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Signature of Author

Signature of Supervisor

Permanent address:
77-7-1, Taman Lita,
Jalan Osman Bin Kadir Lit,
10150 Pulau Pinang

Name of Supervisor
Assoc. Prof. Dr. Tang Tong Boon

Date :

Date :

UNIVERSITI TEKNOLOGI PETRONAS

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY BASED

DYNAMIC DIFFICULTY ADJUSTMENT SYSTEM

FOR COGNITIVE TRAINING AND REHABILITATION

by

UNG WEI CHUN

The undersigned certify that they have read, and recommend to the Postgraduate Studies Programme for acceptance this thesis for the fulfilment of the requirements for the degree stated.

Signature: ______________________________

Main Supervisor: Assoc. Prof. Dr. Tang Tong Boon

Signature: ______________________________

Co-Supervisor: Prof. Dr. Fabrice Meriaudeau

Signature: ______________________________

Head of Department: Assoc. Prof. Ir. Dr. Nursyarizal Mohd Nor

Date: ______________________________

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY BASED DYNAMIC DIFFICULTY ADJUSTMENT SYSTEM FOR COGNITIVE TRAINING AND REHABILITATION

by

UNG WEI CHUN

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BANDAR SERI ISKANDAR,

PERAK

APRIL 2018

DECLARATION OF THESIS

Title of thesis	Functional Near-Infrared Spectroscopy based Dynamic Difficulty Adjustment System for Cognitive Training and Rehabilitation

I UNG WEI CHUN

hereby declare that the thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at UTP or other institutions.

Witnessed by

Signature of Author

Signature of Supervisor

Permanent address:
77-7-1, Taman Lita,
Jalan Osman Bin Kadir Lit,
10150 Pulau Pinang

Name of Supervisor
Assoc. Prof. Dr. Tang Tong Boon

Date :

Date :

DEDICATION

I dedicate my dissertation work to my family and many friends. A special feeling of gratitude to my loving parents, Ung Kheng Seng and Tan Goay Khim whose words of encouragement and push for tenacity ring in my ears. My brother Ung Wei Khye have never left my side and is very special. I also dedicate this dissertation to my many friends and family who have supported me throughout the process.

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ABSTRACT

Mental overload and underload are equally serious conditions that can impinge the gains of cognitive training and rehabilitation. Therefore, it is always better to train at appropriate pace but the challenge to impose the right amount of cognitive workload remains. This thesis reports the designing and development of a functional near-infrared spectroscopy (fNIRS) – dynamic difficulty adjustment (DDA), a closed-loop feedback system, that allows users to train at their appropriate difficulty level and workload, and also aids them in preventing mental overload. Oxygenated hemoglobin signals measured in the dorsolateral prefrontal cortex (DLPFC) are first processed in real time before extracting relevant parameters, which are then compared to assess the mental workload and adjust the task difficulty accordingly. It is based on the theory that there is a linear relationship between workload and hemodynamics where the task difficulty does not exceed the cognitive capacity, however, once there is cognitive overload or mental overload hemodynamics starts to decrease. The first study was a pilot test involving a mild Alzheimer's disease patient and a healthy older individual, which validated the theory and region of interest – DLPFC. In the second study, the functionality of the fNIRS-DDA system was fully explored using 25 healthy university students. They underwent two separate training sessions: *adaptive* (incorporating the fNIRS-DDA system), and *nonadaptive* (where the task difficulty was fixed at optimum). The workload in each condition was assessed using the NASA Task Load Index (NASA-TLX). The significant drop in DLPFC activation and negative quadratic regression model observed only in nonadaptive condition coupled with sustained performance and higher NASA-TLX scores, especially in both mental demand and frustration subscales, might indicate mental overload. Absence of such drop in activation and negative quadratic regression model alongside lower NASA-TLX overall and all subscale scores in adaptive condition suggest that the incorporation of the fNIRS-DDA system indeed optimised the participants' engagement and aided the participants in avoiding mental overload.

ABSTRAK

Kerterlaluan atau kekurangan beban kerja mental boleh memudaratkan manfaat latihan atau pemulihan kognitif. Latihan mengikuti kebolehan individu lebih baik tetapi pengenaan beban kognitif yang sesuai memang mencabar. Tesis ini melaporkan sistem pelarasan kesukaran dinamik berdasarkan Spektroskopi Inframerah-Dekat (fNIRS-DDA), satu sistem kawalan gelung tertutup yang membolehkan pengguna berlatih pada tahap kesukaran dan beban mental yang sesuai dan juga membantu mereka mencegah keletih mental. Pengukuran oksihemoglobin dalam korteks dorsolateral prefrontal (DLPFC) diproses dalam masa nyata sebelum mengekstrak parameter yang kemudiannya dibandingkan untuk menanksir beban kerja mental dan melaraskan kesukaran. Ia berdasarkan teori bahawa terdapatnya hubungan linear antara beban kerja mental dan hemodinamik di mana kesukaran latihan tidak melebihi kapasiti kognitif, namun, kewujudan kerterlaluan beban kognitif atau keletihan mental akan mengurangkan hemodinamik. Kajian pertama adalah ujian perintis yang melibatkan pesakit Alzheimer ringan dan warga emas sihat untuk mengesahkan teori dan bahagian otak berkaitan – DLPFC. Dalam kajian kedua, fungsi sistem fNIRS-DDA telah diterokai sepenuhnya menggunakan 25 pelajar-pelajar universiti. Mereka menjalani dua sesi latihan: kondisi *adaptive* (kesukaran sentiasa dilaraskan menggunakan sistem fNIRS-DDA), dan *nonadptive* (kesukaran ditetapkan). Beban kerja dalam setiap sesi dinilai dengan NASA Task Load Index (NASA-TLX). Penurunan sikinifikan pengaktifan DLPFC dan model regresi kuadratik negatif hanya diperlihatkan dalam kondisi *nonadaptive* bersama dengan prestasi kekal dan skor NASA-TLX yang lebih tinggi, terutamanya dalam permintaan mental dan frustrasi subkelas, mungkin menunjukkan keletihan mental. Ketiadaan penurunan pengaktifan DLPFC dan model regresi kuadratik negatif bersama-sama dengan NASA-TLX yang lebih rendah dalam kondisi *adaptive* menunjukkan bahawa sistem fNIRS-DDA berjaya mengoptimumkan penglibatan para peserta dan menghindari beban kerja mental pada para peserta.

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LIST OF ABBREVIATIONS

CDR	Clinical Dementia Rating
DDA	Dynamic Difficulty Adjustment
deoxy-Hb	Deoxygenated Hemoglobin
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
mAD	Mild Alzheimer's Disease
MMSE	Mini-Mental State Examination (MMSE)
NASA-TLX	NASA Task Load Index
NIR	Near-Infrared
oxy-Hb	Oxygenated Hemoglobin
PFC	Prefrontal Cortex
RT-SSS	Real-Time Scalp Signal Separating
UAVs	Unmanned Air Vehicles

Chapter 1

INTRODUCTION

1.1 Background Study

Neuroplasticity, also known as brain plasticity or neural plasticity, can be considered as the brain's ability to change its molecular and structural features and systems that dictate a specific function [1]. Over the past few decades, advances in the understanding of neuroplasticity have yielded the development of cognitive interventions, aiming to exploit the plasticity of the cortex in order to improve cognitive function. These interventions are often centred on cognitive tasks [2] to stimulate cognitive functioning and can be grouped into two categories: (1) cognitive training, and (2) cognitive rehabilitation [3, 4]. Cognitive training is a guided practice of standard tasks to practise specific cognitive functions to improve performance while cognitive rehabilitation is an approach focused on improving cognitive functioning or reducing functional decline through compensatory or restorative strategies. For instance, if neuronal plasticity still presents, cognitive rehabilitation may be introduced to Alzheimer's disease patients in an attempt to slow down the insidious progression of the disease.

Working memory, where conscious thought and learning occur, is both the bottleneck and the engine of learning. Capacity limit is one of the major features of working memory that are important to learning. However, its capacity to retain information is very limited. It means that working memory can only hold a limited amount of information at one time. Because working memory is where learning processes occur, instructional methods such as practice exercises and graphics can be used to stimulate the kinds of processing that ultimately result in learning. Since working memory has a limited capacity, it will be important to manage the capacity of working memory i.e. to keeping cognitive load appropriate so that the learner can devote scarce working memory capacity to productive learning processes.

Mental workload reflects the amount of cognitive or attentional resources being allocated to meet task demands at a given point in time, in other words, how hard the brain is working to meet task demands. The amount of mental load imposed during any given lesson or training will depend on (1) the complexity of the content, (2) the related experience of the learners, (3) the rate and control of presentation of information, and (4) the instructional modes and methods used to teach the content [5]. Indeed it is the cognitive demands imposed by learning materials on learners that promote the learning objectives. An ideal amount of effective cognitive demand falls just beyond the capacity limits of the learner so that he or she is challenged to invest mental effort in the learning tasks. However, sustained overloading working memory can cause cognitive overload or mental overload, which leads to negative consequences both for learning and for motivation [6]. Cognitive overload or mental overload occurs when the processing demands evoked by the learning task exceed the cognitive capacity. If cognitive load is too high or too low, the leaner is overwhelmed or underwhelmed, and the learning is disrupted. As a result, the gains of cognitive training would be reduced or even eliminated [7, 8] as meaningful learning often requires substantial cognitive processing.

Therefore, it is always better when the learners train at their own pace [9], as compared to when train independently of learner control which can quickly overload working memory capacity. The challenge is to define learning tasks that impose the right amount of productive load and at the same time minimize irrelevant sources of cognitive load. One of the attempts include the implementation of dynamic difficulty adjustment (DDA), a technique for adaptively changing a task to make it easier or harder based on one or more feedback sources. These sources can be critical events, human performance, physiological metrics, models of performance, and combinations of two or more of the above [10]. Among the many methods of measuring mental workload, physiological measures offer promise because they can be more closely linked to brain function. They are more sensitive to the aspects of the task [7] and are known to respond to cognitive demand in a relatively predictable manner [11].

Physiological measures can also index the level of mental demand associated with a given task because they can provide continuous and unobtrusive monitoring of the learner and do not interfere with the learner's ongoing work [12-16]. Accurate assessment of mental workload could allow for pertinent intervention by adapting the intervention when any detrimental state that can arise from either work overload or understimulation is detected [17-21].

Various neuroimaging modalities such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) can be used to provide objective measures of mental workload. Increasing task difficulty, for instance, is known to be associated with EEG changes such as increased power in the beta bandwidth, increased theta activity at frontal sites and the suppression of alpha activity [22, 23]. On the other hand, a fMRI study has reported that there is a linear relationship between task difficulty and activations in regions related to working memory processes [24]. Although EEG offers excellent temporal resolution, its spatial resolution is very limited. Furthermore, the tedious setup and susceptibility to motion artifacts should be considered for minimally intrusive deployment. The fMRI, on the other hand, offers excellent spatial and temporal resolution but the equipment is expensive and not portable, plus the subject constraints are strict. In contrast, one of the relatively new optical imaging techniques, functional near-infrared spectroscopy (fNIRS) is a more viable alternative for cognitive state monitoring.

This thesis presents a new real-time fNIRS-DDA system, which uses fNIRS brain signals as a reference to dynamically adjust the difficulty level of a given task, aiming to improve user engagement and prevent mental overload by imposing the right amount of cognitive load. The fNIRS-DDA system has the flexibility to be used together with any task no matter in cognitive training or cognitive rehabilitation.

1.2 Problem Statement

- Mental overload affects cognitive training or rehabilitation gains

  Cognitive training has the potential to improve or maintain performance in a specific domain while cognitive rehabilitation can help brain-injured or otherwise cognitively impaired individuals to restoral normal functioning, or to compensate for cognitive deficits. However, for both cognitive training and cognitive rehabilitation, a range of difficulty levels may be available. As mentioned previously, different task difficulty levels can result in different mental workload and various cognitive states. The ideal amount of effective cognitive demand falls just beyond the capacity limits of the learner [5] so that he or she is challenged to invest extra mental effort in the learning tasks. However, mental overload and underload are both equally serious conditions that can cause the learner to lose focus, learn less, and is less productive and more error-prone [25, 26]. As a result, the gains of cognitive training would be reduced or even eliminated [7, 8] as meaningful learning often requires substantial cognitive processing. Therefore, it is always better when the learners train at their own pace [9]. The challenge is to impose the right amount of cognitive load. It can be done by adjusting the amount of cognitive load accordingly to metrics of mental workload. The main problems remain how and which metric to use in the implementation of a reliable DDA system that can provide accurate continuous and unobtrusive monitoring of the learner, and do not interfere with the learner's ongoing work.

1.3 Research Hypothesis

Taking mental overload into account, the fNIRS-DDA system developed is designed to maintain a user's engagement and prevent mental overload by imposing the right amount of cognitive load via adapting the challenge of a task automatically based on the user's current mental state. Therefore, it is hypothesized that the use of the fNIRS-DDA system optimizes the user's engagement and prevent mental overload by providing personalized cognitive training.

1.4 Research Objectives

The objectives of the research are as follow:

- To design and develop a fNIRS-DDA system

  This thesis reports the design and development of the fNIRS-DDA system that not only allows users to train at their appropriate level of difficulty and workload but also aids them in preventing mental overload. The system is designed to impose the right amount of cognitive load via adapting the challenge of a task automatically based on the user's current mental state. The fNIRS-DDA system has the flexibility to be used together with any task no matter in cognitive training or cognitive rehabilitation.

- To examine and validate the efficacy of the fNIRS-DDA system

  This thesis also looks into the efficacy of the fNIRS-DDA system in optimizing the user's engagement and preventing mental overload by conducting two separate studies. In these studies, the fNIRS-DDA system was bundled with a well-established cognitive task – mental arithmetic problem solving, aiming to slow down the progression of dementia in Alzheimer's disease patients. However, both of these aforementioned studies were only pre-studies. The first study was a pilot study involving only two older participants (a mild Alzheimer's disease patient and a healthy control) to validate the proposed theory and target region while the other study was conducted solely to fully test the functionality of the fNIRS-DDA system i.e. does it really help to prevent mental overload. The efficacy of the fNIRS-DDA system coupled with the mental arithmetic problem solving cognitive training in slowing down progression of dementia will be assessed in future studies.

1.5 Scope of Study

This work focuses in designing and developing a fNIRS-DDA system to be used along with cognitive training or cognitive rehabilitation, aiming to maintain a user's engagement and prevent mental overload by adapting the challenge automatically based on the user's current mental state, as measured by fNIRS, in order to impose the right amount of cognitive load. By maintaining a user's engagement and preventing mental overload, the gains of cognitive training or rehabilitation can be maximized. First, designing the system consists of selecting the most suitable DDA feedback metrics, identifying the most appropriate neuroimaging modality, defining the target region to acquire the neurophysiological metrics and describing the steps to process and ultimately translate the neurophysiological metrics to feedback for the DDA. Subsequently, a fully automated software was developed using MATLAB (MathWorks, Inc.) accordingly to the system design.

Based on extensive literature review, mental arithmetic problem solving was identified as the task to be used in cognitive rehabilitation for Alzheimer's disease to slow down progression of dementia. A first pilot study was first carried out to validate the proposed theory and target region, followed by a second pilot study to fully test the functionality of the fNIRS-DDA system i.e. does it really help to prevent mental overload. The efficacy of the fNIRS-DDA system coupled with the mental arithmetic problem solving cognitive training in slowing down progression of dementia will be assessed in future studies.

Chapter 2

LITERATURE REVIEW

2.1 Neuroplasticity

Neuroplasticity, also known as brain plasticity or neural plasticity, refers to the ability of the brain, or more precisely the central nervous system, to alter its molecular and structural features and systems that dictate a specific function [1]. Microscopically, neuroplasticity allows the neurons (nerve cells) to change its form and function to adapt in response to new situations, changes in the environment or to compensate for lesions. Some of these alterations include the transfer of brain activity associated with a specific function to other parts of the brain, recruitment of new or different neural networks, thickening or shrinkage of grey matter, and strengthening and weakening of synapses. At the cellular level, changes in membrane excitability, synaptic plasticity, as well as structural changes in dendritic and axonal anatomy are observed in animals and humans [27, 28].

The study of neuroplasticity engages scientists from a vast array of disciplines because of the profound implications it has for understanding the functional underpinnings of action and cognition in the healthy and lesioned brain [29]. Over the past decades, several researches showed that neuroplasticity occurs throughout the life span [30-32]. Therefore, there has been an increased interest in improving cognitive function by exploiting the plasticity of the cortex. These interventions are often centred on cognitive tasks [2] and can be grouped into three categories: (1) cognitive stimulation, (2) cognitive training, and (3) cognitive rehabilitation [3, 4].

Cognitive training is a guided practice of standard tasks to practise specific cognitive functions to improve performance while cognitive rehabilitation is an approach focused on improving cognitive functioning or reducing functional decline through compensatory or restorative strategies. Several studies showed that intensive training of a cognitive or motor process induces plastic changes in underlying cortical structures and representations [33, 34]. On top of that, advances in the understanding of neuroplasticity in the process of functional recovery following brain lesions are starting to lead to the development of more rational strategies to facilitate cognitive rehabilitation [35, 36].

2.2 Working Memory

Working memory involves a total of three subsystems [37]. Two of them are to store and manipulate visual images as well as verbal information, which include visuospatial sketchpad and phonological loop [38, 39]. Last but not least, the third subsystem is known as the central executive – an attentional system that selects goal-relevant behaviour by focusing and switching attention. Therefore, well-coordinated subsystems are able to store and retrieve information from long-term memories [40].

Working memory, where conscious thought and learning occur, is both the bottleneck and the engine of learning. Capacity limit is one of the major features of working memory that are important to learning. However, its capacity to retain information is very limited. It means that working memory can only hold a limited amount of information at one time. Because working memory is where learning processes occur, instructional methods such as practice exercises and graphics can be used to stimulate the kinds of processing that ultimately result in learning. Since working memory has a limited capacity, it will be important to manage the capacity of working memory i.e. to keeping cognitive load appropriate so that the learner can devote scarce working memory capacity to productive learning processes.

As working memory is heavily involved in a vast range of functions, Alzheimer’s disease patients often suffer from cognitive impairments that are associated with deficits in working memory; see 2.6.3.

2.3 Mental Workload

Mental workload reflects the amount of cognitive or attentional resources being allocated to meet task demands at a given point in time, in other words, how hard the brain is working to meet task demands. The amount of mental load imposed during any given lesson or training will depend on (1) the complexity of the content, (2) the related experience of the learners, (3) the rate and control of presentation of information, and (4) the instructional modes and methods used to teach the content [5].

2.3.1 Underload and Overload

Mental overload and underload are both equally serious conditions that can cause the learner to lose focus, learn less, and is less productive and more error-prone [25, 26]. Indeed it is the cognitive demands imposed by learning materials on learners that promote the learning objectives. An ideal amount of effective cognitive demand falls just beyond the capacity limits of the learner [5] so that he or she is challenged to invest mental effort in the learning tasks. However, sustained overloading working memory can cause mental overload, which leads to negative consequences both for learning and for motivation [6]. Mental overload occurs when the processing demands evoked by the learning task exceed the cognitive capacity [41]. Different task difficulty can also result in different mental workload and various cognitive states, which can affect performance and learning. If cognitive load is too high or too low, the leaner is overwhelmed or underwhelmed, and learning is disrupted. As a result, the gains of cognitive training would be reduced or even eliminated [7, 8] as meaningful learning often requires substantial cognitive processing.

Therefore, it is always better when the learners train at their own pace [9], as compared to when train independently of learner control which can quickly overload working memory capacity. The challenge is to define learning tasks that impose the right amount of productive load and at the same time minimize irrelevant sources of cognitive load.

2.4 Dynamic Difficulty Adjustment (DDA)

One of the attempts to impose the right amount of cognitive load include the implementation of DDA, a technique for adaptively changing a task to make it easier or harder based on one or more feedback sources. By monitoring user state and adapting the system when it detects detrimental states, a DDA system improves performance and helps users maximize their amount of productive work. The implementation of DDA can be very beneficial. For instance, DDA can offer personalized learning i.e. the pace of learning or materials can be tailored accordingly to the understanding of each individual. In the gaming world, players reported that they experience faster performance gains and feel more in control when the difficulty adjusts adaptively based on their skill [42]. A previous study also revealed that the players are more engaged when the difficulty is adjusted accordingly to performance, as compared to when the difficulty is simply altered over the course of gameplay [43]. Outside of the gaming world, DDA systems can also be used to facilitate the transition of users from novice to expert [44].

2.5 Metrics of Mental Workload

While there has been considerable research on the topic, various metrics have the potential to be a reliable indicator of mental workload. These metrics can be critical events, human performance, physiological metrics, models of performance, and combinations of two or more of the above [10]. Among the many methods of measuring mental workload, there are three main classifications: performance, physiological, and subjective-based measures.

2.5.1 Performance Measures

It is generally accepted that performance may be indicative of the effectiveness in accomplishing a particular task [45]. These techniques exploit the assumption that people have limited cognitive resources to assess mental workload related to task difficulty. Generally, the two ways to measure workload on the basis of performance include primary and secondary task measures. The former is a more direct than the latter, but both are used and at least moderately accepted. Previous studies utilizing such measures confirmed that they are sensitive to mental demand changes under certain conditions [46, 47], implying that it is possible to estimate workload by measuring the increase/decrease in performance.

The primary task can be measured by recording different variables e.g. number of correct responses, response time and accuracy. However, in accordance to the attentional resources model, the limitations are that optimum performance does not necessarily reflect the optimum task workload. Some other limitations are that such measures cannot accurately assess the amount of workload over a short period of task performance and they do not consider spare mental capacity [48]. Another problem is that the measures cannot be easily applied directly to another task i.e. the primary performance measure must be separately selected for each different course.

The secondary performance measure, an extra measure to the primary task, attempts to assess the residual capacity that is not utilized in performing a task. It compares between the mental capacity consumed by the main task and the total available capacity. According to Multiple Resource Theory, theoretically, since primary task performance takes up a certain amount of cognitive resources, the remaining resources are used on secondary task performance [49]. Such measure is able to capture if there is any spare mental capacity, however, less importance should be placed on it as compared to the primary task and major problem is that the use of secondary tasks may disrupt primary task performance [50].

However, if the task is too easy, both performance measures don’t clearly reflect levels of workload as performance is not lacking in any region. In comparison to secondary task performance, primary task performance is easier to measure and its accuracy is more extensively tested. All in all, primary task performance should be prioritized when it comes to assessing mental workload based on performance.

2.5.2 Physiological Measures

Physiological measures are able to provide objective measurement of mental workload an individual is experiencing on the basis of the physical reactions of the body. Objective measurement is the most exact and therefore the best way to assess workload because it does not require a direct response from the individual, unlike subjective measurements [51]. It has been reported that physiological metrics are sensitive to cognitive workload. Some of the most common physiological metrics used to evaluate mental workload include cardiac activities, eye blink activity, and brain activity.

2.5.2.1 Cardiac Activities

The most common physiological measurement of mental workload is cardiac monitoring. Cardiac measures are often used because they are easy to evaluate and are considered a fairly reliable indicator of workload. Cardiac activity can be measured through heart rate, heart rate variability, and blood pressure.

2.5.2.1.1 Heart Rate (HR) and Heart Rate Variability (HRV)

HR and HRV are widely regarded as reliable physiological measurements of mental workload as the effects of mental workload are often observed in the cardiovascular system. Sympathetic and parasympathetic nervous systems, both part of the autonomic nervous system, work involuntarily and can induce changes on HR and HRV directly when alterations in mental activity take place. HR has been proven to more sensitive to mental demand, as observed in flight control tasks [52], and mental arithmetic task [53]. Meanwhile, HRV, which refer to the variation in the time interval between heartbeats, is sensitive to mental demand changes, particularly those imposed by complex tasks. Changes in heart rate is claimed to be associated with increasing mental effort [54]. HRV is a more sensitive metric than HR, when it comes to measuring the change of mental workload in complex cognitive tasks. One of the biggest advantages of both HR and HRV is the easy and simple recording procedure that does not interfere with the ongoing task. However, both of them are susceptible to other environmental factors such as physical load, noise and temperature [55].

2.5.2.1.2 Blood Pressure

Mental workload can also be evaluated on the basis of blood pressure [53]. Blood pressure refers to the pressure of circulating blood on the walls of large arteries of the systemic circulation. Blood pressure is recorded with two numbers – the systolic (high number) and diastolic pressure (lower number). The former is the force at which the heart pumps blood around the body while the latter is the resistance to the blood flow in the blood vessels. Although blood pressure changes are related to HR changes and thus can be indicative of the effect of workload on the cardiovascular system [56], problem is that not only blood pressure is monitored mainly at discrete time intervals but it also uses an inflatable cuff placed around the arm, which can be uncomfortable. There, blood pressure may not be that suitable to be used in a DDA.

2.5.2.2 Eye Blink Activity

Eye blink activity is obtained by measuring blink frequency (the number of eye closures in a given period of time) and duration. There has been a widespread use of such measure in various studies including flight control tasks [52] and visual monitoring tasks [53]. Both studies pointed out that there is negative relationship between task complexity and blink frequency, and that blink duration is shorter at higher difficulty level. However, depending on the nature of the task, the eye blink rate is not always negatively associated with mental demand [46] and changes in light or air quality may affect the eye blink rate [51].

2.5.2.3 Brain Activity

All the aforementioned physiological metrics employ indirect means to assess mental workload. Cardiac activities and eye blink are all influenced by signals the brain sends when different levels of mental load are imposed. The brain is said to play a pivotal role in processing information, making decisions and initiating actions in response to the external stimuli [22]. Apart from the good temporal resolution of cognitive activity that task-related brain activity offers [57], the measurement procedure is continuous and does not interfere with the task [58]. Some of the most common neuroimaging modalities used to assess workload are fMRI, EEG, and fNIRS. However, these modalities require specialized equipment and special training to operate and interpret the data.

2.5.2.3.1 Functional Magnetic Resonance Imaging (fMRI)

Due to its non-invasiveness and excellent spatial resolution, fMRI is regarded as the most widely used neuroimaging modality in investigating cognitive impairments [59]. By utilizing magnetic resonance imaging (MRI) technique, fMRI detects task-associated changes in blood oxygenation and flow to measure the brain activity. Typical fMRI image is shown in Figure 2.1. fMRI offers excellent spatial and temporal resolution [60].

The working principle of fMRI is exactly the same with that of magnetic resonance imaging. fMRI uses a strong magnetic field and radio waves to image blood flow in the brain. It is based on the fact that oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) behaves differently in a uniform magnetic field; they have distinct magnetic resonance. Hemoglobin turns diamagnetic when oxygenated but paramagnetic when deoxygenated. Such characteristic generates small differences in the magnetic resonance signal of blood, based on the oxygenation level. Since blood oxygenation is associated with neural activity, the differences are claimed to be reflecting brain activity.

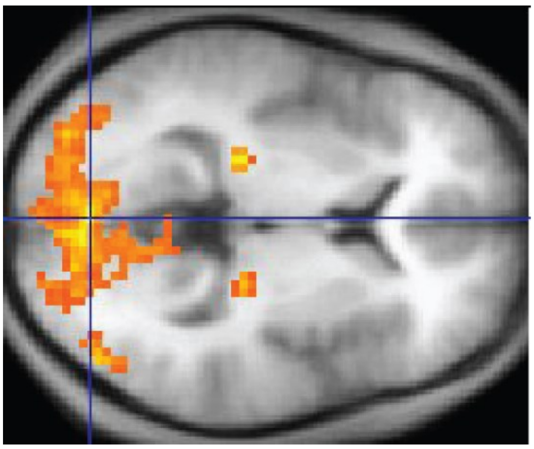


Figure 2.1: A typical fMRI image. Yellow areas indicate increased brain activity compared with a control condition. (credit: “Superborsuk”/Wikimedia Commons)

Since fMRI measures cerebral blood flow in high resolution, it has been claimed that fMRI can be used to provide sensitive objective assessments of variations in mental workload [61]. The use of cerebral blood flow to assess workload is based on the principle that there is a close coupling between neuronal electrical activity, the demands imposed by the associated cellular processes, and regional blood flow in the brain [62]. Several studies agree that there is a linear relationship between fMRI activity and task complexity, as observed in brain regions associated with task-related processes [63-65].

Although fMRI offers various advantages, scanning is taken in a large tunnel-shaped machine which can fill up a room easily (see Figure 2.2). The equipment is expensive and not portable. Before undergoing a fMRI scan, the participants have to be checked for different types of metal in the body and all metal objects such as earrings and necklaces must be removed. The participants are often instructed to remove their clothes and may have to change into a hospital gown. After that, the participants then have to lie down on a table and are restricted to a fixed position throughout the fMRI scan. During the fMRI scan, the table will then slide into and out of the tunnel, stopping at different positions. Unwanted noises and vibrations generated by the machine may cause discomfort or even anxiety. These negative emotional states may influence the study or research. Worse, being confined in the tunnel imposes a significant threat to people who are suffering from claustrophobia [66]. This highlights the need for new neuroimaging technique like fNIRS.

Figure 2.2: fMRI machine in the College of Medicine, Florida State University.

2.5.2.3.2 Electroencephalography (EEG)

EEG uses electrodes affixed to the scalp to detect the electrical activity in the brain. Typical EEG data (waveforms) are illustrated in Figure 2.3. EEG is considered the fastest neuroimaging modality as the sampling rate of EEG is at least 250 Hz; thousands of snapshots per second. In other words, EEG offers excellent temporal resolution. This enables further processing or analysis to be carried out at sub-second timescales or even in real time. Despite having a high temporal resolution, the resistivity of skull greatly limits its spatial resolution [67].

This electrical activity is produced by synchronized activity of billions of nerve cells in the brain. The electrical activity is measured in voltages. These neurons located in the brain produce very small electrical signals that form patterns known as brain wave. The electrodes affixed detects electrical signals along the scalp, digitizes the data and sends the data to an amplifier. The data are then amplified before being displayed or sent to another processing unit. EEG signals are generally divided into four bands: delta waves (up to 4 Hz), theta waves (4–8 Hz), alpha waves (8–13 Hz), and beta waves (more than 13 Hz).

Alpha waves have been reported to disappear and to be replaced by beta waves when mental workload is increased [68]. Generally, both theta and alpha exhibit positive and negative relationship respectively with increasing mental workload [52]. On the other hand, complexity and volume changes affect delta and alpha waves

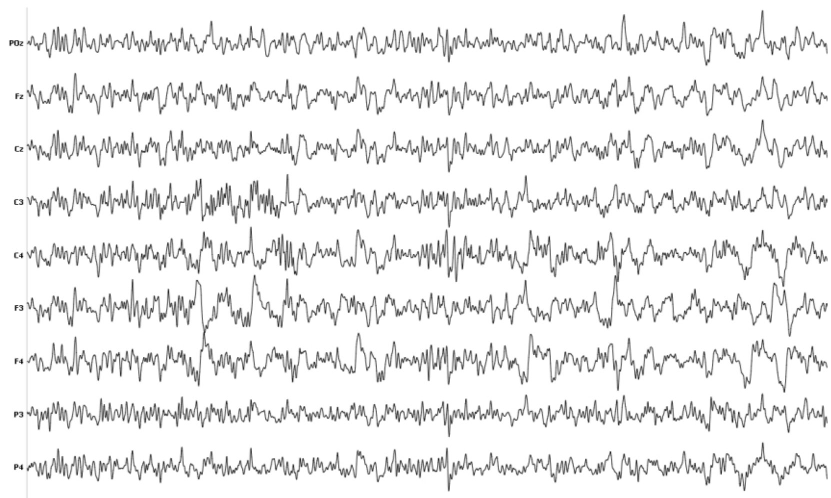


Figure 2.3: Typical EEG data (waveforms).

differently [22]. Although EEG measures can evaluate the relative contributions of different workload, there are a few shortcomings.

EEG is highly prone to multiple forms and sources of noise. They include physiological and non-physiological artifacts, including motion artifacts [69]. Since EEG detects electrical signals along the scalp, it is claimed that only a small proportion of the signals recorded actually originates from the deeper brain layer [70]. EEG's advantages include low costs, ease of use, and high temporal resolution. However, EEG offers poor spatial resolution, which makes it difficult to pinpoint the brain region where the electrical activity is actually coming from. Besides that, it is relatively lengthy and tedious to set up and record an EEG. One can either manually tape the electrodes in place or use an EEG cap (refer to Figure 2.4). Both options often require application of gooey gel-like substance on the scalp of participants via a syringe to enhance the conductivity between the scalp and the electrode. Gel stuck all over the hair of the participants may be messy and may cause discomfort.

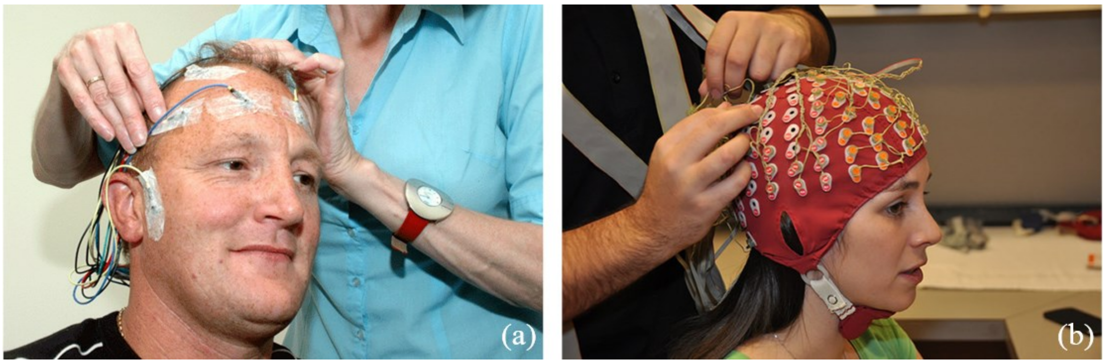


Figure 2.4: Installation of EEG electrodes. (a) Manually taping the electrodes in place. (b) Using an EEG cap.

