Differentiation of Normal Cognition and Early Dementia using fNIRS

by

Ung Wei Chun
17111

Dissertation submitted in partial fulfilment of
the requirement for the
Bachelor of Engineering (Hons)
(Electrical and Electronic)

September 2015

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CERTIFICATION OF APPROVAL

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Approved by,

_____

Dr. Tang Tong Boon

UNIVERSITI TEKNOLOGI PETRONAS

BANDAR SERI ISKANDAR, PERAK

September 2015

CERTIFICATION OF ORIGINALITY

This is to certify that I am responsible for the work submitted in this project, that the original work is my own except as specified in the references and acknowledgements, and that the original work contained herein have not been undertaken or done by unspecified sources or persons.

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Ung Wei Chun

ABSTRACT

This study aimed to assess the effectiveness of functional near-infrared spectroscopy in differentiating normal cognition and early dementia. To date, only pen-and-paper tests, which are time consuming, uneconomical in the sense that the services of psychiatrist or psychologist don't come cheap, and are just behaviour assessments, are used to screen for dementia. The deployment of functional near-infrared spectroscopy not only could study functional connectivity but also could provide the objective confirmation of dementia diagnosis To observe the difference between the brain signal of normal aging individuals and early dementia patients, tasks to activate working memory were designed. A total of 10 subjects (3 healthy controls and 7 early dementia patients) screened using Mini Mental Status Examination and Clinical Dementia Rating underwent three levels of sequencing tasks and three categories of verbal fluency tasks while getting their brain signals measured. The findings showed that the activation level of healthy controls is higher than that of early dementia patients (sequencing tasks – level 1: 0.08 vs 0.04 mM·mm, level 2: 0.07 vs 0.06 mM·mm, level 3: 0.05 vs 0.04 mM·mm; verbal fluency tasks – 0.2 vs 0.1 mM·mm). This activation was found to be in the left and right prefrontal cortex. Besides that, more complicated activations were observed during verbal fluency task as it tests not only working memory but also verbal and executive control abilities. As of now, the sample size is not sufficient enough to conclude this study but the data collection is still on-going. Once the data collection is completed and the sample size is large enough, the role of functional near-infrared spectroscopy in dementia diagnosis can be validated and this study can finally be concluded.

ACKNOWLEDGEMENT

This project was a great chance for learning and professional development. Therefore, I consider myself as a very lucky individual as I was provided with an opportunity to be a part of it. I am also grateful for having a chance to meet so many wonderful people and professionals who led me towards the completion of this project.

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ACRONYMS AND ABBREVIATIONS

AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
CDR	Clinical Dementia Rating
deoxy-Hb	Deoxygenated haemoglobin
ED	Early dementia
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
MMSE	Mini Mental Status Examination
MRI	Magnetic resonance imaging
NC	Normal cognition
NIR	Near-infrared
oxy-Hb	Oxygenated haemoglobin
PET	Positron emission tomography
VaD	Vascular dementia
VFT	Verbal fluency task
WM	Working memory

CHAPTER 1
INTRODUCTION

1.1 BACKGROUND

Aging population is a major issue in most countries, no matter developed, developing or less-developed ones. Among all aging-associated diseases, dementia is the fastest growing brain disorder [1] (see Fig. 1). By 2013, dementia has affected 44.4 million people globally and this figure is expected to rise dramatically in future [2]. Dementia is defined as a neurodegenerative disorder involving the deterioration of multiple cognitive abilities which could affect everyday life. The deterioration is usually progressive, even to the extent that self-care and self-reliance are not possible. There are various forms of dementia. Alzheimer' disease (AD) is the most common form and accounts for 60-80% of dementia cases while vascular dementia (VaD) accounts for another 10% [3]. A European study claimed that the prevalence of dementia doubles every 5 years starting from the age of 65-90 [4]. As a consequence, dementia is regarded as a global health crisis [5].

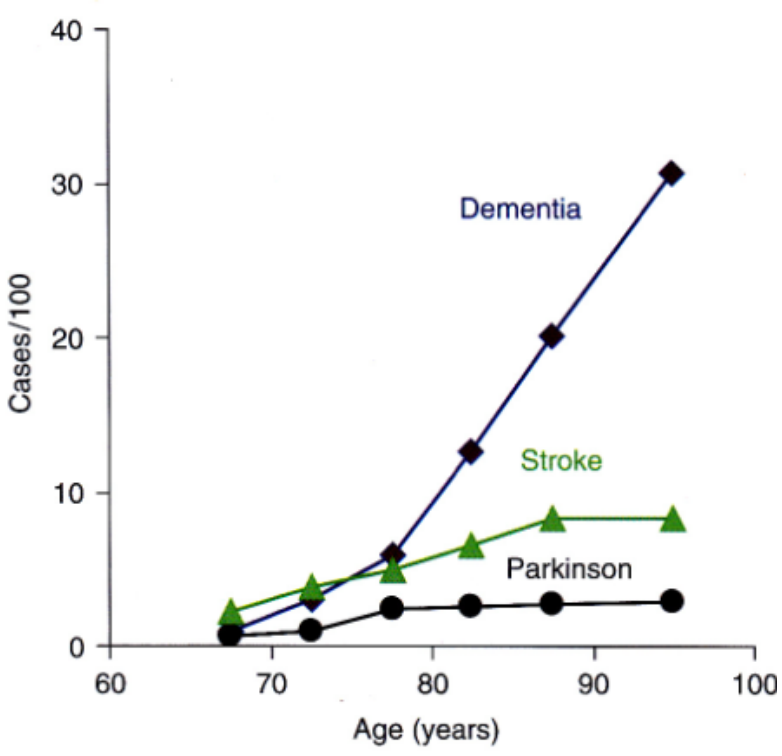


Fig. 1. Dementia shows the highest increase in numbers with advancing age [1].

A wide range of cognitive functions are compromised due to changes in the brain regions in patients with AD [6]. These abnormalities affect not only memory, language, problem solving, judgment, but also calculation and visuospatial awareness. Executive functions are among one of the many impairments found in patients with AD. These functions encompass a number of cognitive abilities responsible for decision making, planning, self-monitoring, and behaviour organization and inhibition [7]. All aforementioned processes often involve working memory (WM), which is reported to be responsible for transient holding and processing of new and stored information [8, 9]. It is also claimed that WM plays a crucial part in the processing of reasoning, comprehension, learning, and memory updating [10].

