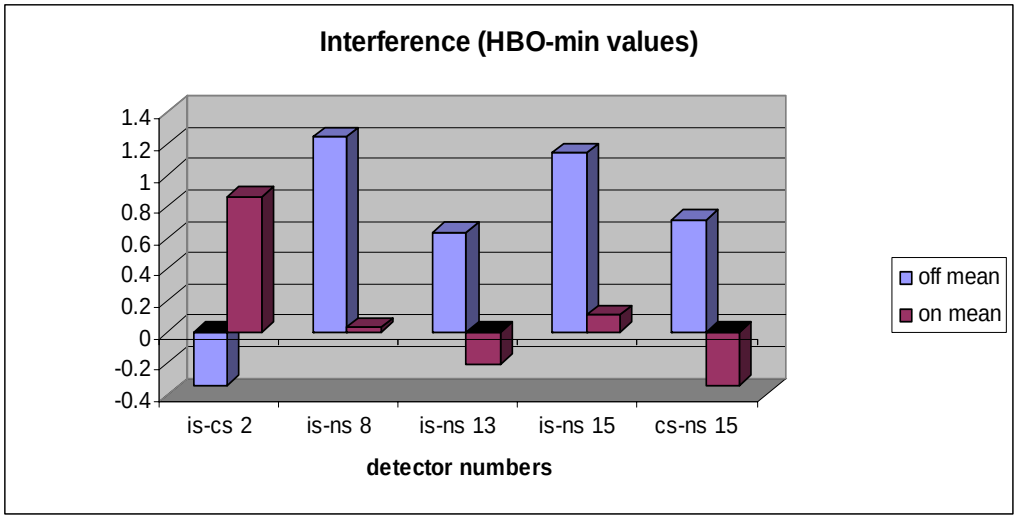

Figure 5.9 Mean values of the significant interference results of the oxyhaemoglobin data (minimum values)

Table 5.8 shows the interference results of maximum oxyhaemoglobin data. These are the significant mean values for the detectors 5, 11 and 13. Here the only significant difference is between the congruent and neutral stimuli. MPH-on data here are negative. But MPH-off data are negative or positive for different detector numbers. These results can be seen more easily in figure 5.10.

Table 5.8 Mean values of the significant interference results of the oxyhaemoglobin data (maximum values)

HBO	**off**	**on**
maximum	**mean**	**mean**
cs-ns 5	-0.1691	-1.0327
cs-ns 11	0.0243	-1.0672
cs-ns 13	0.1579	-0.5919

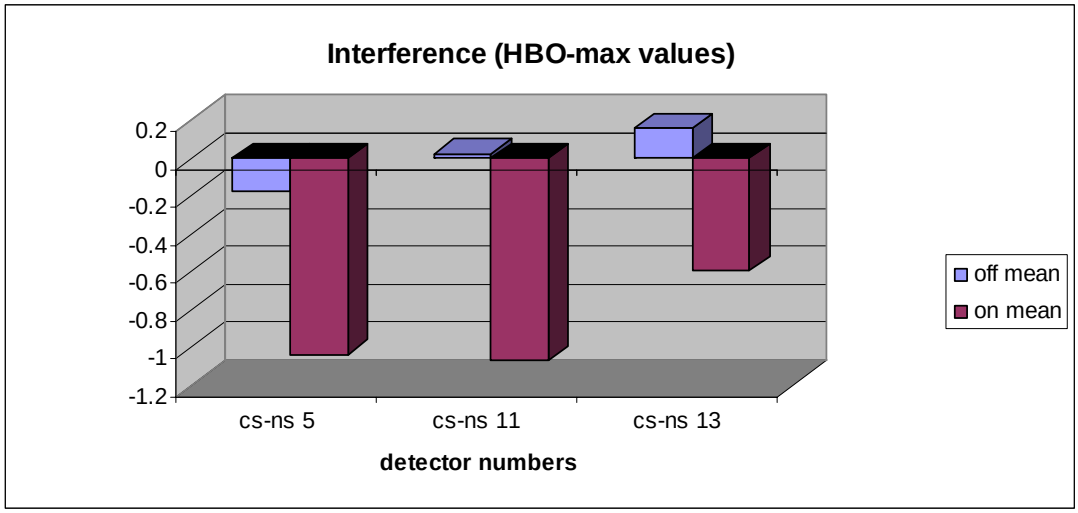

Figure 5.10 Mean values of the significant interference results of the oxyhaemoglobin data (maximum values)

To investigate the behavioral performances of the subjects, the reaction times to all types of questions were calculated. Table 5.9 shows the reaction times before and after medication. Then the mean values of the reaction times were calculated and they were compared with the maximum and minimum HbH and HbO values.

Table 5.9 Reaction times of the subjects for all types of questions before and after medication and their mean and standard deviation values in seconds

subject no	NS		CS		IS	
	off	on	off	on	off	on
1	1.011	0.963	1.178	1.178	1.372	1.332
2	1.488	0.927	1.365	1.097	1.708	1.267
3	0.660	0.623	0.769	0.685	0.871	0.701
4	1.213	1.086	1.256	1.340	1.657	1.510
5	1.157	1.140	1.114	1.330	1.637	1.362
6	0.732	0.850	0.794	0.868	0.925	0.987
7	1.133	0.884	1.186	0.863	1.282	0.887
8	1.252	1.217	1.197	1.237	1.456	1.310
9	0.789	0.943	0.859	1.321	0.967	1.248
10	0.958	0.830	1.080	0.941	1.150	0.953
11	0.973	1.101	1.083	1.142	1.260	1.234
12	1.422	1.325	1.375	1.448	1.502	1.399
13	1.865	1.065	2.018	1.531	2.622	1.261
14	1.028	0.833	1.113	0.970	1.269	1.030
15	0.952	0.841	1.224	1.069	1.546	1.137
mean	**1.109**	**0.975**	**1.174**	**1.135**	**1.415**	**1.174**
std	0.313	0.180	0.297	0.239	0.427	0.220

Figure 5.11 shows the data obtained from the detector 2. In the first part, minimum deoxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum deoxyhaemoglobin data vs reactiom times. To plot these graphs, mean values of the significant data were used. The first point on the lines always shows the reactions to the neutral stimuli, the second point shows the reactions to the congruent stimuli and the last one shows the reactions to the incongruent stimuli. The blue line represents the data obtained before medication. The red one represents the data obtained after medication. It can be seen that the reaction times before medication are always longer than the duration after medication. MPH shortens the durations to answer the questions. As it is known, neutral stimuli are the easiest questions and the incongruent stimuli are the most difficult ones. Therefore, to reply the easiest questions takes much less time than to reply the difficult questions. This result can be seen on the graphs.

