INVESTIGATING BRAIN HEMODYNAMICS OF SCHIZOPHRENIC PATIENTS BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

by

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ABSTRACT

INVESTIGATING BRAIN HEMODYNAMICS OF SCHIZOPHRENIC PATIENTS BY FUNCTIONAL NEAR INFRARED SPECTROSCOPY

People can easily stop talking, walking, singing and so on, in response to changes in internal or environmental states. The ability to respond to a specific dimension of a stimulus while suppressing simultaneous inappropriate or no longer required competing stimulus is known as interference effect. This ability to inhibit inappropriate or irrelevant responses is a hallmark of executive control and is subserved by prefrontal cortex of the brain in healthy subjects. Damage to these prefrontal regions, results in response inhibition deficits and also have been linked to several neurological disorders like schizophrenia and autism.

Schizophrenia is a psychiatric disorder that associated with general cognitive impairments in addition to inhibitory deficits. Onset of these symptoms typically occurs in young adulthood, with approximately 1% of the population affected.

In this study, attentional processes in schizophrenia spectrum have been examined using Stroop task and fNIRS.

Keywords: Functional Near-Infrared Spectroscopy, Schizophrenia, Stroop task, Response inhibition.

ÖZET

İŞLEVSEL YAKIN KIZIL ÖTESİ SPEKTROSKOPİ İLE ŞİZOFREN HASTA GRUPLARINDA BEYİN HEMODİNAMİĞİNİN İNCELENMESİ

İnsanlar iç ve dış uyaranlara bağlı olarak, konuşmak, yürümek veya şarkı söylemek gibi eylemleri rahatça sonlandırabilirler. Uyaranın belirli bir boyutuna yanıt verirken, eş zamanlı oluşan uygunsuz veya kullanılmayan boyutu bastırmak, enterferans etkisi olarak bilinir. Sağlıklı bireylerde uygunsuz veya bağımsız yanıtların inhibisyonu, yönetimsel bir işlevdir ve prefrontal korteks tarafından kontrol edilir. Beynin prefrontal bölgesinde oluşan bazı hasarlar, yanıt inhibisyonu bozulmalarına yol açar, ve şizofreni ve otizim gibi bazı nörolojik bozukluklarla da ilişkilendirilebilir.

Şizofreni sadece yanıt inhibisyonu ile değil, kognitif alandaki bozulmalarla da tanımlanabilen genellikle erken erişkinlik döneminde ortaya çıkan ve toplumun % 1'ini etkileyen psikiyatrik bir bozukluktur.

Bu çalışmanın amacı şizfrenide görülen dikkat bozukluklarının Stroop ve fNIRS yardımıyla analizidir.

Anahtar Sözcükler: İşlevsel Yakın Kızılötesi Spektroskopi, Şizofren, Stroop testi, Yanıt inhibisyonu.

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A	Light extinction
ε	Specific extinction coefficient
c	Substance concentration
d	Distance
B	Differential path length factor
G	Signal loss due to scattering

LIST OF ABBREVIATIONS

ADHD	Attention-Deficit Hyperactivity Disorder
[HbO_2**]** / [Hb]	Concentration of oxy/deoxy-hemoglobin
CBV	Cerebral Blood Volume
CS	Congruent Stimuli
deoxy-Hb	Deoxygenated Hemoglobin
DLPFC	Dorsolateral Prefrontal Cortex
DSM	The Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
HF	High Frequency
IS	Incongruent Stimuli
LED	Light Emitting Diodes
LF	Low Frequency
MEG	Magnetoencephalogram
NIR	Near-Infrared
NIRS	Near-Infrared Spectroscopy
NS	Neutral Stimuli
oxy-Hb	Oxygenated Hemoglobin
PCB	Printed Circuit Board
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
SPECT	Single Photon Emission Computerized Tomography
tot-Hb	Total Hemoglobin
VLF	Very Low Frequemcy
WCS	Wisconsin Card Sort

1. INTRODUCTION

Schizophrenia is characterized by a loss of contact with reality and a disruption of thought, perception, mood and movement. The disorder typically becomes apparent during adolescence or early adulthood and usually persists for life. Descriptions of schizophrenia-like symptoms date back to circa 2000. However, medical studies of the ancient Greek and Roman literature shows some diagnosis of this psychotic disorder, but there was no recorded condition that would meet the modern criteria for schizophrenia. Even though it has been known more than 2000 years and a broad concept has existed for a hundred year; it is still not clear whether what is called schizophrenia is a single disease or group of several diseases.

The computerized tomography, magnetic resonance imaging and cerebral blood flow studies have revealed that the classified negative symptoms of schizophrenia are characterized similarly to the cognitive and behavioral aspects of frontal lobe disease including impaired motivation, paucity of thought, and shallow affect. Frontal lobe impairment has consistently been implicated by the characteristic pattern of cognitive impairment in schizophrenics. Studies of frontal lobe lesions (damage) and brain imaging of regional blood flow have been the significant areas of study. The frontal cortex has also been found to be a heterogeneous region in terms of cognitive and behavioral influences.

To date, several functioning neuroimaging techniques have been tested on schizophrenics while they were performing several cognitive tasks. These imaging methodologies are used to understand the cerebral activity in a particular brain region in terms of its relationship to a specific behavioral state or its interactions with inputs from other regions activities. The challenge, in all these studies, has been to converge to a rapid, non invasive and precise technique.

In this study, we have decided to apply the functional near infrared spectroscopy measurement during cognitive activity to reproduce the similar differences observed by other modalities. Since optical imaging techniques offer rapid and non-invasive access to

brain oxygenation and blood flow, we decided to investigate the cerebral activation during a color-word matching Stroop task.

1.1. Motivation and Objective

Early detection of schizophrenia and understanding its pathophysiology might improve prognosis and guide therapeutic interventions. Among the neuroimaging modalities, fNIRS has been the most liberally utilized for schizophrenia investigations. This may be because fNIRS is a non-invasive, safe and user-friendly method of monitoring brain activity.

In this study, we used fNIRS neuroimaging modality during Stroop task and investigate the oscillatory dynamics between controls and patient groups. For comparing these oscillatory dynamics, we used response inhibition and event-related energy spectrum techniques.

Our results show that there are specific brain areas responsible for generating specific oscillatory patterns and that fNIRS is a valuable tool for investigating these patterns.

2. SCHIZOPHRENIA

Schizophrenia is a psychiatric diagnosis that describes a mental illness characterized by impairments in the perception or expression of reality, most commonly manifesting as auditory hallucinations, paranoid or bizarre delusions or disorganized speech and thinking in the context of significant social or occupational dysfunction.

2.1. The History of Schizophrenia

In 1898, Emil Kraepelin, a German physician, used the term “dementia praecox” to describe the symptoms that are now associated with schizophrenia. The term “dementia” was used to describe the global disruption of perceptual and cognitive processes, while “praecox" referred to the onset of the disorder in early adulthood. Kraepelin characterized the disorder as progressive with no return to premorbid levels of functioning.

A Swiss psychiatrist, Eugen Bleuler, reformulated dementia praecox. In 1911, Bleuler coined the term "schizophrenia“. The word schizophrenia is derived from the Greek roots schizo (split) and phrene (mind). Schizophrenia is often misconceived as multiple personality disorder. However, schizophrenia was intended to describe the fragmented thinking characteristic of people with the disorder.

2.2. Classification and Diagnosis

The most widely used criteria for diagnosing schizophrenia is from DSM-IV-TR. 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.

Diagnosis is based on the self-reported experiences of the person as well as abnormalities in behavior reported by family members, friends or co-workers, followed by secondary signs observed by a psychiatrist, social worker, clinical psychologist or other clinician in a clinical assessment.

2.3. Genetics

Schizophrenia has an important genetic component, which shows that it does "run in the family". Evidence for a genetic component comes from twin studies. Monozygotic twins (identical twins) are those with exactly the same genetic makeup; dizygotic twins (fraternal twins) are those who share only half of their genetic makeup. If genetics was the ONLY factor in developing schizophrenia, then both monozygotic twins should always develop this illness, but this is not true.

Twin studies have shown that the tendency for both monozygotic (identical) twins to develop schizophrenia is between 30-50%. The tendency for dizygotic (fraternal) twins to develop schizophrenia is about 15%. The tendency for siblings who are not twins (such as brothers of different ages) is also about 15%. Remember, schizophrenia is found in the general population at a rate of about 1%. Therefore, because the tendency for monozygotic twins is NOT 100%, genetics cannot be the only factor. However, because the tendency for monozygotic twins to have schizophrenia is much greater than the tendency for dizygotic twins, genetics DOES play a role. [20]

2.4. Importance of Dorsolateral Prefrontal Cortex in Schizophrenia

The dorsolateral prefrontal cortex (DLPFC) is a very unique part of the frontal cortex specific to almost only humans. The DLPFC's relation to schizophrenia is supported by the fact that frontal lobe disease or damage by tumors, aneurysms, infarction or psychosurgery, produces symptoms resembling that of schizophrenia.

The role of the DLPFC is considered very complex and important for higher human brain functions like working memory and conscious control of behavior. What is physically known about the DLPFC is extensive in terms of its neural projections to other parts of the brain and the time period in which these projections develop.