2.5.2.3.3 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is considered a relatively new technology in neuroimaging field. Over the past 20 years, there has been an increasing deployment of fNIRS in various researches. fNIRS is a neuroimaging modality that monitors the brain activity non-invasively through hemodynamic responses [71]. fNIRS possesses excellent temporal resolution (1 ms) with reasonable spatial resolution (1 cm). It offers several advantages such as portability, ease of setup and the subject constraints are more lenient. fNIRS data can be presented in the form of signal or image over a specific area if sufficient channels are used (see Figure 2.5). Subsequent paragraphs discuss the discovery and principles of fNIRS.

One of the earliest fNIRS study was conducted in 1977 [71]. The working principles behind fNIRS include: 1) Human skin, tissues, and bone are relatively transparent, enabling near-infrared (NIR) light to travel through them; 2) Some of the NIR light is absorbed by complex protein in the red blood cells; and 3) The attenuated NIR light then travels through its optical pathway and is picked up by a detector. As arterial bloom volume occupies approximately 30% of the brain volume, fNIRS may be able to quantify hemodynamic changes that occur within the venous compartments. The hemodynamic responses are measured through the changes in the concentration of oxy- and deoxy-Hb. oxy-Hb is the form of hemoglobin with the bound oxygen while deoxy-

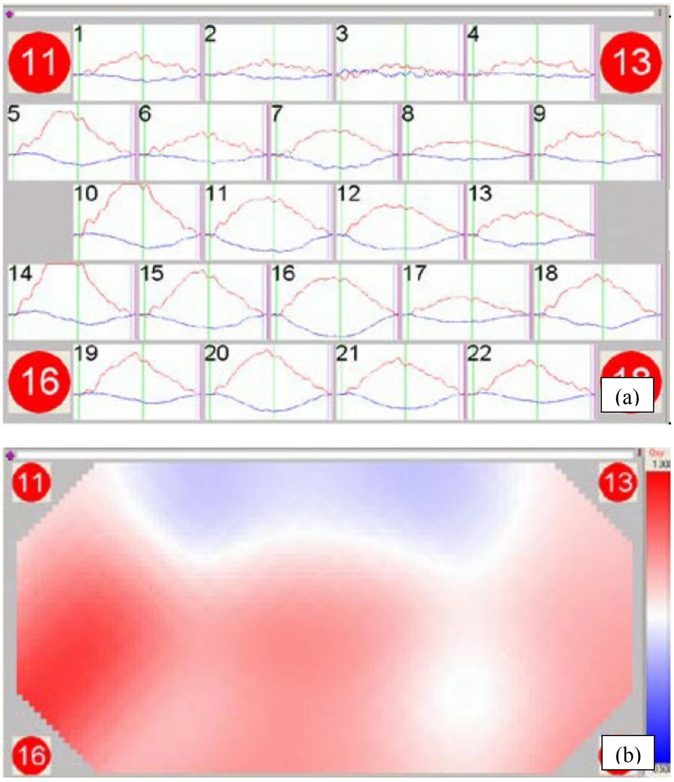


Figure 2.5: Representation of fNIRS data. (a) Waveform where red and blue lines represent concentration changes of oxy-Hb and deoxy-Hb respectively. (b) Map or image where red and blue intensities indicate increase and decrease in concentration respectively.

Hb is the form of hemoglobin without the bound oxygen. Next paragraph looks into the mechanism of fNIRS.

NIR light of two distinctive wavelengths in the spectrum of 700-900 nm is irradiated by an emitter. In this spectrum, the NIR light is able travel through human skin, tissues, and bone while part of the transmitted NIR light is absorbed by oxy- and deoxy-Hb which are stronger absorbers of light. Both oxy- and deoxy-Hb absorb NIR light differently. The absorption spectra of oxy-, deoxy-Hb and where NIR light operates are illustrated in Figure 2.6. The attenuated NIR lights is then picked up by a detector. The distinctive absorption spectra of enable the respective change in NIR light intensity due to the absorption of oxy- and deoxy-Hb to be measured. The entire mechanism is simplified and demonstrated in Figure 2.7. Using the modified Beer-Lambert law, these changes in NIR light intensity are then converted to relative concentration change of oxy- and deoxy-Hb. Concentration changes in both oxy- and deoxy-Hb are calculated based on the NIR light scattering and attenuation.

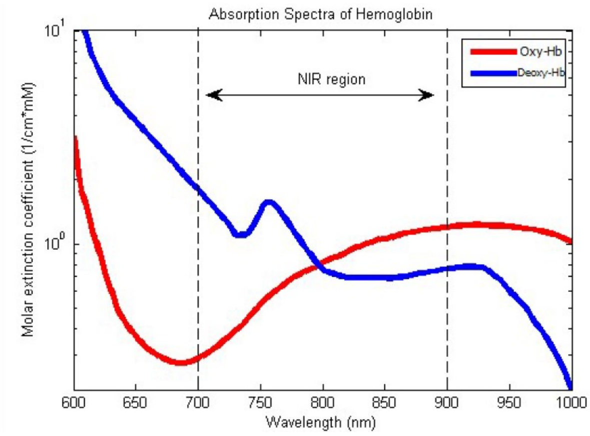


Figure 2.6. Absorption spectra of oxy- and deoxy-Hb for different NIR wavelengths.

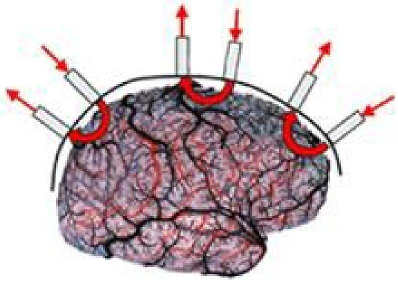


Figure 2.7: How fNIRS works. NIR light is emitted and attenuates when it travels through the brain before being picked up by a detector.

Both oxy- and deoxy-Hb can be used as indicators. Nonetheless, in contrast to deoxy-Hb, oxy-Hb is proven to be more sensitive to cerebral blood changes that are associated with task [72]. This is supported by another study that claims that changes in blood oxygenation reflect neuronal changes [73]. There has been a widespread use of fNIRS in studying different primary brain functions including motor [74], visual [75] and auditory [76]. fNIRS was also deployed to investigate task-associated hemodynamic responses during verbal fluency test [77, 78]. Last but not least, a few researches attempted to utilize fNIRS in treating attention deficit hyperactivity disorder [79, 80] and implementing brain–computer interface [81].

One method to assess changes in workload using fNIRS is to analyse the changes in oxy-Hb. By looking into the changes in this parameter, it is possible to measure the level of brain activity (and thus the workload) in the user's P when he or she is engaged in a complex task. This approach has succeed in detecting the workload level for participants piloting unmanned air vehicles [82], engaging as part of a human-robot team [83], and performing a complex visual task [84]. A linear relationship between task workload and hemodynamics has often been observed [82, 85] where the difficulty of the task at hand does not exceed the cognitive capacity of participant. When cognitive capacity is exceeded the observed effects on hemodynamics conform to the shape reported by the Yerkes–Dodson law (see Figure 2.8) [86]. Workload

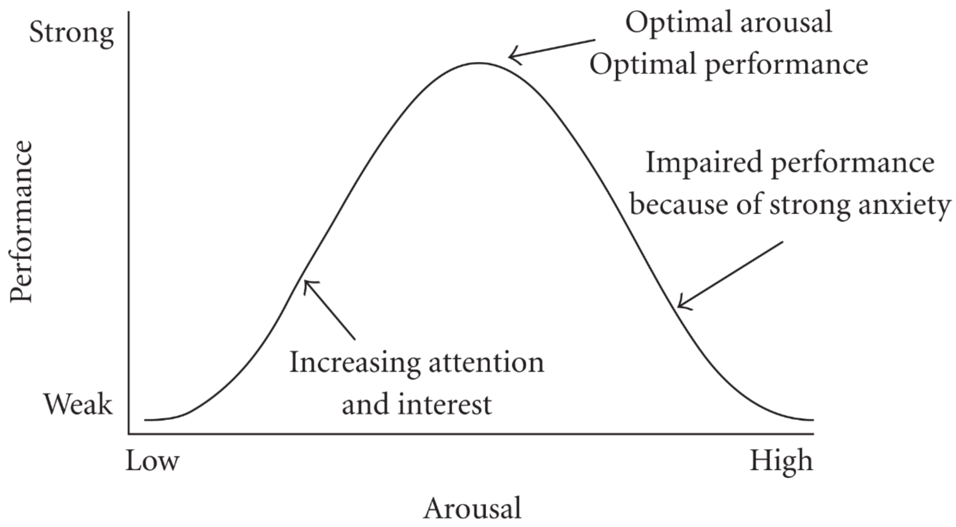


Figure 2.8: The original version of the Yerkes-Dodson law, based on the actual findings and theorizing of Yerkes and Dodson [86].

alone does not have a quadratic relationship with functional hemodynamics, but instead once there is mental overload functional activation decreases. There are evidences from other studies support the above claim i.e. prefrontal activation followed an inverted U-shaped curve (increases with load up to a certain difficulty level then decreases) [87-91]. The presence of a negative quadratic slope or a sudden decrease during monitoring of workload dynamics is indicative of mental overload.

fNIRS equipment is inexpensive, easy to set up, and highly portable. Take Hitachi ETG-4000 fNIRS system as an example (see Figure 2.9(a)), with a volume of 560 mm x 933 mm x 1470 mm and two pairs of 360° rotating wheels, it is considered as a compact and mobile unit. It is fairly easy to move the machine around or load the machine into a moving truck. Apart from that, the machine itself occupies very little space. The lightweight probes (emitters and detectors) of fNIRS can be attached to probe holder(s) which can be positioned on the head of participant easily and quickly (refer to Figure 2.9(b)) while still allowing users to still function normally. Glass or plastic rod can be used to clear away the hair to ensure that the probes are in good contact with the scalp. Last but not least, there are far fewer constraints imposed on the participants. The participants are allowed to wear whatever they and they don't have to prepare anything to undergo fNIRS measurement. Furthermore, the environment is controlled by the operator. These advantages make fNIRS useful and suitable for clinical applications and measuring infants as well as children. Besides that, fNIRS has specific advantages in being applied to DDA systems. Additionally, it has been found to be resistant to movement artifacts in comparison to other modalities [92].

(a) (b)

Figure 2.9: Hitachi ETG-4000 fNIRS system in use. (b) A participant wearing a probe holder that holds all the probes in place.

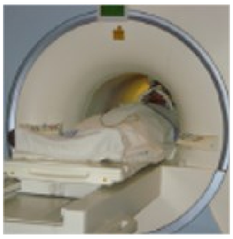
2.5.2.3.4 Comparison

Like fMRI, fNIRS probes the same underlying hemodynamic responses non-invasively. However, fMRI possesses higher spatial but lower temporal resolution than fNIRS. The fMRI equipment is expensive, and not portable. On the other hand, fNIRS equipment is relatively inexpensive, and highly portable. Before undergoing a fMRI scan, the participants have to be checked for different types of metal in the body and all metal objects such as earrings and necklaces must be removed. Sometimes, the participants are instructed to remove their clothes and may have to change into a hospital gown. The participants then have to lie down and stay still throughout the fMRI scan. As mentioned in section 2.5.2.3.1, fMRI scan is taken in a tunnel-shaped machine, which may cause discomfort or even anxiety especially to participants with claustrophobia. Meanwhile, for fNIRS, there are far fewer constraints imposed on the participant than fMRI and the operator can control the environment. Its lightweight and non-intrusive probes still allow user to function normally even when they are affixed to the forehead. Taken together these advantages, the participants may feel more comfortable. These advantages also make fNIRS more useful and suitable for clinical applications and measuring infants as well as children.

EEG measures electrical brain activity through the electrodes affixed to the scalp. fNIRS seems to offer higher spatial resolution than EEG but the temporal resolutions of both modalities are similar. Nevertheless, EEG is susceptible to physiological and non-physiological artifacts, including motion artifacts [69]. Since EEG detects electrical signals along the scalp, it is claimed that only a small proportion of the signals recorded actually originates from the deeper brain layer [70]. EEG is cheaper, as compared to fNIRS. However, it is relatively lengthy and tedious to set up and record an EEG. It often requires application of gel-like substance on the scalp of participants via a syringe to enhance the conductivity between the scalp and the electrode. Gel stuck all over the hair of the participants may make them uncomfortable. On the other hand, fNIRS not only is relatively easy and quick to set up but it has also been found to be resistant to movement artifacts in comparison to other modalities [92].

Table 2.1 summaries and compares the advantages, shortcomings as well as applications of fNIRS, fMRI, and EEG [93]. In comparison to other neuroimaging modalities, good spatial and reasonable temporal resolution, and higher resistance to artifacts [92] coupled with portability, ease of setup, and lenient subject constraints make fNIRS more useful and suitable for clinical applications especially DDA.

Table 2.1: Comparisons of fMRI, EEG and fNIRS [93].

	fMRI	**EEG**	**fNIRS**
			
Underlying signal	Blood oxygenation level dependent contrast (which indirectly relates with neuronal activity)	Electrical activity from pyramidal cells perpendicular to the scalp (mainly gyri)	Volume of oxygenated and/or deoxygenated blood (which indirectly relates with neuronal activity)
Typical feedback signal source	Single brain regions, 3mm x 3mm voxels	One central electrode or a multi-electrode cap	Several sensors over cortex or cortices
Feedback delay	~1.5 s (plus 4-6 s hemodynamic delay)	< 50 ms	~0.5 s (plus 4-6 s hemodynamic delay)
Resolution			
temporal	Seconds	Milliseconds	Seconds
spatial	Millimeters	Centimeters	Centimeters
depth	Deep (any region)	Superficial	Superficial (<4 cm)
Portable	No	Yes	Yes
Cost (USD)			
Initial set-up	500,000-2,000,000	500-50,000	50,000-300,000
Running costs	~500/hour	No extra fees	No extra fees
Relevant literature	Moderate	Plentiful	Emerging
Main applications	Psychological conditions (chronic pain, depression, schizophrenia, etc.) (Experimental)	Paediatric ADHD, epilepsy, various psychological disorders	Brain computer interfaces, stroke rehabilitation (Experimental)

2.5.3 Subjective-Based Measures

Apart from the aforementioned measures, subjective assessment tools can be used to rate mental workload as these tools provide valuable information on perceived workload or other aspects of performance. As of now, all instruments available can be classified into two different categories: unidimensional and multidimensional ratings. The former are regarded as the simplest to use as they only have one dimension and thus no complex analysis techniques are involved while the latter are more complicated and more time-consuming form of measurement, and provide more detailed analysis of the many dimensions of workload. Generally, unidimensional instruments are considered to be too simple to evaluate the complexity of workload while multidimensional form of measuring workload is the most widely used and accepted method. Two of the most commonly used and well-known multidimensional tools are NASA Task Load Index (NASA-TLX) and Subjective Workload Assessment Technique (SWAT).

2.5.3.1 Subjective Workload Assessment Technique (SWAT)

SWAT is another widely used multidimensional scaling method designed to measure mental workload that is split along three dimensions: time load, mental effort load, and psychological stress load [94]. Each of these dimensions is represented by a 3-point ordinal scale: (1) low, (2) medium, and (3) high. Table 2.2 provides the description of the dimensions and levels.

The SWAT administration can be broken down into three steps. First, three levels of each of these three scales create a total of 27 possible combinations, which are presented on individual cards for the rater to sort them accordingly his or her perception of workload. Although the sorting process is time-consuming, it is valuable as it ultimately results in a scale with interval properties that takes the individual differences in workload perception into account. Second, the rater provide subjecting ratings of the workload. In accordance to the scale developed in step one, the last step involves the conversion of the ratings to an absolute score, which lies between 0 and 100.

Although the SWAT scale is useful in estimating changes in mental workload [94], it has been reported that the three dimensions lack subjective orthogonality e.g. it is possible that high levels of time-load will trigger higher level in the mental workload dimension [95]. Furthermore, it has been pointed out that inexperienced rater is likely to encounter high failure rate in performing the sorting step [96] and the SWAT is less sensitive when it comes to evaluating low mental demands [97]. Taken together the NASA-TLX is the better instrument to assess mental workload [98].

Table 2.2: The SWAT scale dimensions and descriptions.

Dimension	Description of Each Level
Time Load	1. Often have spare time. Interruptions or overlap among activities occur infrequently or not at all. 2. Occasionally have spare time. Interruptions or overlap among activities occur frequently. 3. Almost never have spare time. Interruptions or overlap among activities are very frequent, or occur all the time.
Mental Effort Load	1. Very little conscious mental effort or concentration required. Activity is almost automatic, requiring little or no attention. 2. Moderate conscious mental effort or concentration required. Complexity of activity is moderately high due to uncertainty, unpredictability, or unfamiliarity. Considerable attention required. 3. Extensive mental effort and concentration are necessary. Very complex activity requiring total attention.
Psychological Stress Load	1. Little confusion, risk, frustration, or anxiety exists and can be easily accommodated. 2. Moderate stress due to confusion, frustration, or anxiety noticeably adds to workload. Significant compensation is required to maintain adequate performance. 3. High to very intense stress due to confusion, frustration, or anxiety. High extreme determination and self-control required.

2.5.3.2 NASA Task Load Index (NASA-TLX)

NASA-TLX is a widely used, subjective, multidimensional assessment tool that rates perceived workload or other aspects of performance (see Appendix A) [99, 100]. NASA-TLX consists of six subscales (as listed in Table 2.3) which altogether contribute to the overall workload.

The administration of the NASA-TLX is a two-part procedure. First, the rater evaluates the contribution of each factor (its weight) to the workload of the task. There are 15 possible pair-wise comparisons of the six scales e.g. mental demand vs physical demand, overall performance vs effort and so on. The rater has to select the member of each pair that contributed more to the workload of the task. At the end of the session, the number of times that each factor is selected is tallied, which can range from 0 (not relevant) to 5 (more important than any other factor). The second part of the workload assessment involves the rater providing numerical ratings for each of the six subscales, which reflect the magnitude of that factor in the task. Each scale is presented as a horizontal line divided into 20 equal intervals between bipolar

Table 2.3: In the NASA-TLX, the total workload is divided into 6 subscales.

Subscale	Description
Mental Demand	How much mental and perceptual activity was required? Was the task easy or demanding, simple or complex?
Physical Demand	How much physical activity was required? Was the task easy or demanding, slack or strenuous?
Temporal Demand	How much time pressure did you feel due to the pace at which the tasks or task elements occurred? Was the pace slow or rapid?
Overall Performance	How successful were you in performing the task? How satisfied were you with your performance?
Frustration Level	How irritated, stressed, and annoyed versus content, relaxed, and complacent did you feel during the task?
Effort	How hard did you have to work (mentally and physically) to accomplish your level of performance?

descriptors. These are ‘low’ and ‘high’ in all cases except the scale ‘performance’, which extends from ‘good’ to ‘poor’ (and is reverse scored). The overall workload score is calculated by multiplying each raw rating by the weight given to that factor by the rater. The sum of the weighted ratings is then divided by 15 (the sum of the weights) to convert the scores into a 0 to 100 scale. Apart from the overall workload score, it is also very common to compare the raw test scores for each subscale.

The NASA-TLX has been proven to be sensitive to changes in workload [96] and has presented a high reliability [101]. Several precious studies have confirmed that the NASA-TLX is a better subjective workload assessment tool than the SWAT and others.

2.5.4 Conclusions

Table 2.4 presents the benefits and drawbacks of each metric. Among the many methods of measuring mental workload, physiological measures offer promise because they can be more closely linked to brain function. They are more sensitive to the aspects of the task [7] and are known to respond to cognitive demand in a relatively predictable manner [11]. Physiological measures can also index the level of mental demand associated with a given task because they can provide continuous and unobtrusive monitoring of the learner and do not interfere with the learner’s ongoing work [12-16]. Accurate assessment of mental workload could allow for pertinent intervention by adapting the intervention when any detrimental state that can arise from either work overload or understimulation is detected [17-21]. Apart from that, it is possible to assess a user’s affective or emotional state using physiological metrics [102]. A previous study also claimed that the participants’ skills improve more and the participants are more immersed when the level of challenge is altered based on their mental state instead of their performance [103].

In comparison to other neuroimaging modalities, good spatial and reasonable temporal resolution, and higher resistance to artifacts [92] coupled with portability, ease of setup, and lenient subject constraints make fNIRS more useful and suitable for clinical applications especially DDA.

Table 2.4: The benefits and drawbacks of each metric.

Metrics	Result of Increased Workload	Benefits	Drawbacks
Performance			
Primary	Decreases	Accurate to changes in workload	Not accurate when low levels of workload
Secondary	Decreases	Finds spare mental capacity better than Primary	May interfere with task, not accepted
Physiological			
Cardiac Activities			
Heart Rate	Increases	Widely accepted and studied, easy to measure	May not be completely reliable Doesn't measure absolute levels of work
Heart Rate Variability	Decreases	Some studies indicate better accuracy than HR	Not widely studies or accepted Influenced by respiration, equipment requirement
Blood Pressure	Increases	Can be used to calculate modulus	Not widely studied or accepted No more information than HR and HRV
Eye Blink Activity	Rate decreases	Most accurate for visual workload	Not as accurate for other work measures
Brain Activity			
Functional Magnetic Resonance Imaging	Cerebral blood flow increases	Excellent spatial resolution	Poor temporal resolution; Strict subject constraints Large, unmovable, and expensive equipment
Electroencephalography	Alpha waves replaced by Beta waves	Accurate, reliable	Poor spatial resolution; Susceptibility to artifacts Lengthy and tedious setup
Functional Near-Infrared Spectroscopy	Increases when difficulty < capacity Decreases once there is mental overload	Portable, reliable, lenient subject constraints, higher resistance to artifacts, quick and easy setup	Limited penetration depth Rough spatial resolution (vs fMRI)
Subjective			
Subjective Workload Assessment Technique	Higher rating	More sensitive to increases in difficulty than NASA-TLX	High failure in analysis of results No agreement on accuracy or sensitivity
NASA Task Load Index	Higher rating	Accurate, valid	Takes a long time to administer and analyse

2.6 Alzheimer's Disease

Aging population is a major issue in most countries, no matter developed, developing or less-developed ones. In Malaysia, the aging population is expected to rise to 12% by the year 2030 [104]. Among all aging-associated diseases, dementia is the fastest growing brain disorder [105] (see Figure 2.10). By 2013, dementia has affected 44.4 million people globally and this figure is expected to rise dramatically in future [106]. Dementia is defined as a neurodegenerative disorder involving the deterioration of multiple cognitive abilities, which can affect everyday life. The deterioration not only causes memory impairment but also inflicts cognitive disturbances as well as executive dysfunction. Unfortunately, the deterioration is usually progressive, even to the extent that self-care and self-reliance are not possible. A European study claimed that the prevalence of dementia doubles every 5 years starting from the age of 65-90 [107]. Every year, there are 7.7 million new reported cases [108]. This increases not only the demand but also the cost of dementia caregiving [108]. As a consequence, dementia is regarded as a global health crisis [109].

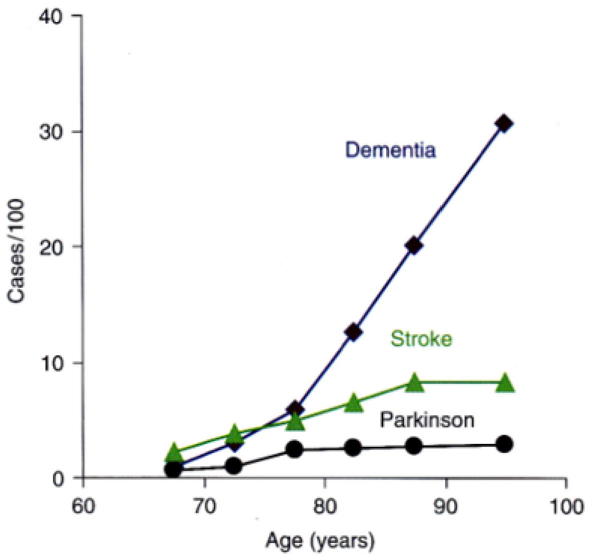


Figure 2.10: Dementia shows the highest increase in incidence rate as people age, compared to Stroke and Parkinson's disease [105].

Various forms of dementia with respective set of symptoms have been identified, with Alzheimer' disease being the most common form and accounts for 60-80% of dementia cases 10% [110]. Alzheimer's disease is a chronic progressive neurodegenerative brain disease that can occur in middle or old age. Microscopically and neuropathologically, Alzheimer's disease patients show large numbers of senile plaques and neurofibrillary tangles.

2.6.1 Risk Factors

The root cause of Alzheimer's disease is poorly understood [111]. Similar to diabetes, heart disease and other common chronic conditions, a number of factors play a role in increasing or decreasing the risk of developing Alzheimer's disease [112]. These risk factors include age, education level, gender, and lifestyle [113]. Some of these factors are controllable while some are not.

2.6.1.1 Age

Age is claimed to be one of the major risk factors for Alzheimer's disease [114]. The incidence rate of Alzheimer's disease increases as people age: 5-8% for individuals over 65 years old, 15-20% for individuals over 75 years old, and 25-50% for individuals over 85 years old [115-117]. However, it is suggested that advanced age itself is insufficient to cause Alzheimer's disease. The increasing incidence rate with age can be explained by the fact that advanced age increases the risk of gene mutation [113]. Advanced age combined with genetic vulnerability synergistically pose higher risk of developing Alzheimer's disease [118].

2.6.1.2 Education Level

People with fewer years of formal education are more likely to develop Alzheimer's disease [119]. It is suggested that higher education level yields higher cognitive reserve, allowing alternate brain networks to compensate for the neuropathological changes caused by Alzheimer's disease [120, 121]. More years of education increases the communications between neurons, allowing the brain to compensate for the early neuropathological changes caused by Alzheimer's disease by rerouting alternate neural pathways to perform a cognitive training task [122]. On the other hand, lower education level may reflect lower socioeconomic status that may be associated with inadequate nutrition and health care, indicating negative environmental factors [123].

2.6.1.3 Gender

There are studies that claimed that there appears to be gender differences in which risk factors for Alzheimer's disease affect men and women. It is estimated that the lifetime risk for developing Alzheimer's disease is 9.1% and 17.2% for men and women respectively [124]. In other words, women are at higher risk of developing Alzheimer's disease, compared to men. Women tend to have longer lifespan, which subjects them to higher risk of developing Alzheimer's disease [125]. Men have higher mortality rate from cardiovascular disease in midlife, which explains their shorter life span and lower risk of developing Alzheimer's disease [125]. Considering low education level as one of the risk factors for Alzheimer's disease, the limited education that women, who born in the first half of 19^{th} century, received may account for women's higher risk of developing Alzheimer's disease [110]. Still, there is no concrete evidence.

2.6.1.4 Lifestyle

Clearly, lifestyle is also a risk factor of Alzheimer's disease. Interpersonal activity and emotional support received by individuals can have a big impact on the risk of developing Alzheimer's disease. It has been proven that more active social engagement and higher levels of exposure to emotional support indeed reduce cognitive decline in older adults [48]. It is also said that regular participation in physical leisure activities may lower the risk of developing Alzheimer's disease [126, 127]. This is supported by a previous study that showed that physical activities indeed help to preserve hippocampal volume in elders [128].

2.6.2 Diagnosis

Intensive studies and guidelines have been established, particularly through assessment tools, to diagnose Alzheimer's disease [129]. The challenges of these cognitive impairment involve identification of the borders of condition: between mild cognitive impairment, an intermediate state of clinical impairment, and mild Alzheimer's disease. The two most widely used assessment tools are the Mini-Mental Status Examination (MMSE), a brief questionnaire designed to measure cognitive impairment [130] (see Appendix B), and the Clinical Dementia Rating (CDR), an observer rating scale designed to rate the severity of dementia [131] (refer to Appendix C).

While the assessment tools including MMSE and CDR are simple and well-formed, they are subjected to several problems: time-consuming interview with a professional in psychology, proneness to subjectivity, and the scores can be influenced by education, socioeconomic status, and gender difference. In addition, these approaches come with their respective weaknesses. The most notable weaknesses for these assessments are as follow: MMSE is associated with its lack of sensitivity to mild Alzheimer's disease; CDR assessment requires the presence of a reliable informant or collateral source. As content of these assessment tools are highly verbal, its utility in detecting the specific brain region subjected to organic diseases such as Alzheimer's disease is not guaranteed [132, 133].

2.6.3 Cognitive Impairments

A wide range of cognitive functions are compromised due to changes in the brain regions in patients with Alzheimer's disease [134, 135]. It has been reported abnormalities such as hippocampal atrophy and ventricular enlargement are associated with Alzheimer's disease. These abnormalities include memory, language, problem-solving skills, judgment, calculation, and visuospatial awareness [135]. Executive functions are among the most significant impaired functions in patients with Alzheimer's disease. These functions encompass a number of cognitive abilities responsible for decision making, planning, self-monitoring, and behaviour organization and inhibition [136]. All aforementioned processes often involve working memory (WM), which is reported to be responsible for transient holding and processing of new and stored information [137, 138]. It is also claimed that WM plays a crucial part in the processing of reasoning, comprehension, learning, and memory updating [139].

Alzheimer's disease patients show broad impairment in the capacity for new learning [140]. This is due to the fact that working memory deficits often result in the inability to retain short-term memory, hindering long-term memory consolidation during the learning process [141]. Apart from that, is well established that mental arithmetic impairment is a common attribute in the early course of Alzheimer's disease [112, 142, 143]. A previous study also correlates this impairment to the stages of dementia [144]. It is also suggested that executive function processes are crucial in math success [145]. In other words, individuals with disturbances of executive function may encounter mathematical difficulties – even if they have a sound understanding of the math concepts.

Neuroimaging studies revealed that working memory deficits found in patients with Alzheimer's disease are associated with neurodegeneration in the prefrontal cortex (PFC) [146-148], particularly the dorsolateral prefrontal cortex (DLFPC) [149, 150]. One previous study show that significant decrease in regional cerebral blood flow is commonly observed in the frontal, parietal, and temporal cortices of Alzheimer's disease patients [151]. Another study proved that Alzheimer's disease patients showed significantly reduced inferior parietal and lateral prefrontal activations when solving math questions [152]. Consistent to the volumetric loss, patients with Alzheimer's disease have poorer performance in working memory because of the atrophy in the PFC. It is suggested that PFC is among the regions vulnerable to neurodegeneration in Alzheimer's disease and the cognitive impairments may well result from dysfunction in those association cortices.

2.6.4 Cognitive Rehabilitation Interventions

Since previous studies showed that the plasticity of working memory does exist and the activity of the brain areas related with working memory can be improved via working memory training [153, 154], there are various nonpharmacologic approaches attempting to treat cognitive impairments associated with dementia. Nonpharmacologic approaches include a vast array of techniques to conduct comprehensive and effective cognitive rehabilitation. Cognitive rehabilitation, a process to help cognitive impaired individuals, is one of the nonpharmacologic approaches. Not long ago there was a debate over the importance of cognitive rehabilitation in dementia patients [155]. Cognitive rehabilitation is introduced to Alzheimer's disease patients, hoping to optimize their brain functions, improve their quality of life, reduce the risk of excess disability, and to minimize the social impact of Alzheimer's disease [156]. It has also been suggested that cognitive rehabilitation can help to preserve brain functionality [157]. It is reported that cognitive training enhances performance in specific cognitive training tasks in healthy people [158]. Nonetheless, there has been a lack of evidence for the efficacy of such training in Alzheimer's disease patients [159].

Cognitive rehabilitation often comprises of cognitive tasks designed to develop the cognition affected by internal or external injury to the brain. An example is the name-face recall training where participants were taught strategies for name-face rehearsal [160]. A summary of studies applying different cognitive rehabilitation interventions using different cognitive task is given in Table 2.5. Some of these interventions successfully trained the participants i.e. improving specific cognitive functions [160-164]. Some even succeed in improving the cognitive status of dementia patients [165, 166], implying that such cognitive rehabilitation may be useful to slowing down the cognitive decline caused by dementia.

2.6.4.1 Identifying Effective Cognitive/Learning Tasks and Region of Interest

Since increased cerebral blood flow and metabolism have been reported to be associated with performance of cognitive tasks [167], cognitive tasks which increase cerebral blood flow of the association cortices mentioned in 2.6.3, particularly the DLFP), can be effective cognitive tasks. Consequently, mental arithmetic was chosen as the cognitive task as it not only activates the DLPFC [168-171] but is also simple enough for Alzheimer's disease patients to follow and perform them. This decision is

Table 2.5: Summary of different cognitive rehabilitation interventions using different cognitive task.