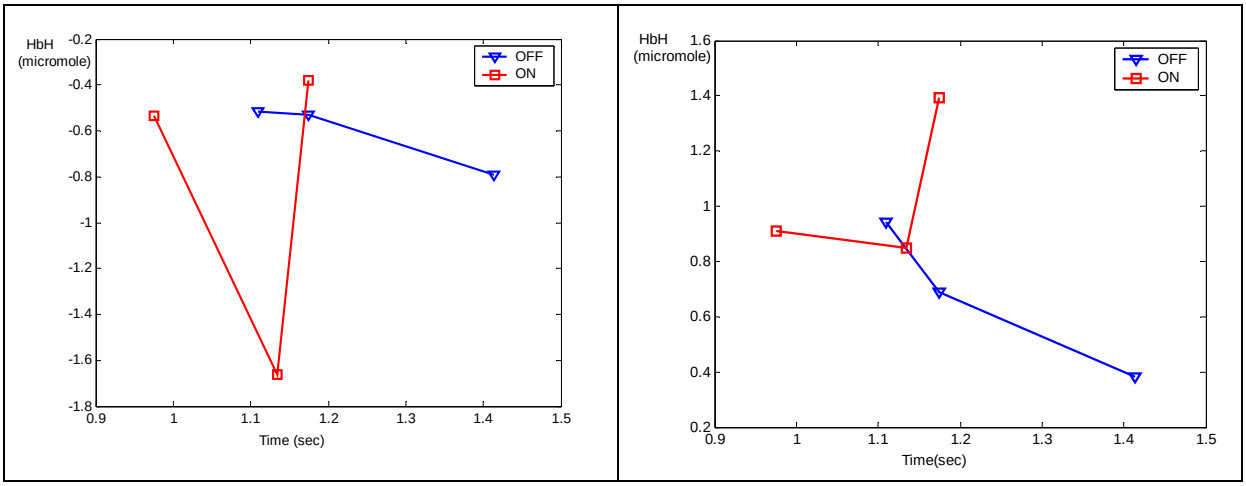

Figure 5.11 a) The graph of the minimum deoxyhaemoglobin data vs. reaction time for the detector 2. b) The graph of the maximum deoxyhaemoglobin data vs. reaction time for the detector 2.

Figure 5.12 shows the data obtained from the detector 6. In the first part, minimum deoxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum deoxyhaemoglobin data vs reactiom times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

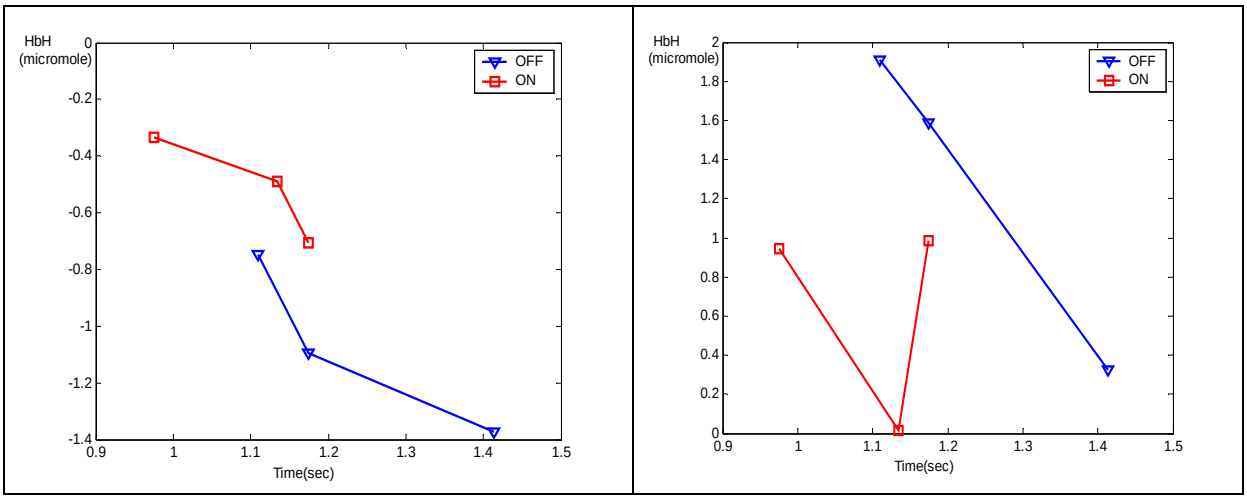

Figure 5.12 a) The graph of the minimum deoxyhaemoglobin data vs. reaction time for the detector 6. b) The graph of the maximum deoxyhaemoglobin data vs. reaction time for the detector 6.

Figure 5.13 shows the data obtained from the detector 10. In the first part, minimum deoxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum deoxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

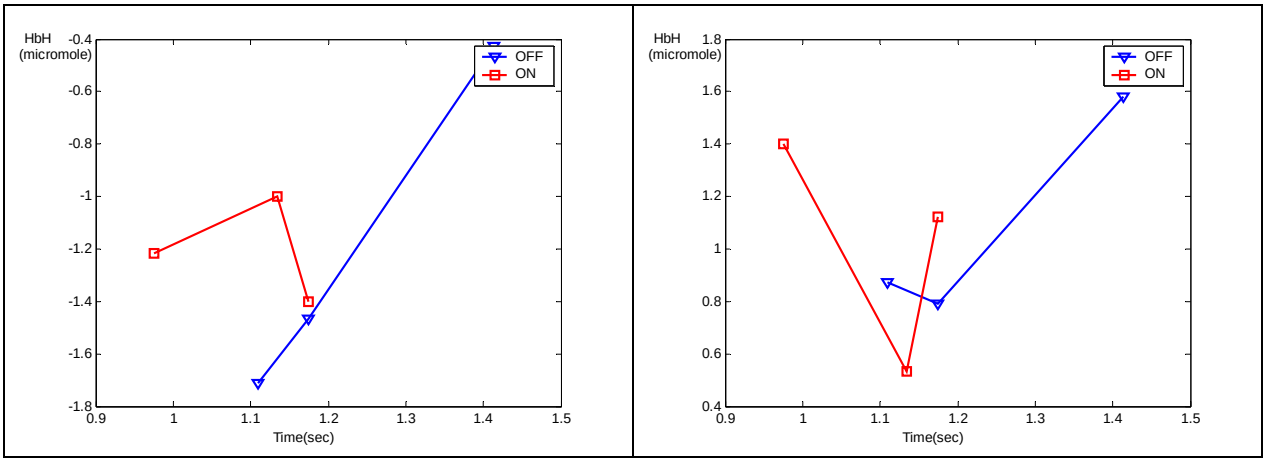

Figure 5.13 a) The graph of the minimum deoxyhaemoglobin data vs. reaction time for the detector 10. b) The graph of the maximum deoxyhaemoglobin data vs. reaction time for the detector 10.