A large portion of schizophrenic symptoms can also be described as reflecting (or contributing to) specific cognitive deficits in memory and reasoning ability (executive functions. The set of cognitive processes used to actively maintain and manipulate information for use in mental abstraction and reasoning or controlling behavior is known as working memory.

As discussed earlier, the DLPFC has been linked to many of the negative symptoms of schizophrenia as also seen in those with DLPFC damage, and with direct DLPFC stress loading through tasks such as: Stroop, delayed-response tasks, and the Wisconsin Card Sort (WCS). The link between DLPFC function, working memory, and negative symptoms of schizophrenia required more than one study. First, Weinberger et al (1986) provided empirical proof of the DLPFC dysfunction in schizophrenics by linking cerebral blood flow (rCBF) deficits to the DLPFC. [23]

Regional cerebral blood flow or rCBF is a measurement of blood circulation levels to specific areas of the brain using a Xenon inhalation technique developed by Orbist et al. The studied participants inhale the Xenon gas and imaging technology can detect where the radioactive chemicals saturated in the blood stream flow throughout the body and brain. By monitoring rCBF while the patients participated in the Wisconsin Card Sort (WCS), a task relying heavily on working memory, Weinberger et al (1986) suggested that

the DLPFC's link to negative symptoms arises from a deficit in blood flow to that region, lowering its activation levels. Patients' performance on the WCS positively correlated with the level of blood flow to the DLPFC suggests that many of the negative symptoms present in schizophrenics may be a function of working memory deficits. [18]

3. PRINCIPLES OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY

The evolution of neuroimaging studies, has been started by the fact that skull is not a natural border for the light. For the nervous system, it was reported as early as 1949 that the activity of nerve cells was associated with changes in their optical properties [3]. Since than, changes in optical properties of brain cells have been reported in cell cultures, bloodless brain slices, as well as in intact cortical tissue.[1, 2] Optical signals have been used to map brain function after surgical exposure of cortical tissue in animals and human subjects. It has been shown that it is possible to extract brain activity through the intact skull in adult human subjects and non-invasive functional brain mapping has been possible. [1, 2, 3]

Functional neuroimaging is a widely accepted technology for understanding relationship between physiological activity in certain brain areas and specific mental functions. Among other physiological systems brain is the only organ that has to be investigataed non-invasively most of the situation. This necessity gave birth to functional neuroimaging methods. Common methods include Positron Emmision Tomography (PET), Electroencephalography (EEG), Magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRs). Among all these methods fNIRs, as an emerging hemodynamic based functional neuroimaging technology, offers a relatively non-invasive, safe, portable method of both direct and indirect method of monitoring brain activity.

Multi-channel NIRS is able to detect spatially relatively specific activation due to cognitive processing. Monitoring this brain activity with optical techniques is associated with a number of physiological changes. These physiological changes during brain activity can be divided into two phases. First phase occurs intracellularly, and second phase occur within vascular space. During brain activity as the associated neurons firing, ions and water fluxes through neuron’s membrane which causes a change in membrane potential as well as magnetic and electrical fields.

In addition to those events taking place intracellularly, local brain activity induces a local arteriolar vasodilation and consequently an increase in local cerebral blood volume (CBV) and blood flow (CBF), termed neurovascular coupling. [2] As this brain activity continues or increases, also an increase in glucose and oxygen consumption occurs. Over periods of several seconds, the increased CBF carries both oxygen and glucose in the blood to the area. During these process oxygen molecule binds to hemoglobin and form oxygenated hemoglobin (oxy-Hb) and unbinds from hemoglobin to form deoxygenated hemoglobin (deoxy-Hb). Functional activation of human cerebral cortex can be assessed using these oxygenated and deoxygenated hemoglobin molecules.

The underlying idea is that when brain activity increases within the particular part of cerebral cortex, blood supply to the area increases as well as does the level of oxy-Hb. The consumption of oxygen during brain activation furthermore leads to an increase in deoxygenated hemoglobin that is, however, soon compensated by the increase in blood supply, and deoxy-Hb usually decreases as a result. In other words, activation of a particular brain region is supposed to be reflected in an increase in oxy-Hb and total-Hb and a corresponding decrease in deoxy-Hb. These changes in the concentration of oxy-Hb and deoxy-Hb can now be detected by means of NIRS. [21].

Most biological tissues are relatively transparent to near-infrared light between 700 -1000 nm. This is due to fact that water and hemoglobin absorption are relatively small within this “optical window”. Above 1000 nm, water absorbs all photons over a path length of less than a few millimeters in normally hydrated tissue. In the visible part of the spectrum, below 700 nm, the intense absorption bands of hemoglobin and increasing light scattering phenomena again prevent transmission over longer path lengths. [19]

Several studies showed that if light range is selected between 700-900 nm then light scattering will be minimized. So in this study we selected 3 different wavelengths as 730, 805 and 850 nm.

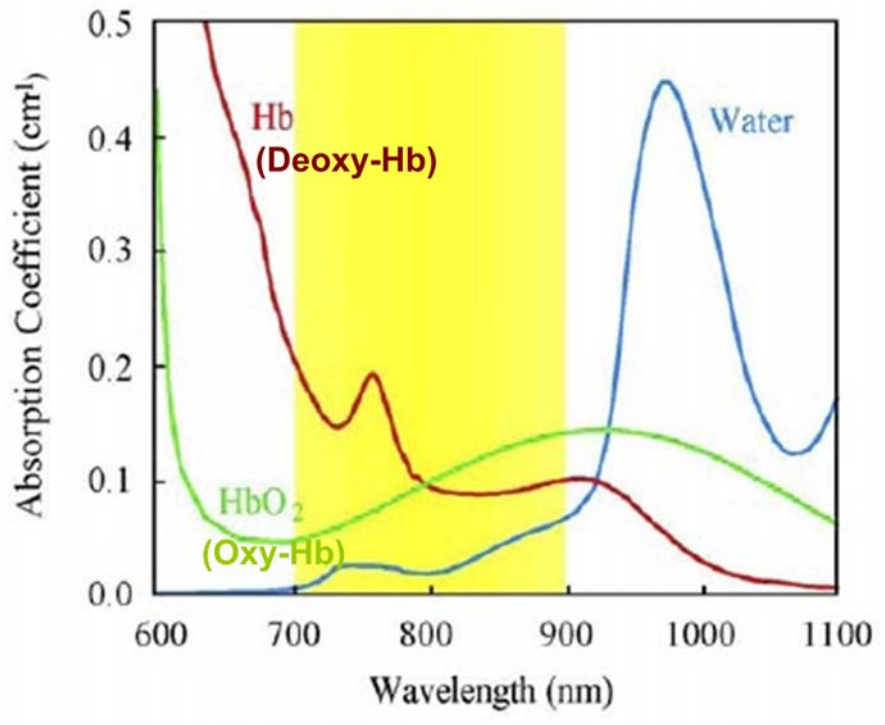

Figure 3.1 The absorption spectrum of water, oxy-Hb,deoxy-Hb in near-infrared window.

The interaction of light to biologic tissue is attenuated mainly by absorption and scattering. Once the photons are transmitted into human head, they are either scattered or absorbed mainly by oxy-Hb and deoxy-Hb. The concentaration of these light absorbing molecules is determined similarly to the determination of a substance concentration in a photometer. As seen from figure 3.1, the absorbed photon (photon 2), or directly transmitted photon (photon 3) concentrations can be calculated by original Beer-Lambert Law:

$$A = \varepsilon \times c \times d \tag{3.1}$$

where A is;

$$A = Log \frac{I_0}{I} \tag{3.2}$$

and ε is specific extinction coefficient, c is substance concentration and d is distance.

Extinction of light(A), is proportional to the concentration (c) of the absorber multiplied by a constant extinction coefficient ($\boldsymbol{\varepsilon}$) for the particular absorber and the distance (d) corresponding to the width of the cuvette. But this calculation holds true only for infinitesimal substance concentrations, and negligible light scattering. With higher substance concentrations and significant light scattering, the formula must be modified to take into account the longer path length (photon 1) and loss of light due to scattering (photon 4). By analogy this light intensity after the photons have interacted with the biological tissue can be expressed mathematically in modified Beer-Lambert Law. Modified Beer- Lambert Law is an empirical description of optical attenuation in highly scattered medium.

$$A = \varepsilon \times c \times d \times B + G \tag{3.3}$$

Where ***B*** is differential path length factor which accounts for longer path-length and ***G*** is signal loss due to scattering which depens mainly on geometrical factors. [18]

In functional optical brain imaging studies, attenuation due to scattering is assumed constant which cancels out the term ***G*** in the formula. This is due to the fact that, the amount of scatterers within different layers of head does not change due to cognitive activity.