Study	**Participants**	**Program**	**Training duration**	**Results**
Hofmann et al. [172]	10 AD patients	Task of relevance in everyday life	3 or 4 times per week for 3 weeks	No general cognitive improvement
Kesslak, Nackoul and Sandman [160]	11 AD patients vs control group	Name-face recall	4 weeks of reviewing photos and personal information at home	Improvement in recalling of names and faces
Cipriani, Bianchetti and Trabucchi [162]	10 AD patients vs 10 MCI vs 3 MSA patients	Cognitive rehabilitation using TNP software [173]	1st training: 13–45 minutes, 4 days per week, for 4 weeks 2nd training: Similar to 1st training but 6 ± 2 weeks apart	AD patients: Improvement in verbal production and executive functions MCI patients: Improvement in behavioural memory
Hofmann et al. [163]	9 AD patients vs 9 MDD patients vs 10 healthy participants	Shopping route simulation, including social competence tasks and tests of orientation and memory	Three times per week, for 4 weeks	AD patients: Significant reduction of mistakes after training, substantial improvement in task performance MDD patients and healthy participants: Improvement in task performance
Brum, Forlenza and Yassuda [161]	16 MCI patients vs control group	Various tasks to exercise orientation in time and space, name-face recall, visual and auditory attention, memory, and training transfer practices.	MCI patients: 2 2-hour sessions per week, for one month, 8 sessions in total Control group: 4 sessions at study endpoint	Improvement in attention, time orientation, shopping skills, dealing with finances and reduced depressive symptoms.
Konsztowicz et al. [164]	15 MCI patients (randomized to two groups: memory training and memory compensation) vs control group	Memory training: Training in selective attention and visual imagery skills, followed by training transfer practices Memory compensation: Integration of external memory support system into everyday life	All except control group: 7 90-minute training sessions and homework assignments	Memory training: Improvement in self-reported memory abilities and satisfaction with memory Memory compensation: Improvement on one memory test but not on any other outcomes
Talassi et al. [166]	MCI patients: 30 training vs 7 control MD patients: 24 training vs 5 control	Training: Cognitive rehabilitation using TNP software [173], occupational therapy and behavioural training Control: Physical rehabilitation, occupational therapy and behavioural training	30–45 minutes per activity , on 4 days per week, for 3 weeks	Training: Improvement in cognitive and affective status of MCI and MD patients
Kawashima et al. [165]	16 AD patients vs 16 control	Reading aloud and arithmetic calculation	20 minutes daily for 19.2 days per month over 6 months	Improvement in several cognitive functions Cognitive ability did not decline during the learning period

AD = Alzheimer's disease, MCI = mild cognitive impairment, MD = mild dementia, MDD = major depressive disorder, MSA = multiple system atrophy in agreement with a previous study providing cognitive rehabilitation using arithmetic calculation which has observed improved cognitive status of dementia patients [165]. DLPFC contributes to higher order or more complex cognitive functions e.g. calculation. DLPFC is said to have a role in a vast array functions such as cognitive flexibility [174], inhibitory control [175], sequential ordering of operations [176], working memory demands coping [177], and updating of arithmetic operations [178]. Taken together, these further implicate that mental arithmetic can be an effective cognitive task and the DLPFC can be a suitable region to acquire the physiological features for DDA (see 2.5.2.3.3).

2.7 Summary

Considering neuroplasticity occurs throughout the lifespan [30-32], cognitive training and cognitive rehabilitation have been proposed to improve cognitive function [3, 4]. Cognitive training is a guided practice of standard tasks to practise specific cognitive functions to improve performance while cognitive rehabilitation is in approach focused on improving cognitive functioning or reducing functional decline through compensatory or restorative strategies. However, since working memory has a limited capacity, it will be important to manage the capacity of working memory i.e. to keeping cognitive load appropriate so that the learner can devote scarce working memory capacity to productive learning processes. Mental overload and underload are both equally serious conditions that can cause the learner to lose focus, learn less, and is less productive and more error-prone [25, 26]. If cognitive load is too high or too low, the leaner is overwhelmed or underwhelmed, and learning is disrupted. As a result, the gains of cognitive training or rehabilitation would be reduced or even eliminated [7, 8].

Therefore, it is always better when the learners train at their own pace [9] i.e. appropriate amount of effective cognitive demand. One of the ways to achieve that is the implementation of DDA, a technique for adaptively changing a task to make it easier or harder when detrimental states are detected. Among the many metrics that can be indicative of mental workload, neurophysiological measures are more task-sensitive [7], are known to respond to cognitive demand predictably [11], and can provide continuous and unobtrusive monitoring of the learner without interference [12-16]. In comparison to other neuroimaging modalities, good spatial and reasonable temporal resolution, and higher resistance to artifacts [92] coupled with portability, ease of setup, and lenient subject constraints make fNIRS more useful and suitable for clinical applications especially DDA.

This thesis presents a new real-time fNIRS-DDA system, which uses fNIRS brain signals as a reference to dynamically adjust the difficulty level of a given task, aiming to improve user engagement and prevent mental overload. Although the fNIRS-DDA system has the flexibility to be used together with any task no matter in cognitive training or cognitive rehabilitation, the entire study focused on Alzheimer's disease as the combination of the system and cognitive rehabilitation has the potential as an alternative treatment for the disease. Mental arithmetic was chosen as the cognitive task and DLPFC was identified as the region of interest.

Chapter 3

METHODOLOGY

A total of two studies were conducted. The first study was a pilot test involving a mild Alzheimer's disease (mAD) patient and a healthy older individual, aiming to validate the theory behind the fNIRS-DDA system and to confirm the region of interest. On the other hand, the second study was like a functionality testing of the fNIRS-DDA system. The goal was to ensure that everything is working as planned before examining the efficacy of such cognitive rehabilitation as an alternative treatment for Alzheimer's disease (next part of research) which requires not only vast resources but also a large sample size and long data collection duration.

3.1 fNIRS-DDA

The potential of fNIRS to detect workload has been thoroughly discussed in 2.5.2.3.3. But can these experimental results be reproduced in real world environments and in real time? As mentioned earlier, fNIRS has the unique advantage of being relatively resistant to movement artifacts in a comparison to other neuroimaging modalities, on top of its high temporal resolution, reasonable spatial resolution, portability, ease of setup, and lenient subject constraints. In this section, necessities and techniques to monitor workload in real time are investigated.

The fNIRS-DDA system proposed is actually a closed-loop feedback system (see Figure 3.1 for the feedback block diagram), consisting of a fNIRS system OT-R40 (Hitachi Medical Corporation, Japan), a computer, a monitor, and a Serial Response Box (Psychology Software Tools, Inc.). Hitachi OT-R40 is deployed to acquire fNIRS data while the computer is responsible to process it and adjust the task difficulty. Arithmetic questions are displayed on the monitor where they have to be solved mentally. Meanwhile, the Serial Response Box is used to obtain the participants' responses. Brain activity in target region (DLPFC) is measured using Hitachi OT-R40. The measured fNIRS signals are then transferred to a computer for signal processing in order to extract useful information to the feed the DDA. Based on this information, the task difficulty is adjusted accordingly. The feedback loop is repeated until the entire training or learning is completed. The schematic diagram of the fNIRS-DDA system is illustrated in Figure 3.2.

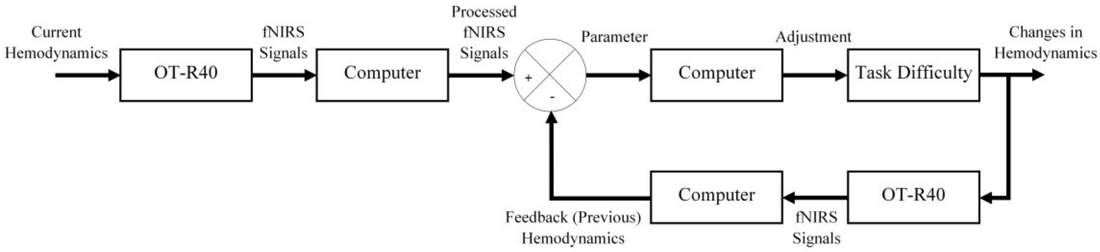


Figure 3.1: The fNIRS-DDA's closed-loop feedback control system block diagram.

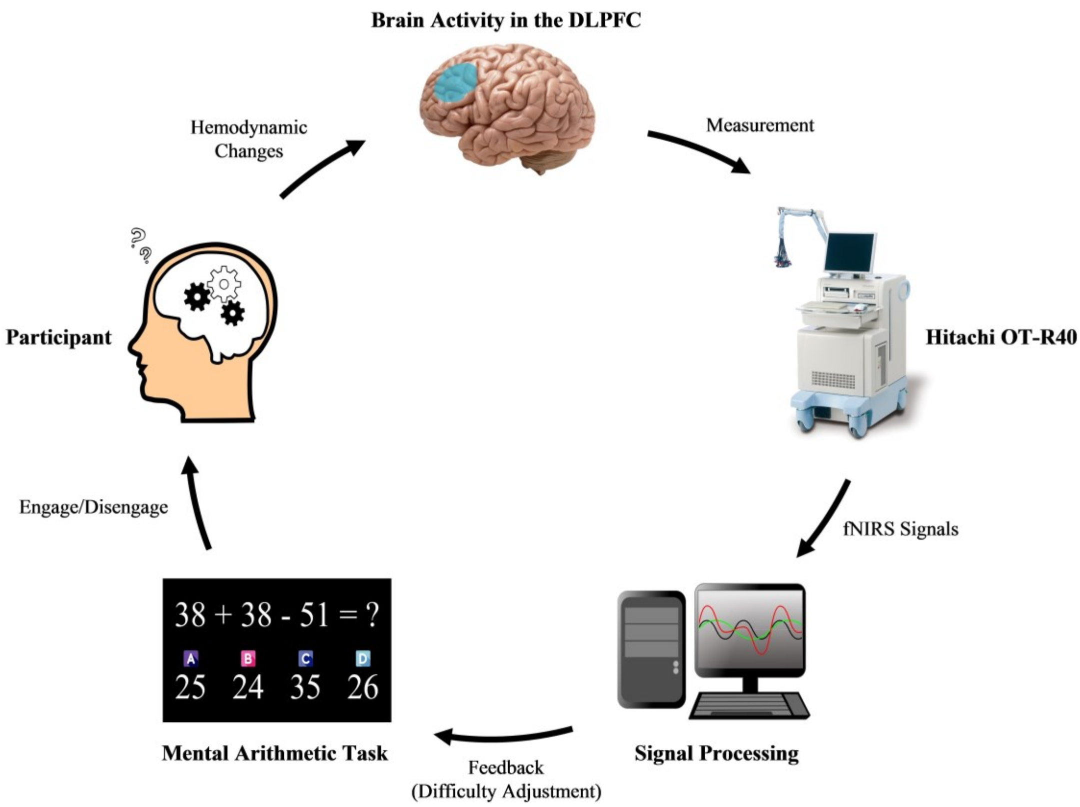


Figure 3.2: The schematic diagram of the fNIRS-DDA system.

3.1.1 Hardware Components

3.1.1.1 OT-R40 fNIRS System

Multichannel OT-R40 fNIRS topography system is one of the components in the fNIRS-DDA system. Hemoglobin signal changes are denoted in arbitrary units of millimolar-millimeter (mM·mm).

3.1.1.1.1 System Composition

The dimensions of OT-R40 are 560 mm long by 933 mm wide by 1470 mm tall, as shown in Figure 3.3. OT-R40 itself occupies very little space. Apart from that, although OT-R40 is weighs around 130 kg, it possesses two pairs of 360° rotating wheels. It is fairly easy to move OT-R40 around or even load the machine into a moving truck. All 4 wheels are also equipped with double stopper to stop swing and wheel rotation, enabling OT-R40 to be securely locked at any location for installation. However, OT-R40 should be installed on a horizontal flat surface. Installation on inclined surface over 5° may cause OT-R40 to fall. Besides that, OT-R40 should not be oppressed against a wall.

Figure 3.4 shows a OT-R40 fNIRS system. The optical fibre cables transmit NIR light to the participant and guide the reflected light to the detectors while the main cabinet houses the control computer and all physical connections. The system control panel consists of a mouse, keyboard, drawer, and phantom. Mouse and keyboard are used to navigate the interface while phantom is used to check if measurement operation is correct. The external output terminal consists of 2 RS-232C, 2 analogue signal input, 4 digital signal input, 4 digital signal output, and 1 LAN ports. The RS-232C is a standard for serial communication transmission of data while LAN connection enables fNIRS data during measurement to be sent in real time.

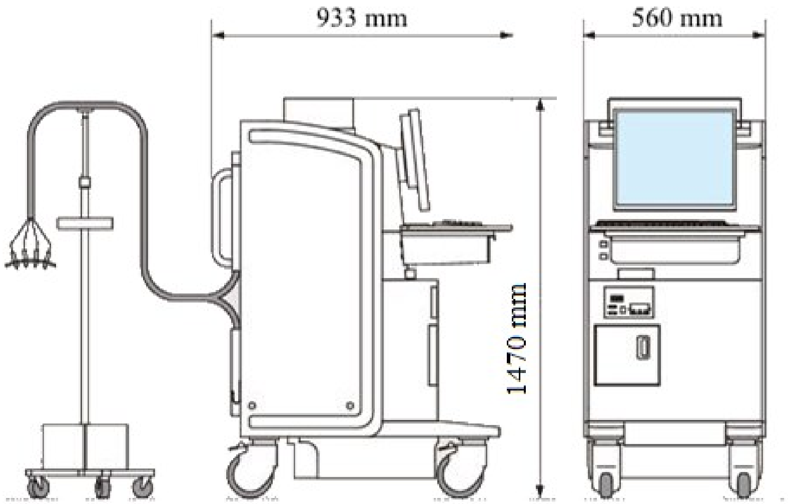


Figure 3.3: OT-R40 has dimensions of 560 mm (length) × 933 mm (width) × 1470 mm (height).

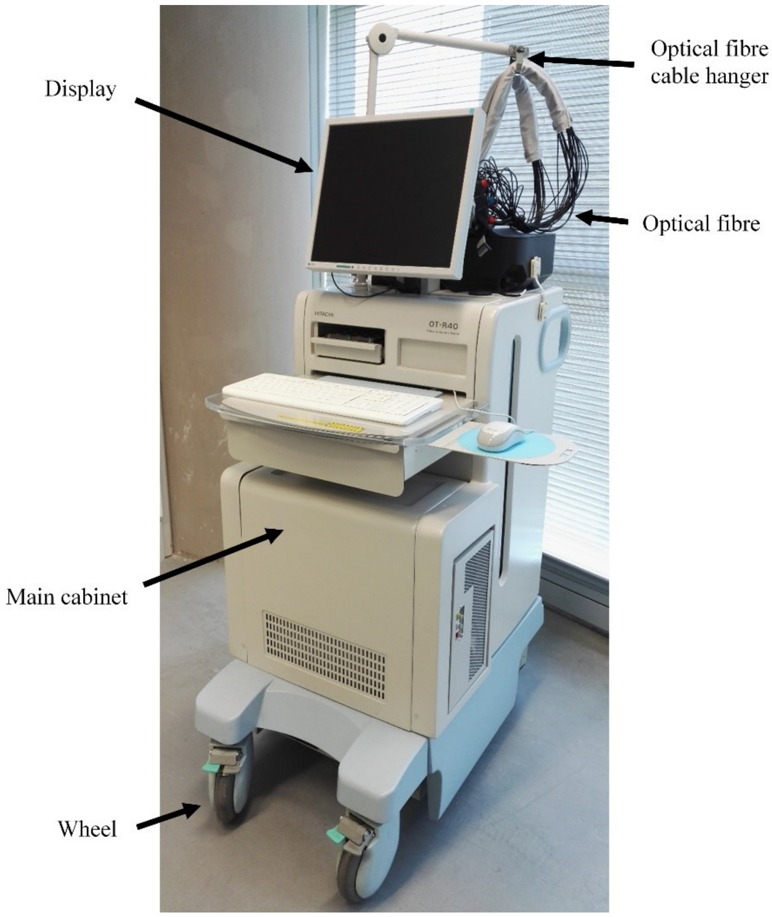


Figure 3.4: OT-R40 (Hitachi Medical Corporation, Japan).

3.1.1.1.2 Data Acquisition

The sampling rate of OT-R40 is 10 Hz (1 sample per 0.1 s). OT-R40 uses laser diodes to emit NIR light of two different wavelengths (695 and 830 nm) through optical fibres and the reflected light is received by avalanche photodiodes which are located 30 mm away from respective emitters. A total of 52 measurement channels was used to measure the brain activity. The probes and channels layout is illustrated in Figure 3.5(a). Such arrangement of the probes is sufficient to cover the entire prefrontal cortex including the target region DLPFC (see Figure 3.5(b)). According to the international 10-20 system [179], emitter 23 and 28 are placed directly at T4 and T3 respectively to ensure that the DLPFC is covered.

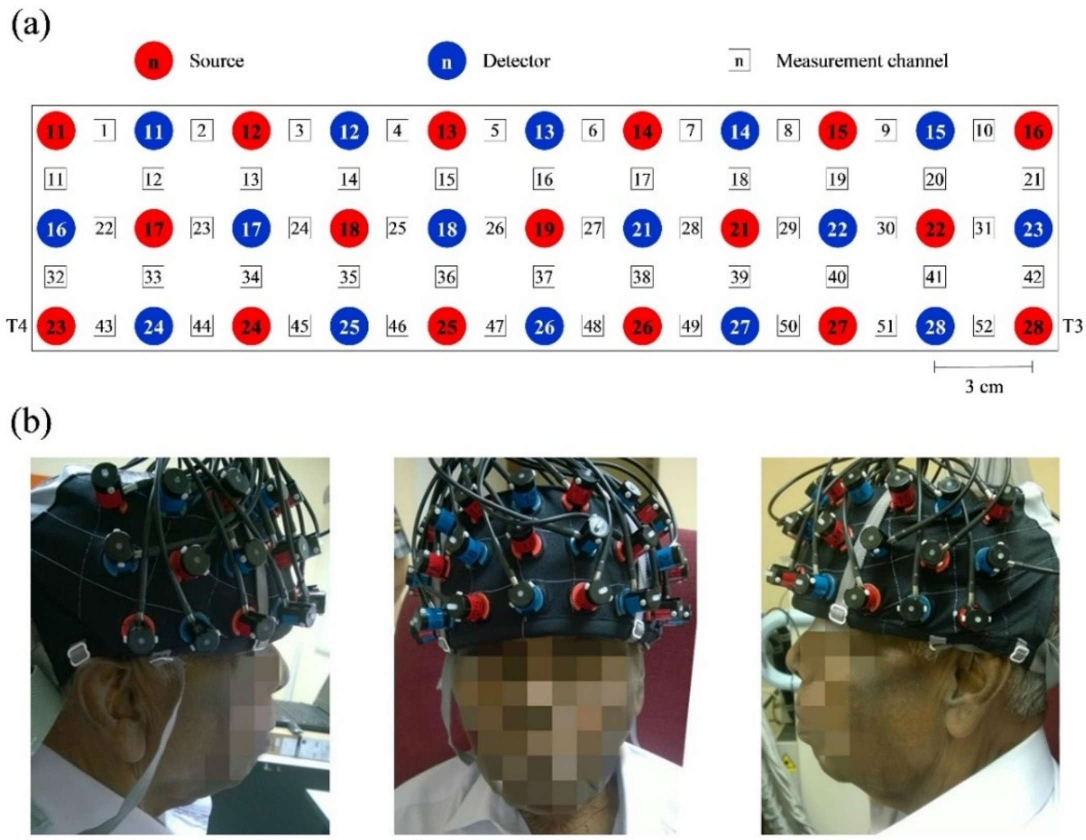


Figure 3.5: Details regarding the probes and measurement channels. (a) 17 emitters and 16 detectors are arranged in such way to form 52 measurement channels. (b) Emitter 23 and 28 are placed directly at T4 and T3 respectively. Such arrangement is sufficient to measure the entire prefrontal cortex including DLPFC.

Since the probes are attached to a flexible head cap, it is relatively easy, fast and convenient to wear the head cap directly on the patients. The optodes contain a spring that pushes the tip to the scalp. Therefore, the force exerted by the spring may cause the participant to feel pain in a particular area as time goes by. All channels have to be checked to ensure that the probes are in contact with the scalp. To improve the contact, accessories such as glass rod or hair manipulator can be used to clear away the hair to ensure that the probes are in good contact with the scalp. The entire process is expected to consume less than 10 minutes.

3.1.1.2 Computer ⇋ OT-R40

OT-R40 cannot perform real time processing on its own. It requires another processing unit to do that. In the fNIRS-DDA system, a separate computer is used to do that. Throughout the cognitive training, both computer and OT-R40 have to communicate between one another all the time. They communicate via two different physical connections: LAN and serial (RS-232C). The former is for real-time transmission of fNIRS data from OT-R40 to the computer while the latter is for the computer to send command to OT-R40.

3.1.1.2.1 Real-Time fNIRS Data Acquisition

In OT-R40, hemoglobin data during measurement are sent to an external computer in real time through a category 5 or higher crossover LAN cable. Both the computer and OT-R40 are assigned two different IP addresses but under the same subnet mask e.g. OT-R40: IP 172.10.101.1, subnet mask 255.255.255.0; Computer: IP 172.10.101.2, subnet mask 255.255.255.0. The computer and OT-R40 are then connected and are able to communicate using TCP/IP with PNET [180]. After establishing the connection, OT-R40 functions as a server while the computer acts as a client. The flowchart for real-time sending and receiving data is shown in Figure 3.6.

The function responsible for receiving oxy- and deoxy-Hb data from OT-R40 is programmed to run in the background so that it will not obtrusively interfere with the cognitive training. The function is also purposely programmed to run every 0.01 s to fetch the data if there is any. By doing so, it is guaranteed that no data will be left out.

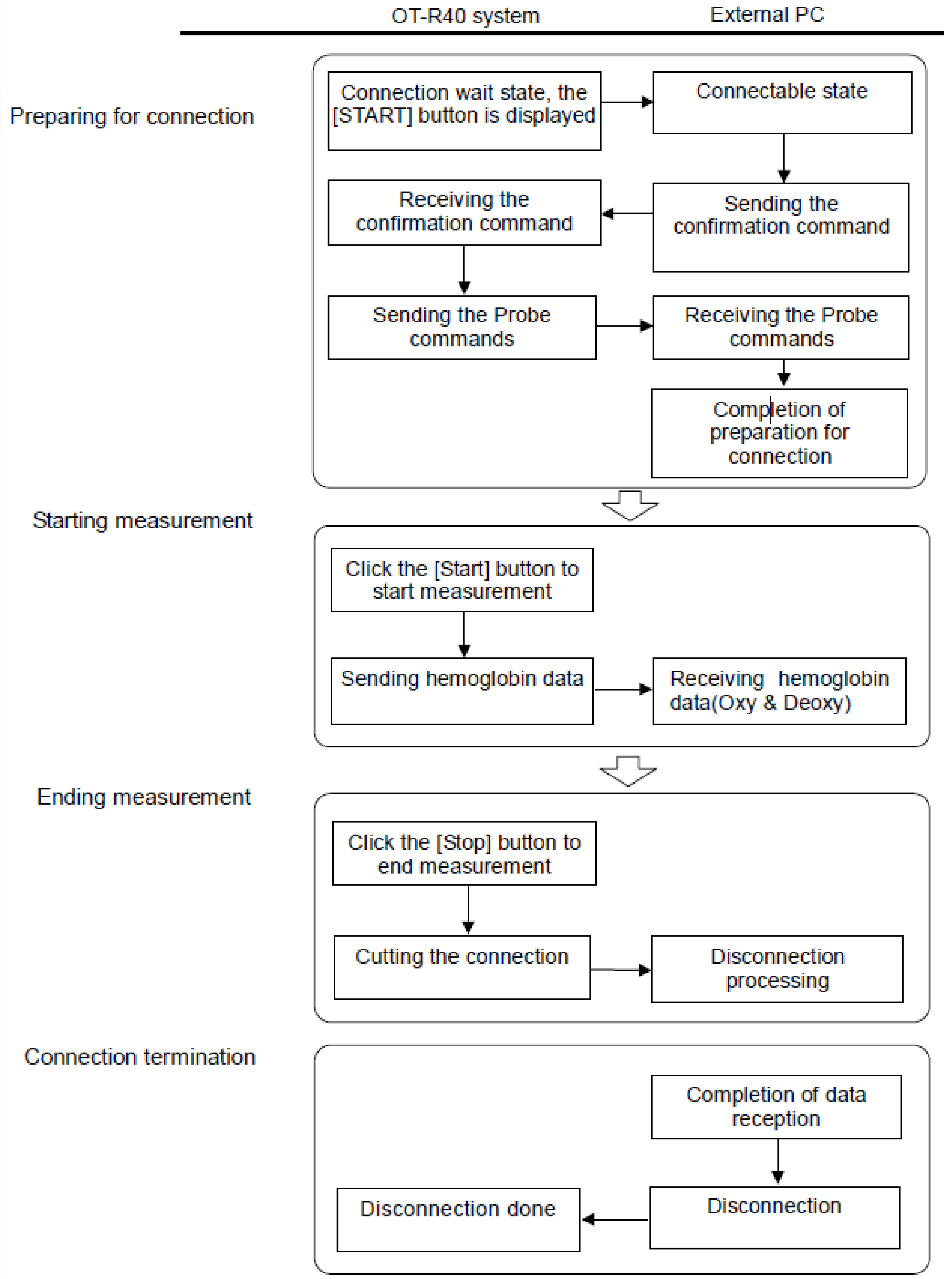


Figure 3.6: Flowchart for sending and receiving fNIRS data between computer and OT-R40 in real time.

3.1.1.2.2 Controlling OT-R40 via the Computer

A RS-232C cable is used to import signals via serial communication from an external computer into OT-R40. After establishing the serial communication link, the computer can now send specific commands to OT-R40, as listed in Table 3.1. OT-R40 executes these commands accordingly. Using these commands, the GUI is programmed to start the measurement when the training begins and end the measurement when the training ends automatically. The GUI is also programmed to mark the task and rest periods. For example, signals recorded when the participant is performing the task is marked with marker A while signals recorded during rest period is marked with marker B. By doing so, it saves a lot of time during real time processing as the task- or rest-related signals can be extracted based on the markers easily and quickly.

Table 3.1: Executable commands that OT-R40 understands.

Received command	**Display character in the mark field**	**Received command (stim measurement)**	**Display character in the mark field (stim measurement)**	**Received command (event measurement)**	**Display character in the mark field (event measurement)**
ST [cr]	START	A [sp] [cr]	A	F1 [cr]	F1
ED [cr]	STOP	B [sp] [cr]	B	F2 [cr]	F2
PS [cr]	PAUSE	C [sp] [cr]	C	F3 [cr]	F3
UP [cr]	UnPAUSE	D [sp] [cr]	D	F4 [cr]	F4
		E [sp] [cr]	E	F5 [cr]	F5
		F [sp] [cr]	F	F6 [cr]	F6
		G [sp] [cr]	G	F7 [cr]	F7
		H [sp] [cr]	H	F8 [cr]	F8
		I [sp] [cr]	I	F9 [cr]	F9
		J [sp] [cr]	J	M [cr]	M

3.1.1.3 Serial Response Box

The Serial Response Box is a relatively simple response collection device that connects directly to the computer through a standard DB25 connector (see Figure 3.7). It communicates with the computer using a universal asynchronous receiver-transmitter with standard RS-232C protocol. The Serial Response Box features 5 keys, 5 lamps, and a voice key. Besides that, the key debounce period and voice key sensitivity can be adjusted via programme. In the fNIRS-DDA, voice key is not deployed and the key debounce is set at default 30 ms. The Serial Response Box is powered by 12V DC power supply. The power supply jack is plugged into the connector on the back of the Serial Response Box.

In the fNIRS-DDA system, since only 4 of the keys are used, minor physical changes are made. A tape is used to cover the fifth key and lamp (keys and lamps are numbered 1-5 from left to right). Four 20 mm × 20 mm alphabetic key labels (A, B, C and D) are also printed and stuck on the keys using double-sided foam. By doing so, the participants not only can see the keys clearly but they also need less effort to press down the keys. Since the same experimental setup will be utilized in future studies, the use of the Serial Response Box and the introduction of such physical modification are to ensure that the response collection process is so simple that the target participants (Alzheimer's disease patients or healthy older adults) are able to follow and perform accordingly. The fifth key and lamp are also covered to avoid causing unnecessary confusion. In current study, the participants were instructed to input their answer by pressing corresponding key e.g. press key A if A was the answer or press key D if D was the answer.

Although MATLAB Psychophysics Toolbox extensions already have built-in function i.e. CMUBox to interact with the Serial Response Box, additional programming was done not only to link the keys to the answer choices but to record the participants' response time once they hit one of the keys. On top of that, the programme also invalidates the participant's response if they press more than one key at the same time or if the duration given to solve a question is way too short.

Figure 3.7: The original Serial Response Box.

3.1.2 Real-Time Monitoring of Workload

If fNIRS is to be deployed to provide real-time monitoring of mental workload, automating manual processes to analyse fNIRS signal is a must. In this section, ways to predict and assess mental workload objectively (and automatically) are discussed.

3.1.2.1 Analysing Changes in Oxy-Hb

Since oxy-Hb is proven to be more sensitive to task-associated changes [72], one of the most widely used method to detect changes in workload is focusing on the changes in oxy-Hb. Generally, oxy-Hb increases when the brain gets more active or stimulated. Thus, by analysing the changes in this parameter when a user is engaged in a task, the level of brain activity (and the workload) in the user's PFC can be estimated. Various studies have investigated workload levels on the basis of changes in oxy-Hb.

Similar approach was deployed by to assess the mental workload for participants piloting unmanned air vehicles (UAVs) [82]. The number of UAVs the participants had to keep track of was varied between trials. The mean change in oxy-Hb was obtained in each trial and increased levels of oxy-Hb was observed in the PFC as the participants tried to pilot of more UAVs. The findings were in identical to the observations during interaction with the n-back task, a common assessment in cognitive neuroscience to measure a part of working memory and working memory capacity. Other than that, increased levels of oxy-Hb also correlated with NASA-TLX workload scores, further validating the detection of signals that point to workload.

3.1.2.2 Configuration of fNIRS Probes

Configurations of fNIRS probes are important because they can impact the accuracy. Using configurations with more measurement channels (source-detector pairs) provides two distinct advantages. First, increasing the number of information (signals) acquired decreases the tendency for one noisy channel to adversely impinge the automated analysis process. Second, these configurations provide better coverage of the PFC. For example, using less source-detector pairs may have problem in assessing region of interest unless they are placed very precisely. However, accuracy also depends heavily on analysis methods and algorithms. As mentioned in 3.1.1.1.2, a total of 52 measurement channels is used to measure the brain activity. Such arrangement of the probes is sufficient to cover the entire prefrontal cortex including the target region DLPFC. According to the international 10-20 system [179], emitter 23 and 28 are placed directly at T4 and T3 respectively to ensure that the DLPFC is covered.

3.1.2.3 Real-Time Signal Processing

The computer processes the fNIRS signals acquired from OT-R40 in real time. A 5^{th} order bandpass filter of 0.01 ~ 0.5 Hz [181] is applied to remove physiological noise. The fNIRS signals are then smoothed using moving average filter of 50 data points (5 s). Since the entire processing has to be repeated on every newly acquired data, it is not possible to do baseline correction in real time. The oxy-Hb signals are then averaged over a total of 8 channels i.e. 4 channels for each left DLPFC (channel 8, 18, 19, 29) and right DLPFC (channel 3, 13, 14, 24) to get an average oxy-Hb signal. This average oxy-Hb signal is used for further analysed (see the following sections).

3.1.2.4 Selecting fNIRS Features

Identifying features of the fNIRS signals that will be fed into models or algorithms are of vital importance. Choosing too few or incorrect features may result in a collection of features that is not truly descriptive of the signal, ultimately impinging the accuracy. However, there is neither standardized method to perform feature extraction nor consensus about the best feature. Based on current fNIRS literature, a widely used approach to extract feature is the use of average signal value, calculated from specific channel(s) over a specific time interval (considering the hemodynamic delay [182]) during each trial [183, 184].