Figure 5.14 shows the data obtained from the detector 12. In the first part, minimum deoxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum deoxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

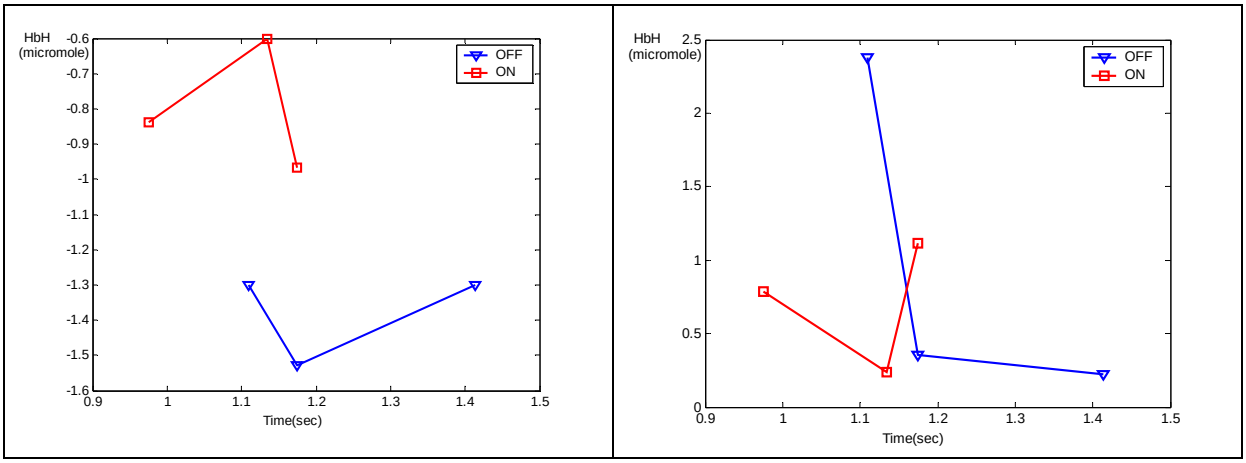

Figure 5.14 a) The graph of the minimum deoxyhaemoglobin data vs. reaction time for the detector 12. b) The graph of the maximum deoxyhaemoglobin data vs. reaction time for the detector 12.

Figure 5.15 shows the data obtained from the detector 16. In the first part, minimum deoxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum deoxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

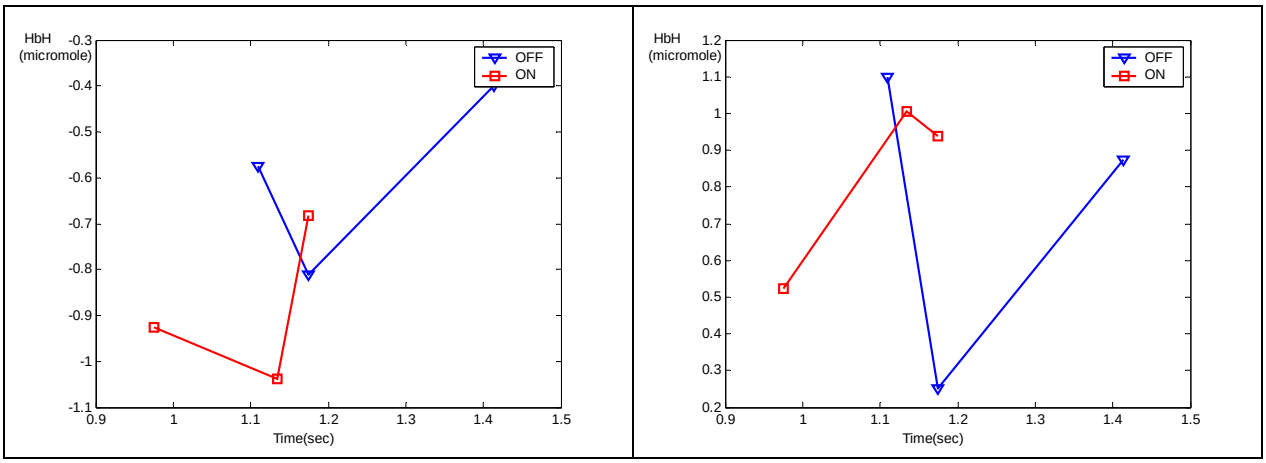

Figure 5.15 a) The graph of the minimum deoxyhaemoglobin data vs. reaction time for the detector 16. b) The graph of the maximum deoxyhaemoglobin data vs. reaction time for the detector 16.

Figure 5.16 shows the data obtained from the detector 2. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. For theoxyhaemoglobin data, the effect of the MPH did not change. It shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

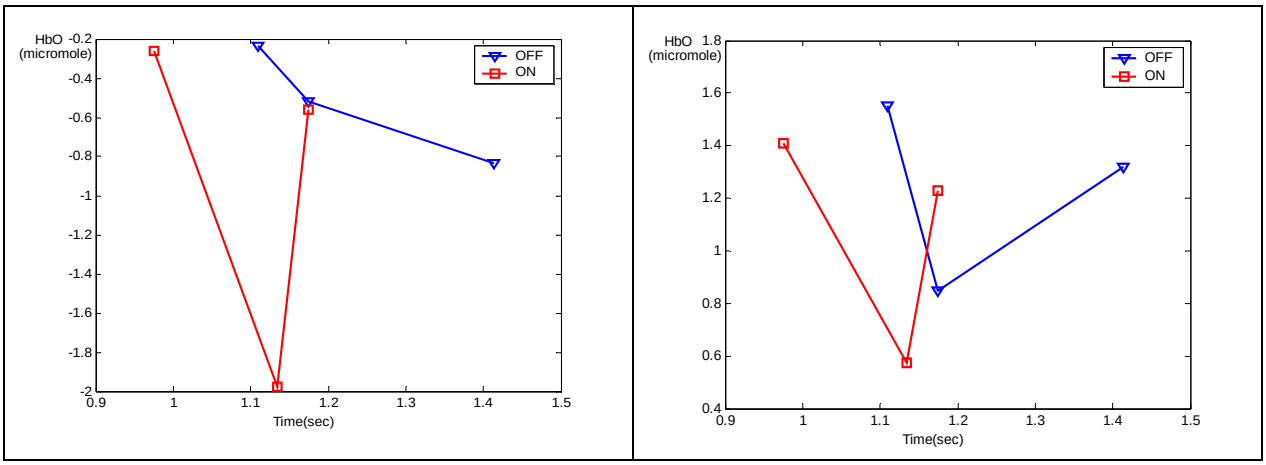

Figure 5.16 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 2. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 2.