As the photon 2 and photon 3 concentrations considered infinitesimal, and photon 4 concentration is placed not taken into account due to scattering, photon 1 is the only photon that dominates concentration, with a certain distance of photo detector placed from a light source, dominated photons (photon 1) traveled along the “banana shaped path” between the source and the detector. [18]

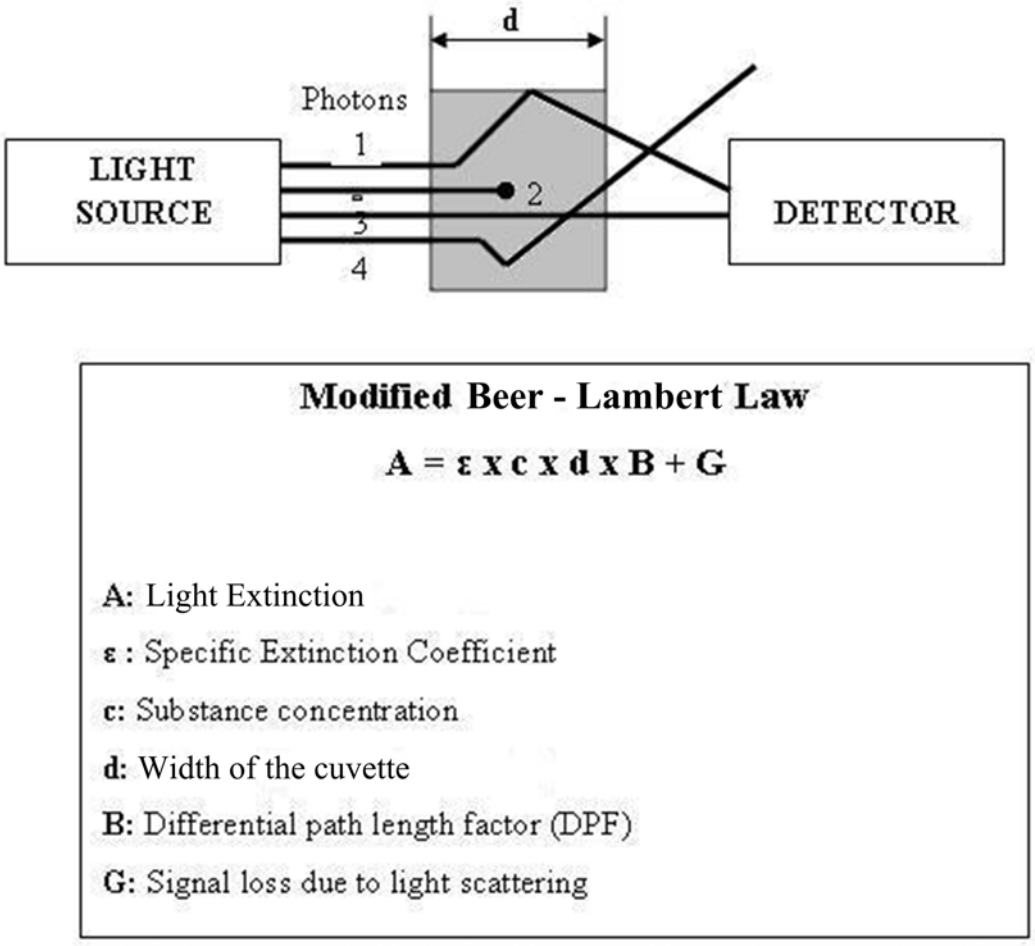

Figure 3.2 Modified Beer-Lmbert Law: Influence of light absorption and scattering on optical measurement.

Detailed explanation of modified Beer-Lambert Law for highly scattered medium, such as brain, can be found in Appendix A.

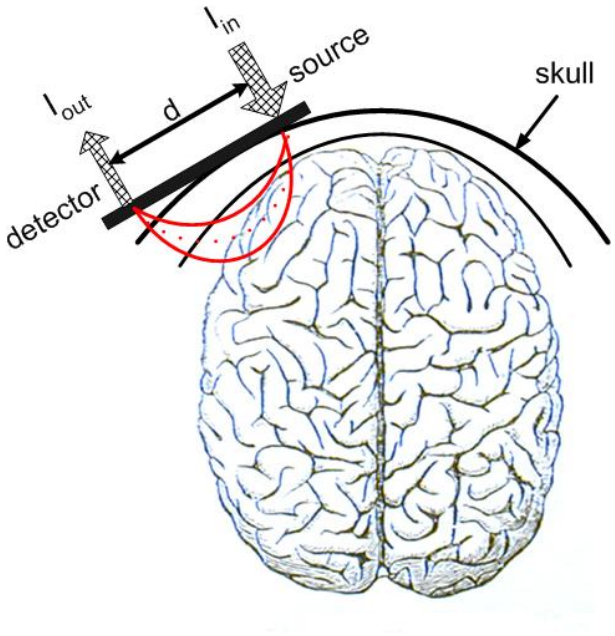

Figure 3.3 Banana shaped propagation of photons between source and detector.

For the consideration of penetration depth of near-infrared light, photon migration models predicted it to be directly proportional to interoptode distance. Because light is scattered after entering the tissue, a photodetector placed 2-7 cm away from the optode can collect light after it has passed through the tissue. When the distance between the source and photodetector is set at 4cm, the fNIRs signal becomes sensitive to hemodynamic changes within the top 2-3 mm of the cortex and extends laterally 1cm either side, perpendicular to the axis of source detector spacing. [8] Studies have shown that at inter-optode distance as short as 2-2.5 cm, gray matter is part of the sample volume. [8] Using this technique, several types of brain activity, including the performance of cognitive tasks, have been assessed. [10]

The underlying idea is that when brain activity increases within the particular part of cerebral cortex, blood supply to the area increases as well as does the level of oxy-Hb. The consumption of oxygen during brain activation furthermore leads to an increase in deoxygenated hemoglobin that is, however, soon compensated by the increase in blood supply, and deoxy-Hb usually decreases as a result. In other words, activation of a particular brain region is supposed to be reflected in an increase in oxy-Hb and total-Hb and a corresponding decrease in deoxy-Hb. These changes in the concentration of oxy-Hb and deoxy-Hb can now be detected by means of NIRS. [5]

4. FUNCTIONAL BRAIN IMAGING STUDIES IN SCHIZOPHRENIA

Functional brain imaging methods have been applied to the study of schizophrenia aiming at elucidating the neurobiology of this complex and heterogeneous disorder. These studies utilize the fact that neuronal activation results in regionally increased blood flow. This activity can be measured either by radiotracer methods, or by a regional effect on the ratio of deoxyhemoglobin to oxyhemoglobin. These measurement methods have included the ^{133}Xenon technique for measuring cerebral blood flow (CBF); positron emission tomography (PET) for assessing metabolism, CBF and neuroreceptor functioning; single photon emission computerized tomography (SPECT) for studying CBF and neuroreceptors; and, more recently, functional magnetic resonance imaging (fMRI) for measuring changes attributable to cerebral blood flow. Studies of cerebral metabolism and blood flow (CBF) can be divided into those measuring the physiologic parameters at a resting state and those introducing a perturbation, or challenge, in the form of a neurobehavioral probe or pharmacologic intervention. [17, 18]

Results of these functional brain imaging studies have revealed that some patients with schizophrenia have one or more major anatomical abnormalities. First, early in the disease there is a reduction in the blood flow to the left globus pallidus, suggestive of a disturbance in the system that connects the basal ganglia to the frontal lobes. PET and SPECT examinations have supported this by showing functional changes in basal ganglia. And several PET studies implicated basal ganglia dysfunction in schizophrenia. [ ] Second, there appears to be a disturbances in the frontal lobes themselves since blood flow does not increase during tests of frontal function involving working memory, as it does in normal subjects. Third, the cortex o the medical temporal lobe is thinner and the anterior portion of the hippocampus is smaller than in normal people, especially on the left side, consistent with PET studies showing the decreased metabolism in hippocampus and anterior cingulate cortex. Finally, the lateral and the third ventricles are enlarged and there is widening of the sulci, especially in the thinner temporal lobe and in the frontal lobe, reflecting a reduction in the volume of this lobe as well.

Links between clinical features of schizophrenia and brain function have been guided by hypotheses that relate behavior to specific brain regions and systems which are implicated in schizophrenia. These links are based on preclinical research and the emergence of symptoms, commonly seen in schizophrenia, that occur following brain lesions. Persistent negative symptoms have been related to frontal lobe dysfunction. Frontal lobe damage has neurobehavioral sequelae, such as impairment in abstraction, verbal fluency, mental flexibility and concept formation. Positive, productive symptoms (hallucinations and delusions) have been related to the temporo-limbic system, with evidence of impaired learning and memory. Subcortical regions, with special emphasis on the basal ganglia, have been examined in the context of the dopamine hypothesis. Across these dimensions, laterality measures of the relation between left and right hemispheric parameters have been compared in patients and normal controls. While necessarily simplistic and not reflecting on other brain systems that modulate normal and pathological psychotic behavior, these dimensions have generated hypotheses that can be examined with functional brain imaging.

4.1. Functional Near Infrared Spectroscopy in Schizophrenia

Among the functional neuroimaging modalities fNIRS is particularly valuable in schizophrenia given its frontally based dysfunction. Although this technology is unlikely to immediately replace fMRI or MRI-based methods due to its current limitations, fNIRS has yet to be fully embraced as a way of further understanding the mechanism underlying schizophrenia and various brain disorders.