At present, there is no cure for dementia but early diagnosis and brain monitoring can be beneficial. Several neuroimaging modalities have been proposed to gain a better understanding. Functional near-infrared spectroscopy (fNIRS) forms an economical way to image the brain, as compared with functional magnetic resonance imaging (fMRI), and has a better spatial resolution than electroencephalography (EEG).

1.2 PROBLEM STATEMENT

For dementia, early diagnosis and brain monitoring can be beneficial. To date, only pen-and-paper tests are used to screen for dementia. These tests can be time consuming, not economical (expense for psychiatrists), and are just behaviour assessments. There is no objective confirmation of clinical diagnosis of dementia. Thus, it has been suggested that fNIRS could be deployed clinically to diagnose dementia by differentiating normal cognition (NC) and early dementia (ED). This not only could study functional connectivity but also could provide the objective confirmation of dementia diagnosis, just like what fNIRS has achieved in differentiating other brain disorders [11].

1.3 OBJECTIVES

The overarching objective was to assess the effectiveness of fNIRS in differentiating NC from ED. By doing so, the role of fNIRS in dementia diagnosis can be validated. To achieve the main objective, the following prior sub-objectives had to be accomplished:

1. To design and develop a protocol consisting of several tasks for memory assessment
2. To collect data from subjects
3. To process fNIRS data to identify subjects into NC and ED categories
4. To run statistical analysis to see how accurate the identification is

1.4 SCOPE OF STUDY

Since the number probes for fNIRS measurement was limited, only certain regions can be measured. Therefore, getting a sound knowledge of pen-and-paper screening tests for dementia was essential not only to decide the regions to be measured but also to develop an effective protocol to differentiate NC from ED using fNIRS.

There exists various neuroimaging modalities such as fNIRS, fMRI, EEG and positron emission tomography (PET) that can be used in this study. Read up on these neuroimaging modalities was done to gain a better understanding in order to justify why fNIRS was preferred in this study.

To observe the difference between the brain signal of normal aging individuals and ED patients, tasks used to test WM were designed. Healthy controls and ED patients underwent the designed tasks while getting their brain signals recorded. Other than pen-and-paper screening tests, this data was processed and analysed to diagnose dementia.

1.5 THE REPORT

This report contains several chapters, ranging from introduction to conclusion.

Chapter 2 outlines what have been done and found by other researchers in the topics which are related to this study, such as neuroimaging modalities, and the difference of NC and ED from the aspects of neuroimaging.

Chapter 3 describes a system of methods which was deployed to achieve the goals of this study. The system of methods includes appropriate subject selection, the protocol, signal processing, and a Gantt chart.

In Chapter 4, results are presented and discussed by commenting on the results obtained, interpreting what the results mean and explaining any results which are unexpected.

Chapter 5 wraps up what have been discussed in this report. Based on the results, Chapter 5 also reaffirms the statement, discusses the issues, and reaches a final judgment.

CHAPTER 2
LITERATURE REVIEW

INTRODUCTION

First, this section briefly discusses some of the neuroimaging modalities which are more commonly used – fNIRS, fMRI and EEG. Other than that, this section also compares the brain function between healthy individuals and ED patients.

2.1 fNIRS AND OTHER NEUROIMAGING MODALITIES

fNIRS is a neuroimaging modality that monitors the brain activity non-invasively through hemodynamic responses [12]. Oxygenated haemoglobin (oxy-Hb) is the form of haemoglobin with the bound oxygen while deoxygenated haemoglobin (deoxy-Hb) is the form of haemoglobin without the bound oxygen. In fNIRS, oxy-Hb and deoxy-Hb absorb the 700-900 nm near-infrared (NIR) light penetrating through skin and skull differently (see Fig. 2). Thus, concentration changes in both oxy-Hb and deoxy-Hb can be calculated based on the NIR light scattering and attenuation. A study has proven that oxy-Hb is more sensitive to cerebral blood volumes changes that are associated with task [13]. Because of the portable equipment, ease of setup and lenient subject constraints, there has been a widespread use of fNIRS, including observing task-associated brain responses [14] and treating attention deficit hyperactivity disorder (ADHD) [15].

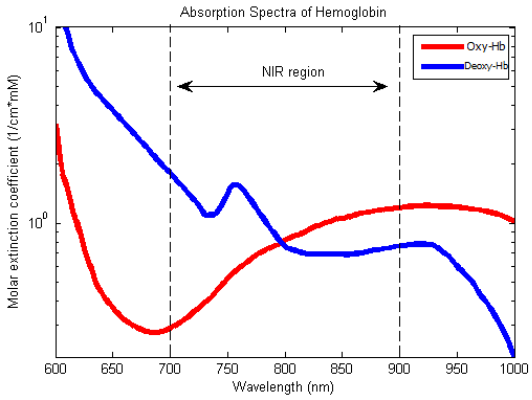


Fig. 2. Absorption spectra of oxy-Hb and deoxy-Hb for NIR wavelengths, by Adrian Curtin – CC-BY-SA-2.1-jp.

Other than fNIRS, there are various non-invasive neuroimaging modalities such as fMRI and EEG. By utilizing magnetic resonance imaging (MRI) technique, fMRI detects task-associated changes in blood oxygenation and flow to measure the brain activity. Although fMRI has excellent spatial and temporal resolution [16], the equipment is large, expensive, and the subject constraints are strict. fMRI neurofeedback system has succeed in controlling brain areas associated with pain processing [17, 18]. On the other hand, EEG uses electrodes affixed to the scalp to detect the electrical activity in the brain. Despite EEG has a high temporal resolution, the resistivity of skull limits its spatial resolution [19] and only a small proportion of the signals recorded originates from the deeper brain layer [20]. Previous studies have showed that neurofeedback system utilizing EEG is effective in treating brain disorders [21, 22].

2.2 WORKING MEMORY

WM involves a total of three subsystems [23]. Two of them are to store and manipulate visual images as well as verbal information, which include visuospatial sketchpad and phonological loop [24, 25]. 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 [26]. As WM is heavily involved in a vast range of functions, the following paragraph will discuss the cognitive impairments in patients with AD that are related to WM deficits.

Patients with AD show broad impairment in the capacity for new learning [27]. This is due to the fact that WM deficits often result in the inability to retain short-term memory, hindering long-term memory consolidation during the learning process [28]. Apart from that, patients with AD suffer from another principal WM deficit – impairment in the access to semantic memory, which is probably caused by declined central executive functions [27]. These reported findings all suggest that WM deficits are associated with the cognitive impairment in AD.