Figure 5.17 shows the data obtained from the detector 5. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

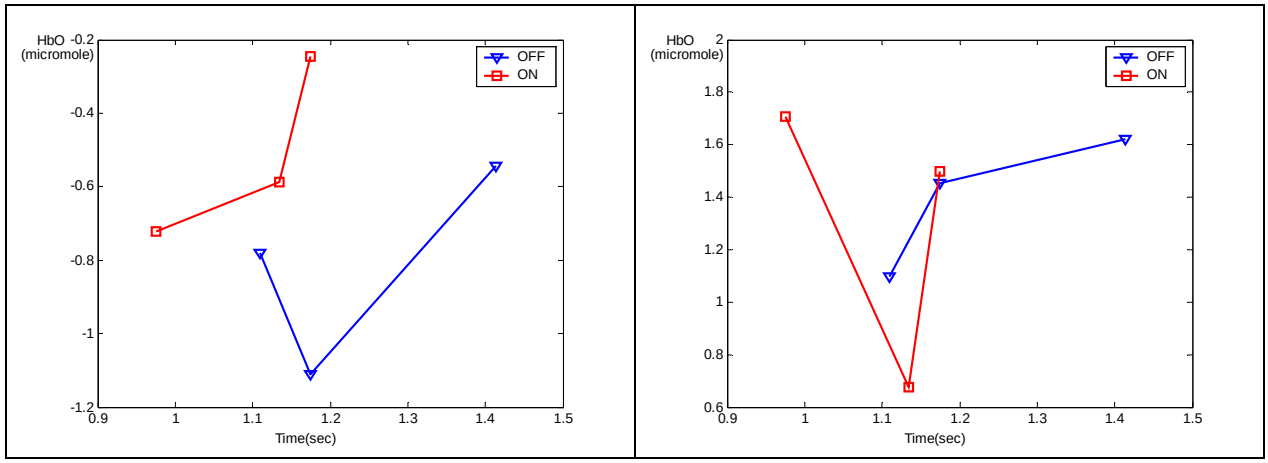

Figure 5.17 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 5. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 5.

Figure 5.18 shows the data obtained from the detector 7. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

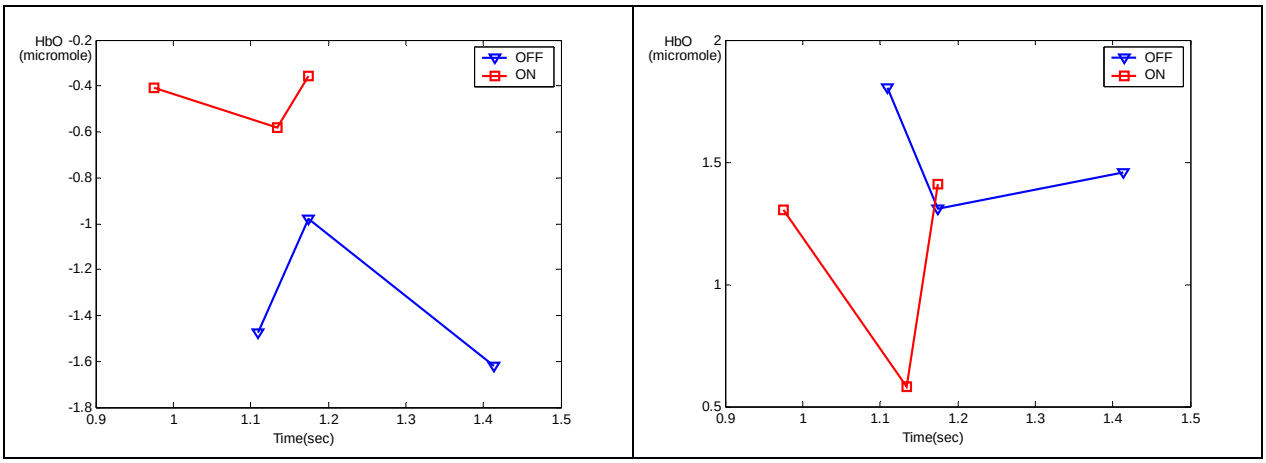

Figure 5.18 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 7. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 7.

Figure 5.19 shows the data obtained from the detector 8. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

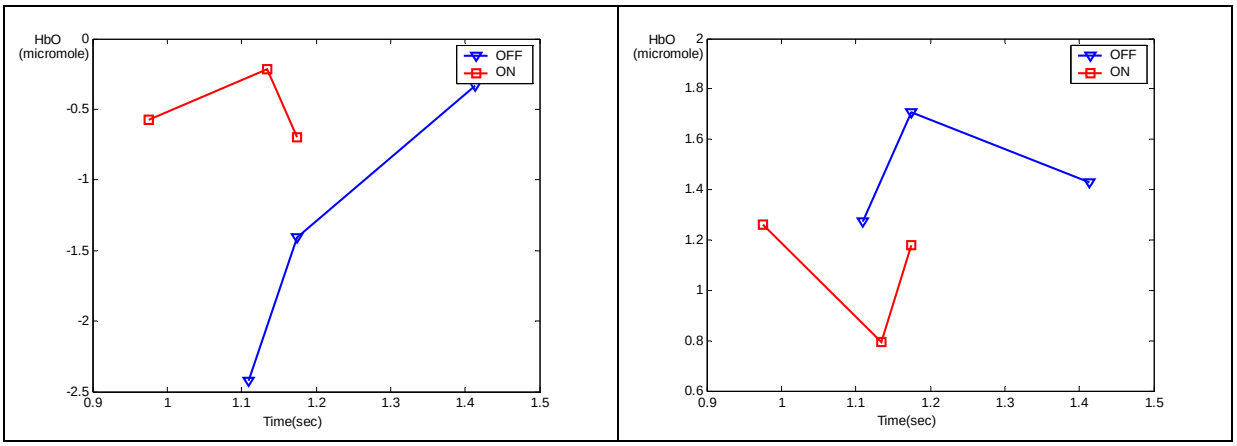

Figure 5.19 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 8. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 8.