Okada et al. utilized multi-channel fNIRS to investigate disturbances in interhemispheric integration of brain oxygen metabolism and hemodynamics. They utilized a mirror drawing task (MDT) and found that controls showed distinct and well integrated patterns of changes in oxy-Hb, deoxy-Hb, and total blood volume during the MDT. In contrast, half of the patients with schizophrenia showed “dysregulated patterns” in the frontal regions between hemispheres, such that increases in oxy-Hb were not paralleled by

decreases in deoxy-Hb. This led the authors to suggest that certain symptoms of schizophrenia might be related to problems in interhemispheric integration. [1]

Similarly, Fallgatter and Strik examined the relationship between lateralized frontal fNIRS activation patterns during the execution of a continuous performance test (CPT). Interestingly, they did not find any overall or hemispheric activation effects in their cohort. However, when compared to healthy controls they found group differences, with a lateralized activation in schizophrenia. Furthermore, a trend towards higher left relative to right oxy-Hb and deoxy-Hb ratios at rest and during activation were observed in subjects with schizophrenia. This led the authors to suggest that there may be a reduced specific lateralized frontal activity, possibly based on a left hemisphere functional deficit in schizophrenia.[2]

Another more recent investigation has utilized frontally based tasks such as random number generation (RNG), ruler-catching (RC), and sequential finger-to-thumb (SFT) tasks to show that there are task dependent functional abnormalities frontal brain metabolism in schizophrenia. Specifically, during the RNG task, total-Hb and oxy-Hb concentrations increased and deoxy-Hb decreased, but the responses were significantly smaller in schizophrenic patients. During RC task, oxy-Hb in patients with schizophrenia tended to decrease, in contrast to the mostly increasing response in control subjects. No group difference was observed during the SFT task. [3]

Verbal fluency tests (VFTs) have also been utilized to clarfy the nature of language-related problems in schizophrenia. Kubota et al. found that while healthy subjects performed both semantic and phonemic fluency equivalently, subjects with schizophrenia showed more compromised performance in semantic VFTs compared to the phonemic VFTs. FNIRS measurement revealed that the pattern of prefrontal cortex (PFC) activation was greater during the phonemic VFT when compared to the semantic VFT in healthy subjects, suggesting more prominent PFC involvement in phonemic-cued retrieval. In contrast, subjects with schizophrenia showed the opposite pattern of activation, implying that the semantic mode of lexical access might impose greater cognitive demands on the PFC for this patient group. [4]

Similarly, another study also utilized VFT to demonstrate characteristic time courses of oxy-Hb changes in the frontal lobe for schizophrenia as compared to a sample of depressed patients.[5] Specifically, depressed patients demonstrated smaller oxy-Hb increases during the first half of the task period, while patients with schizophrenia had a small trough of oxy-Hb at the start of the task period and oxy-Hb re-increase in the post-task period. The decreased oxy-Hb activation in depression was consistent with decreased regional cerebral blood flow and metabolism in the dorsolateral prefrontal cortex in the resting state observed in functional neuroimaging studies using other methodologies such as PET, SPECT, and fMRI. Yet these results did not support the either the hypofrontality [6] observed when the task performances of schizophrenic patients are poorer, or the hyperfrontality observed when the task performances are matched. This might be related to the authors' modification to their VFT task (increased length) due to their interest in monitoring time course changes in blood volume. [7]

In contrast, Watanabe and Kato showed findings consistent with task dependent functional hypofrontality demonstrated by other neuroimaging studies.[8] They found that oxy-Hb increased during VFT and letter–number (LN) sequencing, schizophrenia patients showed lower performance and a smaller increase in oxy-Hb during VFTs than controls. This reduced oxy-Hb response during VFTs in schizophrenia patients was also observed even when their performance was matched with controls' performance. In contrast, increase in oxy-Hb during LN in schizophrenia patients was comparable with that of controls. In addition, patients medicated with atypical antipsychotics showed a larger increase in oxy-Hb during VFT and LN than those medicated with typical antipsychotics.

Perlstein et al. applied n-back sequential-letter working memory task to schizophrenic patients and control subjects. According to fMRI results, schizophrenic patients showed a deficit in physiological activation of the right dorsolateral prefrontal cortex (BA 46/9) in the context of normal task-dependent activity in other regions, but only under the condition that distinguished them from comparison subjects on task performance. Patients with greater dorsolateral prefrontal cortex dysfunction performed more poorly. Dorsolateral prefrontal cortex dysfunction was selectively associated with disorganization symptoms. [15]

5. COLOR-WORD MATCHING STROOP TASK

The color-word matching Stroop interference task [Stroop,1935] is a measure of "inhibition of prepotent response" using color-word matching task. Inhibition of prepotent response is an executive function and is subserved by prefrontal cortex of the brain in healthy subjects. Damage to these regions results in response inhibition deficits.

Cognitive interference occurs when the processing of a specific stimulus feature impedes the simultaneous processing of second stimulus attribute. Traditional stroop task requires a person to respond to a specific dimension of a stimulus while suppressing a competing stimulus dimension. Subjects generate a response to match one dimension of a stimulus while suppressing the irrelevant dimension. A color word such as GREEN appears in an ink color such as red. If the subject's task is to read the word and ignore the color (i.e., say "green"), there is no evidence of difficulty relative to reading the word in standard black ink. However, if the subject's task is to name the ink color and ignore the word (i.e., say "red"), there is considerable difficulty relative to naming a color patch. Reading the word interferes with naming the color, but the color does not interfere with reading the word. In doing this, response preparation and interference processes are within the same modality (verbal) and one can not exclude that these two processes cofound each other. The stimuli interfere at the response preparation level.

In an adapted single trial version of the color-word matching stroop task, interference takes place at a conceptual level and is separated from the preparation. An additional response (button press), which was neither a color nor a word. The modality of the behavioural component of the task is independent of the interfering dimensions. Subjects were presented two words (e.g., GREEN written in blue ink; BLUE written in black ink), and they had to match the color of the first word with the meaning of the second word (e.g., "Does the color of the first word correspond with the meaning of the second word?"). Varying the dimension of the first word (neutral, congruent, or incongruent words to the presented color) allows for the investigation of interference effects. The conceptual interference between the two dimensions of a stimulus within a matching process was separated from the response preparation and execution process. The

main difference between the two tasks is that subjects in the Matching Stroop task compare two attributes of a stimuli while in the traditional Stroop task they generate a response to match one attribute of a stimulus.

6. METHOD

6.1. Subjects

Twenty five schizophrenic patients and twelve ADHD patients and twelve healthy controls were involved in this study. Ratios of men to women between each group were matched (2/3). Patients and controls did not differ significantly regarding their mean age level (age 30.2 ± 10.4 versus 32.6 ± 8.3 versus 31.9 ± 8.6). Data from control subjects were acquired at Biomedical Engineering Laboratories in Bogazici University in Istanbul, Turkey. Data from patient subjects were acquired at Department of Psychiatry of Pamukkale University Medical Faculty in Denizli, Turkey. The protocol has been approved by the Ethics board of Pamukkale and Bogazici Universities. Prior to experiment both groups were given interview to ensure that they met the following inclusion criteria.

- Native Turkish speakers
- Normal or corrected-to-normal vision and normal color vision
- Right handed
- No intelligence deficit
- Controls were reported as no neurological or psychiatric disorder

6.2. Experimental Procedure

Each participant sat on a chair with their eyes open during experiments. Participants were instructed to minimize movement such as head movements during fNIRs measurements because they might produce artifacts or changes in cerebral perfusion unrelated to task. Furthermore experiments were performed in a silent and dimmed room to prevent any other disturbances.

Figure 6.1 A photograph of the experimental setup. In the figure, the computer numbered as 1 was used as a patient computer for Stroop task, number 2 is 16-channeled Niroxcope Probe, number 3 is Control Box and number 4 is the computer for real-time monitoring and storing the data.

6.3. Psychophysical Procedure

In this study, the color-word matching Stroop task was used to explore the differences in frontal lobe functions. During Stroop task two rows of letters appeared on the screen and subjects were instructed to decide whether the color of the top row letters corresponded to the name written on the bottom row.

neutral	congruent	incongruent
XXXX BLUE	RED BLUE	GREEN BLUE
XXXX RED	BLUE BLUE	GREEN BLUE

Figure 6.2 Examples of single trials for the neutral, congruent and incongruent condition of the color–word matching Stroop task. For the upper three examples color of the upper word does not match with the meaning of the lower word, but for the lower three examples it does.

Response was given by pressing the right button of a mouse with index finger (YES-response) and left button of a mouse with middle finger (NO-response) of the right hand. During the neutral trials, the letters in the top row were “XXXX” printed in red, green, blue or yellow, and the bottom row consisted of Turkish names of color words of “RED”, “GREEN”, “BLUE” and “YELLOW” printed in white. For congruent trials, the top row consisted of Turkish names of color words of “RED”, “GREEN”, “BLUE” and “YELLOW” printed in congruent color. For the incongruent condition, the color word was printed in different color to produce interference between coloring the word and naming it.

At the beginning of the experiment, fixation point (“+” sign) was displayed for one minute on the screen. Experimental run consisted of 15 block stimuli (5 neutral, 5 congruent, 5 incongruent) in a random order with an interstimulus interval of 20 sec. Each block consisted of 6 trials and between each block fixation point was displayed until next block appears. Word remained on the computer screen until the response was given with a maximum time of 4 sec. The screen was blank between trials.