3.1.2.5 Assessing Mental Workload and Adapting the System

Each trial can be represented as an epoch. First, considering the 5 – 7 s of hemodynamic delay [182], the period between 8 s after rest onset and the end of rest, and between 8 s after task onset and the end of task are defined as period 1 and 2 respectively (see Figure 3.8). Using the common approach [183, 184], right after each trial, the oxy-Hb signals during period 1 and 2 are averaged to obtain two average values: $oxy\text{-}Hb_{task(n)}$ and $oxy\text{-}Hb_{rest(n)}$ respectively, where n is the trial number. Activation, $oxy\text{-}Hb_{act(n)}$ is defined as the difference between $oxy\text{-}Hb_{task(n)}$ and $oxy\text{-}Hb_{rest(n)}$. The first three trials and following three trials are fixed at level 1 and 2 respectively. Beyond the first six trials, after every three trials, the activation values are further averaged to get $\overline{oxy\text{-}Hb}_{act(n-2:n)}$ using the formula

$$\overline{oxy\text{-}Hb}_{act(n-2:n)} = \frac{oxy\text{-}Hb_{act(n)} + oxy\text{-}Hb_{act(n-1)} + oxy\text{-}Hb_{act(n-2)}}{3}$$

$$= \frac{1}{3} \sum_{\substack{n-2 \\ n \neq 0 \\ \{3n \mid n \in \mathbb{N}\}}}^{n} oxy\text{-}Hb_{act(n)} \tag{1}$$

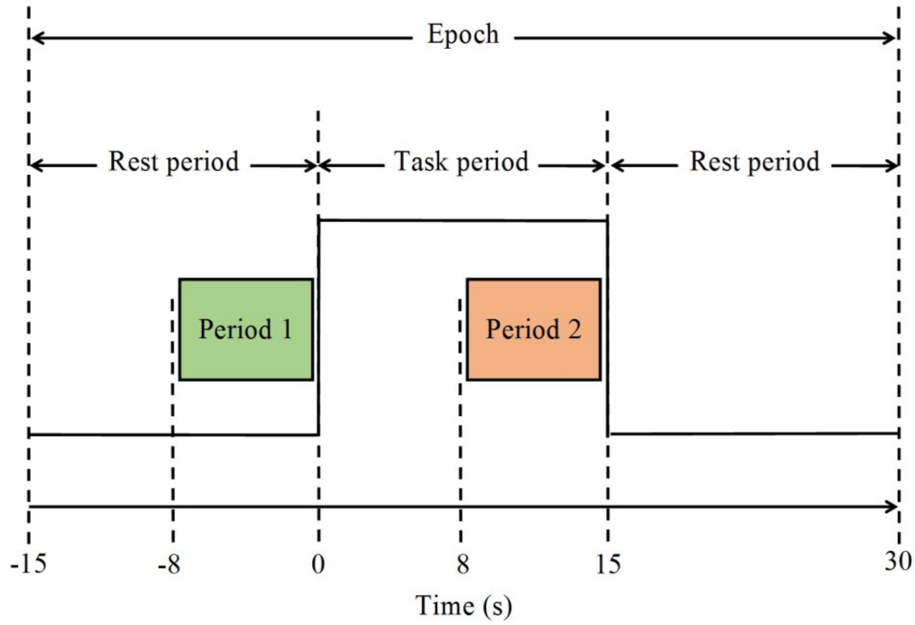


Figure 3.8: Diagram of an epoch, each consisting of 15-s pre-task rest period, 15-s task period and 15-s post-task period. Each trial can be represented as one epoch.

When $n > 6$ and after every three trials, the difficulty level of the next three questions will be adjusted based on the parameter $\overline{oxy\text{-}Hb}_{act(n-2:n)}$. A linear relationship between task workload and hemodynamics has often been observed [82, 85] where the difficulty of the task at hand does not exceed the cognitive capacity of participant. If $\overline{oxy\text{-}Hb}_{act(n-2:n)}$ is larger than $\overline{oxy\text{-}Hb}_{act(n-5:n-3)}$, it implies that the task at hand does not exceed the cognitive capacity of participant. In order to prevent mental underload as well as to impose sufficient amount of effective cognitive load (just beyond the capacity limits) [5], the difficulty level of the next three trials will be raised by one level or remain at the maximum.

When cognitive capacity is exceeded the observed effects on hemodynamics conform to the shape reported by the Yerkes–Dodson law (see Figure 2.8) [86]. Workload alone does not have a quadratic relationship with functional hemodynamics, but instead once there is mental overload functional activation decreases i.e. prefrontal activation followed an inverted U-shaped curve (increases with load up to a certain difficulty level then decreases) [87-91]. The presence of a negative quadratic slope or a sudden decrease during monitoring of workload dynamics is indicative of mental overload. It simply means that if $\overline{oxy\text{-}Hb}_{act(n-2:n)}$ is smaller than $\overline{oxy\text{-}Hb}_{act(n-5:n-3)}$, the processing demands evoked are probably higher than the cognitive capacity. Since sustained overloading working memory can cause mental overload, which leads to negative consequences both for learning and for motivation [6], the next three trials will be made easier or remain at the minimum.

The entire algorithm can be represented using the flowchart depicted in Figure 3.6. Meanwhile, Figure 3.10 shows the pseudocode developed based on the flowchart to facilitate the pre-code planning and organization. By using the algorithm, the effect of baseline shift is reduced and the participants can train at their own pace. This algorithm is mainly designed to impose the right amount of productive load and at the same time minimize irrelevant sources of cognitive load. Its ultimate aim is to prevent mental underload and overload, both of which are equally serious conditions that can impinge the gains of cognitive training or rehabilitation [7, 8, 25, 26].

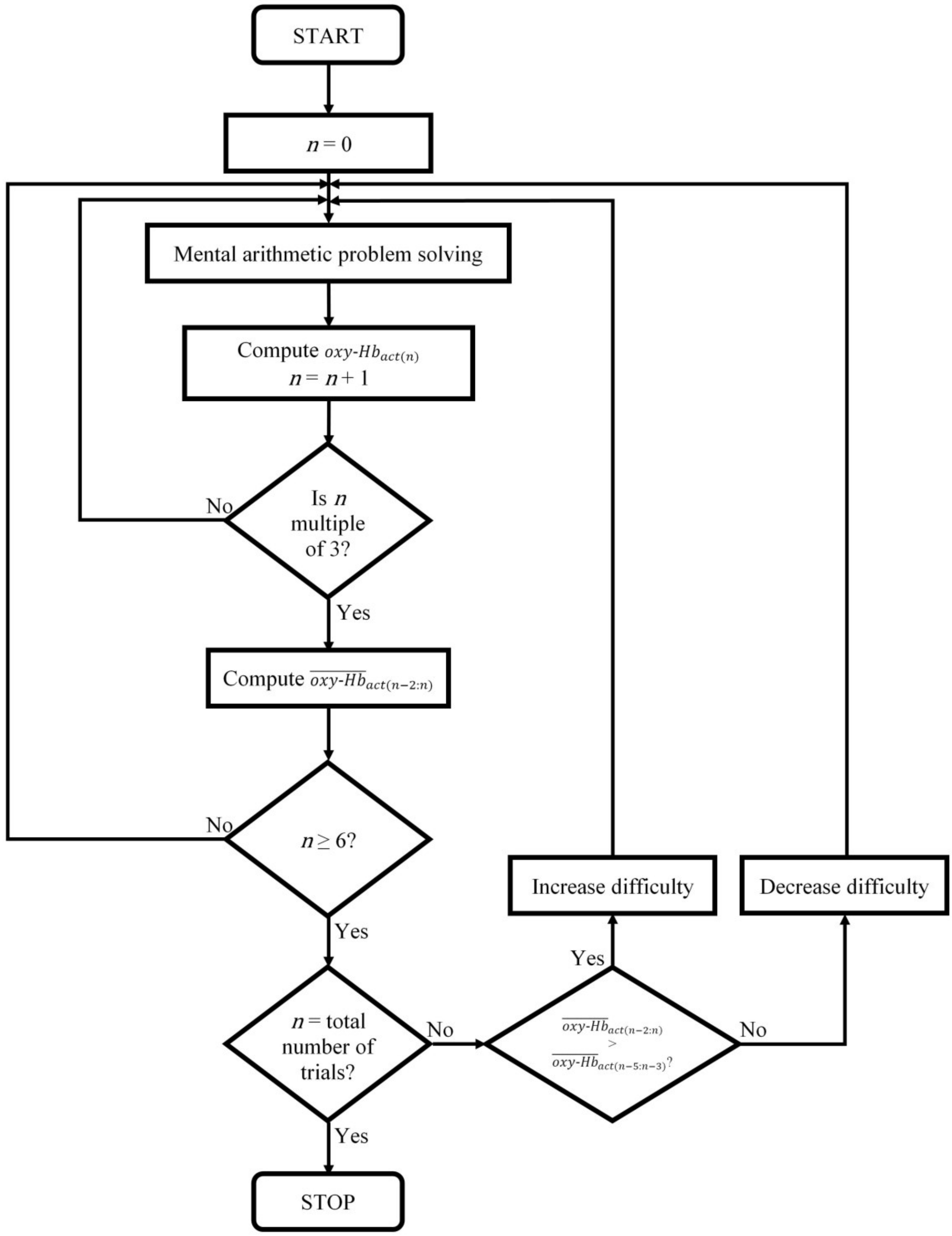


Figure 3.9: The flowchart simplifying the automated algorithm to assess mental workload and adjust task difficulty.

Procedure Algorithm()

- *Total number of trial:* N
- *Trial number:* $n = 0$
- ***Loop*** *if* $n < N$
  1. *Mental arithmetic problem solving while recording fNIRS signals*
  2. $n = n + 1$
  3. *Compute* $oxy\text{-}Hb_{task(n)}$, $oxy\text{-}Hb_{rest(n)}$, *and then* $oxy\text{-}Hb_{act(n)}$
  4. *If* $n \bmod 3 = 0$
     (a) *Compute* $\overline{oxy\text{-}Hb_{act(n-2:n)}}$ *using (1)*
  5. *If* $n \geq 6$
     (a) *If* $n \neq N$
        i. *If* $\overline{oxy\text{-}Hb_{act(n-2:n)}} > \overline{oxy\text{-}Hb_{act(n-5:n-3)}}$
           1. *Increase difficulty of the next 3 trials*
        ii. *Else if* $\overline{oxy\text{-}Hb_{act(n-2:n)}} < \overline{oxy\text{-}Hb_{act(n-5:n-3)}}$
           1. *Decrease difficulty of the next 3 trials*
     (b) *Else if* $n = N$
        i. ***End loop***

Figure 3.10: Pseudocode for the algorithm to assess mental workload and adjust task difficulty.

3.2 Cognitive Task – Mental Arithmetic Problem Solving

As discussed in 2.6.4.1, mental arithmetic may be an effective cognitive task as it not only activates the DLPFC [168-171] but is also simple enough for Alzheimer's disease patients to follow and perform them. Arithmetic calculation has been proven to be effective in improving the cognitive status of dementia patients [165]. A number of studies suggest that the DLPFC can be a suitable region to acquire the physiological features for DDA (see 2.5.2.3.3). The MATLAB Psychophysics Toolbox extensions are used to design and run the entire training [185-187].

3.2.1 Paradigm

After much consideration, in order to make the task more simple enough so that Alzheimer's disease patients to follow and perform, the arithmetic questions come with four choices and only one correct answer. The motive is to ensure that the participants indeed perform as they are expected to – solve the arithmetic questions shown mentally. Without looking at their responses, it is impossible to see whether they actually perform the mental calculations or not.

During the rest periods, the participants are required to keep their vision on the fixation cross (see Figure 3.11(a)) and relax. During the task period, participants are required to solve the arithmetic question shown on the monitor (refer to Figure 3.11(b)) mentally and respond by pressing the corresponding key. The question along with 4 answer choices will be displayed for 15 s unless the participant responds before 15 s. If that is the case, once the participant responds, only the question and the selected answer will remain on screen (see Figure 3.11(c)) for 1 s and he or she will be tested with a new question. In every task period, the participants are given 15 s to solve as many arithmetic questions as possible. The participants are also encouraged to double check their answer by mental calculation again even though they have solved and responded already.

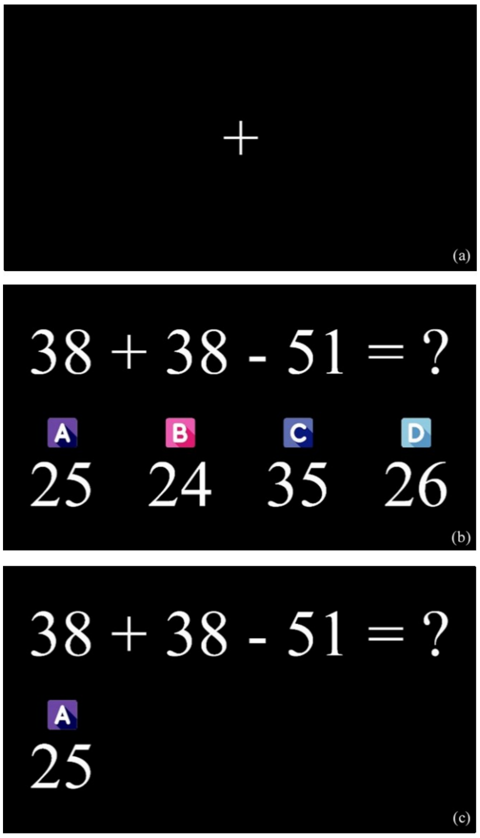


Figure 3.11: What the participants see on the monitor. (a) Fixation cross; cue to relax. (b) Arithmetic question with 4 answer choices. (c) After responding, only the arithmetic question and selected answer will remain on screen for 1 s.

3.2.2 Levels of Difficulty

For the arithmetic problems, there are 6 levels of difficulty, with lowest level being the simplest and the highest level being the most complex. All single-digit operands range from 1 to 9 while double-digit operands range from 10 to 99. Details of these 6 levels are listed in Table 3.2.

Table 3.2: Descriptions of each difficulty level.

Level	Number of Operands		Arithmetic Operations
	Single-digit	Double-digit	
1	2	-	+ and/or −
2	3	-	+ and/or −
3	-	2	+ and/or −
4	2	1	+ and/or −
5	1	2	+ and/or −
6	-	3	+ and/or −

All operands and answers are non-negative.
Single-digit operands ranges from 1 to 9.
Double-digit operands ranges from 10 to 99.

3.2.3 Question Generator

A programme is used to generate the set of questions that would be used in each level based on the criteria: a) no repetition of number(s) in a question, b) answer is non-negative, and c) higher level questions are always more difficult than lower level questions (to avoid cases e.g. level 3 question 30 – 29 is not harder than level 2 question 3 + 9 + 8). For each level, each combination of arithmetic operations, e.g. $s_1 + s_2 + d_1$ and $s_1 + s_2 - d_1$, have equal probability of being picked. That is why the programme extracts a fixed number of questions from every possible combination of arithmetic operations in each level. Take level 4 as an example, both $s_1 - d_1 + s_2$ and $s_1 + s_2 - d_1$ only have 140 possible combinations of numbers and this number is the lowest compared to other combinations of arithmetic operations. Therefore, in level 4, 140 combinations are extracted from each combination of arithmetic operations, forming a final set of 1400 questions for level 4. In this way, each different combination of arithmetic operations stands equal chance (10%) of being picked. For more details, please refer to Table 3.3.

Table 3.3: All possible sets of questions generated using the question generator.

Level	Operands	Arithmetic Operations	Number of Possible Combinations	Number of Questions Included	Total Number of Questions
1	2 single-digit operands	$s_1 + s_2$	72	36	72
		$s_1 - s_2$	36	36	
2	3 single-digit operands	$s_1 + s_2 + s_3$	504	100	400
		$s_1 + s_2 - s_3$	436	100	
		$s_1 - s_2 - s_3$	436	100	
		$s_1 - s_2 + s_3$	100	100	
3	2 double-digit operands	$d_1 + d_2$	7218	2880	5760
		$d_1 - d_2$	2880	2880	
4	2 single-digit, 1 double-digit operands	$s_1 + s_2 + d_1$	6480	140	1400
		$s_1 + s_2 - d_1$	140	140	
		$s_1 - s_2 + d_1$	6480	140	
		$s_1 + d_1 + s_2$	6480	140	
		$s_1 + d_1 - s_2$	6480	140	
		$s_1 - d_1 + s_2$	140	140	
		$d_1 + s_1 + s_2$	6480	140	
		$d_1 + s_1 - s_2$	6480	140	
		$d_1 - s_1 - s_2$	6480	140	
		$d_1 - s_1 + s_2$	6480	140	
5	1 single-digit, 2 double-digit operands	$s_1 + d_1 + d_2$	8010	3321	36531
		$s_1 + d_1 - d_2$	4770	3321	
		$s_1 - d_1 + d_2$	4770	3321	
		$d_1 + s_1 + d_2$	8010	3321	
		$d_1 + s_1 - d_2$	4770	3321	
		$d_1 - s_1 - d_2$	3321	3321	
		$d_1 - s_1 + d_2$	8010	3321	
		$d_1 + d_2 + s_1$	8010	3321	
		$d_1 + d_2 - s_1$	8010	3321	
		$d_1 - d_2 - s_1$	3321	3321	
		$d_1 - d_2 + s_1$	4770	3321	
6	3 double-digit operands	$d_1 + d_2 + d_3$	704880	86920	347680
		$d_1 + d_2 - d_3$	621160	86920	
		$d_1 - d_2 - d_3$	86920	86920	
		$d_1 - d_2 + d_3$	621160	86920	

s_x: Single-digit operand x, ranges from 1 to 9. d_y: Double-digit operand y, ranges from 10 to 99.

3.3 Study 1: Theory and Region Validation

Study 1 was a pilot study involving only two older participants (a mild Alzheimer's disease patient and a healthy control) to validate the proposed theory and target region. In this study, Serial Response Box was not utilized and the questions were not multiple choice; no input was collected from the participants. Apart from that, in this study, the fNIRS-DDA system was of earlier version and it adjusts the task difficulty every trial from the third trial onwards.

3.3.1 Participants

The mAD patient is a 58-years-old woman and the healthy control (HC) is a 50-years-old man. The inclusion criteria for the mAD patient and HC are listed in Table 3.4. The diagnosis were carried out by trained clinicians. The CDR is a structured interview to rate the severity of dementia [131]. Both HC and mAD patient were briefed through the nature of the experimental procedures before any training. Informed consent form was subsequently obtained along with their demographic information. This pilot study was granted necessary permits from the local ethics committee and was performed in compliance with the Declaration of Helsinki. Both participants were not remunerated for their participation.

Table 3.4: Inclusion and exclusion criteria for HC and mAD.

Inclusion criteria for HC	Inclusion criteria for mild AD	Exclusion criteria for both groups
• Right-handed	• Right-handed	• Left-handed
• Able to converse in English	• Able to converse in English	• Unable to converse in English
• No cognitive complaints and no deficits on testing	• No past history of psychiatric or neurological disorder	• Poor eyesight, hearing, and movement
• Independent in activities of daily living	• CDR = 1	• Bed-ridden
• No past history of psychiatric or neurological disorder		• Secondary medical conditions
• CDR = 0		• CDR ≥ 2

3.3.2 Procedure

Before the training, the participants were seated in a comfortable chair, and were also instructed to avoid movement and keep both hands on the armrest. Figure 3.12 shows the experimental setup. Practice was also provided to familiarize the subjects with the experimental procedures. The time course of the cognitive training is illustrated in Fig. 3. In total, subjects underwent 15 math questions (totalled around 8 minute) involving addition and/or subtraction. Each question represents one trial. The training started with a 15-s rest and every task lasted for 15 s, followed by a 15-s rest. The entire training lasted for 7 min 45 s. During the rest periods, subjects were instructed to look at the fixation point (see Figure 3.13(a)) and relax. During the task, they were required to solve the arithmetic question that appears on screen (see Figure 3.13(b)) for 15 s mentally. They were also encouraged to double check after solving. Similarly, for the arithmetic questions, there were six levels of difficulty (refer to 3.2.2).

Figure 3.12: Participants were instructed to avoid movement, keep their hands on the armrest during the training, where they had to solve arithmetic questions mentally.

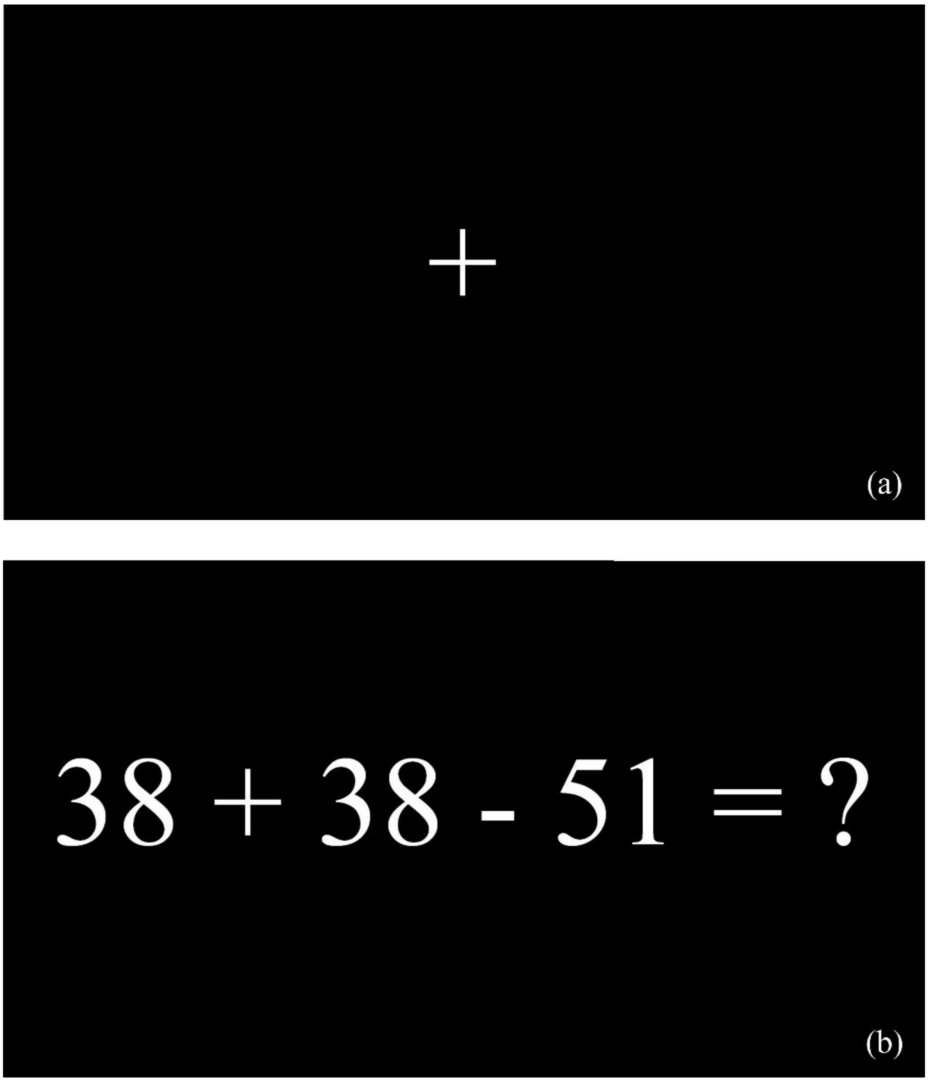


Figure 3.13: The cognitive training task. (a) The fixation point during rest periods. (b) An example of arithmetic question.

3.3.3 Data Analysis

Since Study 1 was just a pilot test and the sample size was extremely small, no statistical analysis could be done. Simple comparison functions e.g. less than, greater than were used to analyse both fNIRS and behavioural data (median of difficulty levels). Even though the results were probably inconclusive, they helped to examine the feasibility of the system that is intended to ultimately be used in a large scale study.

3.4 Study 2: Functionality Testing

Findings from Study 1 warrant a more detailed study focusing on the functionality of the fNIRS-DDA system. The goal was to make sure that everything is working as planned before examining the efficacy of such cognitive rehabilitation as an alternative treatment for Alzheimer's disease (future research) which requires not only vast resources but also a large sample size and long data collection duration.

3.4.1 Participants

Since the purpose of this study was to test the functionality of the fNIRS-DDA system, a total of 25 healthy right-handed university students matched for age (23.44 ± 2.89 years) and gender (13 males; 12 females) was recruited. Through online advertising (circulating poster online; see Appendix D), they were recruited through purposive sampling with specific inclusion criteria: 1) Right-handed; 2) Able to converse in English; 3) No past history of psychiatric or neurological disorder e.g. depression; 4) Able to attend two 1-hour sessions (at least one week apart). No participant had any neurological or psychiatric history, or any medical history affecting cognitive function. Apart from that, all of them had normal or corrected-to-normal vision.

All the participants were briefed through the nature of the experimental procedures prior to any experiment. Apart from that, the participants were required to undergo two training sessions spread over at least two weeks i.e. the second session should be at least one week apart from the first one. In the first session, informed consent form (refer to Appendix E) was obtained along with their demographic information e.g. age, gender, ethnicity, education level, and first language (see Appendix F). This study was granted necessary permits from the local Universiti Teknologi PETRONAS ethics committee and was performed in compliance with the Declaration of Helsinki. All the participants were remunerated for their participation.

3.4.2 Procedure

After much consideration (see 2.6.4.1), mental arithmetic task was selected as the cognitive training task. Participants underwent a series of multiple-choice math questions with four choices and only one correct answer. Before the training, participants were briefed and practice was provided. This was to familiarize the participants with the experimental procedures. Other than that, the participants were be instructed to avoid movement, keep their left hand on the arm rest and their right hand on the Serial Response Box throughout both sessions. shows the experimental setup.

During the pre-task and post-task rest periods, the participants were required to keep their vision on the fixation cross (see Figure 3.11(a)) and relax. During the task period, participants were required to solve the arithmetic question shown on the monitor (refer to Figure 3.11(b)) mentally and respond by pressing the corresponding key. The question along with 4 answer choices would be displayed for 15 s unless the participant responded before 15 s. If that was the case, once the participant responded, only the question and the selected answer would remain on screen (Figure 3.11(c)) for 1 s and a new question would be shown. In every task period, the participants were given 15 s to solve as many arithmetic questions as possible. The participants were also instructed to double check their answer by mental calculation again even though they had solved and responded already.

Figure 3.14: The participants were instructed to avoid movement, keep their left hand on the arm rest and their right hand on the Serial Response Box throughout both experiments, where they had to solve arithmetic questions mentally.

The fNIRS-DDA adaption was compared to a control condition where the participants were tested only arithmetic questions of their optimal level of difficulty throughout the entire training. Thus, there were 2 separate training sessions: *adaptive* and *nonadaptive*.

- In the *adaptive condition*, the training regimen incorporated the fNIRS-DDA system, meaning the level of difficulty was constantly automatically and adaptively adjusted accordingly to the fNIRS signals measured in real time.
- In the *nonadaptive condition*, the training was a two-part procedure. First, a prior screening was conducted to determine the participants' optimal level of difficulty (level that elicited the highest activation value). Subsequently, only arithmetic questions of this level of difficulty were asked throughout the remaining training session.

These training sessions spread across at least 2 weeks. In each session, the participants were required to solve a series of arithmetic questions mentally while getting their brain activity measured using OT-R40. In a counterbalanced design to control for order effects, the participants were randomly assigned to two groups, each group undergoing the aforementioned training conditions in a different order e.g. Group 1 underwent the sessions in the order of nonadaptive, adaptive conditions while Group 2 underwent the sessions in the order of adaptive, nonadaptive conditions (see Figure 3.15). By creating a group for each possible order, the variance due to order effects became a separate source of variance, making for a more powerful experimental design.

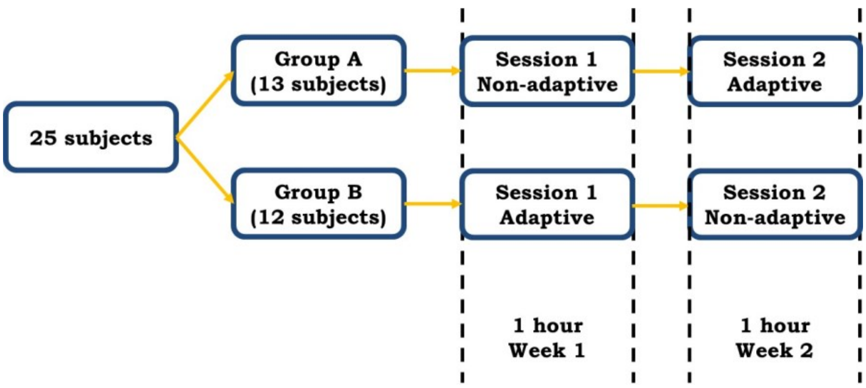


Figure 3.15: The counterbalanced experimental design.

In both conditions, right after the cognitive training, the participants were administered the paper version of the NASA-TLX measure (see Appendix A). NASA-TLX is a widely used, subjective, multidimensional assessment tool that rates perceived workload or other aspects of performance [99, 100]. NASA-TLX consists of six subscales (as listed in Table 2.3) which altogether contribute to the overall workload. The participants were told to read the description for each of these subscales carefully before rating.

3.4.2.1 Nonadaptive Condition

A nonadaptive session consisted of two parts – prior screening and cognitive training. The total duration for a nonadaptive session was around 40 minutes.

3.4.2.1.1 Prior Screening

A prior screening was carried out to determine the participants' optimal level of difficulty based on the fNIRS signals. The screening was preceded by a 15 s pre-task rest period followed by 15 s task and 15 s post-task rest periods (see Figure 3.16). Each task period represents a trial, where the participants had to solve arithmetic questions mentally. The prior screening lasted 9 min 15 s and consisted of 18 trials. In each trial, the participants were given 15 s to answer as many arithmetic questions as possible. There were 6 levels of difficulty, with lowest level being the simplest and the highest level being the most complex. Details of these 6 levels are listed in 3.2.2. In the prior screening, all 6 levels of difficulty were tested (3 trials per level) in a randomized order. In the end, each participant contributed 18 activation values and these values were further averaged down to 6 values (one for each level). The level with the largest activation value was chosen as the participants' optimal level of difficulty. In the end, the participants' optimal level of difficulty was picked based on the amplitude of activation and afterwards, only arithmetic questions of that particular level of difficulty were asked throughout the subsequent training session (refer to 3.4.2.1.2).

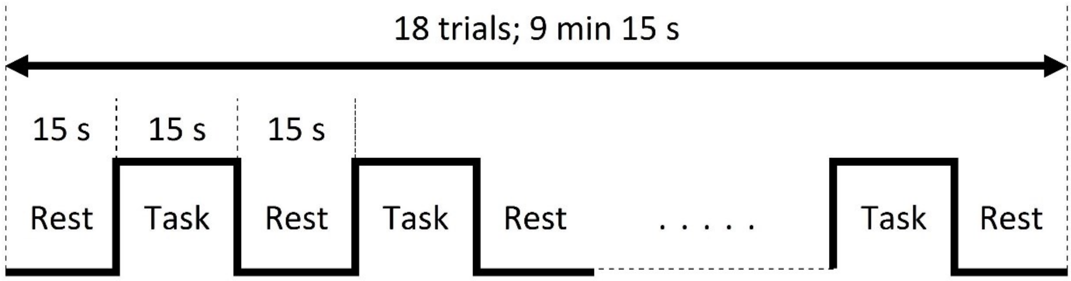


Figure 3.16: The paradigm of the prior screening in nonadaptive condition.

3.4.2.1.2 Cognitive Training

The time course of the cognitive training is illustrated in Figure 3.17. The cognitive training started with a 15-s rest and every task lasted 15 s, followed by a 15-s rest. In the cognitive training, each task period represents a trial, where the participants had to solve arithmetic questions mentally. The cognitive training lasted 30 min 15 s and consisted of a total of 60 trials. In each trial, the participants were given 15 s to answer as many arithmetic questions as possible. Throughout the cognitive training, only arithmetic questions from a particular level (selected in the prior screening; refer to) were asked.

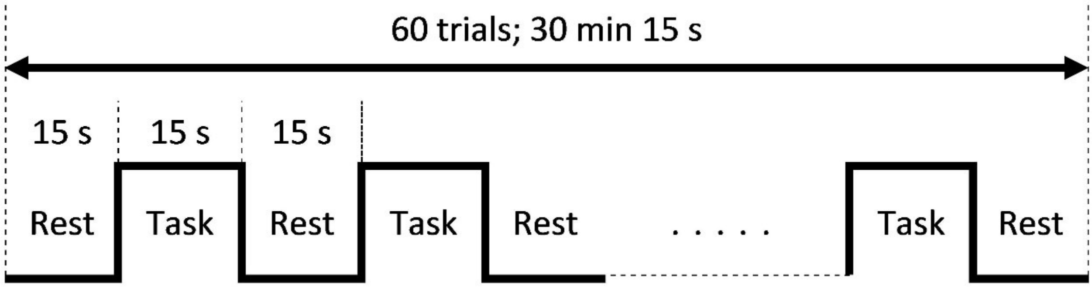


Figure 3.17: The paradigm of the cognitive training session.

3.4.2.2 Adaptive Condition

An adaptive session lasted approximately 30 minutes and consisted only of one part – cognitive training session. The adaptive training regimen incorporated the fNIRS-DDA system (see 3.1), meaning the level of difficulty was constantly automatically and adaptively adjusted accordingly to the fNIRS signals measured in real time. In adaptive condition, the cognitive training was exactly the same as the one used in nonadaptive condition (see Figure 3.17) except that fNIRS-DDA was incorporated.

The cognitive training started with a 15-s rest and every task lasted 15 s, followed by a 15-s rest. In the cognitive training, each task period represents a trial, where the participants had to solve arithmetic questions mentally. The cognitive training lasted 30 min 15 s and consisted of a total of 60 trials. In each trial, the participants were given 15 s to answer as many arithmetic questions as possible. There were 6 levels of difficulty, with lowest level being the simplest and the highest level being the most complex. Details of these 6 levels are further elaborated in section 3.2.2. Since fNIRS-DDA was incorporated, arithmetic questions of appropriate degree of difficulty that were constantly tailored to the participants' current cognitive workload were asked throughout the cognitive training. The session started with three level 1 questions, followed by three level 2 questions. From there onwards, the difficulty level of subsequent questions was adjusted based on their processed fNIRS signals every three. Detailed description of the algorithm is written in 3.1.2.5.