Figure 5.20 shows the data obtained from the detector 11. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

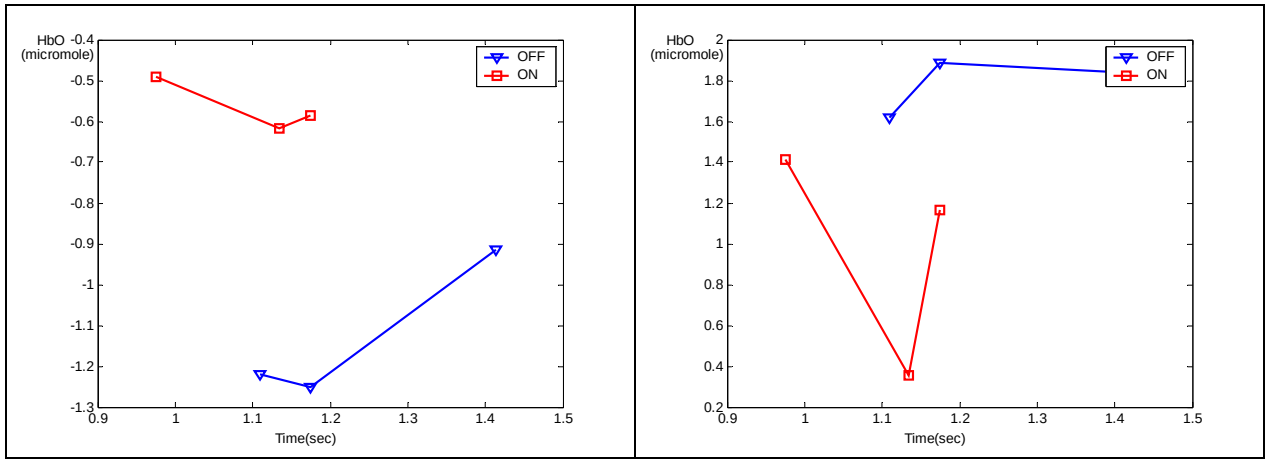

Figure 5.20 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 11. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 11.

Figure 5.21 shows the data obtained from the detector 12. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

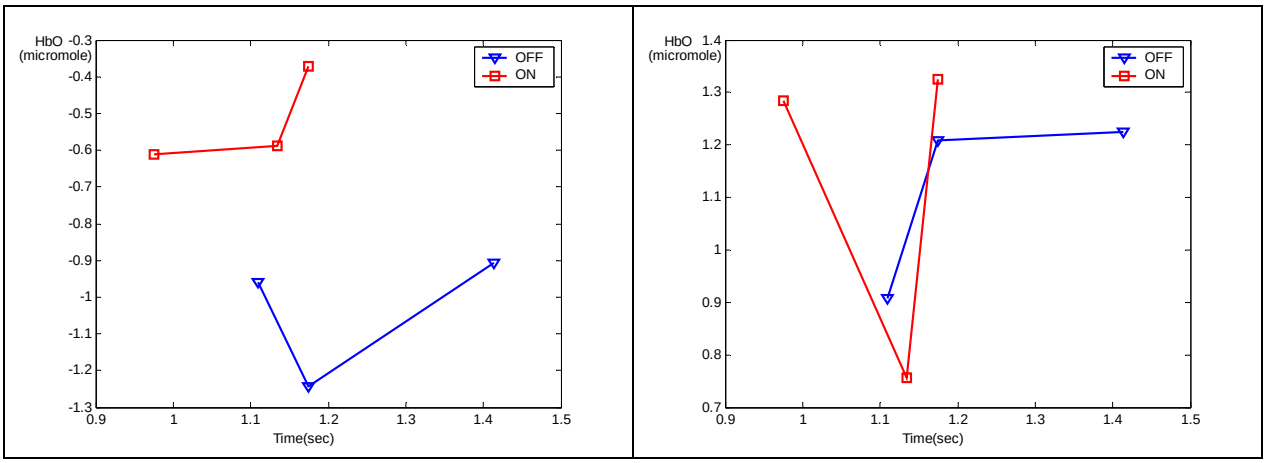

Figure 5.21 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 12. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 12.

Figure 5.22 shows the data obtained from the detector 13. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

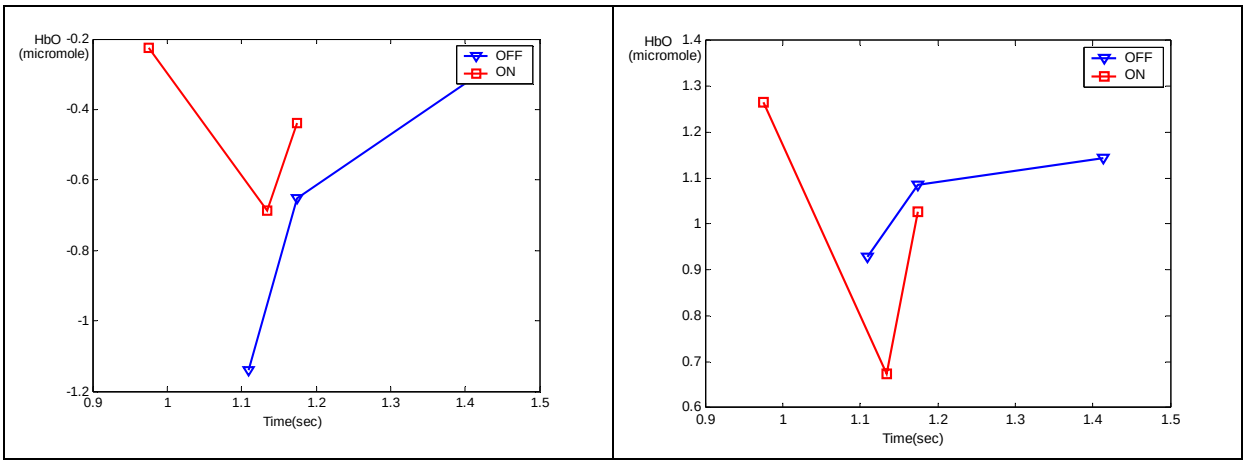

Figure 5.22 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 13. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 13.

Figure 5.23 shows the data obtained from the detector 15. In the first part, minimum oxyhaemoglobin data was compared with reaction times. The second part is the graph of the maximum oxyhaemoglobin data vs reaction times. Again, mean values of the significant data were used. The first point is the reactions to the neutral stimuli; the second point is the reactions to the congruent stimuli and the last one is the reactions to the incongruent stimuli. In this graph, it is also seen that MPH shortens the durations to answer the questions. The reaction times to neutral stimuli are again shorter and the reaction times to incongruent stimuli are again longer than the others.