Prior to the experiment subjects were tested with a shortest version of the task for training.

6.4. Data Collection

Hemodynamic changes in the prefrontal cortex were measured using NIROXCOPE 301 which was developed at the Biophotonics Lab of the Institute of Biomedical Engineering in Boğaziçi University. This device is composed of:

- 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 can emit at three wavelengths of 730 nm, 805 nm and 850 nm. 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 5.3.

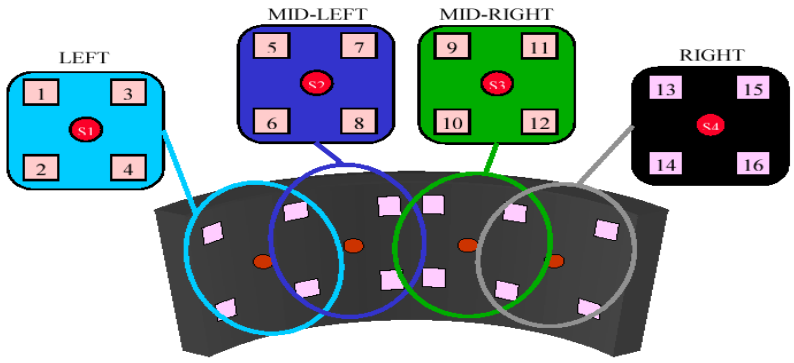

Figure 6.3 Source-detector configurations on the brain probe and nomenclature of photodetectors.

NIROXCOPE 301 is composed of:

- Flexible sensor that consists of four LED light sources and ten detectors.
- 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.

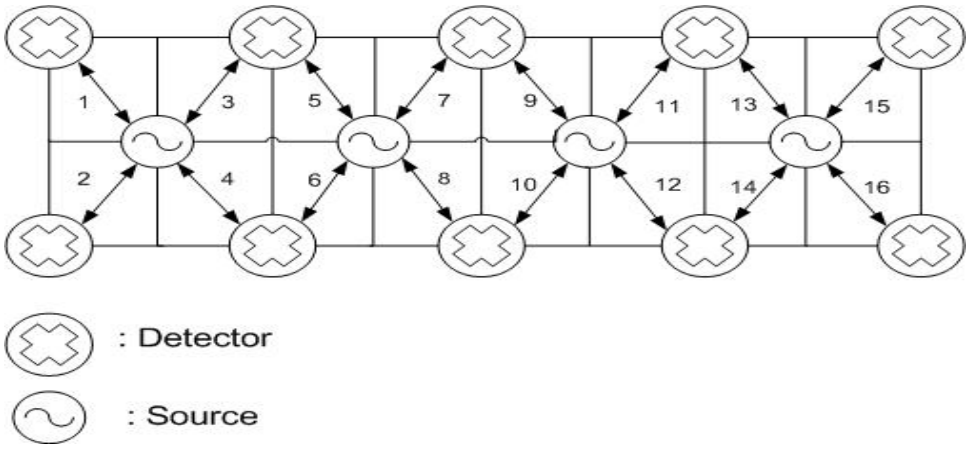

Figure 6.4 Design of fNIRs probes.

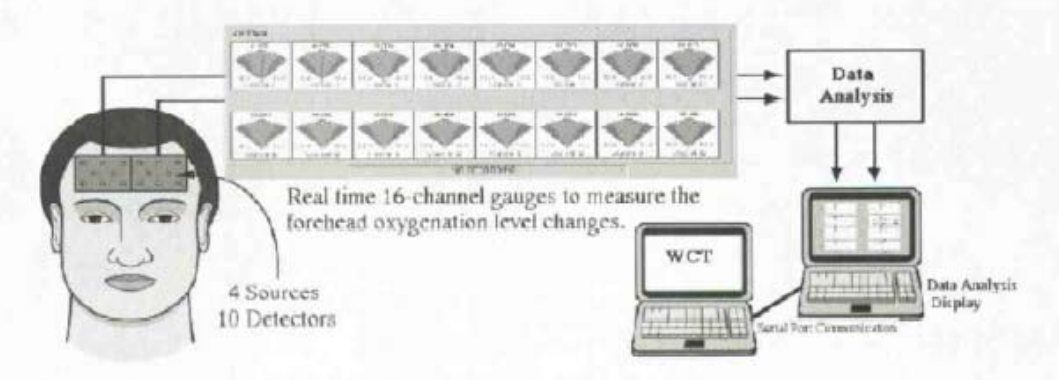

Figure 6.5 Data analysis and system flow.

6.5. Data Analysis

Signal changes at the detectors during the Stroop task were collected by means of NIROXCOPE 301. Oy-Hb and deoxy-Hb changes were calculated using the modified Beer-Lambert Law. Figure 5.6 and 5.7 show the oxy-Hb and deoxy-Hb changes of a schizophrenic patient and a control subject during Stroop task respectively. The red lines show the time stimulus was applied. To enable group comparisons, the length of all recording segments of both schizophrenia patients and controls were normalized to 700 seconds overall and 4 seconds maximum for the task.

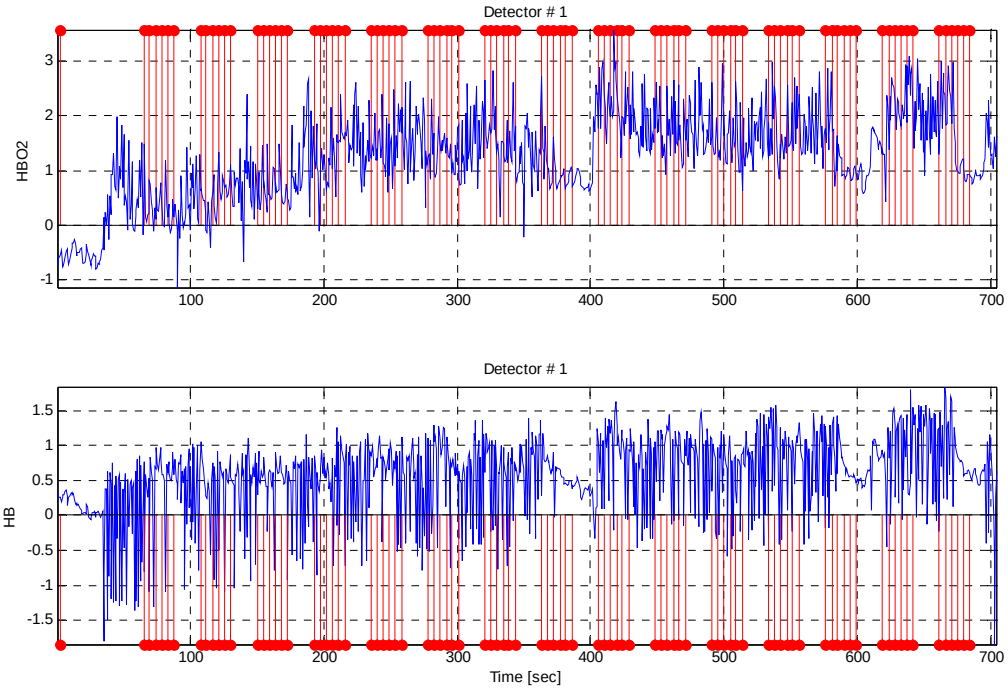

Figure 6.6 Raw data from schizophrenic patient.

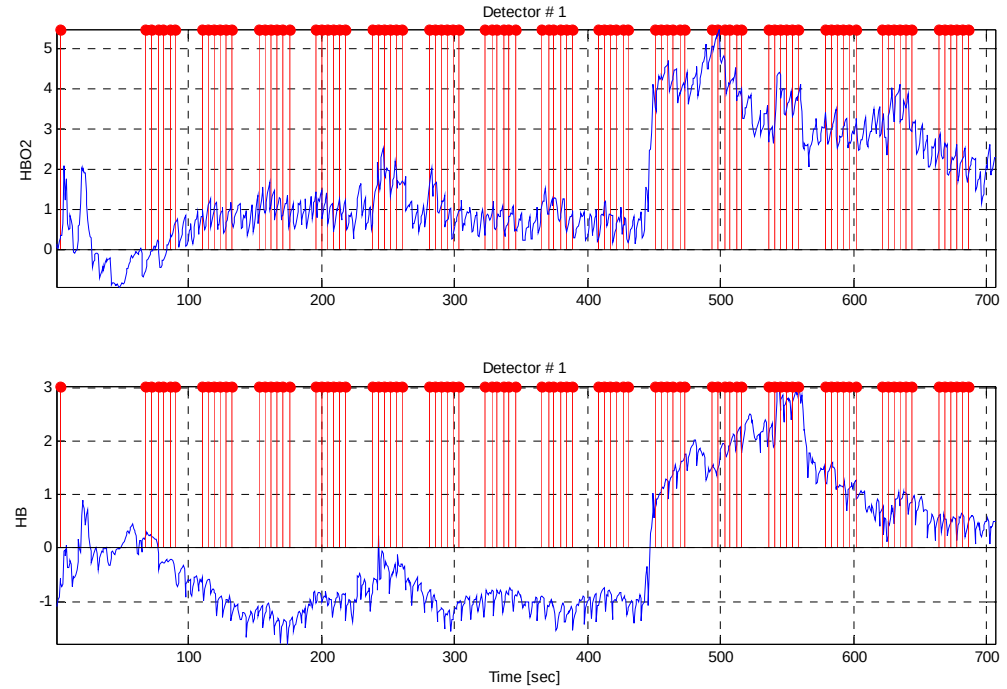

Figure 6.7 Raw data from control group.