3.4.3 Data Analysis

3.4.3.1 fNIRS Data

For each participant, the fNIRS time series were then epoched into 60 smaller blocks (one block for each trial). Each block consisted of a 15-s pre-task rest period, a 15-s task period followed by a 15-s post-task period. In reality a few participants' fNIRS data were subjected to baseline drift even though attempts have been made to reduce the effects of baseline drift. The baseline drift was more obvious as the training progressed. Therefore, it was not appropriate to calculate the block average of fNIRS signals directly by averaging all the activation values. Instead, all the fNIRS data were normalized using min-max normalization in order to reduce all the participants' data to the same scale, aiming to create a fairer comparison. Min-max normalization is a normalization strategy or feature scaling which linearly transforms a property (values of a numeric range of a feature of data) to a scale between 0 and 1 using the formula

$$z_i = \frac{x_i - \min(x)}{\max(x) - \min(x)} \qquad (2)$$

where $x = (x_{participant\ 01}, \dots, x_{participant\ 20})$, $x_i = i^{\text{th}}$ observed data, and $z_i = i^{\text{th}}$ normalized data. After normalizing the data, block average of fNIRS signals was calculated by averaging the relevant fNIRS data.

For each training condition, each participant contributed a total of 60 activation values (one value per trial; see 3.1.2.5). These 60 values were then averaged and divided into 4 time intervals (each of 7.5 min or 15 trials) not only to investigate the time-on-task effects i.e. any fall off in performance with time on task but also to study how well the fNIRS-DDA worked. The same analysis technique was applied to the behavioural data i.e. response time, answer accuracy and difficulty level as well.

3.4.3.2 Statistics

Non-parametric Mann-Whitney U tests with Bonferroni-Holm correction were employed to compare the NASA-TLX scores including both overall and subscale scores. On the other hand, the exact test was repeated multiple times to test the intra- and inter-condition differences in difficulty levels. A total of 12 (e.g. nonadaptive condition: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min; adaptive condition: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min) and 4 ($nonadaptive_{(0–7.5\ \text{min})}$ vs $adaptive_{(0–7.5\ \text{min})}$, … , $nonadaptive_{(22.5–30\ \text{min})}$ vs $adaptive_{(22.5–30\ \text{min})}$) pairwise Mann-Whitney U tests with Bonferroni-Holm correction were carried out to determine intra- and inter-condition differences respectively in difficulty levels. The Bonferroni-Holm correction would test each individual hypothesis in a sequential rejective manner at

$$\frac{\alpha}{n - rank\ number\ of\ the\ pair\ (by\ degree\ of\ significance) + 1} \qquad (3)$$

where α is the desired significance level (0.05) and n is the number of comparisons.

Other behavioural data that were statistically assessed included the response time and answer accuracy. Both the response time and answer accuracy were not good parameters for inter-condition comparison and it made no sense to compare them directly as the difficulty levels were designed to alter regularly in adaptive condition, so both the parameters were expected to affected in adaptive condition. Instead, the response time and answer accuracy, which were directly related with performance, were analysed only to investigate the time-on-task effects i.e. any increase in the parameters over increasing time on task. As a consequence, for each of these parameters, only intra-condition statistical significance was estimated using 6 pairwise one-sample t-tests with similar Bonferroni-Holm correction per training condition (e.g. nonadaptive: $nonadaptive_{(0–7.5\ min)}$ vs $nonadaptive_{(7.5–15\ min)}$, … , $nonadaptive_{(15–22.5\ min)}$ vs $nonadaptive_{(22.5–30\ min)}$; adaptive condition: $adaptive_{(0–7.5\ min)}$ vs $adaptive_{(7.5–15\ min)}$, … , $adaptive_{(15–22.5\ min)}$ vs $adaptive_{(22.5–30\ min)}$) and 4 ($nonadaptive_{(0–7.5\ min)}$ vs $adaptive_{(0–7.5\ min)}$, … , $nonadaptive_{(22.5–30\ min)}$ vs $adaptive_{(22.5–30\ min)}$).

The same number of test were repeated to assess whether there were any intra-condition differences in the normalized fNIRS activations. On top of that, inter-condition statistical significance in the fNIRS parameter was estimated using 4 pairwise comparisons between the two training conditions at each time interval, with one-sample t-test with Bonferroni-Holm correction (e.g. $nonadaptive_{(0–7.5\ min)}$ vs $adaptive_{(0–7.5\ min)}$, … , $nonadaptive_{(22.5–30\ min)}$ vs $adaptive_{(22.5–30\ min)}$). Finally, to investigate the relationship between time on task and normalized fNIRS activation, quadratic regression analyses were performed using the time on task as a continuous independent variable. All the statistical tests performed are summarized in Table 3.5.

Table 3.5: The statistical tests performed on the parameters: NASA-TLX scores, difficulty level, response time, answer accuracy and normalized activation.

Parameters
NASA-TLX scores
Inter-condition differences
Mann–Whitney U tests with Bonferroni-Holm correction
7 pairwise comparisons (one for each subscale and another one for overall score)
Mental demand$_{(nonadaptive)}$ vs Mental demand$_{(adaptive)}$, … , Overall$_{(nonadaptive)}$ vs Overall$_{(adaptive)}$
Difficulty level
Intra-condition differences
Mann–Whitney U tests with Bonferroni-Holm correction
0 pairwise comparisons for nonadaptive condition since difficulty level remained constant
6 pairwise comparisons for adaptive condition only
adaptive$_{(0\text{–}7.5\ \text{min})}$ vs *adaptive*$_{(7.5\text{–}15\ \text{min})}$, … , *adaptive*$_{(15\text{–}22.5\ \text{min})}$ vs *adaptive*$_{(22.5\text{–}30\ \text{min})}$
Inter-condition differences
Mann–Whitney U tests with Bonferroni-Holm correction
4 pairwise comparisons
nonadaptive$_{(0\text{–}7.5\ \text{min})}$ vs *adaptive*$_{(0\text{–}7.5\ \text{min})}$, … , *nonadaptive*$_{(22.5\text{–}30\ \text{min})}$ vs *adaptive*$_{(22.5\text{–}30\ \text{min})}$
In nonadaptive condition, difficulty level was constant
Response time
Intra-condition differences
One-sample t-tests with Bonferroni-Holm correction
6 pairwise comparisons per training condition
Nonadaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Adaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Answer accuracy
Intra-condition differences
One-sample t-tests with Bonferroni-Holm correction
6 pairwise comparisons per training condition
Nonadaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Adaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Normalized Activation
Intra-condition differences
One-sample t-tests with Bonferroni-Holm correction
6 pairwise comparisons per training condition
Nonadaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Adaptive: 0–7.5 min vs 7.5–15 min, … , 15–22.5 min vs 22.5–30 min
Inter-condition differences
One-sample t-tests with Bonferroni-Holm correction
4 pairwise comparisons
nonadaptive$_{(0\text{–}7.5\ \text{min})}$ vs *adaptive*$_{(0\text{–}7.5\ \text{min})}$, … , *nonadaptive*$_{(22.5\text{–}30\ \text{min})}$ vs *adaptive*$_{(22.5\text{–}30\ \text{min})}$
Relationship with time on task
Quadratic regression using the time on task as a continuous independent variable

3.5 Summary

The fNIRS-DDA system developed is actually a closed-loop feedback system, consisting of a multichannel fNIRS system OT-R40, a computer, a monitor, and a Serial Response Box. Brain activity in target region (DLPFC) is measured using OT-R40. The measured fNIRS signals are then transferred to a computer for signal processing in order to extract useful information to the feed the DDA. Based on this information, the task difficulty is adjusted accordingly. The feedback loop is repeated until the entire training or learning is completed.

Since oxy-Hb is more sensitive to task-associated changes, the fNIRS-DDA assesses mental workload objectively based on specific features of oxy-Hb. oxy-Hb signals are first processed in real time before extracting relevant parameters. These parameters are compared in order to assess the mental workload and adjust the task difficulty accordingly. It is based on the theory that there is a linear relationship between workload and hemodynamics where the difficulty of the task at hand does not exceed the cognitive capacity, however, once there is cognitive overload or mental overload, functional hemodynamics starts to decrease, resulting in an invert U-shaped activation.

A total of two studies were conducted. The first study was a pilot test involving a mAD patient and a healthy older individual, aiming to validate the theory behind the fNIRS-DDA system and to confirm the region of interest. On the other hand, the second study was like a functionality testing of the fNIRS-DDA system. The goal was to ensure that everything is working as planned before applying the system in future studies.

Chapter 4

RESULTS AND DISCUSSION

4.1 Study 1: Theory and Region Validation

The aim of this pilot test was to validate the theory behind the fNIRS-DDA system and to confirm the region of interest.

4.1.1 Results

4.1.1.1 Sample Characteristics

There were only two participants (one mAD patient and one HC). Demographic information about age, gender, and education level collected were tabulated in Table 4.1, along with their behavioral data. Apart from that, mAD patient had a MMSE score of 14 and CDR rating of 1 while HC had a MMSE score of 26 and CDR rating of 0.

Table 4.1: Participants' demographic information and behavioural data.

	HC (n=1)	mAD (n = 1)
Characteristic	Mean	Mean
Age, years	50	58
Gender, M/F	M	F
Education level, P/S/T	S	S
CDR rating	0	1
MMSE score	26	14
Level of difficulty (easiest 1, hardest 6)		
Median	3	2
Peak	5	3

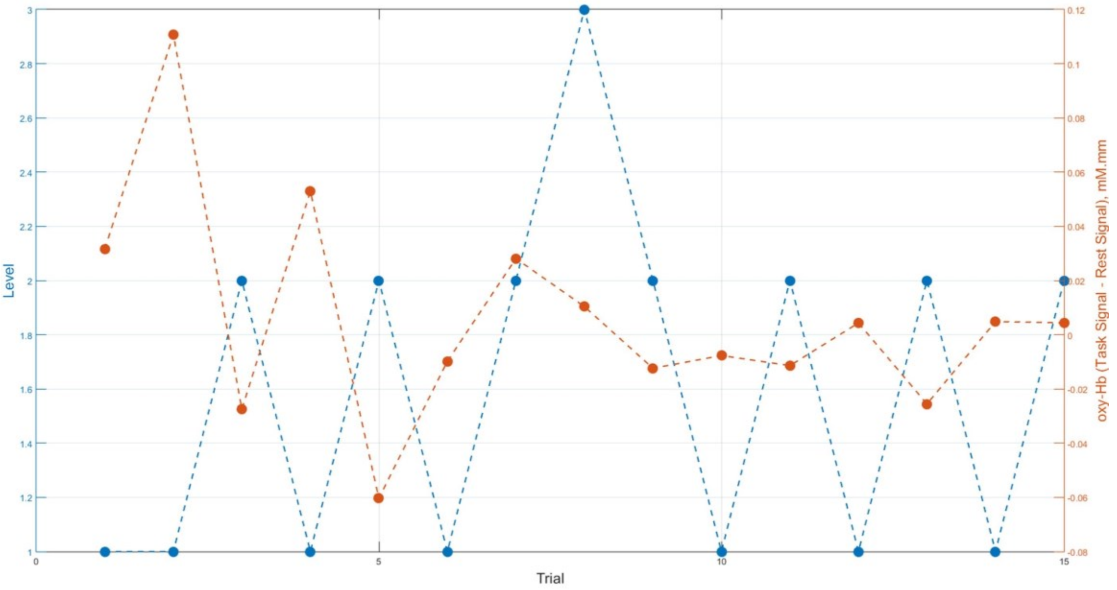
M = male; F = female; P = primary; S = secondary; T = tertiary.

4.1.1.2 Behavioural Data: Difficulty Level

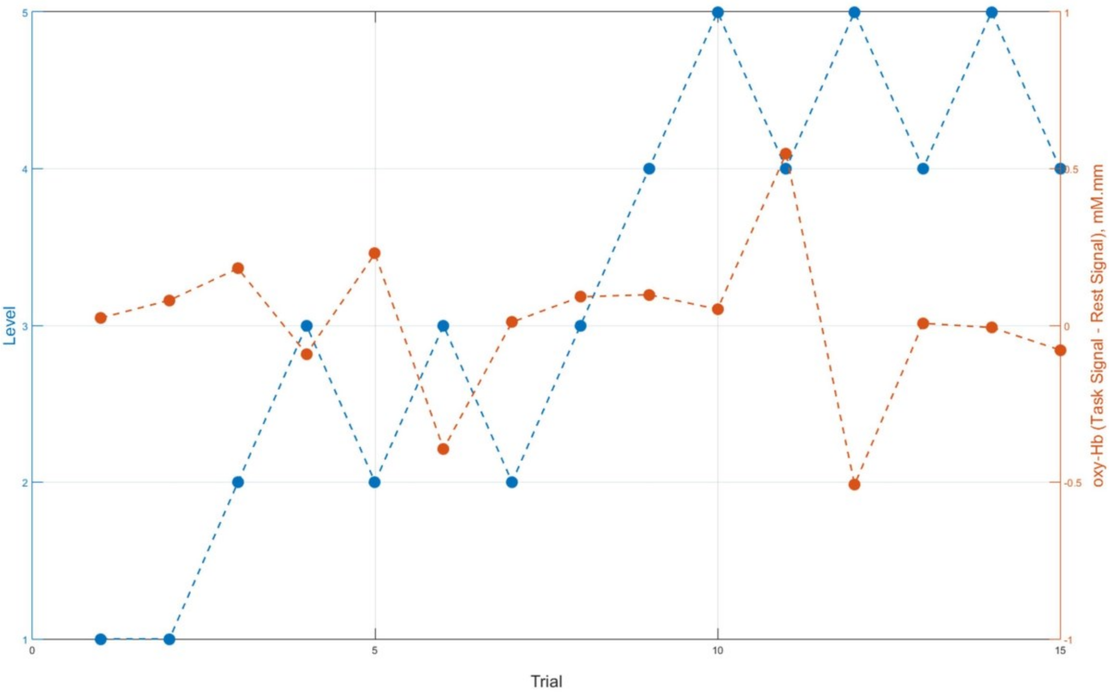
It was expected that the HC with no mental calculation impairment would perform better than the mAD patient. The fNIRS-DDA system picked up the difference in cognition between the two participants as intended. Referring to Figure 4.1(a), the highest level that the mAD patient achieved was only level 3 and the patient also fluctuated between level 1 and 2 throughout the training. Perhaps level 3 and 2 questions were too difficult for the mAD patient, prompting the patient to give up more easily. Level 1 is possibly the appropriate degree of difficulty for the mAD patient. However, the fNIRS-DDA system is designed to prevent mental underload as well as to impose sufficient amount of effective cognitive load. That was why the mAD patient fluctuates between level 1 and 2.

On the other hand, in the beginning of the training, the HC fluctuated between level 2 and 3 for several trials. Subsequently, he successfully progressed to level 4 and 5 and maintained his performance. The HC's progress is illustrated in Figure 4.1(b). With no deficit in mental calculation abilities, the HC should have no problem in performing calculations mentally. However, level 5 questions may be too hard for the HC to solve within 15 s, which explains why the HC fluctuated between level 4 and 5 towards the end of the training.

Based on these results, the fNIRS-DDA system succeed in allowing participants to train at their appropriate degree of difficulty. This might avoid causing any detrimental cognitive overload/underload which can affect the cognitive training gains.



(a)



(b)

Figure 4.1: The participants' performance and hemodynamics. (a) mAD. (b) HC.

4.1.1.3 fNIRS Data

Bandpass filter was used to remove physiological noise while moving average filter was applied to smooth the signal. Figure 4.2 shows the raw/contaminated fNIRS signal with signals after removing physiological noise and smoothing in channel 14 of the HC. As discussed in 3.1.2.4, the oxy-Hb signals were averaged over the DLPFC (4 channels for each left and right DLPFC) to get an average oxy-Hb signal. The average oxy-Hb with standard deviations in eight channels over the DLPFC of the HC are illustrated in Figure 4.3. The task difficulty level was adjusted based on this average oxy-Hb signal. All these were done in real time. HC showed higher average activation across blocks (0.0163 mM·mm) than mAD (0.0062 mM·mm), thereby in consistent with the hypothesis through demonstration of the trend.

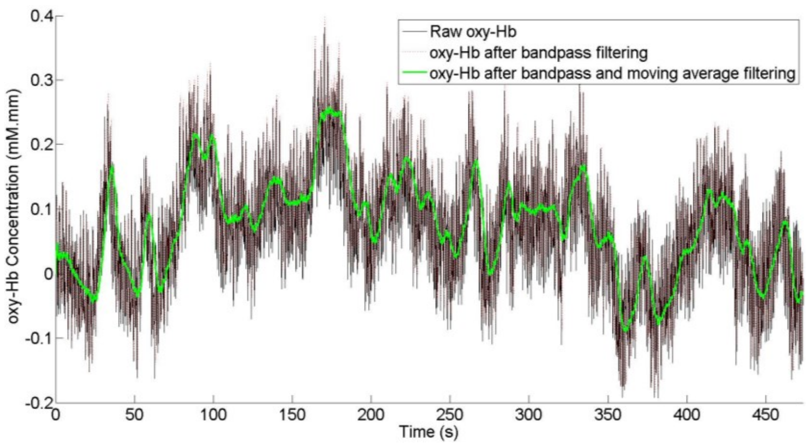


Figure 4.2: Raw and processed fNIRS signal sampled from channel 14 of the HC.

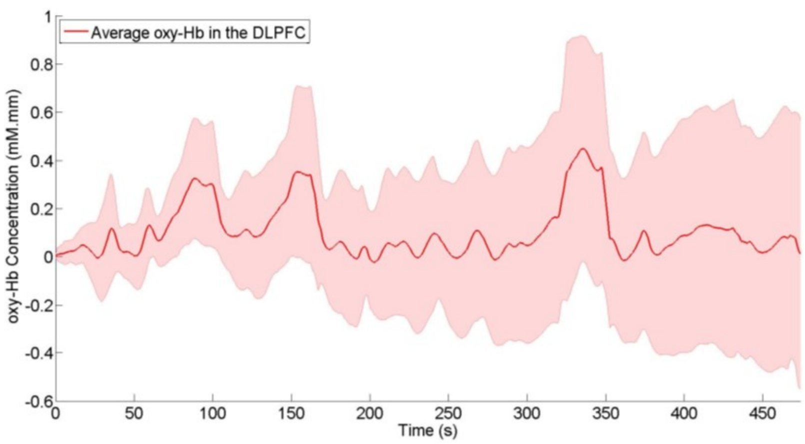


Figure 4.3: The average oxy-Hb signal (red line) with standard deviations (shaded region) in eight channels over the DLPFC of the HC.

4.1.2 Discussion

Higher and lower average activation observed in HC and mAD respectively coupled with HC's higher performance and mAD's poorer performance suggests that using the fNIRS-DDA system, the participants actually trained at their appropriate degree of difficulty. This finding is further supported as patients with AD were identified with lower activation in the PFC compared to HC during cognitive tasks, while HC performed also better on the tasks [188-190]. However, instead of the fNIRS-DDA system, it is possible that the finding could also be due to the difference in neurological status. Several MRI studies revealed that deficits found in patients with AD are associated with volumetric changes in the prefrontal cortex (PFC) [191-193]. It has been suggested that cognitive decline related to normal aging is attributed to the reduction of white matter rather than the reduction of grey matter [194]. In contrast, significant loss of grey matter which is composed of cortical neurons and glia was evidenced in Alzheimer's disease, and led to reduced neuronal activation in the PFC of Alzheimer's disease, when compared to HC [195]. These results warrant a more detailed study focusing on the functionality of the fNIRS-DDA system (Study 2; see 3.4), aiming to make sure that everything is working as planned before examining the efficacy of such cognitive rehabilitation as an alternative treatment for Alzheimer's disease (future research) which requires not only vast resources but also a large sample size and long data collection duration.

4.1.3 Conclusion

Based on the experiment results, the proposed fNIRS-DDA system allows the participants to train at their appropriate degree of difficulty and workload. This may help in avoiding causing any mental overload which can affect the cognitive training gains. Future study will explore the functionality of the fNIRS-DDA system.

4.2 Study 2: Functionality Testing

The second study was a functionality testing of the fNIRS-DDA system to ensure that everything is working as planned.

4.2.1 Results

4.2.1.1 Sample Characteristics

A total of 25 healthy university students participated in current study (age range, 20–29 years; mean ± standard deviation age, 23.44 ± 2.89 years). However, the data collected from a particular participant was excluded as he did not complete his second training session due to a technical error and four more participants whose fNIRS data were noisy (contained high amount of spikes, and abnormality in activations and deactivations). After excluding those data, the final group of participants consisted of 20 individuals (11 females; mean ± standard deviation age, 22.7000 ± 2.4301 years). Demographic information about age, gender, and education level was collected (see Table 4.2). No participant had any neurological or psychiatric history, or any medical history affecting cognitive function. Apart from that, all of them had normal or corrected-to-normal vision. All of the participants completed the second session training session at least a week apart from the first one but one. He underwent the second training session 6 days after completing the first training session.

Table 4.2: The participants' demographic information.

	n = 20
Characteristic	**Mean (SD)**
Age, years	22.7000 (2.4301)
Gender, M/F	9/11
Education level, P/S/T	0/0/20
Days between 1st and 2nd session	8.0500 (3.3635)

M = male; F = female; P = primary; S = secondary; T = tertiary.

4.2.1.2 Subjective Perception of Workload

The participants' NASA-TLX scores are illustrated in Figure 4.4. On average, the participants reported higher ratings not only in all of the subscales but also in the overall workload score in nonadaptive condition. Despite not being statistically significant, these results might be of clinical significance, especially the mental demand (p = 0.0955) and frustration (p = 0.0684) subscale scores where the p-values are close to the significance level (0.05). As expected, adaptive condition yielded lower workload because the difficulty of the arithmetic questions were constantly tailored to the participants' cognitive state. In contrast, nonadaptive condition might be more cognitively taxing (as reflected in the mental demand subscale score) as the participants only underwent arithmetic questions from their optimal difficulty level that elicited highest activation as compared to other levels. In addition to that, the higher frustration subscale score might be indicative of higher degree of frustration which is possibly indicative of mental overload triggered by problem-solving tasks like math. Increasing the sample size would probably uncover significant inter-condition differences in both of these subscale scores as it more reliably reflects the population mean.

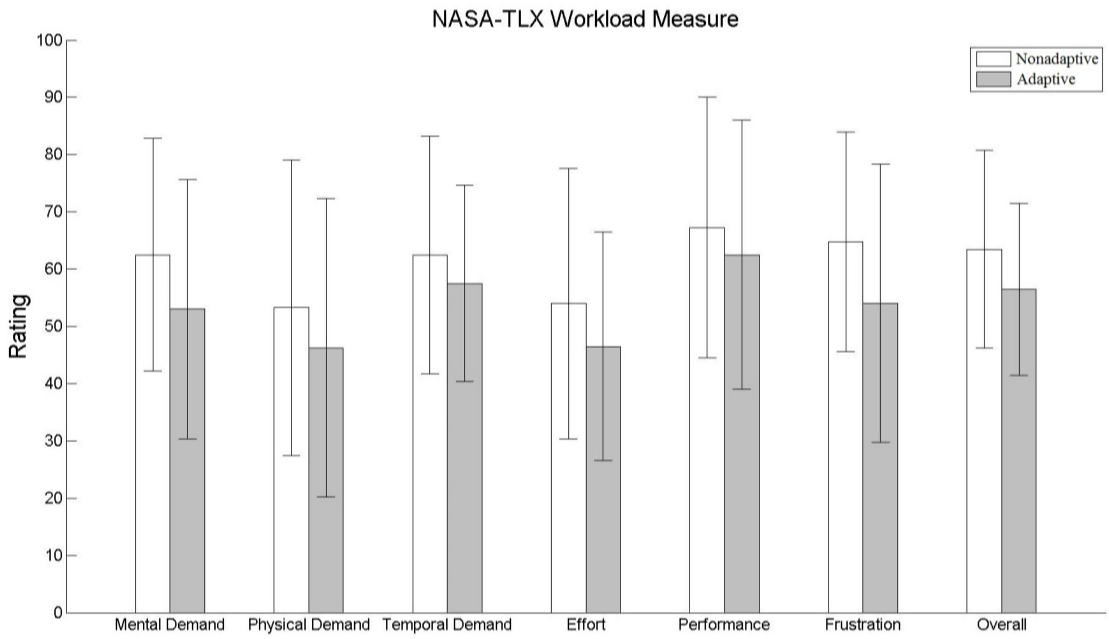


Figure 4.4: The participants' mental workload assessment scores, using the NASA-TLX. Ratings are provided on a scale from 0 (low) to 100 (high).

4.2.1.3 Behavioural Data

The behavioural results (difficulty level, response time and answer accuracy) are summarized in Table 4.3.

Table 4.3: The behavioural data i.e. difficulty level, response time and answer accuracy as well as the fNIRS data i.e. normalized activation.

	Time on task (min)			
	0 to 7.5	**7.5 to 15**	**15 to 22.5**	**22.5 to 30**
Parameters	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Difficulty level; 1 (easiest) to 6 (hardest)				
Nonadaptive	3.9000 (1.6827)	3.9000 (1.6827)	3.9000 (1.6827)	3.9000 (1.6827)
Adaptive	2.4000 (0.5982)	2.8000 (0.8944)	3.05000 (0.9445)	3.6000 (1.0463)
Response time (s)				
Nonadaptive	5.0212 (2.8155)	5.1413 (2.8732)	4.7940 (2.7348)	4.9952 (2.9022)
Adaptive	2.1926 (0.8803)	2.4197 (0.9129)	2.5860 (0.9784)	3.2929 (1.6572)
Answer accuracy (%)				
Nonadaptive	60.9905 (19.9898)	59.5099 (21.8201)	61.5187 (22.0473)	60.7286 (21.8842)
Adaptive	82.7829 (7.8399)	80.4365 (7.8158)	76.7329 (8.9605)	73.7940 (13.8909)
Normalized Activation (a.u.)				
Nonadaptive	0.4227 (0.0664)	0.4328 (0.0474)	0.4891 (0.0539)	0.4654 (0.0596)
Adaptive	0.4578 (0.0735)	0.4495 (0.0821)	0.4880 (0.0725)	0.4879 (0.0664)

4.2.1.3.1 Difficulty Level

The peak difficulty levels that the participants underwent are shown in Table 4.3 Figure 4.4. In nonadaptive condition, the participants were tested with only arithmetic questions from a particular level. On the other hand, in nonadaptive condition, initially (0 to 7.5 min), the participants trained a significantly lower level than that in nonadaptive condition (p = 0.0028). As the training went on, the participants progressed steadily to higher levels. In the end (22.5 to 30 min), the participants reached significantly higher levels as compared to the initial level during 0 to 7.5 min (p = 0.0002). In other words, in adaptive condition, the participants started with significantly lower levels and eventually progressed to significantly higher levels of difficulty (comparable to adaptive condition). However, it is noticeable that the standard deviation in adaptive condition was large as some participants showed higher activation in lower difficulty levels even though normally higher levels of difficulty would elicit higher activations (see section 4.2.1.4.1).

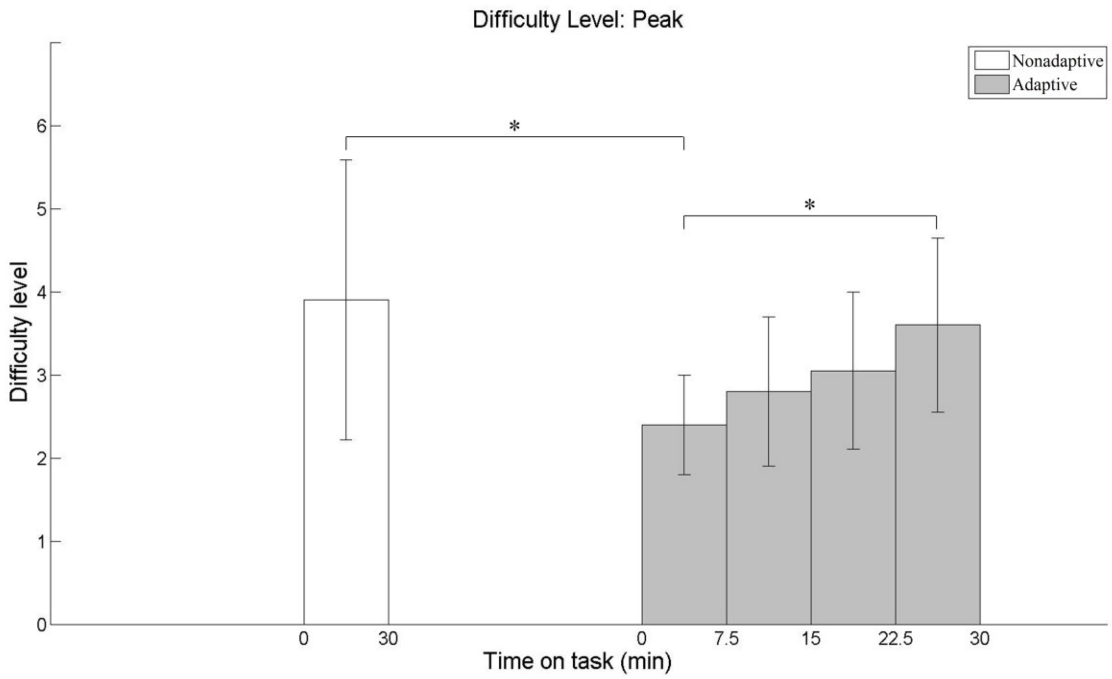


Figure 4.5: Peak difficulty levels that the participants underwent in different time intervals. Statistical analysis was performed using Mann-Whitney U test. *$p < 0.05$ with Bonferroni-Holm correction.

4.2.1.3.2 Response Time

Response time was the time taken for the participants' to hit one of the keys on the Serial Response Box, regardless of correct or incorrect answer. Referring to Table 4.3 and Figure 4.6, in nonadaptive condition, the participants' response time remained almost constant throughout the entire session. However, the standard deviation was large, possibly due to the differences in the difficulty level. The higher the difficulty level, the longer it took to solve the arithmetic questions as the questions were more complex. According to Table 4.4, in nonadaptive condition, 5%, 20%, 25%, 5%, 20% and 25% of the participants underwent difficulty level 1, 2, 3, 4, 5 and 6 respectively. This could explain the large standard deviation in response time only in nonadaptive condition but not in adaptive condition. In adaptive condition, all the participants started with three trials of level 1 followed by three trials of level 2 within the first 7.5 min. As mentioned in 0 not all but majority of the participants eventually progressed to higher difficulty levels as the training went on, hence the increase in the mean and standard deviation in response time.

As mentioned in section 3.4.3.2, the response time was not a good parameter for inter-condition comparison and it made no sense to compare them as the difficulty levels kept changing in adaptive condition, so did the response time. Instead, the response time, which was directly related with performance, was analysed to investigate the time-on-task effects i.e. any increase in the response time over increasing time on task.

4.2.1.3.3 Answer Accuracy

Answer accuracy was calculated by diving the number of questions answered correctly by the number of questions attempted. In accordance Table 4.3 to Figure 4.7, the participants' accuracy remained unchanged throughout the entire training in nonadaptive condition. The large standard deviation can be attributed to the differences in the difficulty level. The higher the difficulty level, the more complex the arithmetic questions were and the participants were more prone to error. Some participants underwent lower difficulty levels while the rest were tested with

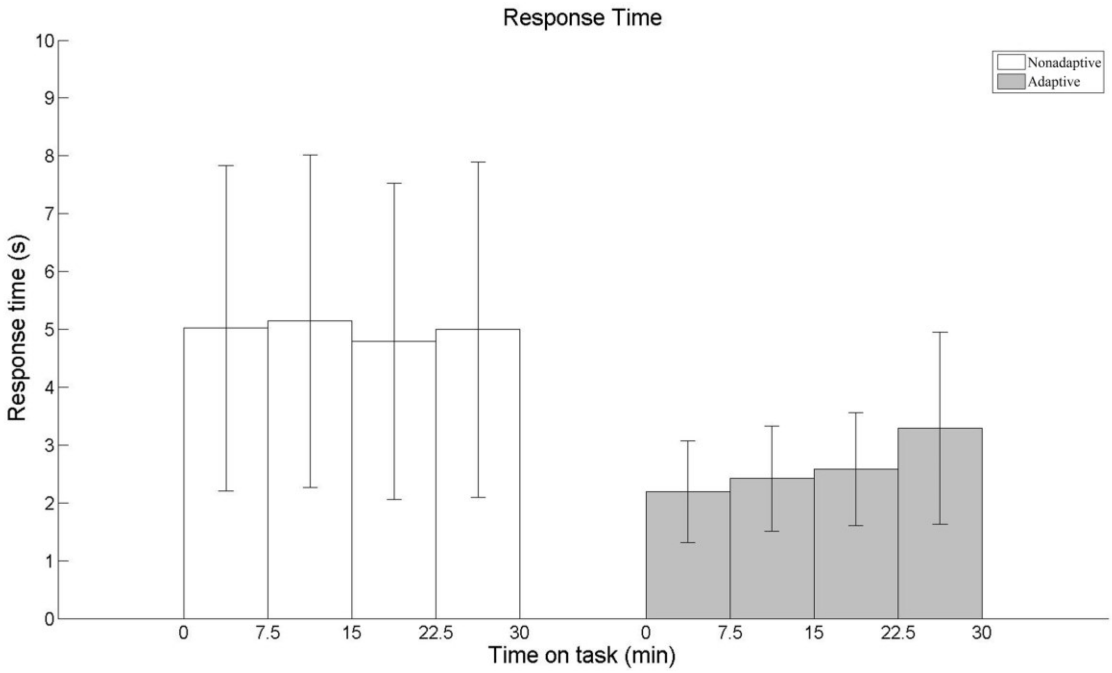


Figure 4.6: The participants' response time in different time intervals. Statistical analysis was performed using one-sample t-test with Bonferroni-Holm correction only to estimate the intra-condition differences.