2.3 DIFFERENTIATING NC FROM ED

Currently, only pen-and-paper tests are deployed to diagnose dementia. Mini Mental Status Examination (MMSE) is a tool designed to screen for cognitive impairment [29] (refer to APPENDIX A) while Clinical Dementia Rating (CDR) is an observer rating scale developed to rate the severity of dementia [30] (refer to APPENDIX B). The CDR requires not only the dementia patient but also a reliable informant or collateral source (usually a family member). Besides that, other limitations of the CDR include its length of administration, reliance on clinical judgment, and relative insensitivity as a measure of change in interventional studies. The last point is vital when it comes to monitoring the progress of ED. In this case, CDR is definitely less sensitive.

The prefrontal cortex of the brain is shown in red in Fig. 3. Apart from pen-and-paper tests, previous study comparing brain function between AD patients and healthy elderly people showed that the most significant differences in activation during avoiding collision in simulated driving were observed in the prefrontal cortex [31]. Another research, in which letter verbal fluency task (VFT) was used as an activation task, revealed that AD patients have lower activation level in the frontal, left and right parietal, and occipital areas, as compared with healthy elderly people [32]. Contradictory, it was found that healthy elderly individuals showed increases in oxy-Hb in both left prefrontal and left superior parietal cortices, and AD patients showed simultaneous decreases and increases in oxy-Hb in the left parietal and left prefrontal cortices respectively during letter VFT [33]. Besides that, previous research claimed that predominantly left hemispheric activation can affect the performance of VFT significantly [34]. Last but not least, a previous study has reported that VFT activates several regions including the left prefrontal cortex [35].

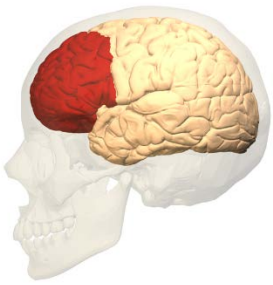


Fig. 3. Prefrontal cortex shown in red, by Database Center for Life Science (DBCLS) and BodyParts3D – CC-BY-SA-2.1-jp.

SUMMARY

fNIRS was utilized throughout this study. Previous studies have claimed that WM deficits are associated with the cognitive impairment in AD. Besides that, it has been reported that both frontal and parietal regions shows prominent differences in brain function between healthy individuals and AD patients. These regions are responsible for WM. Therefore, a protocol testing WM and focusing on frontal region was developed to differentiate NC from ED clinically using fNIRS.

CHAPTER 3
METHODOLOGY

3.1 SUBJECTS

The experiment involved two group of subjects: healthy controls and ED patients. A total of 10 subjects (3 healthy individuals and 7 ED patients) participated in this study. The mean (± standard deviation) ages of healthy controls and ED patients were 71 (± 6) and 74.9 (± 9.6) years respectively. The inclusion criteria for participation are shown in Table 1. All subjects were briefed through the nature of the experimental procedures prior to the experiment. Following the receipt of subject information (refer to APPENDIX C) and informed consent form (refer to APPENDIX D), subjects were administered the MMSE and CDR by the investigator or a trained member of the study team. All the tests and experiment were completed on the same day with a break in between the tests and experiment. Demographic information that were collected include age, gender, ethnicity, education level, first language, employment status, and diagnosis.

Table 1. The inclusion criteria for participation in this study.

Inclusion Criteria	
Healthy Controls	ED Patients
• Above 60 years old [4] • Right-handed • Able to converse in English • No cognitive complaints and no deficits on testing • Independent in activities of daily living • No past history of psychiatric or neurological disorder • CDR = 0 **[30]** • MMSE score ≥ 24 **[29]**	• Above 60 years old [4] • Right-handed • Able to converse in English • CDR = 1 [30] • MMSE score < 24 [29]

3.2 DEMENTIA SCREENING INSTRUMENT

The instruments that were administered in this study include both MMSE and CDR. For MMSE, it scores from 0 to 30 where the higher scores indicate better cognition. The cut off of 17 was set for cognitive impairment. On the other hand, the CDR tests 6 performance areas: memory, orientation, judgment, problem-solving, community affairs, home and hobbies, and personal care. In each area there is a 5 point scale where 0 represents the absence of dementia, 0.5 for questionable, 1 for mild, 2 for moderate, and 3 for severe dementia. The sum of box in these 6 areas will be used in this study. Having completed the online Washington University training module for CDR assessment, a few investigators or members of the study team were eligible to conduct CDR assessment.

3.3 FNIRS SYSTEM

In this study, 52-channel OT-R40 fNIRS topography system (Hitachi Medical Corporation, Japan; see Fig. 4) was used to measure the brain activity. The probes and channels layout is illustrated in Fig. 5. According to international 10-20 system [36], emitter 23 and 28 were placed directly at T4 and T3 respectively. 52 measurement channels are sufficient to cover the prefrontal cortex. Since the probes were attached to a flexible head cap (see Fig. 6), it was relatively easy, fast and convenient to wear the head cap directly on the subjects. All channels had to be checked to ensure that the probes are in contact with the scalp. The entire process consumed less than 10 minutes.

Fig. 4. OT-R40 fNIRS topography system used throughout this study.

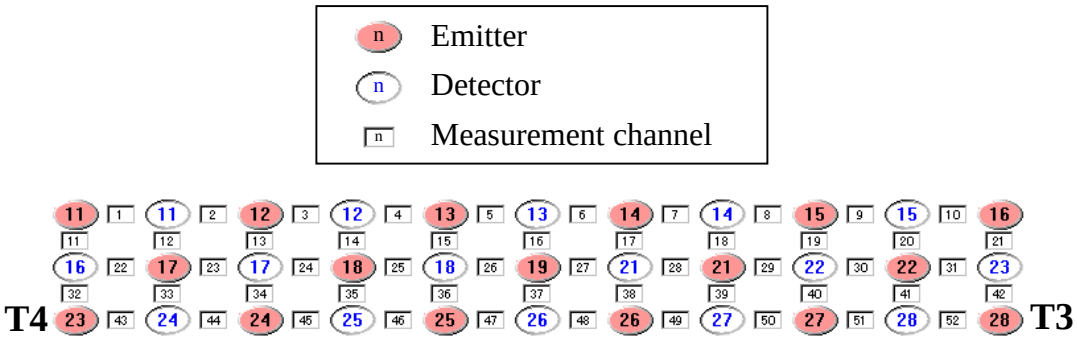


Fig. 5. The probe and channel layout, creating 52 measurement channels.