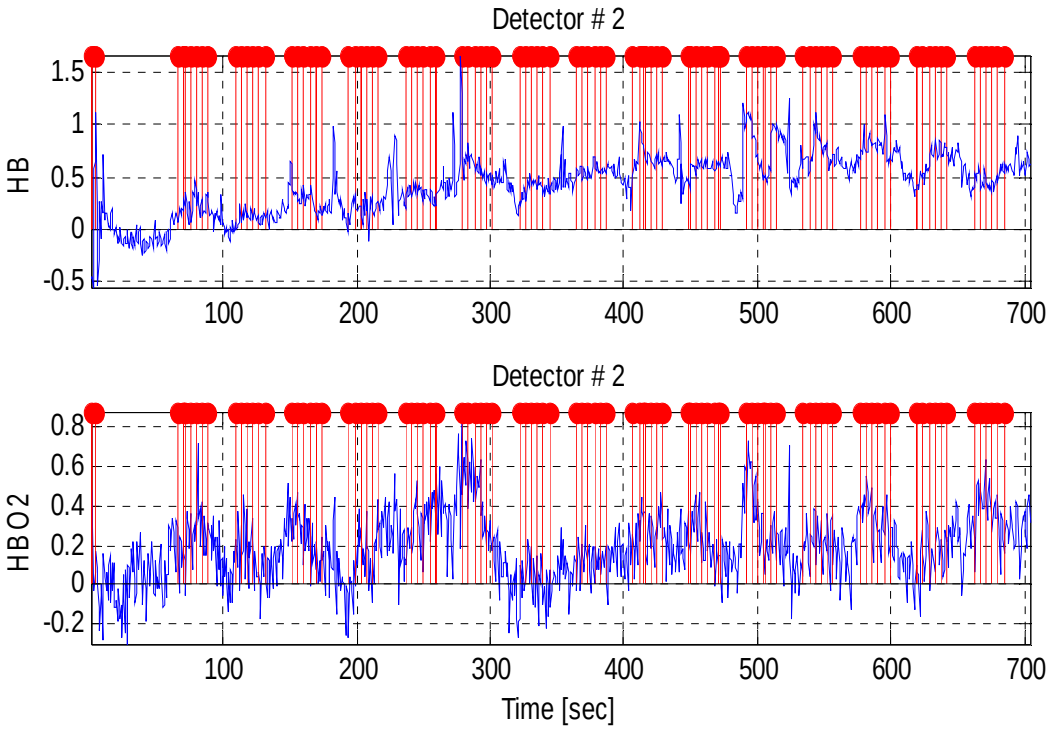

Figure 6.8 Raw data from ADHD patient soon after having medication.

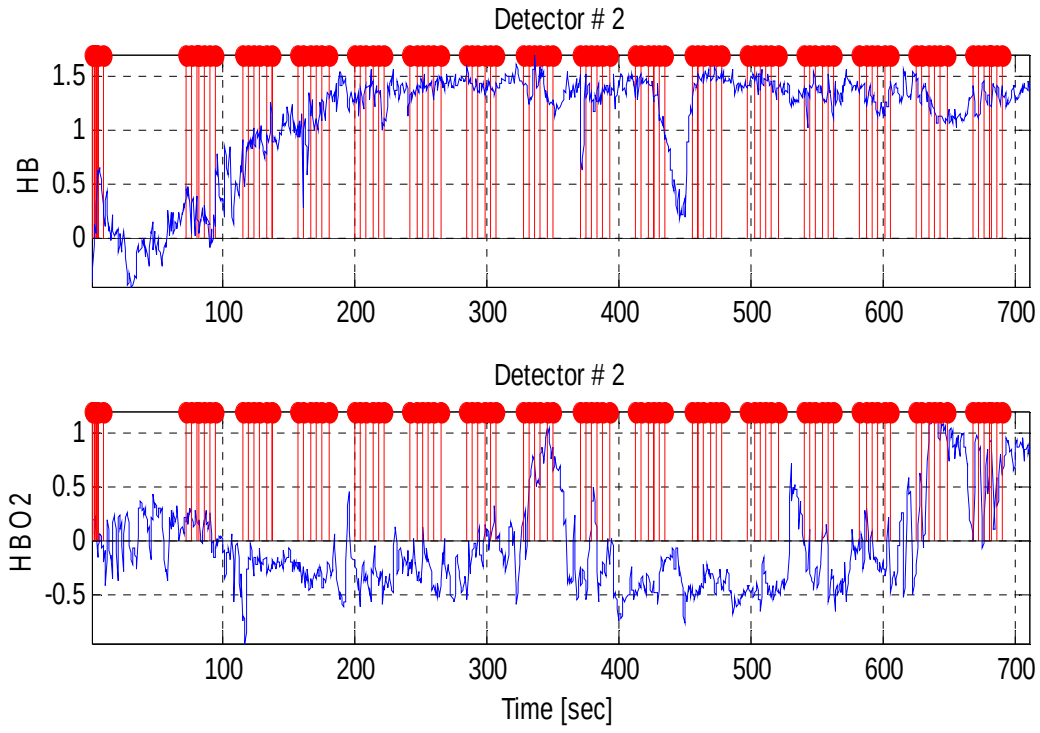

Figure 6.9 Raw data from same ADHD patient without medication.

In the first part of study, analysis of hemodynamic signals in the frequency domain was performed. After the calculation of oxy-Hb and deoxy-Hb signals, the Butterworth low pass filter with cut off frequency of 0.25 Hz was used to remove baseline drift and to eliminate the fluctuations due to heart rate, respiration etc.. Fourth order band pass Butterworth filter was used to separate the oxy-Hb and deoxy-Hb signals into very low frequency (VLF) (0.02-0.05 Hz), low frequency (LF) (0.08-0.12 Hz), and high frequency (HF) (0.12-0.18 Hz) bands. These bands were found partly from literature and partly as a result of retrospective spectral analysis. The VLF band has been shown to carry information regarding the main frequency lobe of the hemodynamic response by several authors. While the LF band is known to represent the vasomotor activity. The third band was not investigated much but in a one study it was mentioned that this band reflects the control of autonomic nervous system on vasomotor dynamics.

7. RESULTS AND DISCUSSION

7.1. Behavioral Results

Behavioral results were studied in two parts. In the first part mean reaction times(RT) and error rates were compared within the group and between the subjects. Studying reaction time is important because it is a measure of cognitive difficulty and efficiency of processing. In the second part response inhibition, which is a measurement of both the speed of behavioral inhibitory process and the ability to effectively trigger inhibitory process, were analyzed.

For the Color Stroop task mean reaction times were analyzed using ANOVA. As expected prior to analyses mean reaction times were found shorter in controls then ADHD and then schizophrenic patients. In controls and schizophrenics mean reaction times within the groups were shorter for neutral stimulus than the congruent or incongruent stimulus, but for ADHD patients mean reaction times were shorter for congruent stimulus than the neutral or incongruent stimulus.

Table 7.1 Reaction time and error rates for the Stroop task averaged over controls and schizophrenics.

Reaction Times	Patients		Controls		Anova Results	
	Mean	Std. Dev.	Mean	Std. Dev.	F Value	P Value
Neutral Stimulus	1,7	0,38	1,09	0,27	36,44	p<0,05
Congruent Stimulus	1,76	0,33	1,32	0,36	59,23	p<0,05
Incongruent Stimulus	2,18	0,29	1,36	0,35	89,31	p<0,05
Error Rates	Mean	Std. Dev.	Mean	Std. Dev.		
Neutral Stimulus	0,08	0,14	0,03	0,02	2,78	1,109
Congruent Stimulus	0,1	0,12	0,04	0,05	3,08	0,094
Incongruent Stimulus	0,3	0,2	0,08	0,08	14,27	p<0,05

Table 7.2 Reaction time and error rates for the Stroop task averaged over controls and off-medicated ADHD patients.

Reaction Times	ADHD_off			Controls		Anova Results	
	Mean	Std. Dev.		Mean	Std. Dev.	F Value	P Value
Neutral Stimulus	1,45	0,3		1,09	0,27	6,44	p>0,05
Congruent Stimulus	1,34	0,26		1,32	0,36	0,263	p>0,05
Incongruent Stimulus	1,625	0,41		1,36	0,35	2,582	p>0,05
Error Rates	Mean	Std. Dev.		Mean	Std. Dev.		
Neutral Stimulus	0,04	0,04		0,03	0,02	2,8	p>0,05
Congruent Stimulus	0,08	0,1		0,04	0,05	3,01	p>0,05
Incongruent Stimulus	0,35	0,2		0,08	0,08	14,27	p<0,05

Reaction times were calculated as the average of answered questions; not answered questions were not included in the reaction times because we did not know whether the subject spend more than 4 seconds on the task or just shift the attention towards something else. As shown in Table7.1 and Figure 7.1, reaction times differed significantly for controls and schizophrenics (for neutral P= 0,02; for congruent P = 0,019 ; for incongruent P=0,0001), but did not differ significantly for controls and ADHDs (P>0,05). The interference effect between congruent and incongruent remained significant over the entire period of the experiment for both controls and schizophrenics. The mean error rates of schizophrenic patients are higher than that of control groups (Table7.1), but only in incongruent stimulus significant difference was seen. This was because the hemodynamic response was stronger during incongruent compared to congruent and neutral trials of the Stroop task in the lateral prefrontal cortex bilaterally. This stronger hemodynamic response was interpreted as stronger brain activation during incongruent trials of the Stroop task.