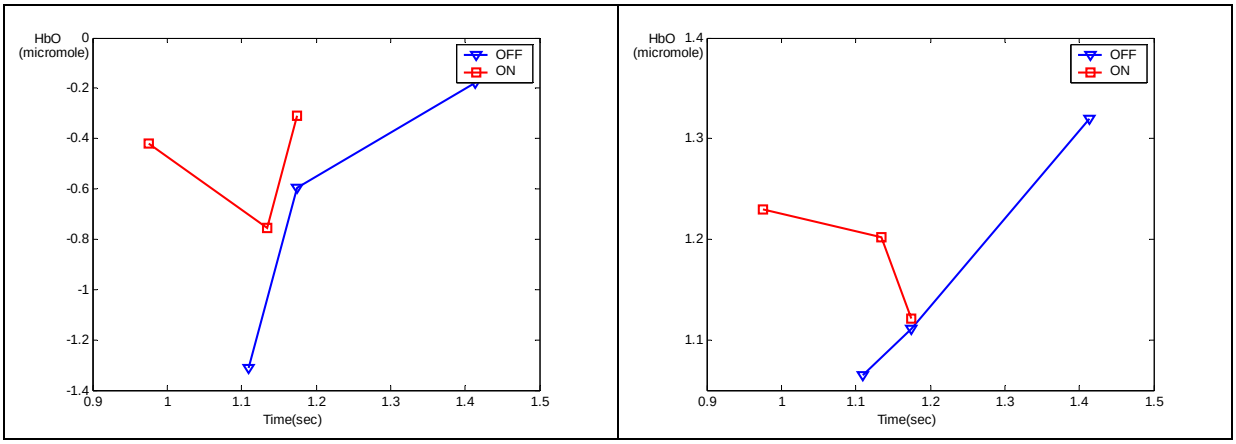

Figure 5.23 a) The graph of the minimum oxyhaemoglobin data vs. reaction time for the detector 15. b) The graph of the maximum oxyhaemoglobin data vs. reaction time for the detector 15.

While investigating the reaction times of the subjects, only some of the detectors which gave significant results were used. For the deoxyhaemoglobin data, the signals from the detectors 2, 6, 10, 12, 16 were analysed. For the oxyhaemoglobin data, the signals from the detectors 2, 5, 7, 8, 11, 12, 13, 15 were analysed. As it is seen from the detector numbers which gave significant results, right lateral and bilateral medial prefrontal regions were activated.

For the ADHD subjects off MPH, HbH generally decreased during CS and IS when compared to NS. HbO generally increased during CS, but increased during IS when compared to NS.

For the ADHD subjects on MPH, HbH generally decreased during CS, but increased during IS when compared to NS. This situation also holds for HbO. It generally decrased during CS, increased during IS when compared to NS.

ADHD subjects on MPH during IS and NS when compared with CS, blood flow was effectively increased during the test with highest cognitive load. However, this situation did not hold for unmedicated ADHD subjects. IS, NS and CS have different patterns for different detectors numbers. But when cognitive loads were compared between on and off-medication groups, HbH generally increased, but HbO generally decreased after medication. Several previous studies have shown that cognitive activity leads to increased forebrain HbO levels, thus increased HbO levels during the IS suggests that in this condition ADHD subjects on MPH effectively increased bilateral frontal HbO levels [58, 59]. In this project, we found that MPH effectively decreased HbO levels. The reason of the decreased level of HbO after medication is vasoconstriction.

When we consider behavioral performance of ADHD subjects on MPH and ADHD subjects off MPH, MPH normalized the behavior during an executive function test but not the related brain activity. It is clearly seen on all of the graphs that MPH has a great effect on the response time of the subjects to NS, CS, and IS. MPH always shortens the durations of the reaction times. This means that subjects answered the questions more quickly after medication.

fNIRS has been used to study deoxy- and oxyhaemoglobin changes in ADHDs and changes were related with MPH use. Firstly, it can be said that the behavioral performance of ADHD subjects improved when medicated. Stroop performance of these patients was improved, as in previous literature.

Many neuroimaging studies have reported that prefrontal cortex activity increases during Stroop test performance. However, unmedicated ADHD patients failed to activate the prefrontal region. This was consistent with previous studies which showed that ADHD subjects had hypofrontality during Stroop task.

In literature, it is said that brain activity increased in medicated ADHD subjects. MPH was believed to increase brain activity and blood flow. But it is not consistent with our study. Increase in brain activity and blood flow means increase in signal obtained by fNIRS. In our results, the signal generally decreased in MPH-on case which means reduced blood volume.

It is known that MPH has vasoconstriction effect via blockade of dopamine mechanism [54]. Vasoconstriction means reduced blood volume. Therefore, we believed that vasoconstriction effect is the reason for the decrease in MPH-on signal.

An analogy is to an engine. There is always a maximum revolution per minute (RPM) for an engine. Nevertheless, one controls the RPM with respect to the steeps (up or down). If the resting engine RPM is too high, the system will consume large amount of gas and will be hyperly active. But if a certain adjustment is made (taking medications) the resting RPM will slow down and the system will be more efficient. Signal to noise ratio will increase hence the desired area will be heard well.

6. CONCLUSION

In this study, fNIRS was used. It is a non-invasive, relatively cheap and portable functional neuroimaging technique to study the differences of prefrontal cortex hemodynamics during Stroop task between adult ADHD subjects on MPH and off MPH. The effects of MPH on hemodynamic variables in the ADHD subjects were examined.

15 right-handed subjets with ADHD were included in this study. The effect of methylphenidate on brain hemodynamics was examined. Data obtained from 16 detectors were statistically analysed for oxyhaemoglobin and deoxyhaemoglobin. The responses to incongruent, congruent and neutral stimuli were compared.

The behavioral performance of ADHD subjects on MPH on Stroop test was better than ADHD subjects off MPH, in terms of response time. During the IS, bilateral prefrontal HbO levels were decreased and HbH levels were increased in ADHD subjects on MPH. Previous studies say that ADHD subjects have functional hypofrontality during the Stroop test and methyphenidate increases the brain activity, thus blood flow. In our study, the signal decreased after the MPH treatment. This means that blood flow decreased, consequently the concentration of deoxyhaemoglobin and oxyhaemoglobin decrased. Decline in the signal was the result of the less absorbtion of the light by HbO_2 and HHb. Nevertheless MPH helped to overcome hyperactivity and inattention problems, increase the efficiency of the brain by controlling the blood vessel more properly.

fNIRS method has some limitations including low spatial resolution, difficulty to measure hemodynamic changes in deeper brain regions, and the measured changes might include data from extracerebral structures (i.e. the scalp and skull and arachnoid space). Thus, the reported changes in hemodynamic variables could be poorly localized. Besides, the reported changes in the prefrontal cortex could reflect changes in other brain regions, like basal ganglia, which could not be evaluated. We did not use another imaging method like fMRI to validate the results. The probe is designed to cover an adult's forehead from hairline to eyebrows. A narrow forehead means loss of signal, since several of the top layer detectors will be sitting on hair and not receiving any light. Hence, small variations in misplacement of the probe that are in 3-5 mm range should be tolerated in activity localization.

The sample was not large, but the statistical differences were quite significant. To have better results, the number of the subjects should be increased.