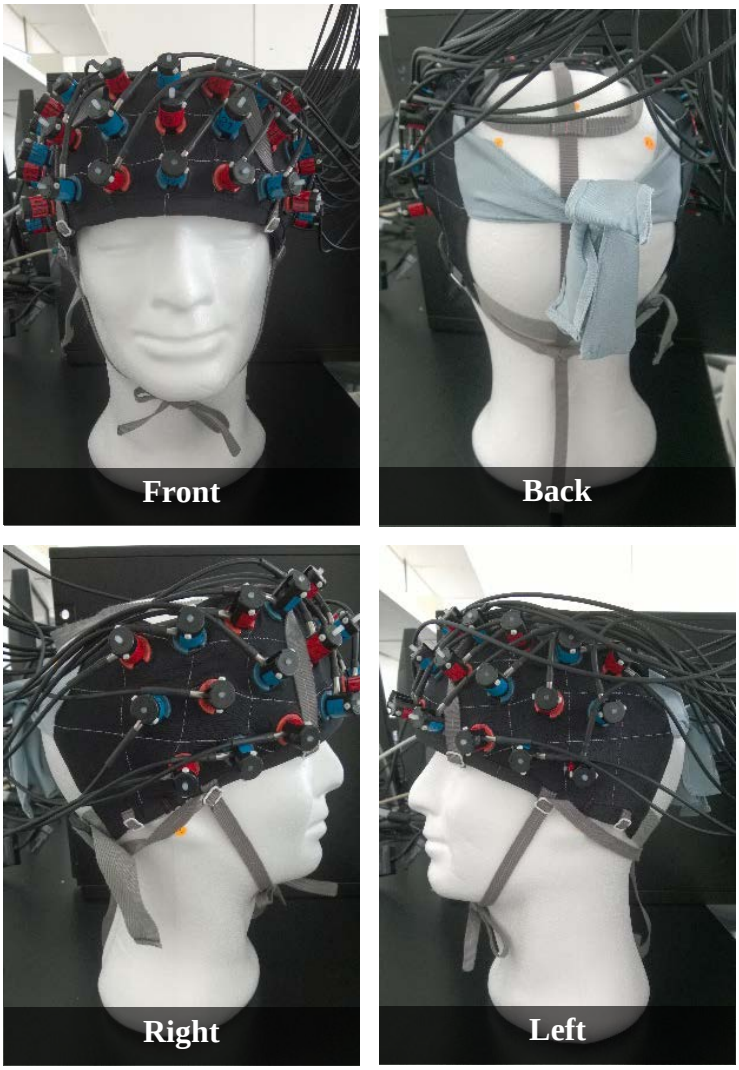


Fig. 6. A mannequin head wearing the elastic cap which holds the probes. It is relatively fast and easy to wear it directly on the subjects.

Serial communication was used to allow remote triggering (START/STOP, marker set etc) and control of the OT-R40 from an external PC. After connecting the OT-R40 and an external PC using a serial cable, the OT-R40 can receive specific commands from the external PC and execute them accordingly. These commands are listed in Table 2. With these commands, markers were sent to do data logging. These markers were then used during the data extraction process, which will be explained in detail later. Coloured regions (each colour representing a specific marker) will appear on marked data, as shown in Fig. 7.

Table 2. Received command and display character in mark field.

Received Command	Display Character in the Mark field	Received Command	Display Character in the Mark field (Stim Measurement)
ST [cr]	START	A [sp] [cr]	A
ED [cr]	STOP	B [sp] [cr]	B
PS [cr]	PAUSE	C [sp] [cr]	C
UP [cr]	unPAUSE	D [sp] [cr]	D
		E [sp] [cr]	E
		F [sp] [cr]	F
		G [sp] [cr]	G
		H [sp] [cr]	H
		I [sp] [cr]	I
		J [sp] [cr]	J

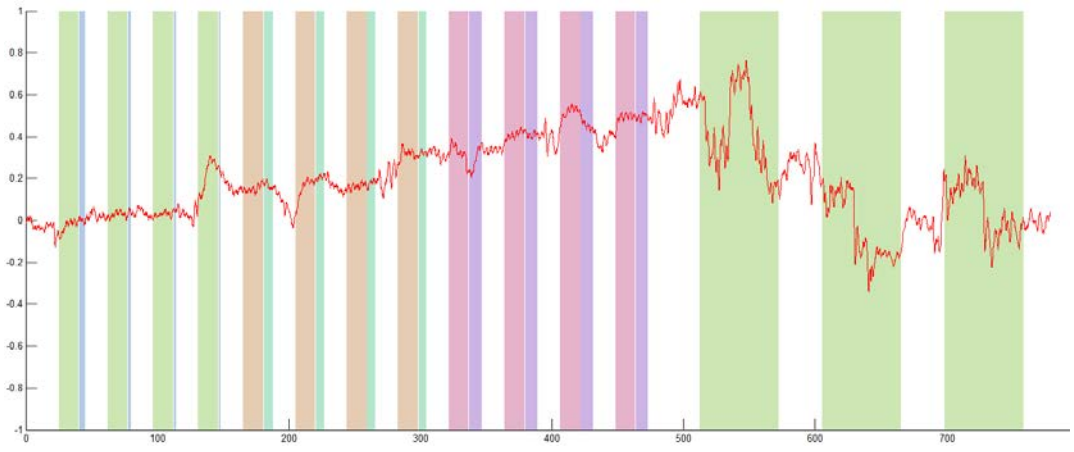


Fig. 7. An example marked data. The coloured regions are the markers.

3.4 TASK PARADIGM

A MATLAB-based program was developed. There were two types of task-sequencing and verbal fluency. Both tasks were carried out in English language. The sequencing tasks were similar to the game “Remember The Sequence” designed by Alzheimer’s Disease Association [37]. The subjects were given briefing and training before any measurement. This was to familiarize the subjects with the experimental procedures. Other than that, the subjects were instructed to avoid movement, keep their left hand on the arm rest and their right hand on the mouse. After doing so, the brain activity was recorded when the subjects were carrying out the tasks. Fig. 8 shows the experimental setup. There were three levels of sequencing tasks – Level 1, 2 and 3. In each level, there were four rounds. On the other hand, verbal fluency for the categories fruits, food, and animals were included. The time course of the tasks was plotted in Fig. 9(a). During the pre-task and post-task rest periods, the subjects were required to keep their eyes on the fixation point as shown in Fig. 9(b).