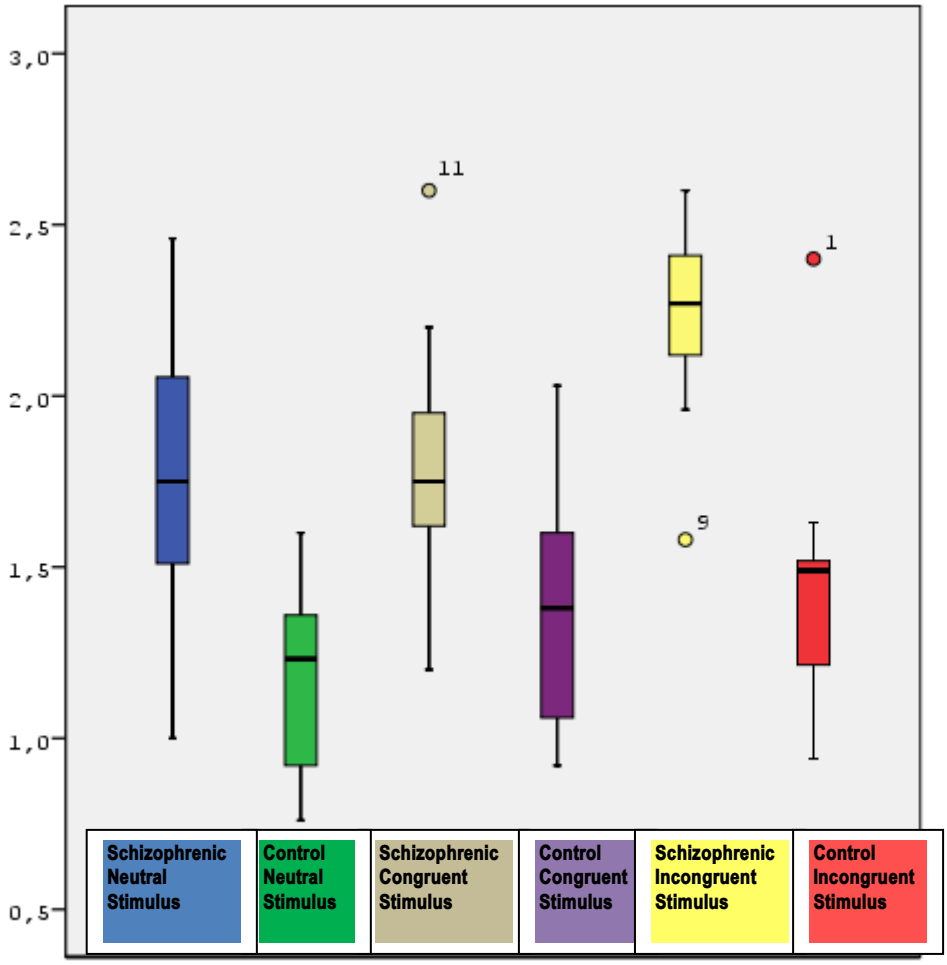

Figure 7.1 Mean and standard deviation of response times between and within controls and schizophrenic patients groups.

Response inhibition is a key determinant of successful cognitive and motor control. More research on response inhibition was done by measuring Go/NoGo and Stop-signal tasks. Up to date a couple of study was done with Stroop paradigim; but like in Go/NoGo tasks, congruent (like Go) and incongruent (like NoGo) stimulus activates the prefrontal cortex. The index of inhibitory control (i.e., inhibition of a prepotent response) is the duration of the stopping process, that is the slowing time from incongruent stimulus to congruent stimulus.

The amount of Stroop inhibition was calculated by examining incongruent RT – congruent RT over congruent RT. ANOVA was used to determine whether schizophrenia and/or ADHD is associated with impaired response inhibition.

Table7.3 and Figure 7.2 show the inhibition index between controls and schizophrenics. As expected patients with schizophrenia presented with increased stop signal reaction time, suggesting slower inhibitory processes. A one-way ANOVA revealed a significant inhibition between two groups.

Table 7.3 Summary of Stroop inhibition for controls and schizophrenics.

Response Inhibition Index			Anova Results	
	Mean	Std. Dev.	Fvalue	Pvalue
Schizophrenia	0.255	0.189	6.312	0.011
Control	0.104	0.146		

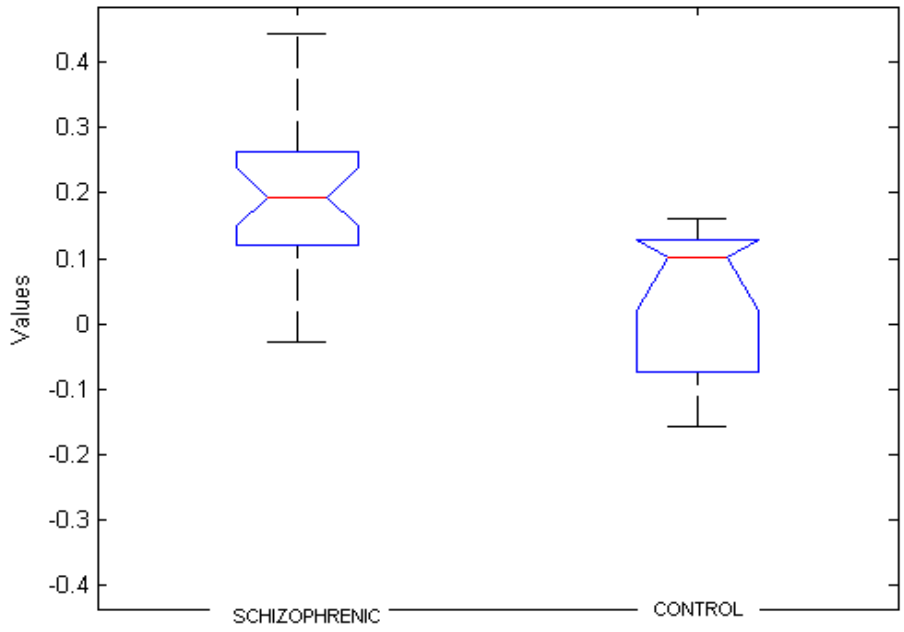

Figure 7.2 Mean and standard deviation of response inhibition between schizophrenics and controls.

Table7.4 shows the inhibition index of ADHD patient before and after medication (ADHD_off vs ADHD_on). ANOVA result shows an critically significant value between two groups,which gives us no information whether ADHD is associated with response inhibition or not.

Table 7.4 Summary of Stroop inhibition for ADHD patient before and after medication.

Response Inhibition Index			Anova Results	
	Mean	Std. Dev.	Fvalue	Pvalue
ADHD_Off	0.225	0.138	3.956	0.059
ADHD_On	0.105	0.155		

Table7.5 and Table7.6 show the inhibition index of control with ADHD patient before medication and ADHD patient after medication respectively. In parallel to the previous studies ANOVA result shows inhibition deficiency in unmedicated ADHD patients. Even though response inhibition has emerged as one of the principal paradigms for studying ADHD, but we could only find the difference between controls and ADHD patients.

Table 7.5 Summary of Stroop inhibition for unmedicated ADHD patients with controls.

Response Inhibition Index			Anova Results	
	Mean	Std. Dev.	Fvalue	Pvalue
Control	0.104	0.146	4.483	0.045
ADHD_Off	0.225	0.138		

Table 7.6 Summary of Stroop inhibition for controls and medicated ADHD patients.

Response Inhibition Index			Anova Results	
	Mean	Std. Dev.	Fvalue	Pvalue
Control	0.104	0.146	44.83	0.980
ADHD_On	0.105	0.155		

7.2. NIRS Results

The main contrast of interest in the Color-Word Matching Stroop task was the incongruent condition against congruent condition. The data from the energies between different conditions were captured and statistically evaluated in SPSS 15.0 by using one-way Welch-ANOVA. Since all data groups have different number of subjects,the Levene test confirms the suspicion that the variances of the groups are different or not. If the the variances and the group sizes are unequal, Welch statistic is more powerful than the standard F or Brown-Forsythe statistics. As with the standard F statistic, the Welch statistic is not significant below 0.05. The result in the tables are calculated using Welch-ANOVA, and by eliminating outliers.

The following tables from Table7.7 to Table7.9 shows the response inhibition energies between controls, schizophrenic patients and ADHD patients in different manner. Only in Table7.10 there is a comparison between all three groups.