APPENDIX A – MATLAB CODES

```
load ADHD

ADHD=struct('hb',struct('vlf',[],'lf',[],'hf',[]),'hbo',struct('vlf',[],'lf',[],'hf',[]),'targets',struct('ns',[]
,'cs',[],'is',[]),'t',[]);

for i=1:20
   % Outlier elimination begins
   [bo,ao]=butter(4,0.25/(adhd(i).fs/2));
   adhd(i).hb=filtfilt(bo,ao,adhd(i).hb);
   adhd(i).hbo2=filtfilt(bo,ao,adhd(i).hbo2);
   for j=1:16
      adhd(i).hb(:,j)=adhd(i).hb(:,j)-smooth(adhd(i).hb(:,j),100);
      adhd(i).hbo2(:,j)=adhd(i).hbo2(:,j)-smooth(adhd(i).hbo2(:,j),100);
   end
   % Outlier elimination ends

   % Filtering down to various bands starts
   [bh,ah]=butter(4,[0.12 0.18]/(adhd(i).fs/2)); % High frequency filter settings
   [bm,am]=butter(4,[0.08 0.12]/(adhd(i).fs/2)); % Low frequency filter settings
   [bl,al]=butter(4,0.08/(adhd(i).fs/2)); % Very low frequency filter settings

   % Filtering starts
   ADHD(i).hbo.vlf=filtfilt(bl,al,adhd(i).hbo2);
   ADHD(i).hbo.lf=filtfilt(bm,am,adhd(i).hbo2);
   ADHD(i).hbo.hf=filtfilt(bh,ah,adhd(i).hbo2);

   ADHD(i).hb.vlf=filtfilt(bl,al,adhd(i).hb);
   ADHD(i).hb.lf=filtfilt(bm,am,adhd(i).hb);
   ADHD(i).hb.hf=filtfilt(bh,ah,adhd(i).hb);
   % Filtering ends

   % Finding the question times
```

```
ns=floor(union(adhd(i).markers{1},adhd(i).markers{2})*adhd(i).fs);
cs=floor(union(adhd(i).markers{3},adhd(i).markers{4})*adhd(i).fs);
is=floor(union(adhd(i).markers{5},adhd(i).markers{6})*adhd(i).fs);

%    t=[ns(1)-tpre:ns(6)];
%    tns=t(1:40);
%    t=[cs(1)-tpre:cs(6)];
%    tcs=t(1:40);
%    t=[is(1)-tpre:is(6)];
%    tis=t(1:40);

tpre=round(5*adhd(i).fs);
tdur=round(20*adhd(i).fs);
trec=round(15*adhd(i).fs);
Ldur=tpre+tdur+trec;

tns=[ns(1)-tpre:ns(1)-tpre+Ldur];
tcs=[cs(1)-tpre:cs(1)-tpre+Ldur];
tis=[is(1)-tpre:is(1)-tpre+Ldur];

A(i).ADHD.hb.vlf.ns=ADHD(i).hb.vlf(tns,:);
A(i).ADHD.hb.vlf.cs=ADHD(i).hb.vlf(tcs,:);
A(i).ADHD.hb.vlf.is=ADHD(i).hb.vlf(tis,:);

A(i).ADHD.hb.lf.ns=ADHD(i).hb.lf(tns,:);
A(i).ADHD.hb.lf.cs=ADHD(i).hb.lf(tcs,:);
A(i).ADHD.hb.lf.is=ADHD(i).hb.lf(tis,:);

A(i).ADHD.hb.hf.ns=ADHD(i).hb.hf(tns,:);
A(i).ADHD.hb.hf.cs=ADHD(i).hb.hf(tcs,:);
A(i).ADHD.hb.hf.is=ADHD(i).hb.hf(tis,:);



A(i).ADHD.hbo.vlf.ns=ADHD(i).hbo.vlf(tns,:);
```

```
A(i).ADHD.hbo.vlf.cs=ADHD(i).hbo.vlf(tcs,:);
A(i).ADHD.hbo.vlf.is=ADHD(i).hbo.vlf(tis,:);

A(i).ADHD.hbo.lf.ns=ADHD(i).hbo.lf(tns,:);
A(i).ADHD.hbo.lf.cs=ADHD(i).hbo.lf(tcs,:);
A(i).ADHD.hbo.lf.is=ADHD(i).hbo.lf(tis,:);

A(i).ADHD.hbo.hf.ns=ADHD(i).hbo.hf(tns,:);
A(i).ADHD.hbo.hf.cs=ADHD(i).hbo.hf(tcs,:);
A(i).ADHD.hbo.hf.is=ADHD(i).hbo.hf(tis,:);

for j=1:4
   %
   %       t=[ns(j*6+1)-tpre:ns((j+1)*6)];
   %       tns=t(1:40);
   %       t=[cs(j*6+1)-tpre:cs((j+1)*6)];
   %       tcs=t(1:40);
   %       is((j+1)*6)=is((j+1)*6)+1;
   %       t=[is(j*6+1)-tpre:is((j+1)*6)];
   %       tis=t(1:40);

   tns=[ns(j*6+1)-tpre:ns(j*6+1)-tpre+Ldur];
   tcs=[cs(j*6+1)-tpre:cs(j*6+1)-tpre+Ldur];
   tis=[is(j*6+1)-tpre:is(j*6+1)-tpre+Ldur];

   A(i).ADHD.hb.vlf.ns=A(i).ADHD.hb.vlf.ns+ADHD(i).hb.vlf(tns,:);
   A(i).ADHD.hb.vlf.cs=A(i).ADHD.hb.vlf.cs+ADHD(i).hb.vlf(tcs,:);
   A(i).ADHD.hb.vlf.is=A(i).ADHD.hb.vlf.is+ADHD(i).hb.vlf(tis,:);

   A(i).ADHD.hb.lf.ns=A(i).ADHD.hb.lf.ns+ADHD(i).hb.lf(tns,:);
   A(i).ADHD.hb.lf.cs=A(i).ADHD.hb.lf.cs+ADHD(i).hb.lf(tcs,:);
   A(i).ADHD.hb.lf.is=A(i).ADHD.hb.lf.is+ADHD(i).hb.lf(tis,:);

   A(i).ADHD.hb.hf.ns=A(i).ADHD.hb.hf.ns+ADHD(i).hb.hf(tns,:);
```

```
        A(i).ADHD.hb.hf.cs=A(i).ADHD.hb.hf.cs+ADHD(i).hb.hf(tcs,:);
        A(i).ADHD.hb.hf.is=A(i).ADHD.hb.hf.is+ADHD(i).hb.hf(tis,:);

        A(i).ADHD.hbo.vlf.ns=A(i).ADHD.hbo.vlf.ns+ADHD(i).hbo.vlf(tns,:);