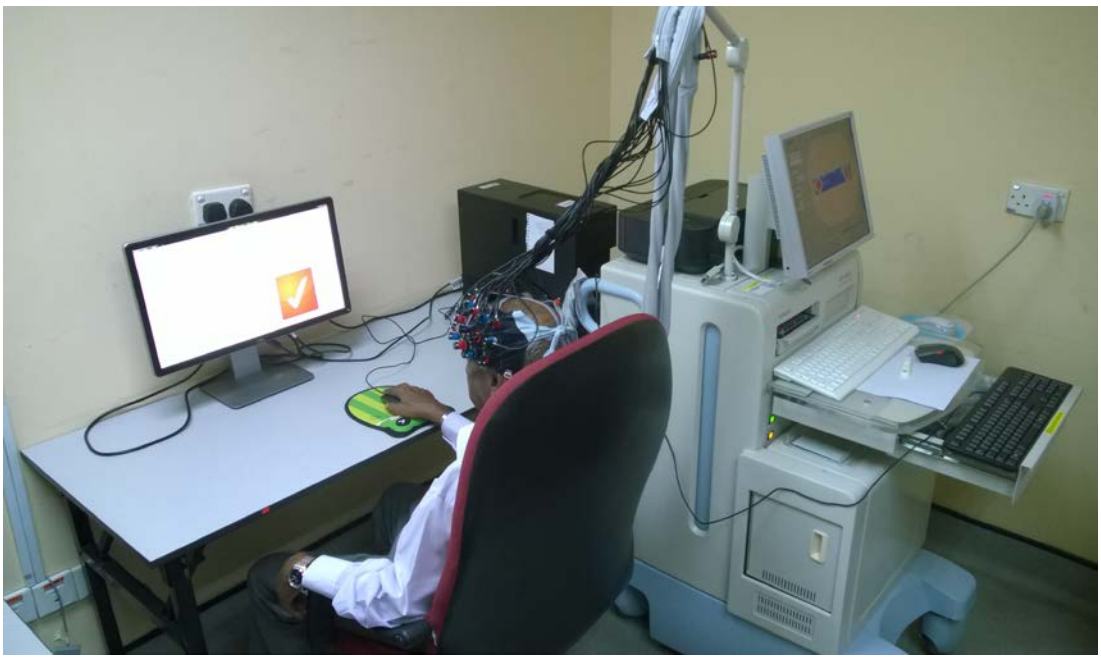
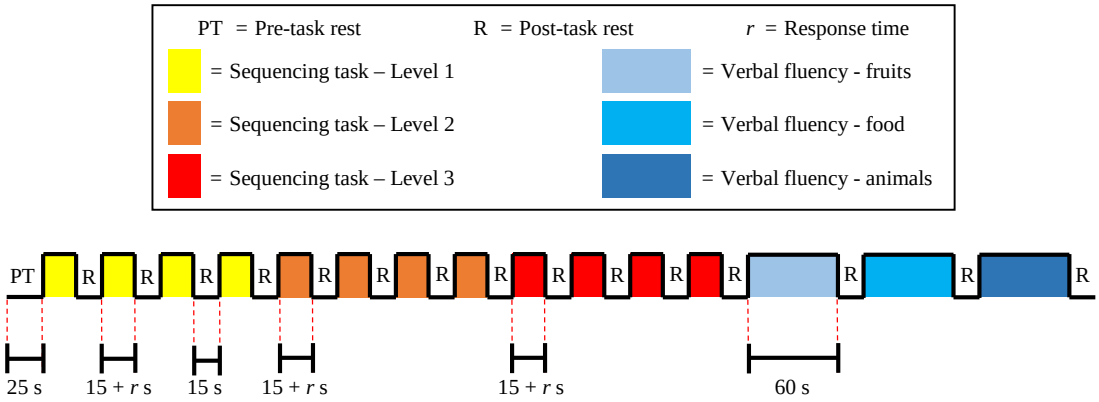
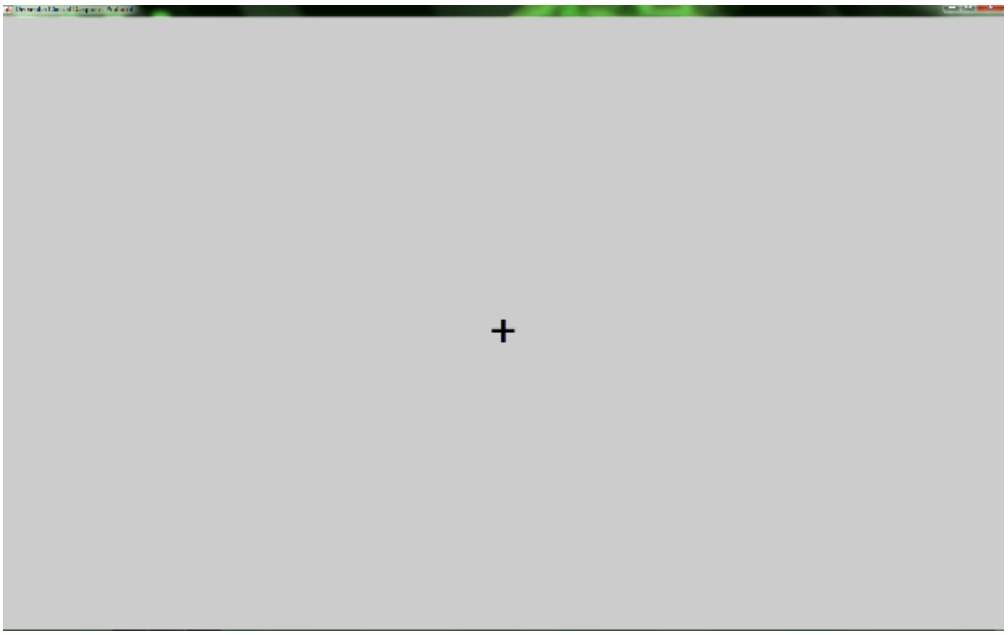


Fig. 8. Each subject was instructed to avoid movement, keep their left hand on the arm rest and their right hand on the mouse during the experiment while carrying out the tasks and getting his or her brain activity recorded.



(a)



(b)

Fig. 9. (a) The time course of the tasks.
(b) The fixation point where the subjects have to keep their eyes on during rest.

3.4.1 Sequencing tasks

With accordance to Fig. 10, the subjects were required to remember series of images shown during the consolidation period and identify them by clicking on the boxes accordingly to the sequences during the response period. The response time (*r*) was recorded. Subjects only had one attempt per round. Specific instructions were listed in Table 3 while the time course of each level was illustrated in Fig. 10.

Table 3. Instructions for the sequencing tasks.

Level	Description
1	The subject is shown a shape momentarily. The subject has to identify the correct shape shown. See Fig. 10(a).
2	The subject is shown two fruits momentarily. The subject has to identify the two fruits in the correct sequence. See Fig. 10(b).
3	The subject is shown three animals momentarily. The subject has to identify the three animals in the correct sequence. See Fig. 10(c).