The underlying idea of calculating response inhibition by using reaction times and energies were the same. In calculating response inhibition using reaction times we averaged RTs in all detectors, so it gives us an overall idea of inhibition occurred in the whole prefrontal cortex. Calculating response inhibition using energies makes us to differentiate prefrontal cortex in four regions, and makes it easier to understand if some part of the brain region is more responsible for inhibitory behavior.

Adapted version of the Stroop task helps us to separate response preparation and interference process. In the traditional Stroop task, generating the verbal response to match a stimulus is interfered by the second dimension of the stimulus (or the dimension of a second stimulus). Response preparation and the interference process itself are confounded by this. With the presently used task, these processes are separated. The manual response preparation processes are separated from the matching process, where interference has to be reduced.

In bi-group comparison all significant results were found in VLF and LF bands, which show us inhibition occurs in low or very low frequency energies. Table7.7 to Table7.9 shows us that the strongest activations corresponded to regions in the lateral PFC, extending along the banks of the IFS. Further, when contrasting only congruent vs. incongruent conditions, only activation in the left IFS remained, this is a clear argument in favor of the relevance of the IFS for interference reduction.

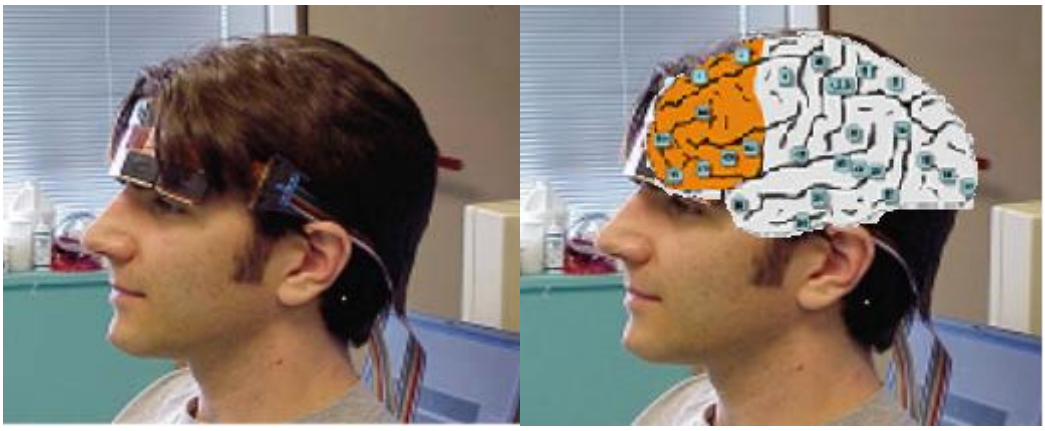

Figure 7.3 Results from the detectors 1 to 4 corresponds to Inferior Frontal Sulcus of Prefrontal Cortex.

This result is not consistent with the other studies that found the right IFS is involved in inhibition. But consistent with our previous studies and Matching Stroop task studies that showed activation in left frontal lobe.

Table 7.7 Summary of response inhibition energies for detector quadruples for VLF,LF and HF energy bands in deoxy-hemoglobin and oxy-hemoglobin for controls and schizophrenic patients

CONTROL VS. SIZO

HbO	VLF	LF	HF
1-4	0.231	0.348	0.279
5-8	0.952	0.173	0.340
9-12	0.942	0.526	0.776
13-16	0.356	0.781	0.861

Hb	VLF	LF	HF
1-4	0.155	0.036	0.099
5-8	0.942	0.175	0.257
9-12	0.894	0.07	0.141
13-16	0.437	0.370	0.388

Table 7.8 Summary of response inhibition energies for detector quadruples for VLF,LF and HF energy bands in deoxy-hemoglobin and oxy-hemoglobin for ADHD medicated and unmedicated

ADHD_ON VS. ADHD_OFF

HbO	VLF	LF	HF
1-4	0.274	0.033	0.179
5-8	0.655	0.451	0.324
9-12	0.382	0.397	0.099
13-16	0.585	0.063	0.251

Hb	VLF	LF	HF
1-4	0.352	0.842	0.549
5-8	0.283	0.958	0.231
9-12	0.100	0.728	0.650
13-16	0.765	0.260	0.420

Table 7.9 Summary of response inhibition energies for detector quadruples for VLF,LF and HF energy bands in deoxy-hemoglobin and oxy-hemoglobin for controls and ADHD unmedicated.

CONTROL VS. ADHD_OFF

HbO	VLF	LF	HF
1-4	0.038	0.997	0.148
5-8	0.782	0.514	0.203
9-12	0.852	0.447	0.286
13-16	0.636	0.938	0.683

Hb	VLF	LF	HF
1-4	0.249	0.144	0.178
5-8	0.904	0.760	0.260
9-12	0.512	0.679	0.298
13-16	0.545	0.448	0.502

Table 7.10 Summary of response inhibition energies for detector quadruples for VLF,LF and HF energy bands in deoxy-hemoglobin and oxy-hemoglobin for controls, schizophrenic patients and ADHD unmedicated.

CONTROL VS. SIZO VS. ADHD_OFF

HbO	VLF	LF	HF
1-4	0.328	0.175	0.470
5-8	0.924	0.116	0.553
9-12	0.990	0.738	0.768
13-16	0.112	0.851	0.675

Hb	VLF	LF	HF
1-4	0.314	0.79	0.114
5-8	0.833	0.221	0.426
9-12	0.987	0.029	0.315
13-16	0.959	0.517	0.948

8. CONCLUSION

In this study a multichannel fNIRS device and a variation of the Stroop task was used to compare schizophrenic patients with those healthy controls during cognitive task. In this Color-Word Matching Stroop version, interference takes place at a conceptual level and is separated from the response preparation. An additional matching process added and subjects gave a constant response (button press), which was neither a color nor a word. The modality of the behavioral component of the task is independent of the interfering dimensions. Varying the dimension of the first word (neutral, congruent, or incongruent words to the presented color) allows for the investigation of the interference effects. The conceptual interference between the two dimensions of a within a matching process was separated from the response preparation and execution process. The main difference between the two tasks is that subjects in the Matching Stroop task compare two attributes of a stimulus while in the traditional Stroop task they generate a response to match one attribute of a stimulus. The results were somehow consistent with the previous studies. Although it appears likely that schizophrenia is associated with reduced response inhibition, the specific nature of this impairment is complicated. Slower reaction times are result of attentional difficulty rather than general slowness of the patients with schizophrenia. Significant results were found mainly in the lateral prefrontal cortex because we selected a STROOP task that mainly activates this region as frontmedain regions cannot be captured by fNIRS due to limited depth of penetration.

APPENDIX A. The Modified Beer Lambert Law

In highly scattered medium such as brain, the oxy-Hb and deoxy-Hb concentration changes was calculated using modified beer lambert law. This law states that optical density (OD) is proportional to the concentration of deoxy-Hb (ε_{Hb}), oxy-Hb (ε_{HbO_2}) and the optical pathlength (L) :

$$OD(\lambda_1) = \log\left[\frac{I_0(\lambda_1)}{I(\lambda_1)}\right] = \varepsilon_{HbO_2}(\lambda_1).[HbO_2].L + \varepsilon_{Hb}(\lambda_1).[Hb].L \qquad \text{(A.1)}$$

$$OD(\lambda_1) = \log\left[\frac{I_0(\lambda_1)}{I(\lambda_1)}\right] = \varepsilon_{HbO_2}(\lambda_1).[HbO_2].L + \varepsilon_{Hb}(\lambda_1).[Hb].L \qquad \text{(A.2)}$$

Where I_0 is the received light intensity, I is the transmitted light intensity, λ_1 is wavelength1 and λ_2 is wavelength2. The oxy-Hb and deoxy-Hb changes in the brain can be calculated as follows:

$$\Delta OD(\lambda_1) = \varepsilon_{HbO_2}(\lambda_1).\Delta[Hbo_2].L + \varepsilon_{Hb}(\lambda_1).\Delta[Hb].L \qquad \text{(A.3)}$$

$$\Delta OD(\lambda_2) = \varepsilon_{HbO_2}(\lambda_2).\Delta[Hbo_2].L + \varepsilon_{Hb}(\lambda_2).\Delta[Hb].L \qquad \text{(A.4)}$$

$$\begin{pmatrix} \Delta OD(\lambda_1) \\ \Delta OD(\lambda_2) \end{pmatrix} = \begin{pmatrix} \varepsilon_{HbO_2(\lambda_1)} & \varepsilon_{Hb(\lambda_1)} \\ \varepsilon_{HbO_2(\lambda_2)} & \varepsilon_{Hb(\lambda_2)} \end{pmatrix} \begin{pmatrix} \Delta[HbO_2] \\ \Delta[Hb] \end{pmatrix} L \tag{A.5}$$

$$\begin{pmatrix} \Delta[HbO_2] \\ \Delta[Hb] \end{pmatrix} = \begin{pmatrix} \varepsilon_{HbO_2(\lambda_1)} & \varepsilon_{Hb(\lambda_1)} \\ \varepsilon_{HbO_2(\lambda_2)} & \varepsilon_{Hb(\lambda_2)} \end{pmatrix}^{-1} \begin{pmatrix} \Delta OD(\lambda_1) \\ \Delta OD(\lambda_2) \end{pmatrix} \frac{1}{L} \tag{A.6}$$

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