        A(i).ADHD.hbo.vlf.cs=A(i).ADHD.hbo.vlf.cs+ADHD(i).hbo.vlf(tcs,:);
        A(i).ADHD.hbo.vlf.is=A(i).ADHD.hbo.vlf.is+ADHD(i).hbo.vlf(tis,:);

        A(i).ADHD.hbo.lf.ns=A(i).ADHD.hbo.lf.ns+ADHD(i).hbo.lf(tns,:);
        A(i).ADHD.hbo.lf.cs=A(i).ADHD.hbo.lf.cs+ADHD(i).hbo.lf(tcs,:);
        A(i).ADHD.hbo.lf.is=A(i).ADHD.hbo.lf.is+ADHD(i).hbo.lf(tis,:);

        A(i).ADHD.hbo.hf.ns=A(i).ADHD.hbo.hf.ns+ADHD(i).hbo.hf(tns,:);
        A(i).ADHD.hbo.hf.cs=A(i).ADHD.hbo.hf.cs+ADHD(i).hbo.hf(tcs,:);
        A(i).ADHD.hbo.hf.is=A(i).ADHD.hbo.hf.is+ADHD(i).hbo.hf(tis,:);
    end

% Find averages to all the question types

M.ADHD.hb.vlf.ns=A(1).ADHD.hb.vlf.ns;
M.ADHD.hb.vlf.cs=A(1).ADHD.hb.vlf.cs;
M.ADHD.hb.vlf.is=A(1).ADHD.hb.vlf.is;

M.ADHD.hb.lf.ns=A(1).ADHD.hb.lf.ns;
M.ADHD.hb.lf.cs=A(1).ADHD.hb.lf.cs;
M.ADHD.hb.lf.is=A(1).ADHD.hb.lf.is;

M.ADHD.hb.hf.ns=A(1).ADHD.hb.hf.ns;
M.ADHD.hb.hf.cs=A(1).ADHD.hb.hf.cs;
M.ADHD.hb.hf.is=A(1).ADHD.hb.hf.is;

M.ADHD.hbo.vlf.ns=A(1).ADHD.hbo.vlf.ns;
M.ADHD.hbo.vlf.cs=A(1).ADHD.hbo.vlf.cs;
M.ADHD.hbo.vlf.is=A(1).ADHD.hbo.vlf.is;
```

```
M.ADHD.hbo.lf.ns=A(1).ADHD.hbo.lf.ns;
M.ADHD.hbo.lf.cs=A(1).ADHD.hbo.lf.cs;
M.ADHD.hbo.lf.is=A(1).ADHD.hbo.lf.is;

M.ADHD.hbo.hf.ns=A(1).ADHD.hbo.hf.ns;
M.ADHD.hbo.hf.cs=A(1).ADHD.hbo.hf.cs;
M.ADHD.hbo.hf.is=A(1).ADHD.hbo.hf.is;

for i=2:20

   M.ADHD.hb.vlf.ns=[M.ADHD.hb.vlf.ns A(i).ADHD.hb.vlf.ns];
   M.ADHD.hb.vlf.cs=[M.ADHD.hb.vlf.cs A(i).ADHD.hb.vlf.cs];
   M.ADHD.hb.vlf.is=[M.ADHD.hb.vlf.is A(i).ADHD.hb.vlf.is];

   M.ADHD.hb.lf.ns=[M.ADHD.hb.lf.ns A(i).ADHD.hb.lf.ns];
   M.ADHD.hb.lf.cs=[M.ADHD.hb.lf.cs A(i).ADHD.hb.lf.cs];
   M.ADHD.hb.lf.is=[M.ADHD.hb.lf.is A(i).ADHD.hb.lf.is];

   M.ADHD.hb.hf.ns=[M.ADHD.hb.hf.ns A(i).ADHD.hb.hf.ns];
   M.ADHD.hb.hf.cs=[M.ADHD.hb.hf.cs A(i).ADHD.hb.hf.cs];
   M.ADHD.hb.hf.is=[M.ADHD.hb.hf.is A(i).ADHD.hb.hf.is];

   M.ADHD.hbo.vlf.ns=[M.ADHD.hbo.vlf.ns A(i).ADHD.hbo.vlf.ns];
   M.ADHD.hbo.vlf.cs=[M.ADHD.hbo.vlf.cs A(i).ADHD.hbo.vlf.cs];
   M.ADHD.hbo.vlf.is=[M.ADHD.hbo.vlf.is A(i).ADHD.hbo.vlf.is];

   M.ADHD.hbo.lf.ns=[M.ADHD.hbo.lf.ns A(i).ADHD.hbo.lf.ns];
   M.ADHD.hbo.lf.cs=[M.ADHD.hbo.lf.cs A(i).ADHD.hbo.lf.cs];
   M.ADHD.hbo.lf.is=[M.ADHD.hbo.lf.is A(i).ADHD.hbo.lf.is];

   M.ADHD.hbo.hf.ns=[M.ADHD.hbo.hf.ns A(i).ADHD.hbo.hf.ns];
   M.ADHD.hbo.hf.cs=[M.ADHD.hbo.hf.cs A(i).ADHD.hbo.hf.cs];
   M.ADHD.hbo.hf.is=[M.ADHD.hbo.hf.is A(i).ADHD.hbo.hf.is];
end
```

```
% Averaging ends
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
d=1:16:208-15;

doff=1:32:320-31;
don=17:32:320-15;

tt=linspace(0,Ldur/1.8,Ldur+1);
x=10;
figure
plot(tt,mean(M.control.hbo.vlf.is(:,d+x),2),'b',tt,mean(M.ADHD.hbo.vlf.is(:,doff+x),2),'r','line
width',2)
plot(tt,mean(M.control.hbo.vlf.is(:,d+x),2),'b',tt,mean(M.migren.hbo.vlf.is(:,dm+x),2),'r',tt,me
an(M.ADHD.hbo.vlf.is(:,doff+x),2),'g',tt,mean(M.ADHD.hbo.vlf.is(:,don+x),2),'m','linewidth'
,2)
plot(tt,M.control.hb.vlf.is(:,1),'linewidth',2)
plot(tt,M.control.hb.vlf.is(:,1+16),'linewidth',2)
plot(tt,M.ADHD.hb.vlf.is(:,1),'linewidth',2)
plot(tt,M.ADHD.hb.vlf.is(:,1+32),'linewidth',2)
plot(tt,M.ADHD.hb.vlf.is(:,17),'linewidth',2)
plot(tt,M.ADHD.hb.vlf.is(:,17+32),'linewidth',2)
plot(tt,mean(M.control.hbo.vlf.ns(:,d+x),2),'b',tt,mean(M.ADHD.hbo.vlf.ns(:,doff+x),2),'r',tt,
mean(M.ADHD.hbo.vlf.ns(:,don+x),2),'g','linewidth',2)
legend('Control','ADHD OFF','ADHD ON')

for ii=1:16
figure(ii)
plot(tt,M.ADHD.hbo.vlf.ns(:,ii+32),'linewidth',2)
[X Y]= ginput(2);
maximum=Y(1)
minimum=Y(2);
nermin(ii,:)=[maximum minimum];
end
```

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