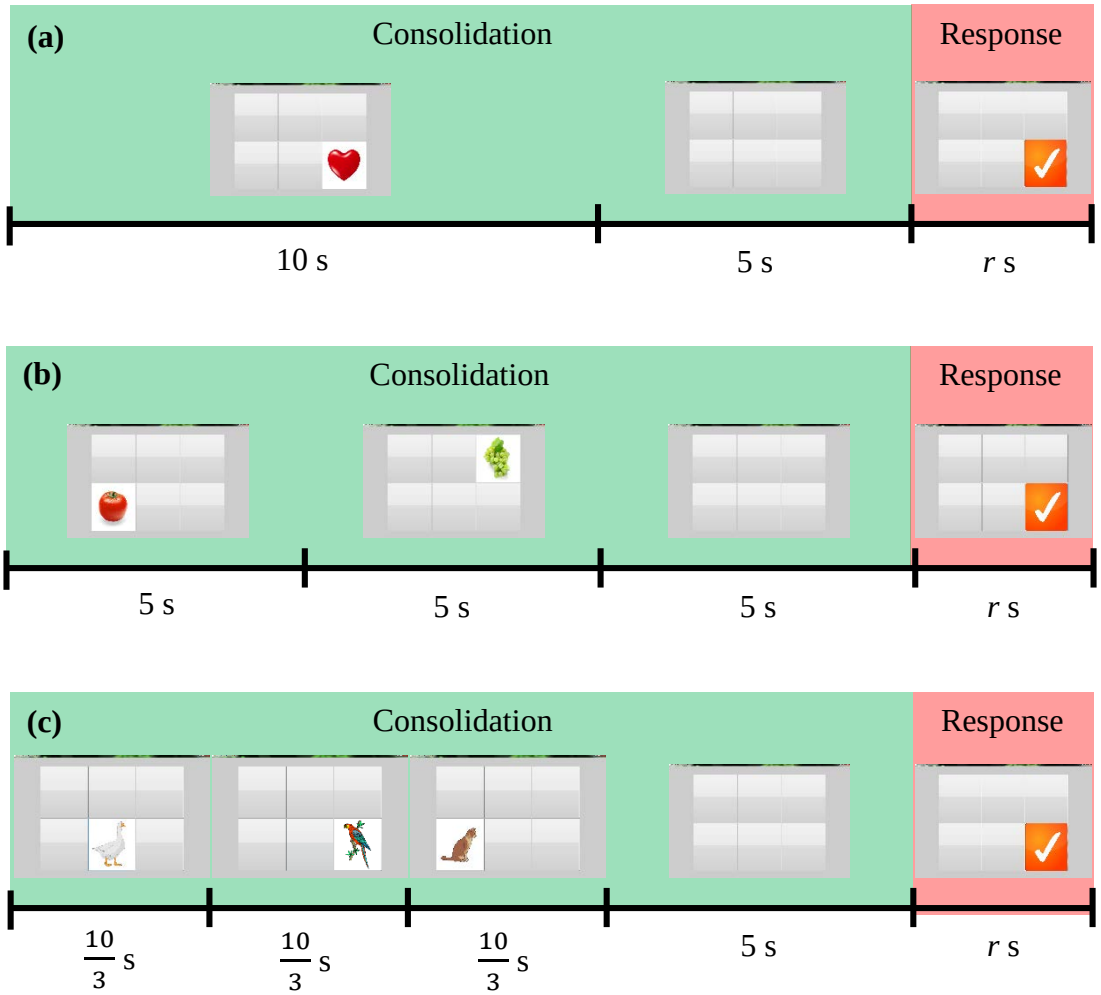


Fig. 10. Time course of the sequencing tasks. (a) Level 1 (b) Level 2 (c) Level 3

3.4.2 VFT

In previous studies using fNIRS, VFT has been widely used as an activation task for patients with Alzheimer's disease [32-34]. There are two versions of VFT: letter and category fluency task [38]. In this study, the latter was included as one of the tasks. Three categories including fruits, food, and animals were assessed in three sessions respectively. In each assessment, each subject was given 1 minute to come up with as many words as possible within that particular category. The total number of words given was recorded by the end of 1 minute. Besides that, subjects were also told to avoid repetition of words. For example, if fruits is selected to be the category, then the subject has to give words such as apple, banana, orange etc. verbally.

3.4.3 Omitted tasks

Initially, apart from the sequencing tasks and VFT, two other tasks were developed using MATLAB. They were known as "Where's The Twin?" and "Match Them Up". For the former, level 1, 2 and 3 contain 4, 3 and 2 rounds respectively while for the latter, level 1, 2 and 3 consist of 7, 5 and 3 rounds respectively. "Where's The Twin" was designed specifically to test working memory [37]. The instructions are listed in Table 4 and the screenshots are displayed in Fig. 11. On the other hand, "Match Them Up" aimed to test logical thinking [37]. The instructions are shown in Table 5 and the screenshots are illustrated in Fig. 12. Both of the tasks were tested using several university students who are in their twenties. However, considering the duration of the entire experiment, only one task was picked. Both of these tasks gave not much positive findings as compared to the sequencing task. As a result, the sequencing task was selected to feature in the experiment

Table 4. Instructions for the “Where’s The Twin” task.

Level	Description	Rounds
1	Four cards with two pairs of fruits will flip open on screen for a moment before closing again. The player has to remember the positions of pictures and match the same pictures.	4
2	Six cards with three pairs of animals will flip open on screen for a moment before closing again. The player has to remember the positions of pictures and match the same pictures.	3
3	Eight cards with four pairs of objects will flip open on screen for a moment before closing again. The player has to remember the positions of pictures and match the same pictures.	2

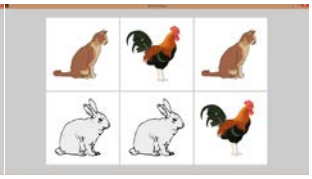
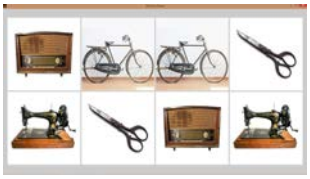
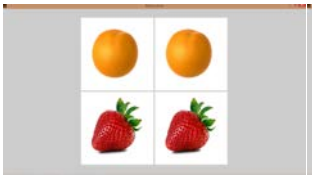
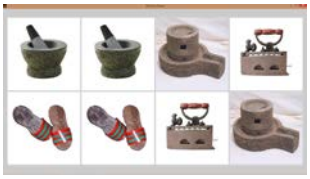
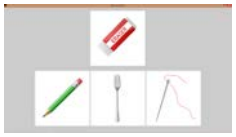
Round	**Level**		
	1	2	3
1			
2			
3			
4			

Fig. 11. Details and screenshots for each round of each level of the "Where's The Twin" task.