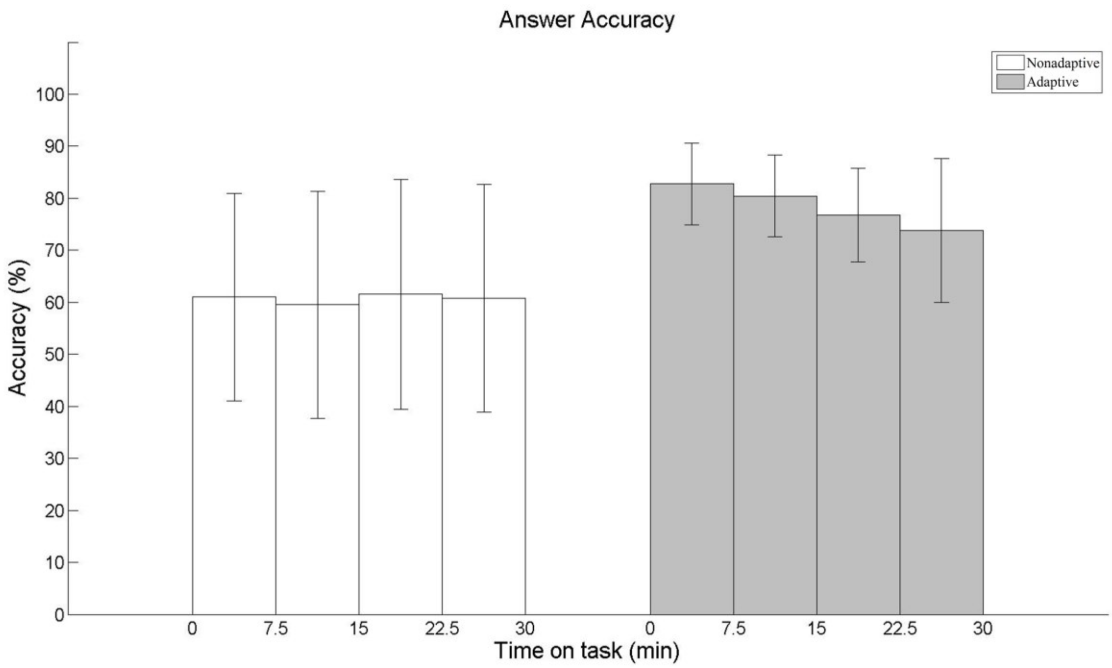


Figure 4.7: The participants' answer accuracy in different time intervals. Statistical analysis was performed using one-sample t-test with Bonferroni-Holm only to investigate the intra-condition differences.

questions of higher difficulty. This could explain why such large standard deviation was not observed in adaptive condition but only in nonadaptive condition. On the other hand, all the participants started the adaptive condition training the same way i.e. same difficulty levels. Afterwards, it all depended on their own hemodynamics. Not all but most of the participants succeed in progressing to higher difficulty levels as the training went on, hence the decreased accuracy and increased standard deviation.

Referring to 3.4.3.2, it was inappropriate to compare both conditions directly on the basis of answer accuracy. The difficulty levels was designed to alter regularly in adaptive condition, so the answer accuracy was expected to be affected. Finally, the aim of looking at the answer accuracy was solely to investigate the time-on-task effects.

4.2.1.4 fNIRS Data

A raw fNIRS signal sampled from channel 2 of one of the participant is shown in Figure 4.8. Apparently, the signal is noisy and full of artifacts, highlighting the important of processing in order to extract maximum amount of useful information.

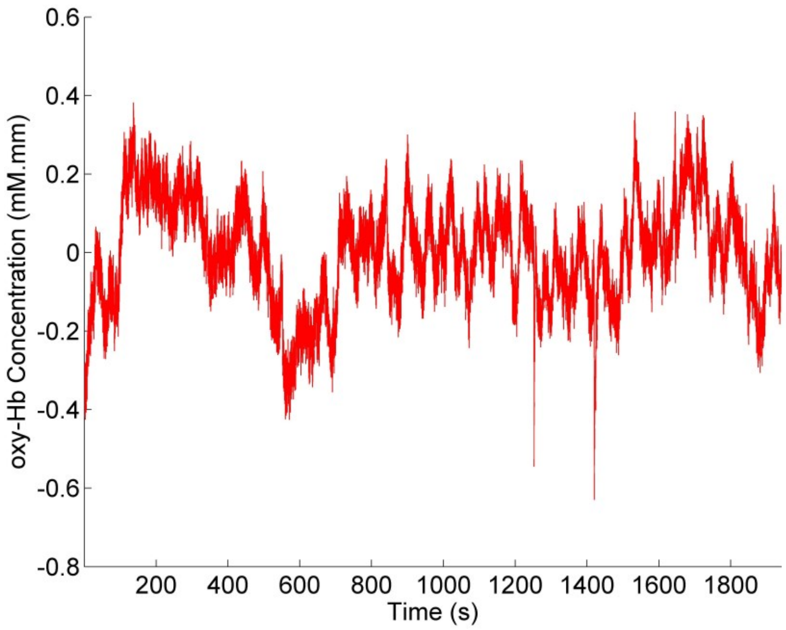


Figure 4.8: Raw fNIRS signal sampled from channel 2 of one of the participants.

4.2.1.4.1 Nonadaptive Condition – Prior Screening

As mentioned in section 3.4.2.1.1, for each participant, the level with the largest $oxy\text{-}Hb_{activation,level}$ was assumed to be the participant's optimal level of difficulty. Subsequently, only arithmetic questions of that particular difficulty level were asked throughout the cognitive training session. $oxy\text{-}Hb_{activation,level}$ for each participant and level are tabulated in Table 4.4, together with the level selected (shaded).

Table 4.4: $oxy\text{-}Hb_{activation,level}$ for each participant and level in the prior screening.

	$oxy\text{-}Hb_{activation,level}$ (mM·mm)					
ID	**1**	**2**	**3**	**4**	**5**	**6**
01	0.0382	0.1136	0.1355	0.1301	0.1752	0.1325
02	0.1316	0.0509	-0.1086	-0.1094	-0.1566	-0.1740
03	0.0518	-0.0185	0.0982	-0.0004	-0.0048	0.0682
04	0.0690	0.1063	0.0364	0.0192	0.0416	0.0190
05	0.0698	0.0375	0.0177	0.0821	0.1365	0.0005
06	0.1453	0.0982	0.0695	0.0550	0.1599	0.1280
07	0.0386	0.0787	0.1532	0.0296	0.0169	0.0763
08	0.0509	0.0538	0.0445	0.0792	0.0008	0.1305
09	0.0299	0.0353	0.1043	0.0429	0.0682	0.0734
10	-0.0085	0.1217	0.0756	-0.0020	0.0659	0.0085
11	0.0099	0.0459	0.0120	-0.0088	0.0246	0.0081
12	0.0254	0.0473	0.0730	0.0408	-0.0236	0.0873
13	-0.0028	0.0059	0.0274	0.0044	0.0250	0.0091
14	0.0520	0.0924	0.0266	0.0118	0.0617	-0.0727
15	0.0760	0.0004	-0.0060	0.0149	0.1194	0.0846
16	0.0053	0.0198	0.0194	-0.0316	0.0256	0.1361
17	0.1729	0.0130	0.3103	-0.1367	0.1513	-0.0671
18	-0.0346	-0.0206	-0.1282	0.0421	0.1610	0.4560
19	0.0440	0.0364	0.0020	0.0499	0.0059	0.0183
20	0.0459	0.1335	0.1114	0.0905	0.1118	0.1948

The optimal level selected i.e. the maximum value is denoted by the grey shade.

4.2.1.4.2 Normalized Activation

Originally, the epoched oxy- and deoxy-Hb signals sampled over the DLPFC (channel 8, 18, 19, 29, 3 13, 14, 24) were measured in units of mM·mm. The signals then underwent min-max normalization, where both the numerator and denominator were in the same units (mM·mm), leaving the resulting signals in arbitrary units (a.u.). After that, the signals were averaged to obtain an overall signal for nonadaptive and adaptive conditions (see Figure 4.9 and Figure 4.10 respectively). In both figures, an increase in oxy-Hb was accompanied by a decrease in deoxy-Hb. This observation was consistent with previous studies that have shown that this is the typical hemodynamic response to neural activation [196, 197] as a result of neurovascular coupling [198, 199].

After min-max normalization, the normalized activation were also calculated in a.u. Figure 4.11 shows the normalized activation for both training conditions in different time intervals while the exact values are recorded in Table 4.3. Multiple one-sample t-tests with Bonferroni-Holm correction revealed some significant intra-condition differences in both nonadaptive and adaptive conditions. In the latter, an overall increasing trend was observed and it was found that the activation in 15–22.5 min was significantly larger than that in 7.5–15 min ($p = 0.0046$), suggesting that the participants were more engaged from 15 min onwards. In addition, the activation in adaptive condition did not show any sign of decreasing.

Meanwhile, in nonadaptive condition, statistical tests revealed multiple intra-condition significant differences in activation. It was evident that the participants' activation peaked in 15–22.5 min as its amplitude was significantly larger than both the activation in 0–7.5 min ($p < 0.0001$) and 7.5–15 min ($p < 0.\ 0001$). This interpretation was further supported as the activation in 22.5–30 min dropped significantly as compared to the activation in 15–22.5 min ($p = 0.0117$). However, albeit the significant drop, the activation in 22.5–30 min was still significantly higher in than that in 0–7.5 min ($p = 0.0061$) and 7.5–15 min ($p = 0.0146$). These significant differences across time intervals hint that the participants' DLPFC activation actually followed a quadratic trend, suggesting the need of a more detailed regression analysis for estimating the relationship between activation and time on task.

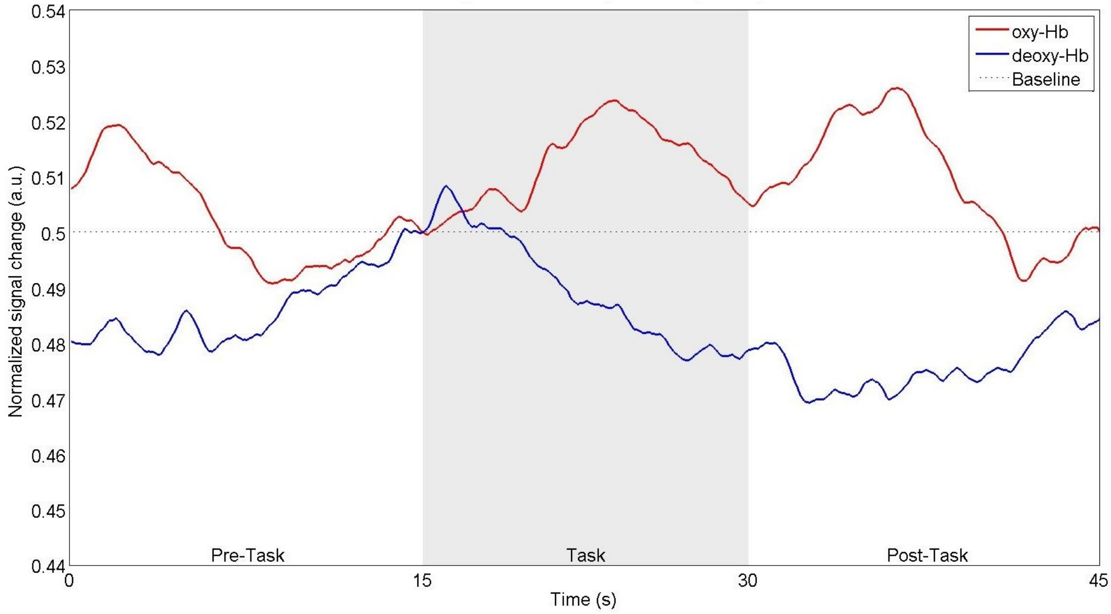


Figure 4.9: The overall normalized oxy- and deoxy-Hb signals for nonadaptive condition.

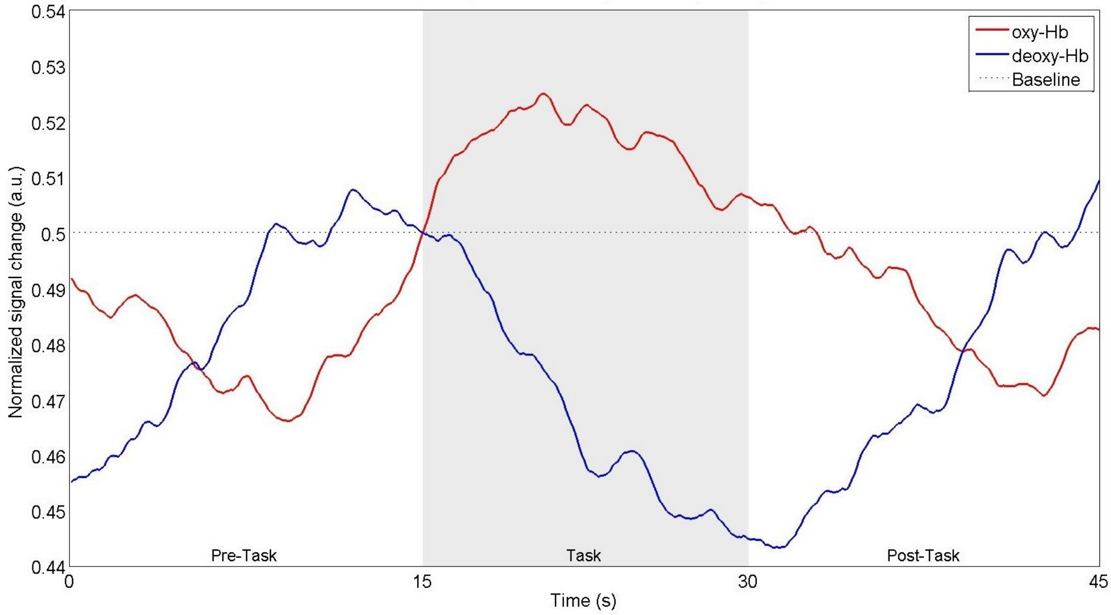


Figure 4.10: The overall normalized oxy- and deoxy-Hb signals for adaptive condition.

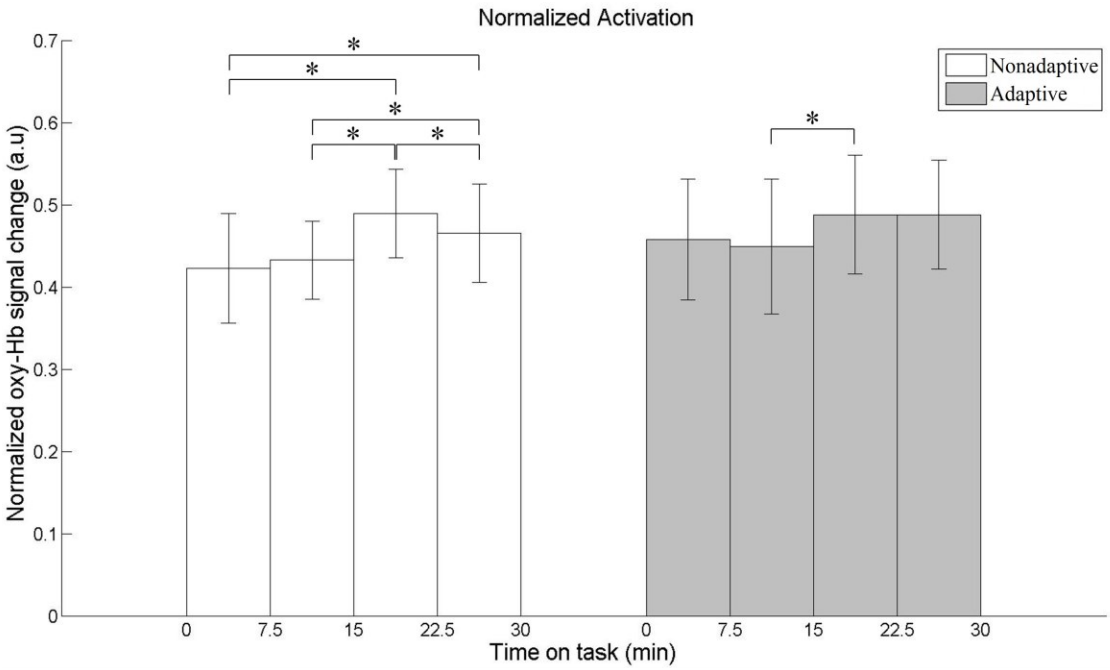


Figure 4.11: The participants' normalized activation in different time intervals. Statistical analysis was performed using one-sample t-test. *$p < 0.05$ with Bonferroni-Holm correction.

4.2.1.4.3 Quadratic Regression Analyses

Quadratic regression analyses were performed using the time on task as a continuous independent variable, resulting in Figure 4.12. It has been reported that evaluating the fit of nonlinear regressions using R-squared often leads to incorrect conclusions [200]. Instead, the standard error of the regression (S) was compared. The regression model of nonadaptive and adaptive conditions produced S of 1.4034 and 1.0901 respectively. S must be ≤ 2.5 to produce a sufficiently narrow 95% prediction interval. At a glance, both of the models were precise enough. Nonadaptive condition's regression model suggests that the participants' DLPFC activation actually followed an inverted U-shape curve (increased with time on task up to around 25 min then decreased). However, the same trend was not observed in adaptive condition.

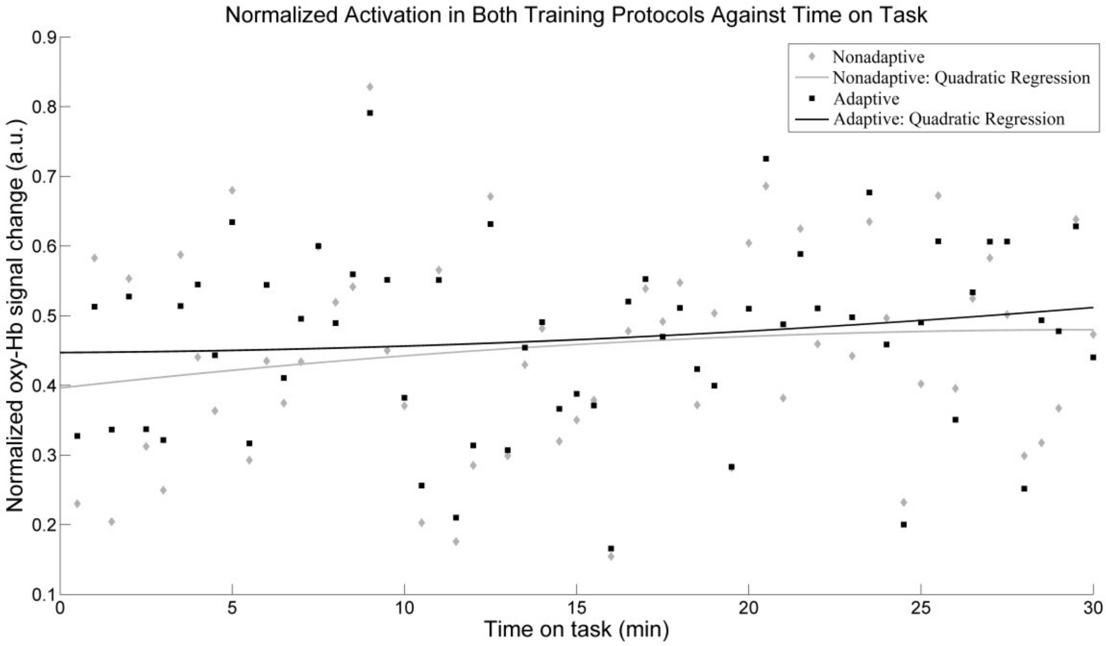


Figure 4.12: Change in normalized oxy-Hb level in both training conditions against time on task, along with their respective quadratic fit.

4.2.2 Discussion

Three possible explanations have been proposed for the above observations (inverted U-shape curve in the participants' activation observed in nonadaptive condition but not in adaptive condition).

4.2.2.1 Boredom

The first explanation was boredom, which is defined as an aversive emotional or psychological state experienced when an individual wants to, but is unable to engage in satisfying activity. The result was in agreement with previous studies, utilizing various neuroimaging modalities, which have demonstrated findings i.e. decrease in oxy-Hb concentration [201] and reduced α, β and γ power [202] in boredom condition. Apart from that, it is also claimed that users have problem in focusing on their task, learn less, are less productive, and more error-prone when they are in boredom state [25]. If so, this is a not a likely explanation for the observations as there was not any fall off in performance (in terms of response time and answer accuracy) albeit the drop in activation.

4.2.2.2 Training Effect

It is further proposed that the inverted U-shape curve can be explained using the training effect hypothesis. A recent study examined the effects of training on an n-back task over a period of 4 weeks. They observed initial increases in activation in task-specific areas followed by decreases in activation by the end of training [203]. They suggest that decreases in activation values are associated with the consolidation of performance gains after extensive practice and conclude that training-related changes in activation follow an inverse U-shaped quadratic function, with initial increases followed by later decreases. The same interpretation may apply to the data from another study [153], which, despite being characterized as demonstrating working memory practice-related increases in activation, are suggestive of a quadratic function with a relative reduction in activation in the last scanning session (5 weeks apart) compared to the penultimate one. In spite of that, both studies examined the training effects over weeks while the nonadaptive condition lasted only 30 minutes. Therefore, the results might not be due to the so-called training effects as it takes some time (much longer than 30 minutes) for such effects to take place.

4.2.2.3 Mental Overload

Last but not least, the inverted U-shaped curve observed might be related to mental overload. A linear relationship between task workload and hemodynamics has often been observed [82, 85] where the difficulty of the task at hand does not exceed the cognitive capacity of participant. When cognitive capacity is exceeded, the observed effects on hemodynamics conform to the shape reported by the Yerkes–Dodson law (see) [86]. The law dictates that human performance at any task varies with arousal in a predictable parabolic curve. The performance increases with physiological or mental arousal, but only up to a certain point. Exceeding that point i.e. when levels of arousal become too high, performance starts to follow a decreasing trend. According to Figure 2.8, the upward part of the inverted U can be thought of as the energizing effect of arousal. The downward part is caused by negative effects of arousal (or stress) on cognitive processes like attention, memory, and problem-solving.

On a supervisory control task a negative quadratic relationship (inverted U) between workload and DLPFC activation was observed [204]. It was also noted that there was a strong correlation between increased DLPFC activation in the highest workload condition and performance. This suggests that workload alone does not have a quadratic relationship with functional hemodynamics, but instead once there exists mental overload functional activation decreases. There are evidences from other studies to support the above claim i.e. prefrontal activation followed an inverted U-shaped curve (increases with load up to a certain workload or limit then decreases) [87-91].

In nonadaptive condition, the task was definitely more cognitively taxing and induced more frustration than adaptive condition since it yielded higher NASA-TLX scores especially in both mental demand and frustration subscales. Frustration triggered by problem-solving tasks like math is said to be one of the manifestations of mental overload. During sustained periods of a taxing cognitive workload, humans typically display time-on-task effects, in which mental overload increases while the performance maintains [205, 206]. Taken together these findings suggest that the presence of a negative quadratic slope during fNIRS monitoring of workload dynamics is indicative of mental overload. The results point more toward the last explanation as it was found that the participants not only exhibited negative quadratic activation coupled with sustained performance during nonadaptive condition but they also registered higher NASA-TLX scores especially in both mental demand and frustration subscales in nonadaptive condition.

4.2.3 Conclusion

In comparison to adaptive condition, it was found that nonadaptive condition yielded higher workload and higher level of frustration (as measured using NASA-TLX), implying that adaptive condition might be more cognitively taxing. During sustained periods of a taxing cognitive workload, humans typically display time-on-task effects, in which mental overload increases while the performance maintains [205, 206]. Quadratic regression showed that the participants' DLPFC activation followed an inverted U-shape curve (increased with time on task up to a limit then decreased) in nonadaptive condition, consistent to the claim that functional activation decreased once mental overload is reached. Several previous studies also reported similar observations [87-91]. Taken together these findings reveal that the presence of a negative quadratic slope during fNIRS monitoring of workload dynamics is indicative of mental overload. However, such negative quadratic slope was only evident in nonadaptive condition but not in adaptive condition, further suggesting that the incorporation of the fNIRS-DDA system in adaptive condition indeed aided the participants in avoiding mental overload. As a consequence of the combination of more cognitively taxing task difficulty level and time-on-task effect, the participants suffered mental overload approaching the end of nonadaptive condition (22.5–30 min).

Chapter 5

CONCLUSION

5.1 Conclusion

A fNIRS-DDA system was successfully designed and developed. It is actually a closed-loop feedback system, consisting of a multichannel fNIRS system OT-R40, a computer, a monitor, and a Serial Response Box. Brain activity in target region (DLPFC) is measured using OT-R40. Since oxy-Hb is more sensitive to task-associated changes, the measured oxy-Hb signals are then transferred to a computer for signal processing in order to extract relevant parameters. These parameters are compared in order to assess the mental workload and adjust the task difficulty accordingly. It is based on the theory that there is a linear relationship between workload and hemodynamics where the difficulty of the task at hand does not exceed the cognitive capacity, however, once there is cognitive overload or mental overload, functional hemodynamics starts to decrease, resulting in an invert U-shaped activation.

A total of two studies were conducted. The first study was a pilot test involving a mAD patient and a healthy older individual, which not only validated the theory behind the fNIRS-DDA system and region of interest (DLPFC) but also warranted a more detailed study on the functionality of the system – Study 2.

In the second study, the functionality of the fNIRS-DDA system was fully explored using 25 healthy university students. In comparison to adaptive condition, nonadaptive condition yielded higher workload and higher level of frustration (as measured using NASA-TLX), implying that nonadaptive condition might be more cognitively taxing. During sustained periods of a taxing cognitive workload, humans typically display time-on-task effects, in which mental overload increases while the performance maintains [205, 206]. Quadratic regression showed that the participants' DLPFC activation followed an inverted U-shape curve (increased with time on task up to a limit then decreased) in nonadaptive condition, consistent to the claim that functional activation decreased once mental overload is reached. Several previous studies also reported similar observations [87-91]. Taken together these findings reveal that the presence of a negative quadratic slope during fNIRS monitoring of workload dynamics is indicative of mental overload. However, such negative quadratic slope was only evident in nonadaptive condition but not in adaptive condition, further suggesting that the incorporation of the fNIRS-DDA system in adaptive condition indeed aided the participants in avoiding mental overload. As a consequence of the more cognitively taxing task difficulty level alongside time-on-task effect, the participants suffered mental overload approaching the end of nonadaptive condition (22.5–30 min).

Adaptive condition, where the fNIRS-DDA system was used, succeed in optimising the participants' engagement. In adaptive condition, the participants were allowed to train at their optimal level of difficulty and workload to maximize their gains. In conclusion, the fNIRS-DDA system succeed in helping the participants to avoid mental overload, which can possibly reduce or even eliminate the gains of cognitive training [8]. The same training regimen coupled with the fNIRS-DDA system will be applied in an upcoming study to preserve working memory in mAD patients in order to slow down the progression of dementia.

5.2 Research Contributions

This MSc research achieved the objectives delineated in section 1.4. The most significant research contribution of this research is the development of the fNIRS-DDA system, utilizing the relatively new neuroimaging modality and a novel algorithm. Apart from being helpful in imposing sufficient amount of effective cognitive load and preventing mental overload, the system has the flexibility to be used together with any task or regimen no matter in cognitive training or cognitive rehabilitation. Such flexibility coupled with the advantages of fNIRS make the system suitable and useful for clinical applications and interventions.

5.3 Limitation

Due to the time constraints as well as resource constraints, the participants involved in Study 2 were only local university students instead of the target audience – the mAD patients, who are not readily and widely available. The patients are usually recruited through a local dementia day-care centre and from the local community. It took a long time not only to screen and recruit the patients but also to transport the entire technology to the nearest city, where both subject recruitment and data collection are more convenient to perform. In the end, Study 2 involved only local university students considering current study was mainly to test the functionality and robustness of the fNIRS-DDA system developed.

Another limitation is that individual difference in math abilities was neglected in current study. Different individuals possess different math abilities. It is worth noting that math skills also affect mental arithmetic strategies [207] and that the level of one's computational estimation strategy increases as one's numeracy skills develop [208]. In current study, the potential effects of differences in numeracy skills were excluded. Last but not least, to substantiate the findings, a larger sample size might help ensure that participants of inadequate math abilities can be excluded and that participants with different math abilities can be assessed separately.

5.4 Future Work and Recommendations

Even though fNIRS is more resistant to artifacts [92], a change in the superficial signals (from the scalp) may thus affect the NIRS signals significantly [209, 210]. The multi-distance real-time scalp signal separating (RT-SSS) algorithm is one of the very few methods to compensate the effect in real time [211]. It will be useful to incorporate the algorithm into the fNIRS-DDA system in order to obtain more accurate and reliable signals from the cerebral cortex.

In this research, the fNIRS-DDA was bundled with mental arithmetic problem solving as the cognitive task. In reality, the system has the flexibility and potential to be used together with any task or regimen no matter in cognitive training or cognitive rehabilitation, not only to personalize the training regimen but also to maximize the gains.

The combination of the fNIRS-DDA system and cognitive rehabilitation (mental arithmetic as the cognitive task) has the potential as an alternative treatment for Alzheimer's disease. An upcoming research, currently in the planning stage, will focus on using the combination to slow down the progression of dementia in Alzheimer's disease patients by preserving their working memory.

REFERENCES

[1] S. C. Cramer, M. Sur, B. H. Dobkin, C. O'Brien, T. D. Sanger, J. Q. Trojanowski*, et al.*, "Harnessing neuroplasticity for clinical applications," *Brain,* vol. 134, pp. 1591-609, 2011.

[2] A. Bahar-Fuchs, L. Clare, and B. Woods, "Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review," *Alzheimer's Research & Therapy,* vol. 5, pp. 35-35, 2013.

[3] J. Choi and E. W. Twamley, "Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy," *Neuropsychol Rev,* vol. 23, pp. 48-62, 2013.

[4] S. Kim, "Cognitive rehabilitation for elderly people with early-stage Alzheimer's disease," *Journal of Physical Therapy Science,* vol. 27, pp. 543-546, 2015.

[5] R. C. Clark, *Building Expertise: Cognitive Methods for Training and Performance Improvement*: Wiley, 2008.

[6] P. Hamilton, G. Hockey, and M. Rejman, "The place of the concept of activation in human information processing theory: An integrative approach," *Attention and performance,* vol. 6, pp. 463-486, 1977.

[7] C. L. Baldwin and B. N. Penaranda, "Adaptive training using an artificial neural network and EEG metrics for within- and cross-task workload classification," *Neuroimage,* vol. 59, pp. 48-56, 2012.

[8] F. Taya, Y. Sun, F. Babiloni, N. Thakor, and A. Bezerianos, "Brain enhancement through cognitive training: a new insight from brain connectome," *Frontiers in Systems Neuroscience,* vol. 9, p. 44, 2015.

[9] R. Mayer and P. Chandler, *When Learning Is Just a Click Away: Does Simple User Interaction Foster Deeper Understanding of Multimedia Messages?* vol. 93, 2001.

[10] R. Parasuraman, M. Mouloua, and R. Molloy, "Effects of adaptive task allocation on monitoring of automated systems," *Hum Factors,* vol. 38, pp. 665-79, 1996.

[11] S. H. Fairclough, L. Venables, and A. Tattersall, "The influence of task demand and learning on the psychophysiological response," *International Journal of Psychophysiology,* vol. 56, pp. 171-184, 2005.

[12] A. Gevins, M. E. Smith, L. McEvoy, and D. Yu, "High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice," *Cereb Cortex,* vol. 7, pp. 374-85, 1997.

[13] A. Gevins and M. E. Smith, "Neurophysiological measures of cognitive workload during human-computer interaction," *Theoretical Issues in Ergonomics Science,* vol. 4, pp. 113-131, 2003.

[14] V. Duffy, *Stress, workload, and fatigue, Eds. Peter A. Hancock and Paula A. Desmond, Lawrence Erlbaum Associates, Publishers, Mahwah, NJ, 2001, 682 pp., Hardcover: ISBN 0-8058-3178-9, $75* vol. 11, 2001.

[15] M. Scerbo, F. G. Freeman, and P. Mikulka, *A brain-based system for adaptive automation* vol. 4, 2003.

[16] G. F. Wilson and C. A. Russell, "Operator functional state classification using multiple psychophysiological features in an air traffic control task," *Hum Factors,* vol. 45, pp. 381-9, 2003.

[17] P. A. Hancock and R. Parasuraman, "Human factors and safety in the design of intelligent vehicle-highway systems (IVHS)," *Journal of Safety Research,* vol. 23, pp. 181-198, 1992.

[18] P. A. Hancock and W. B. Verwey, "Fatigue, workload and adaptive driver systems," *Accident Analysis & Prevention,* vol. 29, pp. 495-506, 1997/07/01/ 1997.

[19] N. Meshkati, P. Hancock, M. Rahimi, and S. M. Dawes, *Techniques in mental workload assessment*, 1995.

[20] R. Parasuraman, J. Christensen, and S. Grafton, *Neuroergonomics: The brain in action and at work* vol. 59, 2011.