Table 5. Instructions for the “Match Them Up” task.

Level	Description	Rounds
1	The player is shown a frequently used item. The player has to identify another item associated with the item shown.	7
2	The player is shown a frequently used item. The player has to identify two other items associated with the item shown.	5
3	The player is shown a frequently used item. The player has to identify three other items associated with the item shown.	3

Round	**Level**		
	1	2	3
1		 	  
2		 	  

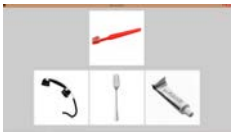
3		 	  
4		 	
5		 	
6			
7			

Fig. 12. Details and screenshots for each round of each level of the "Match Them Up" task.

3.5 DATA ANALYSIS

The Platform for Optical Topography Analysis Tools (Research & Development Group, Hitachi, Ltd.) or POTATo is a MATLAB-based graphical user interface (GUI) to serve as an analysis platform which is capable of carrying out a diversity of data processing methods (see Fig. 13). The raw data from fNIRS was first pre-processed using POTATo to remove artefacts due to body motion, heartbeat, breathing, and random noise. Next, temporal features were extracted from the corresponding fNIRS channels. Subsequently a classifier was implemented to identify subjects into NC and ED categories.

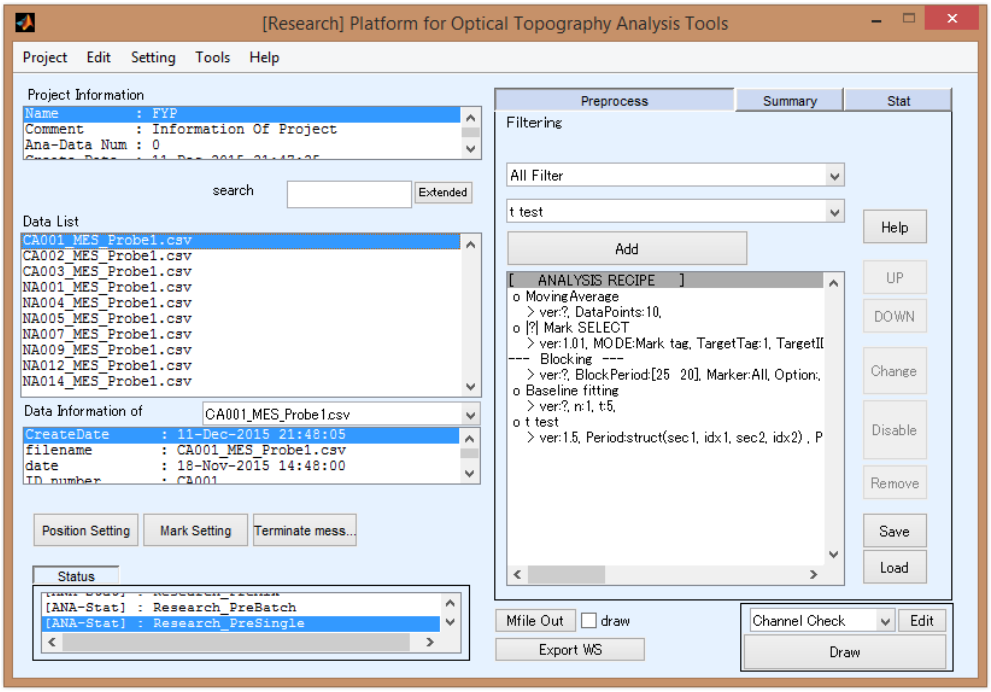
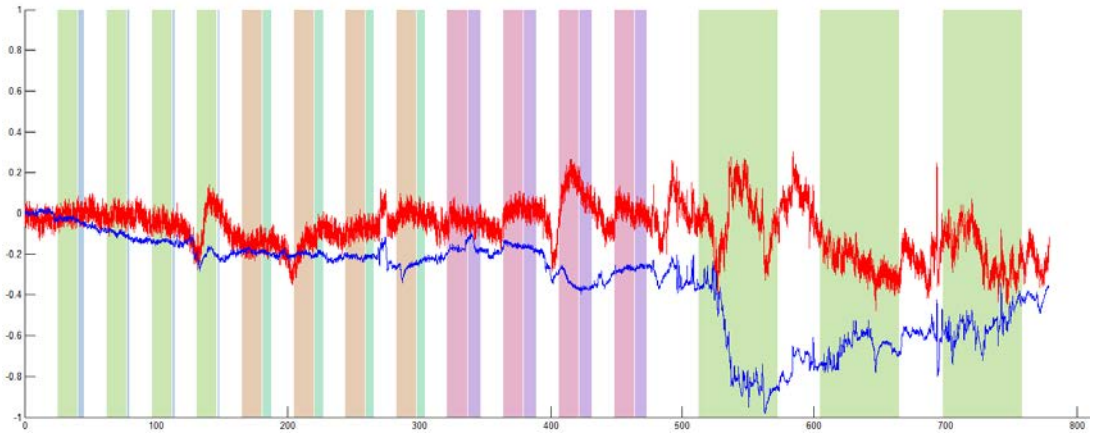
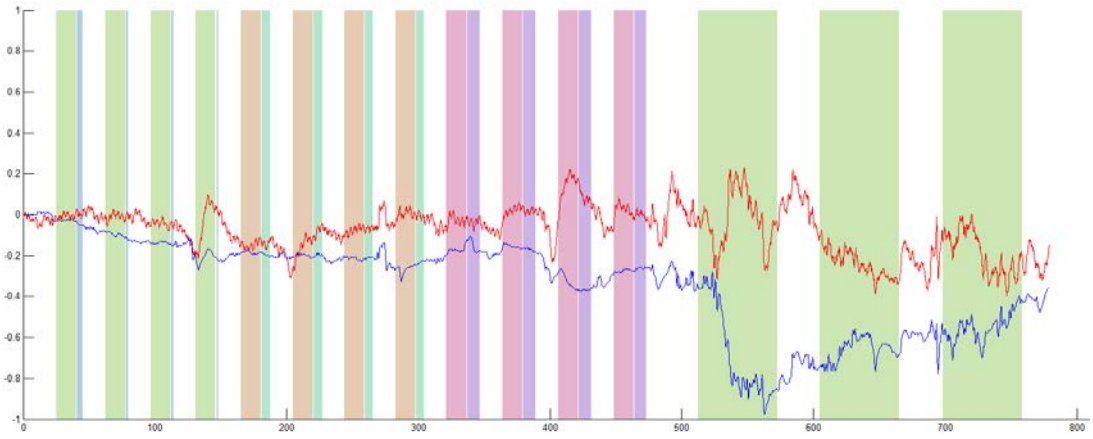


Fig. 13. POTATo, the tool used to facilitate data processing and analysis.