[21] R. Parasuraman and G. F. Wilson, "Putting the brain to work: neuroergonomics past, present, and future," *Hum Factors,* vol. 50, pp. 468-74, 2008.

[22] J. B. Brookings, G. F. Wilson, and C. R. Swain, "Psychophysiological responses to changes in workload during simulated air traffic control," *Biol Psychol,* vol. 42, pp. 361-77, 1996.

[23] A. Gevins, M. E. Smith, H. Leong, L. McEvoy, S. Whitfield, R. Du*, et al.*, "Monitoring working memory load during computer-based tasks with EEG pattern recognition methods," *Hum Factors,* vol. 40, pp. 79-91, 1998.

[24] M. Lewandowska, E. Piatkowska-Janko, P. Bogorodzki, T. Wolak, and E. Szelag, *Changes in fMRI BOLD response to increasing and decreasing task difficulty during auditory perception of temporal order* vol. 94, 2010.

[25] R. Pekrun, T. Goetz, L. M. Daniels, R. H. Stupnisky, and R. P. Perry, "Boredom in achievement settings: Exploring control-value antecedents and performance outcomes of a neglected emotion," *Contemporary educational psychology,* vol. 36, pp. 36-48, 2011.

[26] M. S. Young and N. A. Stanton, "It's all relative: defining mental workload in the light of Annett's paper," *Ergonomics,* vol. 45, pp. 1018-20; discussion 1042-6, 2002.

[27] A. N. Clarkson, B. S. Huang, S. E. Macisaac, I. Mody, and S. T. Carmichael, "Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke," *Nature,* vol. 468, pp. 305-9, 2010.

[28] S. Li, J. J. Overman, D. Katsman, S. V. Kozlov, C. J. Donnelly, J. L. Twiss*, et al.*, "An age-related sprouting transcriptome provides molecular control of axonal sprouting after stroke," *Nat Neurosci,* vol. 13, pp. 1496-504, 2010.

[29] M. A. Dimyan and L. G. Cohen, "Contribution of transcranial magnetic stimulation to the understanding of mechanisms of functional recovery after stroke," *Neurorehabilitation and neural repair,* vol. 24, pp. 125-135, 2010.

[30] E. L. Bennett, M. C. Diamond, D. Krech, and M. R. Rosenzweig, "Chemical and Anatomical Plasticity of Brain," *Changes in brain through experience, demanded by learning theories, are found in experiments with rats,* vol. 146, pp. 610-619, 1964.

[31] P. Rakic, "Neurogenesis in adult primate neocortex: an evaluation of the evidence," *Nature Reviews Neuroscience,* vol. 3, p. 65, 2002.

[32] J. W. Elias and M. V. Wagster, "Developing context and background underlying cognitive intervention/training studies in older populations," *J Gerontol B Psychol Sci Soc Sci,* vol. 62 Spec No 1, pp. 5-10, 2007.

[33] E. A. Maguire, D. G. Gadian, I. S. Johnsrude, C. D. Good, J. Ashburner, R. S. Frackowiak*, et al.*, "Navigation-related structural change in the hippocampi of taxi drivers," *Proc Natl Acad Sci U S A,* vol. 97, pp. 4398-403, 2000.

[34] R. J. Zatorre, R. D. Fields, and H. Johansen-Berg, "Plasticity in gray and white: neuroimaging changes in brain structure during learning," *Nature Neuroscience,* vol. 15, p. 528, 2012.

[35] E. Taub, G. Uswatte, and T. Elbert, "New treatments in neurorehabilitation founded on basic research," *Nat Rev Neurosci,* vol. 3, pp. 228-36, 2002.

[36] B. Cheeran, L. Cohen, B. Dobkin, G. Ford, R. Greenwood, D. Howard, *et al.*, "The future of restorative neurosciences in stroke: driving the translational research pipeline from basic science to rehabilitation of people after stroke," *Neurorehabil Neural Repair,* vol. 23, pp. 97-107, 2009.

[37] A. Baddeley, "Exploring the Central Executive," *The Quarterly Journal of Experimental Psychology Section A,* vol. 49, pp. 5-28, 1996.

[38] A. Baddeley, "The episodic buffer: a new component of working memory?," *Trends Cogn Sci,* vol. 4, pp. 417-423, 2000.

[39] A. Baddeley, S. Gathercole, and C. Papagno, "The phonological loop as a language learning device," *Psychol Rev,* vol. 105, pp. 158-73, 1998.

[40] D. Norman and T. Shallice, "Attention to Action," in *Consciousness and Self-Regulation*, R. Davidson, G. Schwartz, and D. Shapiro, Eds., ed: Springer US, 1986, pp. 1-18.

[41] R. E. Mayer and R. Moreno, "Nine Ways to Reduce Cognitive Load in Multimedia Learning," *Educational Psychologist,* vol. 38, pp. 43-52, 2003.

[42] K. Jegers, "Pervasive game flow: understanding player enjoyment in pervasive gaming," *Computers in Entertainment (CIE),* vol. 5, p. 9, 2007.

[43] H. Qin, P.-L. P. Rau, and G. Salvendy, "Effects of different scenarios of game difficulty on player immersion," *Interacting with Computers,* vol. 22, pp. 230-239, 2009.

[44] B. B. Bederson, "Interfaces for staying in the flow," *Ubiquity,* vol. 2004, pp. 1-1, 2004.

[45] G. W. C. P. Fred and J. G. V. M. Jeroen, "The Efficiency of Instructional Conditions: An Approach to Combine Mental Effort and Performance Measures," *Human Factors,* vol. 35, pp. 737-743, 1993.

[46] T. Megaw, *The definition and measurement of mental workload*, 2005.

[47] M. D. Lee, "Multichannel auditory search: toward understanding control processes in polychotic auditory listening," *Hum Factors,* vol. 43, pp. 328-42, 2001.

[48] E. J. Sirevaag, A. F. Kramer, C. D. Wickens, M. Reisweber, D. L. Strayer, and J. F. Grenell, "Assessment of pilot performance and mental workload in rotary wing aircraft," *Ergonomics,* vol. 36, pp. 1121-40, 1993.

[49] C. D. Wickens, "An introduction to human factors engineering," 1998.

[50] H. A. Colle and G. B. Reid, "Double trade-off curves with different cognitive processing combinations: testing the cancellation axiom of mental workload measurement theory," *Hum Factors,* vol. 41, pp. 35-50, 1999.

[51] D. De Waard, *The measurement of drivers' mental workload*, 1996.

[52] T. C. Hankins and G. F. Wilson, "A comparison of heart rate, eye activity, EEG and subjective measures of pilot mental workload during flight," *Aviat Space Environ Med,* vol. 69, pp. 360-7, Apr 1998.

[53] S.-L. Hwang, Y.-J. Yau, Y.-T. Lin, J.-H. Chen, T.-H. Huang, T.-C. Yenn*, et al.*, "Predicting work performance in nuclear power plants," *Safety Science,* vol. 46, pp. 1115-1124, 2008.

[54] J. A. Veltman and A. W. Gaillard, "Physiological indices of workload in a simulated flight task," *Biol Psychol,* vol. 42, pp. 323-42, 1996.

[55] A. L. Hansen, B. H. Johnsen, and J. F. Thayer, "Vagal influence on working memory and attention," *Int J Psychophysiol,* vol. 48, pp. 263-74, 2003.

[56] T. K. Fredericks, S. D. Choi, J. Hart, S. E. Butt, and A. Mital, "An investigation of myocardial aerobic capacity as a measure of both physical and cognitive workloads," *International Journal of Industrial Ergonomics,* vol. 35, pp. 1097-1107, 2005.

[57] L. R. Fournier, G. F. Wilson, and C. R. Swain, "Electrophysiological, behavioral, and subjective indexes of workload when performing multiple

tasks: manipulations of task difficulty and training," *Int J Psychophysiol,* vol. 31, pp. 129-45, 1999.

[58] A. Gevins, H. Leong, R. Du, M. E. Smith, J. Le, D. DuRousseau*, et al.*, "Towards measurement of brain function in operational environments," *Biological Psychology,* vol. 40, pp. 169-186, 1995.

[59] B. Crosson, A. Ford, K. M. McGregor, M. Meinzer, S. Cheshkov, X. Li*, et al.*, "Functional Imaging and Related Techniques: An Introduction for Rehabilitation Researchers," *Journal of rehabilitation research and development,* vol. 47, pp. vii-xxxiv, 2010.

[60] N. Weiskopf, R. Sitaram, O. Josephs, R. Veit, F. Scharnowski, R. Goebel*, et al.*, "Real-time functional magnetic resonance imaging: methods and applications," *Magn Reson Imaging,* vol. 25, pp. 989-1003, 2007.

[61] M. A. Just, P. A. Carpenter, and A. Miyake, "Neuroindices of cognitive workload: Neuroimaging, pupillometric and event-related potential studies of brain work," *Theoretical Issues in Ergonomics Science,* vol. 4, pp. 56-88, 2003.

[62] C. S. Roy and C. S. Sherrington, "On the Regulation of the Blood-supply of the Brain," *The Journal of Physiology,* vol. 11, pp. 85-158.17, 1890.

[63] M. A. Just, P. A. Carpenter, T. A. Keller, W. F. Eddy, and K. R. Thulborn, "Brain activation modulated by sentence comprehension," *Science,* vol. 274, pp. 114-6, 1996.

[64] J. M. Jansma, N. F. Ramsey, R. Coppola, and R. S. Kahn, "Specific versus nonspecific brain activity in a parametric N-back task," *Neuroimage,* vol. 12, pp. 688-97, 2000.

[65] D. J. Veltman, S. A. Rombouts, and R. J. Dolan, "Maintenance versus manipulation in verbal working memory revisited: an fMRI study," *Neuroimage,* vol. 18, pp. 247-56, 2003.

[66] A. J. Szameitat, S. Shen, and A. Sterr, "The functional magnetic resonance imaging (fMRI) procedure as experienced by healthy participants and stroke patients--a pilot study," *BMC Med Imaging,* vol. 9, p. 14, 2009.

[67] J. A. Malmivuo and V. E. Suihko, "Effect of skull resistivity on the spatial resolutions of EEG and MEG," *IEEE Trans Biomed Eng,* vol. 51, pp. 1276-80, 2004.

[68] R. M. Sabbatini, "The history of the electroencephalogram," 1997.

[69] K. Nathan and J. L. Contreras-Vidal, "Negligible Motion Artifacts in Scalp Electroencephalography (EEG) During Treadmill Walking," *Frontiers in Human Neuroscience,* vol. 9, p. 708, 2015.

[70] R. Srinivasan and "Methods to Improve the Spatial Resolution of EEG," *International Journal of Bioelectromagnetism,* vol. 1, pp. 102-111, 1999.

[71] F. F. Jobsis, "Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters," *Science,* vol. 198, pp. 1264-7, 1977.

[72] H. Sato, M. Kiguchi, A. Maki, Y. Fuchino, A. Obata, T. Yoro*, et al.*, "Within-subject reproducibility of near-infrared spectroscopy signals in sensorimotor activation after 6 months," *J Biomed Opt,* vol. 11, p. 014021, 2006.

[73] S. Heinzel, F. B. Haeussinger, T. Hahn, A. C. Ehlis, M. M. Plichta, and A. J. Fallgatter, "Variability of (functional) hemodynamics as measured with simultaneous fNIRS and fMRI during intertemporal choice," *Neuroimage,* vol. 71, pp. 125-34, 2013.

[74] A. Kleinschmidt, H. Obrig, M. Requardt, K.-D. Merboldt, U. Dirnagl, A. Villringer*, et al.*, "Simultaneous Recording of Cerebral Blood Oxygenation Changes during Human Brain Activation by Magnetic Resonance Imaging and Near-Infrared Spectroscopy," *Journal of Cerebral Blood Flow & Metabolism,* vol. 16, pp. 817-826, 1996.

[75] A. Villringer, J. Planck, C. Hock, L. Schleinkofer, and U. Dirnagl, "Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults," *Neurosci Lett,* vol. 154, pp. 101-4, 1993.

[76] Y. Hoshi and M. Tamura, "Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in man," *Neurosci Lett,* vol. 150, pp. 5-8, 1993.

[77] M. Schecklmann, A. C. Ehlis, M. M. Plichta, and A. J. Fallgatter, "Influence of muscle activity on brain oxygenation during verbal fluency assessed with functional near-infrared spectroscopy," *Neuroscience,* vol. 171, pp. 434-442, 2010.

[78] K. H. Yap, W. C. Ung, E. G. M. Ebenezer, N. Nordin, P. S. Chin, S. Sugathan*, et al.*, "Visualizing Hyperactivation in Neurodegeneration Based on Prefrontal Oxygenation: A Comparative Study of Mild Alzheimer's Disease, Mild Cognitive Impairment, and Healthy Controls," *Frontiers in Aging Neuroscience,* vol. 9, 2017.

[79] A. M. Marx, A. C. Ehlis, A. Furdea, M. Holtmann, T. Banaschewski, D. Brandeis*, et al.*, "Near-infrared spectroscopy (NIRS) neurofeedback as a treatment for children with attention deficit hyperactivity disorder (ADHD)-a pilot study," *Front Hum Neurosci,* vol. 8, p. 1038, 2014.

[80] K. Mayer, S. N. Wyckoff, A. J. Fallgatter, A.-C. Ehlis, and U. Strehl, "Neurofeedback as a nonpharmacological treatment for adults with attention-deficit/hyperactivity disorder (ADHD): study protocol for a randomized controlled trial," *Trials,* vol. 16, pp. 1-14, 2015.

[81] G. Aranyi, M. Cavazza, and F. Charles, "Using fNIRS for Prefrontal-Asymmetry Neurofeedback: Methods and Challenges," in *Symbiotic Interaction: 4th International Workshop, Symbiotic 2015, Berlin, Germany, October 7–8, 2015, Proceedings*, B. Blankertz, G. Jacucci, L. Gamberini, A.

Spagnolli, and J. Freeman, Eds., ed Cham: Springer International Publishing, 2015, pp. 7-20.

[82] H. Ayaz, P. A. Shewokis, S. Bunce, K. Izzetoglu, B. Willems, and B. Onaral, "Optical brain monitoring for operator training and mental workload assessment," *Neuroimage,* vol. 59, pp. 36-47, 2012.

[83] E. T. Solovey, F. Lalooses, K. Chauncey, D. Weaver, M. Parasi, M. Scheutz*, et al.*, "Sensing cognitive multitasking for a brain-based adaptive user interface," in *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*, 2011, pp. 383-392.

[84] E. M. M. Peck, B. F. Yuksel, A. Ottley, R. J. Jacob, and R. Chang, "Using fNIRS brain sensing to evaluate information visualization interfaces," in *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*, 2013, pp. 473-482.

[85] F. A. Fishburn, M. E. Norr, A. V. Medvedev, and C. J. Vaidya, "Sensitivity of fNIRS to cognitive state and load," *Front Hum Neurosci,* vol. 8, p. 76, 2014.

[86] R. M. Yerkes and J. D. Dodson, "The relation of strength of stimulus to rapidity of habit-formation," *Journal of Comparative Neurology and Psychology,* vol. 18, pp. 459-482, 1908.

[87] Y. Yamauchi, S. Kikuchi, F. Miwakeichi, K. Matsumoto, M. Nishida, M. Ishiguro*, et al.*, "Relation between parametric change of the workload and prefrontal cortex activity during a modified version of the 'rock, paper, scissors' task," *Neuropsychobiology,* vol. 68, pp. 24-33, 2013.

[88] R. McKendrick, H. Ayaz, R. Olmstead, and R. Parasuraman, "Enhancing dual-task performance with verbal and spatial working memory training: continuous monitoring of cerebral hemodynamics with NIRS," *Neuroimage,* vol. 85 Pt 3, pp. 1014-26, 2014.

[89] J. H. Callicott, V. S. Mattay, A. Bertolino, K. Finn, R. Coppola, J. A. Frank*, et al.*, "Physiological characteristics of capacity constraints in working memory as revealed by functional MRI," *Cereb Cortex,* vol. 9, pp. 20-6, 1999.

[90] L. Nyberg, E. Dahlin, A. Stigsdotter Neely, and L. Backman, "Neural correlates of variable working memory load across adult age and skill: dissociative patterns within the fronto-parietal network," *Scand J Psychol,* vol. 50, pp. 41-6, 2009.

[91] N. J. Schneider-Garces, B. A. Gordon, C. R. Brumback-Peltz, E. Shin, Y. Lee, B. P. Sutton*, et al.*, "Span, CRUNCH, and beyond: working memory capacity and the aging brain," *J Cogn Neurosci,* vol. 22, pp. 655-69, Apr 2010.

[92] E. T. Solovey, A. Girouard, K. Chauncey, L. M. Hirshfield, A. Sassaroli, F. Zheng*, et al.*, "Using fNIRS brain sensing in realistic HCI settings: experiments and guidelines," in *Proceedings of the 22nd annual ACM symposium on User interface software and technology*, 2009, pp. 157-166.

[93] R. T. Thibault, M. Lifshitz, and A. Raz, "The self-regulating brain and neurofeedback: Experimental science and clinical promise," *Cortex,* vol. 74, pp. 247-61, 2016.

[94] G. B. Reid and T. E. Nygren, "The Subjective Workload Assessment Technique: A Scaling Procedure for Measuring Mental Workload," in *Advances in Psychology*. vol. 52, P. A. Hancock and N. Meshkati, Eds., ed: North-Holland, 1988, pp. 185-218.

[95] P. B. Stephen, "Assessing the Validity of SWAT as a Workload Measurement Instrument," *Proceedings of the Human Factors Society Annual Meeting,* vol. 27, pp. 124-128, 1983.

[96] G. H. Susan, P. I. Helene, C. B. James, Alvah C. Bittner, Jr., L. Z. Allen, and E. C. Richard, "Comparison of Four Subjective Workload Rating Scales," *Human Factors,* vol. 34, pp. 429-439, 1992.

[97] A. Luximon and R. S. Goonetilleke, "Simplified subjective workload assessment technique," *Ergonomics,* vol. 44, pp. 229-243, 2001.

[98] P. C. PARK, "Comparison of subjective mental workload assessment techniques for the evaluation of in-vehicle navigation systems usability," in *TOWARDS THE NEW HORIZON TOGETHER. PROCEEDINGS OF THE 5TH WORLD CONGRESS ON INTELLIGENT TRANSPORT SYSTEMS, HELD 12-16 OCTOBER 1998, SEOUL, KOREA. PAPER NO. 4006*, 1998.

[99] S. G. Hart, "NASA Task load Index (TLX). Volume 1.0; Paper and pencil package," 1986.

[100] S. G. Hart and L. E. Staveland, "Development of NASA-TLX (Task Load Index): Results of Empirical and Theoretical Research," *Advances in Psychology,* vol. 52, pp. 139-183, 1988.

[101] A. Cao, K. K. Chintamani, A. K. Pandya, and R. D. Ellis, "NASA TLX: Software for assessing subjective mental workload," *Behavior research methods,* vol. 41, pp. 113-117, 2009.

[102] S. H. Fairclough, K. Gilleade, K. C. Ewing, and J. Roberts, "Capturing user engagement via psychophysiology: measures and mechanisms for biocybernetic adaptation," *International Journal of Autonomous and Adaptive Communications Systems,* vol. 6, pp. 63-79, 2013.

[103] P. Rani, N. Sarkar, and C. Liu, "Maintaining optimal challenge in computer games through real-time physiological feedback," presented at the 11th International Conference on Human Computer Interaction with Mobile Devices and Services, 2017.

[104] R. Mat and H. M. Taha, "Socio-economic characteristics of the elderly in Malaysia," in *21st Population Census Conference*, Kyoto, Japan, 2003.

[105] F. Barkhof, N. C. Fox, A. J. Bastos-Leite, and P. Scheltens, *Neuroimaging in Dementia*: Springer-Verlag Berlin Heidelberg, 2011.

[106] Alzheimer's Disease International. (16 June). *Dementia statistics*. Available: http://www.alz.co.uk/research/statistics

[107] A. Lobo, L. J. Launer, L. Fratiglioni, K. Andersen, A. Di Carlo, M. M. Breteler*, et al.*, "Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group," *Neurology,* vol. 54, pp. S4-9, 2000.

[108] W. H. Organization. (2016, 10 March). *Dementia Fact Sheet*. Available: http://www.who.int/mediacentre/factsheets/fs362/en/

[109] M. Boustani, B. Peterson, L. Hanson, R. Harris, and K. N. Lohr, "Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force," *Ann Intern Med,* vol. 138, pp. 927-37, 2003.

[110] Alzheimer's Association. *Types of Dementia*. Available: http://www.alz.org/dementia/types-of-dementia.asp

[111] A. Burns and S. Iliffe, "Dementia," *BMJ,* vol. 338, p. b75, 2009.

[112] K. Alkadhi and J. Eriksen, "The Complex and Multifactorial Nature of Alzheimer's Disease," *Current Neuropharmacology,* vol. 9, pp. 586-586, 2011.

[113] A. Alzheimer's, "2015 Alzheimer's disease facts and figures," *Alzheimers Dement,* vol. 11, pp. 332-84, 2015.

[114] J. Lindsay, D. Laurin, R. Verreault, R. Hebert, B. Helliwell, G. B. Hill*, et al.*, "Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging," *Am J Epidemiol,* vol. 156, pp. 445-53, 2002.

[115] B. Duthey, "Background paper 6.11: Alzheimer disease and other dementias," *A Public Health Approach to Innovation,* pp. 1-74, 2013.

[116] L. E. Hebert, J. Weuve, P. A. Scherr, and D. A. Evans, "Alzheimer disease in the United States (2010-2050) estimated using the 2010 census," *Neurology,* vol. 80, pp. 1778-83, 2013.

[117] H. Braak and K. Del Tredici, "Where, when, and in what form does sporadic Alzheimer's disease begin?," *Curr Opin Neurol,* vol. 25, pp. 708-14, 2012.

[118] L. A. Farrer, "Genetics and the dementia patient," *The Neurologist,* vol. 3, pp. 13-30, 1997.

[119] Y. Stern, "Cognitive reserve in ageing and Alzheimer's disease," *Lancet Neurol,* vol. 11, pp. 1006-12, 2012.

[120] C. M. Roe, C. Xiong, J. P. Miller, and J. C. Morris, "Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis," *Neurology,* vol. 68, pp. 223-8, 2007.

[121] J. T. Coyle "Use It or Lose It — Do Effortful Mental Activities Protect against Dementia?," *New England Journal of Medicine,* vol. 348, pp. 2489-2490, 2003.

[122] T. Ngandu, E. von Strauss, E. L. Helkala, B. Winblad, A. Nissinen, J. Tuomilehto*, et al.*, "Education and dementia: what lies behind the association?," *Neurology,* vol. 69, pp. 1442-50, 2007.

[123] I. McDowell, G. Xi, J. Lindsay, and M. Tierney, "Mapping the connections between education and dementia," *J Clin Exp Neuropsychol,* vol. 29, pp. 127-41, 2007.

[124] S. Seshadri, A. Beiser, M. Kelly-Hayes, C. S. Kase, R. Au, W. B. Kannel*, et al.*, "The lifetime risk of stroke: estimates from the Framingham Study," *Stroke,* vol. 37, pp. 345-50, 2006.

[125] G. Chene, A. Beiser, R. Au, S. R. Preis, P. A. Wolf, C. Dufouil*, et al.*, "Gender and incidence of dementia in the Framingham Heart Study from mid-adult life," *Alzheimers Dement,* vol. 11, pp. 310-20, 2015.

[126] M. Crowe, R. Andel, N. L. Pedersen, B. Johansson, and M. Gatz, "Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins," *J Gerontol B Psychol Sci Soc Sci,* vol. 58, pp. P249-55, 2003.

[127] G. Grande, N. Vanacore, L. Maggiore, V. Cucumo, R. Ghiretti, D. Galimberti*, et al.*, "Physical activity reduces the risk of dementia in mild cognitive impairment subjects: a cohort study," *J Alzheimers Dis,* vol. 39, pp. 833-9, 2014.

[128] J. C. Smith, K. A. Nielson, J. L. Woodard, M. Seidenberg, S. Durgerian, K. E. Hazlett*, et al.*, "Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease," *Frontiers in Aging Neuroscience,* vol. 6, p. 61, 2014.

[129] G. M. McKhann, D. S. Knopman, H. Chertkow, B. T. Hyman, C. R. Jack, Jr., C. H. Kawas*, et al.*, "The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimers Dement,* vol. 7, pp. 263-9, 2011.

[130] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician," *J Psychiatr Res,* vol. 12, pp. 189-98, 1975.

[131] J. C. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology,* vol. 43, pp. 2412-4, 1993.

[132] T. N. Tombaugh and N. J. McIntyre, "The mini-mental state examination: a comprehensive review," *J Am Geriatr Soc,* vol. 40, pp. 922-35, 1992.

[133] J. E. Galvin, T. M. Meuser, M. A. Coats, D. A. Bakal, and J. C. Morris, "The "portable" CDR: translating the clinical dementia rating interview into a PDA format," *Alzheimer Dis Assoc Disord,* vol. 23, pp. 44-9, Jan-Mar 2009.

[134] A. Burns and S. Iliffe, "Alzheimer's disease," *Bmj,* vol. 338, p. b158, 2009.

[135] S. Karantzoulis and J. E. Galvin, "Distinguishing Alzheimer's disease from other major forms of dementia," *Expert Rev Neurother,* vol. 11, pp. 1579-91, 2011.

[136] S. W. Anderson and D. Tranel, "Neuropsychological consequences of dysfunction in human dorsolateral prefrontal cortex," *Handbook of neuropsychology,* vol. 7, pp. 145-156, 2002.

[137] N. Cowan, "What are the differences between long-term, short-term, and working memory?," *Progress in brain research,* vol. 169, pp. 323-338, 2008.

[138] K. Oberauer, "Access to information in working memory: exploring the focus of attention," *J Exp Psychol Learn Mem Cogn,* vol. 28, pp. 411-21, 2002.

[139] N. Cowan, *Attention and memory: An integrated framework.* . New York: Oxford University Press, 1995.

[140] H. Spinnler, S. D. Sala, R. Bandera, and A. Baddeley, "Dementia, ageing, and the structure of human memory," *Cognitive Neuropsychology,* vol. 5, pp. 193-211, 1988.

[141] S. E. Gathercole and T. P. Alloway, *Working Memory and Learning: A Practical Guide for Teachers*: SAGE, 2008.

[142] V. Parlato, O. L. Lopez, M. Panisset, A. Iavarone, J. Grafman, and F. Boller, "Mental calculation in mild Alzheimer's disease: A pilot study," *International Journal of Geriatric Psychiatry,* vol. 7, pp. 599-602, 1992.

[143] J. E. McNeil and P. W. Burgess, "The Selective Impairment of Arithmetical Procedures," *Cortex,* vol. 38, pp. 569-587, 2002.

[144] A. Marterer, W. Danielczyk, M. Simanyi, and P. Fischer, "Calculation abilities in dementia of Alzheimer's type and in vascular dementia," *Archives of Gerontology and Geriatrics,* vol. 23, pp. 189-197, 1996.

[145] L. Cragg and C. Gilmore, "Skills underlying mathematics: The role of executive function in the development of mathematics proficiency," *Trends in Neuroscience and Education,* vol. 3, pp. 63-68, 2014.

[146] D. H. Salat, J. A. Kaye, and J. S. Janowsky, "Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease," *Arch Neurol,* vol. 58, pp. 1403-8, 2001.

[147] M. Hornberger, B. Yew, S. Gilardoni, E. Mioshi, E. Gleichgerrcht, F. Manes*, et al.*, "Ventromedial-frontopolar prefrontal cortex atrophy correlates with insight loss in frontotemporal dementia and Alzheimer's disease," *Hum Brain Mapp,* vol. 35, pp. 616-26, Feb 2014.

[148] A. Bakkour, J. C. Morris, D. A. Wolk, and B. C. Dickerson, "The effects of aging and Alzheimer's disease on cerebral cortical anatomy: specificity and differential relationships with cognition," *Neuroimage,* vol. 76, pp. 332-344, 2013.

[149] A. Baddeley, "Working memory," *Science,* vol. 255, pp. 556-559, 1992.

[150] A. Baddeley and B. Wilson, "Frontal amnesia and the dysexecutive syndrome," *Brain Cogn,* vol. 7, pp. 212-30, 1988.

[151] M. B. Imran, R. Kawashima, S. Awata, K. Sato, S. Kinomura, S. Ono*, et al.*, "Parametric mapping of cerebral blood flow deficits in Alzheimer's disease: a SPECT study using HMPAO and image standardization technique," *J Nucl Med,* vol. 40, pp. 244-9, 1999.

[152] F. Remy, F. Mirrashed, B. Campbell, and W. Richter, "Mental calculation impairment in Alzheimer's disease: a functional magnetic resonance imaging study," *Neurosci Lett,* vol. 358, pp. 25-8, 2004.

[153] P. J. Olesen, H. Westerberg, and T. Klingberg, "Increased prefrontal and parietal activity after training of working memory," *Nat Neurosci,* vol. 7, pp. 75-9, 2004.

[154] H. Westerberg and T. Klingberg, "Changes in cortical activity after training of working memory--a single-subject analysis," *Physiol Behav,* vol. 92, pp. 186-92, 2007.

[155] C. J. Camp, "Memory Interventions for Normal and Pathological Older Adults," *Annual Review of Gerontology and Geriatrics,* vol. 18, pp. 155-189, 1998.

[156] L. Clare and B. Woods, "A role for cognitive rehabilitation in dementia care," *Neuropsychological Rehabilitation,* vol. 11, pp. 193-196, 2001.

[157] M. Boccardi and G. B. Frisoni, "Cognitive rehabilitation for severe dementia: critical observations for better use of existing knowledge," *Mech Ageing Dev,* vol. 127, pp. 166-72, 2006.

[158] K. Ball, D. B. Berch, K. F. Helmers, J. B. Jobe, M. D. Leveck, M. Marsiske*, et al.*, "Effects of cognitive training interventions with older adults: a randomized controlled trial," *Jama,* vol. 288, pp. 2271-81, 2002.

[159] A. Bahar-Fuchs, L. Clare, and B. Woods, "Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia," *Cochrane Database Syst Rev,* p. CD003260, 2013.

[160] J. P. Kesslak, K. Nackoul, and C. A. Sandman, "Memory training for individuals with Alzheimer's disease improves name recall," *Behav Neurol,* vol. 10, pp. 137-42, 1997.

[161] P. S. Brum, O. Forlenza, and M. S. Yassuda, "Cognitive training in older adults with Mild Cognitive Impairment: Impact on cognitive and functional performance," *Dementia e Neuropsychologia,* vol. 3, pp. 124-131, 2009.

[162] G. Cipriani, A. Bianchetti, and M. Trabucchi, "Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment," *Arch Gerontol Geriatr,* vol. 43, pp. 327-35, 2006.

[163] M. Hofmann, A. Rosler, W. Schwarz, F. Muller-Spahn, K. Krauchi, C. Hock*, et al.*, "Interactive computer-training as a therapeutic tool in Alzheimer's disease," *Compr Psychiatry,* vol. 44, pp. 213-9, 2003.

[164] S. Konsztowicz, J. Anton, J. Crane, P. Moafmashhadi, and L. Koski, "A pilot study of training and compensation interventions for mild cognitive impairment," *Dement Geriatr Cogn Dis Extra,* vol. 3, pp. 192-201, 2013.

[165] R. Kawashima, K. Okita, R. Yamazaki, N. Tajima, H. Yoshida, M. Taira*, et al.*, "Reading aloud and arithmetic calculation improve frontal function of people with dementia," *J Gerontol A Biol Sci Med Sci,* vol. 60, pp. 380-4, 2005.

[166] E. Talassi, M. Guerreschi, M. Feriani, V. Fedi, A. Bianchetti, and M. Trabucchi, "Effectiveness of a cognitive rehabilitation program in mild dementia (MD) and mild cognitive impairment (MCI): a case control study," *Arch Gerontol Geriatr,* vol. 44 Suppl 1, pp. 391-9, 2007.

[167] P. E. Roland, *Brain Activation*: Wiley, 1997.

[168] E. Vassena, R. Gerrits, T. Verguts, J. Demanet, and R. Siugzdaite, *Preparation for mental effort recruits Dorsolateral Prefrontal Cortex: an fNIRS investigation*, 2017.

[169] E. Vassena, M. Silvetti, C. N. Boehler, E. Achten, W. Fias, and T. Verguts, "Overlapping Neural Systems Represent Cognitive Effort and Reward Anticipation," *PLOS ONE,* vol. 9, p. e91008, 2014.

[170] M. Tanida, K. Sakatani, R. Takano, and K. Tagai, "Relation between asymmetry of prefrontal cortex activities and the autonomic nervous system during a mental arithmetic task: near infrared spectroscopy study," *Neurosci Lett,* vol. 369, pp. 69-74, 2004.

[171] H. Yang, Y. Wang, Z. Zhou, H. Gong, Q. Luo, Y. Wang*, et al.*, "Sex differences in prefrontal hemodynamic response to mental arithmetic as assessed by near-infrared spectroscopy," *Gend Med,* vol. 6, pp. 565-74, 2009.

[172] M. Hofmann, C. Hock, A. Kuhler, and F. Muller-Spahn, "Interactive computer-based cognitive training in patients with Alzheimer's disease," *J Psychiatr Res,* vol. 30, pp. 493-501, 1996.

[173] M. Tonetta, *Riabilitazione neuropsicologica e TNP (training neuropsicologico). Aspetti teorici e pragmatici*: New Magazine, 1998.

[174] J. T. Kaplan, S. I. Gimbel, and S. Harris, "Neural correlates of maintaining one's political beliefs in the face of counterevidence," *Scientific Reports,* vol. 6, p. 39589, 2016.

[175] B. L. Miller and J. L. Cummings, *The Human Frontal Lobes: Functions and Disorders*: Guilford Press, 2007.

[176] T. C. Rickard, S. G. Romero, G. Basso, C. Wharton, S. Flitman, and J. Grafman, "The calculating brain: an fMRI study," *Neuropsychologia,* vol. 38, pp. 325-35, 2000.

[177] V. Menon, S. M. Rivera, C. D. White, S. Eliez, G. H. Glover, and A. L. Reiss, "Functional optimization of arithmetic processing in perfect performers," *Cognitive Brain Research,* vol. 9, pp. 343-345, 2000.

[178] C. Montojo and S. M. Courtney, "Differential neural activation for updating rule versus stimulus information in working memory," *Neuron,* vol. 59, pp. 173-182, 2008.

[179] G. H. Klem, H. O. Luders, H. H. Jasper, and C. Elger, "The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology," *Electroencephalogr Clin Neurophysiol Suppl,* vol. 52, pp. 3-6, 1999.

[180] P. Rydesäter. (2001). *TCP/UDP/IP Toolbox 2.0.6*. Available: https://www.mathworks.com/matlabcentral/fileexchange/345-tcp-udp-ip-toolbox-2-0-6

[181] X. Cui, S. Bray, and A. L. Reiss, "Functional Near Infrared Spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics," *NeuroImage,* vol. 49, pp. 3039-46, 2010.

[182] S. H. Fairclough and K. Gilleade, *Advances in Physiological Computing*: Springer Publishing Company, Incorporated, 2014.

[183] S. Luu and T. Chau, "Decoding subjective preference from single-trial near-infrared spectroscopy signals," *Journal of neural engineering,* vol. 6, p. 016003, 2008.

[184] S. Moghimi, A. Kushki, S. Power, A. M. Guerguerian, and T. Chau, "Automatic detection of a prefrontal cortical response to emotionally rated music using multi-channel near-infrared spectroscopy," *Journal of neural engineering,* vol. 9, p. 026022, 2012.

[185] D. H. Brainard, "The Psychophysics Toolbox," *Spat Vis,* vol. 10, pp. 433-6, 1997.

[186] D. G. Pelli, "The VideoToolbox software for visual psychophysics: transforming numbers into movies," *Spat Vis,* vol. 10, pp. 437-42, 1997.

[187] M. Kleiner, D. Brainard, D. Pelli, A. Ingling, R. Murray, and C. Broussard, "What's new in Psychtoolbox-3."

[188] H. Arai, M. Takano, K. Miyakawa, T. Ota, T. Takahashi, H. Asaka*, et al.*, "A quantitative near-infrared spectroscopy study: a decrease in cerebral hemoglobin oxygenation in Alzheimer's disease and mild cognitive impairment," *Brain and cognition,* vol. 61, pp. 189-194, 2006.

[189] A. Fallgatter, M. Roesler, a. Sitzmann, A. Heidrich, T. Mueller, and W. Strik, "Loss of functional hemispheric asymmetry in Alzheimer's dementia assessed with near-infrared spectroscopy," *Cognitive Brain Research,* vol. 6, pp. 67-72, 1997.

[190] M. J. Herrmann, J. B. Langer, C. Jacob, A.-C. Ehlis, and A. J. Fallgatter, "Reduced prefrontal oxygenation in Alzheimer disease during verbal fluency tasks," *The American Journal of Geriatric Psychiatry,* vol. 16, pp. 125-135, 2008.

[191] F. McNab and T. Klingberg, "Prefrontal cortex and basal ganglia control access to working memory," *Nature neuroscience,* vol. 11, pp. 103-107, 2008.

[192] D. H. Salat, J. A. Kaye, and J. S. Janowsky, "Selective preservation and degeneration within the prefrontal cortex in aging and Alzheimer disease," *Archives of neurology,* vol. 58, pp. 1403-1408, 2001.

[193] T. P. Zanto, M. T. Rubens, A. Thangavel, and A. Gazzaley, "Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory," *Nature neuroscience,* vol. 14, pp. 656-661, 2011.

[194] L. Marner, J. R. Nyengaard, Y. Tang, and B. Pakkenberg, "Marked loss of myelinated nerve fibers in the human brain with age," *J Comp Neurol,* vol. 462, pp. 144-52, Jul 21 2003.

[195] B. A. Yankner, T. Lu, and P. Loerch, "The aging brain," *Annu Rev Pathol,* vol. 3, pp. 41-66, 2008.

[196] H. Watanabe, Y. Shitara, Y. Aoki, T. Inoue, S. Tsuchida, N. Takahashi*, et al.*, "Hemoglobin phase of oxygenation and deoxygenation in early brain development measured using fNIRS," *Proceedings of the National Academy of Sciences,* vol. 114, pp. E1737-E1744, 2017.

[197] A. Villringer and B. Chance, "Non-invasive optical spectroscopy and imaging of human brain function," *Trends Neurosci,* vol. 20, pp. 435-42, 1997.

[198] A. Villringer and U. Dirnagl, "Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging," *Cerebrovasc Brain Metab Rev,* vol. 7, pp. 240-76, 1995.

[199] G. Gratton, M. R. Goodman-Wood, and M. Fabiani, "Comparison of neuronal and hemodynamic measures of the brain response to visual stimulation: An optical imaging study," *Human Brain Mapping,* vol. 13, pp. 13-25, 2001.

[200] A.-N. Spiess and N. Neumeyer, "An evaluation of R(2)as an inadequate measure for nonlinear models in pharmacological and biochemical research: a Monte Carlo approach," *BMC Pharmacology,* vol. 10, pp. 6-6, 2010.

[201] K. Yoshida, D. Sawamura, Y. Inagaki, K. Ogawa, K. Ikoma, and S. Sakai, "Brain activity during the flow experience: a functional near-infrared spectroscopy study," *Neurosci Lett,* vol. 573, pp. 30-4, 2014.

[202] T. Katayama and K. Natsume, "The Change in EEG When We Are Bored," *Journal of Signal Processing,* vol. 16, pp. 637-641, 2012.

[203] A. Hempel, F. L. Giesel, N. M. Garcia Caraballo, M. Amann, H. Meyer, T. Wustenberg*, et al.*, "Plasticity of cortical activation related to working memory during training," *Am J Psychiatry,* vol. 161, pp. 745-7, 2004.

[204] G. Durantin, J. F. Gagnon, S. Tremblay, and F. Dehais, "Using near infrared spectroscopy and heart rate variability to detect mental overload," *Behav Brain Res,* vol. 259, pp. 16-23, 2014.

[205] T. Möckel, C. Beste, and E. Wascher, "The Effects of Time on Task in Response Selection - An ERP Study of Mental Fatigue," vol. 5, p. 10113, 2015.

[206] J. Lim, W. C. Wu, J. Wang, J. A. Detre, D. F. Dinges, and H. Rao, "Imaging brain fatigue from sustained mental workload: an ASL perfusion study of the time-on-task effect," *Neuroimage,* vol. 49, pp. 3426-35, 2010.

[207] I. Imbo and A. Vandierendonck, "The development of strategy use in elementary school children: Working memory and individual differences," *Journal of Experimental Child Psychology,* vol. 96, pp. 284-309, 2007.

[208] A. Dowker, "Young Children's Addition Estimates," *Mathematical Cognition,* vol. 3, pp. 140-153, 1997.

[209] P. Smielewski, M. Czosnyka, J. D. Pickard, and P. Kirkpatrick, "Clinical evaluation of near-infrared spectroscopy for testing cerebrovascular reactivity in patients with carotid artery disease," *Stroke,* vol. 28, pp. 331-8, 1997.

[210] L. Minati, I. U. Kress, E. Visani, N. Medford, and H. D. Critchley, "Intra- and extra-cranial effects of transient blood pressure changes on brain near-infrared spectroscopy (NIRS) measurements," *J Neurosci Methods,* vol. 197, pp. 283-8, 2011.

[211] W. C. Ung, T. Funane, T. Katura, H. Sato, T. B. Tang, A. F. M. Hani*, et al.*, "Effectiveness evaluation of real-time scalp signal separating algorithm on near-infrared spectroscopy neurofeedback," *IEEE journal of biomedical and health informatics,* 2017.

APPENDICES

Appendix A:
NASA Task Load Index (NASA-TLX)

Hart and Staveland's NASA Task Load Index (TLX) method assesses work load on five 7-point scales. Increments of high, medium and low estimates for each point result in 21 gradations on the scales.

Name	Task	Date

Mental Demand — How mentally demanding was the task?

Very Low — Very High

Physical Demand — How physically demanding was the task?

Very Low — Very High

Temporal Demand — How hurried or rushed was the pace of the task?

Very Low — Very High

Performance — How successful were you in accomplishing what you were asked to do?

Perfect — Failure

Effort — How hard did you have to work to accomplish your level of performance?

Very Low — Very High

Frustration — How insecure, discouraged, irritated, stressed, and annoyed wereyou?

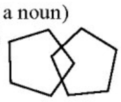
Very Low — Very High

Appendix B:

Mini-Mental State Examination (MMSE)

'Mini-Mental State Examination' (MMSE)

Date : ______________

No	Subject	Maximum Score	Score
1	**Orientation** What is the (year/ month/ date/ day & time of the day) Where are we: (country/ state/ town/ hospital/ floor or ward or clinic)	 5 5	 ( ) ( )
2	**Registration** Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer on the first attempt. If can't remember then repeat them until he/she learns all the 3 objects. Count trials and record. No. of trials:	 3	 ( )
3	**Attention and calculation** i) Serial seven: (100 – 7 = 93/ 93 – 7 = 86/ 86 – 7 = 79/ 79 – 7 = 72/ 72 – 7 = 65) (Stop after five answers) ii) Alternatively spell "WORLD" backwards	5	( )
4	**Recall** Ask for the 3 objects repeated above. Give 1 point for each correct	 3	 ( )
5	**Language** Show and name two objects (pencil, and watch) Repeated the e.g. following **"No ifs, ands or buts,"** Follow a 3 stage command. Take the paper in your hand, fold it into half, and put it on the floor" **Close your eyes** Write a sentence → (must contain a verb and a noun) Copy design → (must overlap pentagons) 	 2 1 3 1 1 1	 ( ) ( ) ( ) ( ) ( ) ( )
	*** Total score**	30	

Source: Folstein MF, Folstein SE, McHugh PR, et al 'Mini Mental State' A practical method for grading the cognitive state of patients for the clinician. J Psy. Research 1975; 12: 189 – 98.

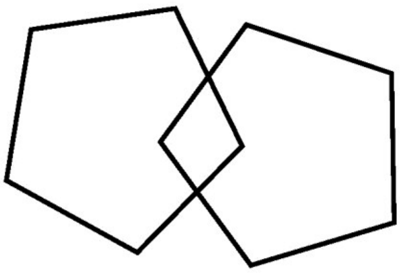
RN	
Name	
DOB	
Sex	
Unit	

Read and obey:

CLOSE YOUR EYES

Write a complete sentence:

Copy this design:



Clock Drawing Test (CDT); [10 minutes past 11 O' clock]:

Appendix C:
Clinical Dementia Rating (CDR)

Subject Initials ________

Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? ☐ Yes ☐ No

1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐ Yes ☐ No

2. Can he/she recall recent events? ☐ Usually ☐ Sometimes ☐ Rarely

3. Can he/she remember a short list of items (shopping)? ☐ Usually ☐ Sometimes ☐ Rarely

4. Has there been some decline in memory during the past year? ☐ Yes ☐ No

5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion) ☐ Yes ☐ No

6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event? ☐ Usually ☐ Sometimes ☐ Rarely

7. Does he/she forget pertinent details of the major event? ☐ Usually ☐ Sometimes ☐ Rarely

8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? ☐ Usually ☐ Sometimes ☐ Rarely

9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

   Within 1 week: ______________________________

   ____

   ____

   Within 1 month: ______________________________

   ____

   ____

10. When was he/she born? ______________________________

11. Where was he/she born? ______________________________

12. What was the last school he/she attended? ______________________________

    Name ______________________________

    Place ______________________________

    Grade ______________________________

13. What was his/her main occupation/job (or spouse's job if subject was not employed)? ________

14. What was his/her last major job (or spouse's job if subject was not employed? ________

15. When did he/she (or spouse) retire and why? ______________________________

1

Subject Initials _________

Clinical Dementia Rating Worksheet

Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

Subject Initials ________

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

   - ☐ As good as they have ever been
   - ☐ Good, but not as good as before
   - ☐ Fair
   - ☐ Poor
   - ☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

   - ☐ No loss
   - ☐ Some loss
   - ☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):

   - ☐ No loss
   - ☐ Some loss
   - ☐ Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

   - ☐ As well as before
   - ☐ Worse than before because of trouble thinking
   - ☐ Worse then before, another reason (why) ____________________

   ____

   ____

5. Can he/she understand situations or explanations?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

____

*This item rates behavior, not appearance.

3

Subject Initials ________

Clinical Dementia Rating Worksheet

Community Affairs Questions for Informant:

Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
   If not applicable, proceed to item 4
   If yes, proceed to item 3
   If no, proceed to item 2

2. Did memory or thinking problems contribute to the subject's decision To retire? (Question 4 is next) ☐ Yes ☐ No ☐ D/K

3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?

   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social

4. Did he/she ever drive a car? ☐ Yes ☐ No

   Does the subject drive a car now? ☐ Yes ☐ No

   If no, is this because of memory or thinking problems? ☐ Yes ☐ No

5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No

*6. Is he/she able to independently shop for needs?
   ☐ Rarely or Never (**Needs to be accompanied on any shopping trip**) ☐ Sometimes (**Shops for limited number of items; buys duplicate items or forgets needed items**) ☐ Usually ☐ Don't Know

7. Is he/she able to independently carry out activities outside the home?
   ☐ Rarely or Never (**Generally unable to perform activities without help**) ☐ Sometimes (**Limited and/or routine, e.g., superficial participation in church or meetings; trips to beauty parlor**) ☐ Usually (**Meaningful participation in activities, e.g., voting**) ☐ Don't Know

8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
   If no, why not? ____

9. Would a casual observer of the subject's behavior think the subject was ill? ☐ Yes ☐ No

10. If in nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
<u>If not, please probe further</u>.

<u>Community Affairs</u>: Such as going to church, visiting with friends or family, political activities, professional organizations such as bas association, other professional groups, social clubs, service organizations, educational programs.

____

***Please add notes if needed to clarify subject's level of functioning in this area.**

4

Subject Initials ________

Clinical Dementia Rating Worksheet

Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores? ________

1b. What can he/she still do well? ________

2a. What changes have occurred in his/her abilities to perform hobbies? ________

2b. What can he/she still do well? ________

3. If in nursing home, what can he/she no longer do well (H and H)? ________

Everyday Activities (Blessed):

	No Loss		Severe Loss
4. Ability to perform household tasks	0	0.5	1

Please describe: ________

5. Is he/she able to perform household chores at the level of:
(Pick one. Informant does not need to be asked directly).

☐ No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)

☐ Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)

☐ Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

☐ Functions in usual activities but not at usual level.

☐ Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple car maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theater or symphony, woodworking, participation in sports.

Subject Initials _________

Clinical Dementia Rating Worksheet

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable to dress
A. Dressing (Blessed)	0	1	2	3

	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3

	Cleanly; proper utensils	Messily; spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3

	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Sphincter control (Blessed)	0	1	2	3

*A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

Subject Initials ________

Clinical Dementia Rating Worksheet

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No

2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct ________
0.5 ________
0.0 – Largely incorrect ________

Within 1 month

1.0 – Largely correct ________
0.5 ________
0.0 – Largely incorrect ________

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. When were you born? ________

5. Where were you born? ________

6. What was the last school you attended?
   Name ________
   Place ________ Grade ________

7. What was your main occupation job (or spouse if not employed)? ________

8. What was your last major job (or spouse if not employed)? ________

9. When did you (or spouse) retire and why? ________

10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

Subject Initials _________

Clinical Dementia Rating Worksheet

Orientation Questions for Subject

Record the subject's answer verbatim for each question

1. What is the date today? ☐ Correct ☐ Incorrect

____

2. What day of the week is it? ☐ Correct ☐ Incorrect

____

3. What is the month? ☐ Correct ☐ Incorrect

____

4. What is the year? ☐ Correct ☐ Incorrect

____

5. What is the name of this place? ☐ Correct ☐ Incorrect

____

6. What town or city are we in? ☐ Correct ☐ Incorrect

____

7. What time is it? ☐ Correct ☐ Incorrect

____

8. Does the subject know who the informant is (in your judgment)? ☐ Correct ☐ Incorrect

____

Subject Initials _________

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. turnip……cauliflower ______________________________
   (0 = vegetables)
   (1 = edible foods, living things, can be cooked, etc.)
   (2 = answers not pertinent; differences; buy them)

2. desk……bookcase ______________________________
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?

3. lie……mistake ______________________________
   (0 = one deliberate, one unintentional)
   (1 = one bad the other good – or explains only one)
   (2 = anything else, similarities)

4. river……canal ______________________________
   (0 = natural - artificial)
   (1 = anything else)

Calculations:

5. How many nickels in a dollar? ☐ Correct ☐ Incorrect
6. How many quarters in $6.75? ☐ Correct ☐ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?

   (0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)
   (1 = call the police, call operator (usually will not give address)
   (2 = no clear response)

9. Subject's assessment of disability and station in life and understanding of why she/she is present at the examination (may have covered, but rate here):

   ☐ Good Insight ☐ Partial Insight ☐ Little Insight

Subject Initials ________

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

10

Appendix D:

Recruitment poster for Study 2

Appendix E:

Informed consent form used in Study 2

ATTACHMENT B

RESEARCH INFORMATION

Research Title: Functional Near-Infrared Spectroscopy (fNIRS) Neurofeedback to Slow Down the Progression of Dementia in Early Dementia Patients

Researcher's Name:
[a] **Ung Wei Chun**
[a] **Assoc. Prof. Dr. Tang Tong Boon**
[a] **Prof. Dr. Fabrice Meriaudeau**
[b] **Prof. Dr. Esther Gunaseli M. Ebenezer**

Researcher Affiliation: [a] Center for Intelligent Signal & Imaging Research (CISIR), Universiti Teknologi PETRONAS, Malaysia.
[b] Medicine Based Department Royal College of Medicine, Universiti Kuala Lumpur Ipoh, Perak, Malaysia

INTRODUCTION

You are invited to voluntarily participate in 2 study sessions spread across 2 weeks (1 session per week). Each session may take up to a maximum duration of 1 hour. In these sessions, you will be required to solve a series of arithmetic questions mentally while getting their brain activity measured using a functional near-infrared spectroscopy (fNIRS) system – Hitachi OT-R40.

PURPOSE OF THE STUDY

This study attempts to validate the fNIRS neurofeedback system we have developed to optimize the mental workload dynamically for the purpose of cognitive rehabilitation before testing on our targeted individuals – the early dementia patients. The aim is to have participants trained at their optimal level of difficulty and workload to maximize their gains.

A mixed population of university subjects will undergo the experimental procedures which will be briefly explained prior to any experiment. Subjects, who have given consent to participate in this study, will be asked to provide demographic information that includes age, gender, ethnicity, education level, first language, etc, as listed in **ATTACHMENT 1**.

As mentioned, there will be 2 sessions of experiment, spread across 2 weeks. In each session, subjects will be required to solve a series of arithmetic questions mentally while getting their brain activity measured using a fNIRS system – Hitachi OT-R40. However, there are two protocols: (P1) a prior screening will be conducted to choose the subjects' optimal level of difficulty and only arithmetic questions of this level of difficulty will be asked throughout the session; (P2) protocol that adjusts the level of difficulty automatically and adaptively. In a counterbalanced design to control for order effects, subjects will be assigned to two groups, each group undergoing the aforementioned protocols in a different order e.g. Group 1 undergoes the sessions in the order of P1,P2 while Group 2 undergoes the sessions in the order P2,P1 (see Figure 1). By creating a group for each possible order, the variance due to order effects becomes a separate source of variance, making for a more powerful experimental design.

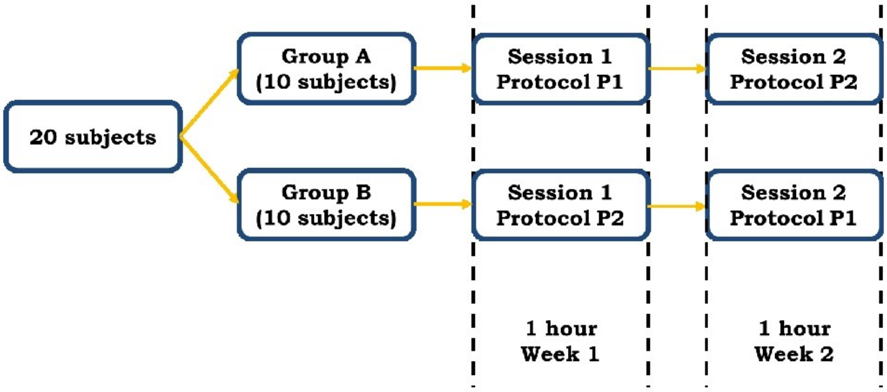


Figure 1. The counterbalanced experimental design.

In Protocol P1, prior screening (10 minutes; see Figure 2) will be carried out to determine the subjects' optimal level of difficulty based on the fNIRS signals. Afterwards, only arithmetic questions of this level of difficulty will be asked throughout the session (Task; 30 minutes; see Figure 3). The total duration for a session using P1 is 40 minutes.

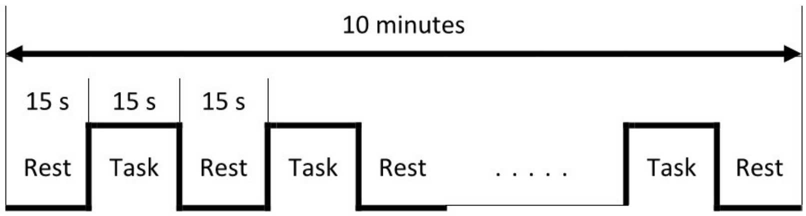


Figure 2. The paradigm of the prior screening used in Protocol P1.

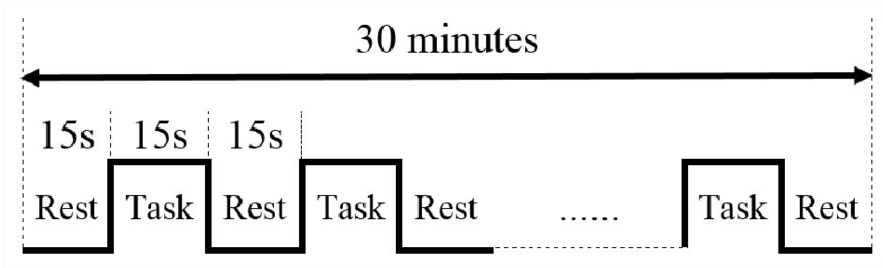


Figure 3. The paradigm of the actual task used in both protocols.

On the hand, Protocol P2 is a protocol that adjusts task level difficulty adaptively based on the fNIRS signals. Therefore, arithmetic questions of appropriate degree of difficulty that are constantly tailored to a subject's current cognitive workload will be asked throughout the session (Task; 30 minutes; see Figure 3). A session employing Protocol P2 is only 30 minutes long.

After undergoing the experimental procedures, subjects will then be administered the NASA Task Load Index (NASA-TLX; see **ATTACHMENT 2**). NASA-TLX is a widely used, subjective, multidimensional assessment tool that rates perceived workload or other aspects of performance.

QUALIFICATIONS FOR PARTICIPATION

Inclusion criteria

- Right-handed
- Able to converse in English
- No past history of psychiatric or neurological disorder

Exclusion criteria:

- Left-handed
- Unable to converse in English
- Poor eyesight, hearing and movement
- Secondary medical conditions e.g. kidney failure, stroke, etc

PROCEDURE

Step 1: Briefing (5 minutes)
Subjects will be briefed through the nature of the experimental procedures prior to any experiment. Following the receipt of informed consent form, subjects will be asked to provide demographic information that includes age, gender, ethnicity, education level, first language, etc. Subjects will also be given practice to familiarize themselves with the experimental procedures that they will go through.

Step 2: Experimental Setup (10 minutes)
Subjects will be seated in a comfortable chair and they will be instructed to avoid movement, keep their left hand on the arm rest and their right hand on the response box throughout the experiment. Since the fNIRS probes are attached to a flexible head cap, it will be relatively easy, fast and convenient to wear the head cap directly on the subjects. All channels have to be checked to ensure that the probes are in contact with the scalp. The entire process is expected to consume less than 10 minutes.

Step 3: Experiment (40 minutes)
The duration depends on the group and session. Regardless of group and session, subjects will be required to solve a series of arithmetic questions mentally while getting their brain activity measured.

- Group A
  - Session 1 (40 minutes)
    Prior screening (10 minutes) will be carried out to determine the subjects' optimal level of difficulty. After that, only arithmetic questions of this level of difficulty will be asked throughout the session (30 minutes).

  - Session 2 (30 minutes)
    Protocol that adjusts task level difficulty automatically and adaptively will be used, allowing the task difficulty level to be adjusted based on the subjects' cognitive workload. Therefore, arithmetic questions of appropriate degree of difficulty that are constantly tailored to a subject's optimum will be asked throughout the session (30 minutes).

- Group B
  - Session 1 (30 minutes)
    Protocol that adjusts task level difficulty automatically and adaptively will be used, allowing the task difficulty level to be adjusted based on the subjects' cognitive workload. Therefore, arithmetic questions of appropriate degree of difficulty that are constantly tailored to a subject's optimum will be asked throughout the session (30 minutes).

  - Session 2 (40 minutes)
    Prior screening (10 minutes) will be carried out to determine the subjects' optimal level of difficulty. After that, only arithmetic questions of this level of difficulty will be asked throughout the session (30 minutes).

Step 4: Post-Experiment Questionnaire (5 minutes)
After undergoing the experimental procedures, subjects will then be administered the NASA-TLX, a widely used, subjective, multidimensional assessment tool that rates perceived workload or other aspects of performance.

VOLUNTARINESS

Your participation in this study is voluntary. You may refuse to participate, discontinue participation, or skip any questions you do not wish to answer at any time without any penalty.

RISKS AND BENEFITS

You may experience some mild, temporary discomfort relating to undergoing the experiments. You will receive remuneration of RM40 after completing both sessions in this study. Furthermore, your participation may help researchers understand the underlying mechanisms of this study.

CONFIDENTIALITY

Only the principal researchers will have access to research results associated with your identity. In the event of publication of this study, no personally identifying information will be disclosed. To make sure your participation is confidential, your personal identity will never be revealed. You have the right to have any unprocessed data withdrawn and destroyed, provided it can be reliably identified, and provided that doing so does not increase your level or risk.

QUESTIONS

Who to contact with questions: You are given the right to have any questions answered at any time. You may discuss these concerns confidentially with the investigators:

Associate Professor Dr. Tang Tong Boon
Contact no.: 012 - 7336653
Email: tongboon.tang@utp.edu.my
Department of Electrical and Electronic Engineering
Universiti of Teknologi PETRONAS

Ung Wei Chun
Contact no.: 016 - 4242549
Email: ungweichun@gmail.com
Department of Electrical and Electronic Engineering
Universiti of Teknologi PETRONAS

SIGNATURES

To give your consent to participate in this study, you or a legal representative must complete and sign **ATTACHMENT 1**, **2**, **3** and **4**.

Subject Information and Consent Form

Research Title: **Functional Near-Infrared Spectroscopy (fNIRS) Neurofeedback to Slow Down the Progression of Dementia in Early Dementia Patients**

Researcher's Name: **Ung Wei Chun, Assoc. Prof. Dr. Tang Tong Boon, Prof. Dr. Fabrice Meriaudeau, Prof. Dr. Esther Gunaseli M. Ebenezer**

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- I have read all of the information in this Subject Information and Consent Form **including any information regarding the risk in this study** and I have had time to think about it.
- All of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
- I may freely choose to stop being a part of this study at any time.

______________________________ ______________________________

Subject Name (Print or type) **Subject I.C** No. (New)

______________________________ ______________________________

Signature of Subject or Legal Representative **Date** (dd/MM/yy)

Ung Wei Chun______________________________
Name of Individual
Conducting Consent Discussion (Print or Type)

______________________________ ______________________________

Signature of Individual
Conducting Consent Discussion

Date (dd/MM/yy)

Note: i) All subject/subjects who are involved in this study will not be covered by insurance.

Subject's Material Publication Consent Form

Research Title: **Functional Near-Infrared Spectroscopy (fNIRS) Neurofeedback to Slow Down the Progression of Dementia in Early Dementia Patients**

Researcher's Name: **Ung Wei Chun, Assoc. Prof. Dr. Tang Tong Boon, Prof. Dr. Fabrice Meriaudeau, Prof. Dr. Esther Gunaseli M. Ebenezer**

To become a part this study, you or your legal representative must sign this page.

By signing this page, I am confirming the following:

- I understood that my name will not appear on the materials published and there has been an effort to make sure that the privacy of my name is kept confidential although the confidentiality is not completely guaranteed due to unexpected circumstances.
- I have read the materials or general description of what the material contains and reviewed all photographs and figures in which I am included that could be published.
- I have been offered the opportunity to read the manuscript and to see all materials in which I am included, but I agreed to waive my right from doing so.
- All the published materials can be shared among the medical practitioners, scientists and researchers worldwide.
- The materials will also be used in local publications, book publications and may access by others locally or internationally.
- I hereby agree and allow the materials to be used in other publications required by other publishers with these conditions:
    - The materials will not be used as advertisement purposes or as packaging materials.
    - The materials will not be used out of context – i.e.: subject's images will not be used in an article which is unrelated to the study.
- If there is any financial implication associated with the data or findings of this study, I agreed that I will not be entitled to receive any financial compensation or claim any financial value except the agreed honorarium for participation in this study.

______________________________	______________________________
Subject Name (Print or type)	**Subject I.C No.**
______________________________	______________________________
Subject Signature	**Date** (dd/MM/yy)
Ung Wei Chun	______________________________
Name and Signature of Individual Conducting Consent Discussion	**Date** (dd/MM/yy)

Note: i) All subject/subjects who are involved in this study will not be covered by insurance.

Appendix F:

Participant information form used in Study 2

ATTACHMENT 1

Participant Information Form

Full Name:			
Email:		Assigned ID:	

Personal Information			
Nationality:		NRIC/Passport No.:	
Phone No.:			
Mailing Address:			

Research Related Information			
Date of Birth:	__(dd) __ (mm) __ (yy) Age: ( )	First Language:	
Gender:		Highest Education Level:	
Ethnicity:		SPM Maths Grade:	
Dominant Hand:		SPM Add Maths Grade:	
On a scale of 1-10, rate your mental calculation ability:			
Smoking?	No: ☐ Yes: ☐ (Hours:___) ago	Caffeine Intake?	No: ☐ Yes: ☐ (Hours:___) ago

Health Condition – Interview Log (To be filled by researcher)	
Physical Condition: Are you feeling well? Tired? Etc.	No. Hours of Sleep: Hrs
Mental Condition: (suffering from chronic stress / emotional trauma for the past few days?)	
Family history related to Neurological, psychiatrical illnesses? If yes please state	
Drug abuse experience / currently under medication? If yes please state	

Experiment Details		
Session	1	2
Date & Time		

Yellow Channels		**Level of P1**

Appendix G:

CD containing all the raw data from both Study 1 and 2

LIST OF PUBLICATIONS

Work presented in the thesis:

- **W. C. Ung**, T. B. Tang, F. Meriaudeau, and E. G. M. Ebenezer, "Dynamic optimization of mental workload in fNIRS-BCI system for cognitive rehabilitation," in *2017 IEEE International Conference on Signal and Image Processing Applications (ICSIPA)*, pp. 320-323, 2017.

  Description: This published conference paper was written based on Study 1.

Indirectly related work:

- K. H. Yap*, **W. C. Ung***, E. G. Ebenezer, N. Nordin, P. S. Chin, S. Sugathan*, et al.*, "Visualizing Hyperactivation in Neurodegeneration Based on Prefrontal Oxygenation: A Comparative Study of Mild Alzheimer's Disease, Mild Cognitive Impairment, and Healthy Controls," *Frontiers in Aging Neuroscience,* vol. 9, p. 287, 2017. * DENOTES EQUAL CONTRIBUTION

  Description: This study was conducted to explore fNIRS alongside a semantic verbal fluency task to investigate any compensation exhibited by the PFC in mild cognitive impairment and mild Alzheimer's disease. This study generally established the foundation to kick-start the work presented in the thesis.

- **W. C. Ung**, T. Funane, T. Katura, H. Sato, T. B. Tang, A. F. M. Hani*, et al.*, "Effectiveness Evaluation of Real-time Scalp Signal Separating Algorithm on Near-infrared Spectroscopy Neurofeedback," *IEEE Journal of Biomedical and Health Informatics,* vol. PP, pp. 1-1, 2018.

  Description: This study was to demonstrate the effectiveness of RT-SSS algorithm to minimize the superficial interference. Such verification is vital in order to apply the algorithm together with the fNIRS-DDA system in future studies.