An example of raw signal from a single channel is shown in Fig. 14(a). Time (s) is plotted on the horizontal axis while oxy-Hb is plotted on the vertical axis. The red and blue signals represent oxy- and deoxy-Hb respectively. Each distinct coloured region represent a different task period. Raw signal is always noisier. Therefore, signal pre-processing was essential. First, moving average filter was applied to smooth the raw signal. Each data point was replaced by the average of the 10 neighbouring data points, resulting in a smoother and cleaner signal (see Fig. 14(b)).



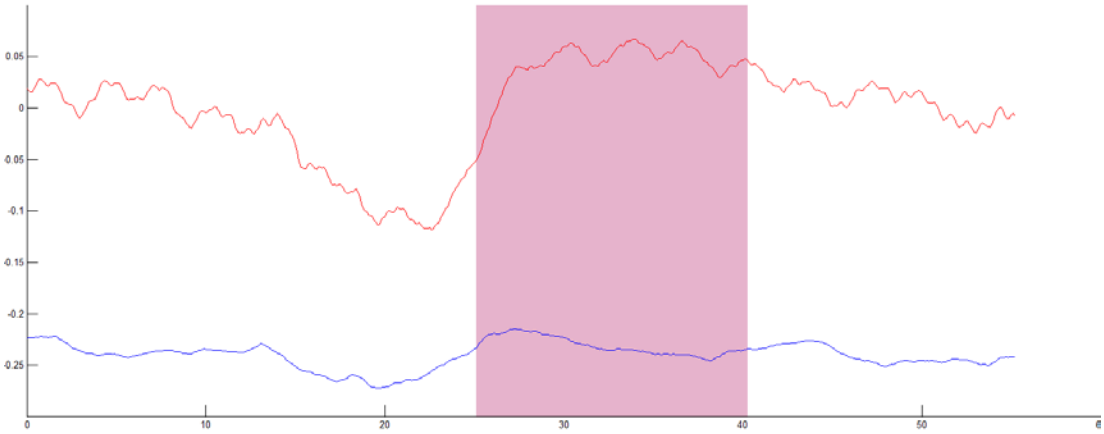
(a)



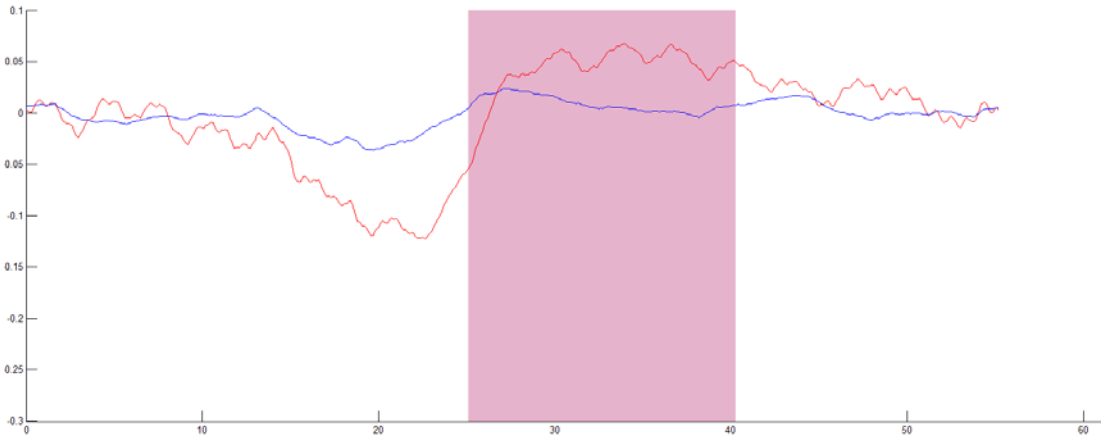
(b)

Fig. 14. Signal analysis: (a) raw signal (b) moving averaged signal

Then, signal during desired tasks was extracted and averaged to produce a blocked signal. For example, signal obtained during all 4 cognition periods of sequencing task level 3 can be extracted and averaged to produce the signal displayed in Fig. 15(a). The red region indicates the desired task period. After blocking, the signal was fitted accordingly to the baseline which was measured in the starting 10 seconds. The baseline-fitted signal is showed in Fig. 15(b).



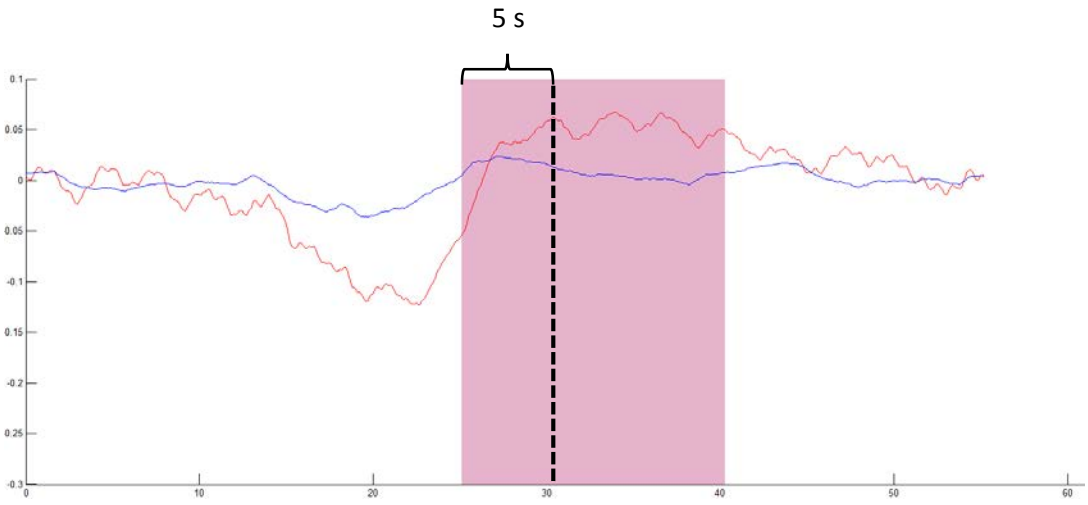
(a)



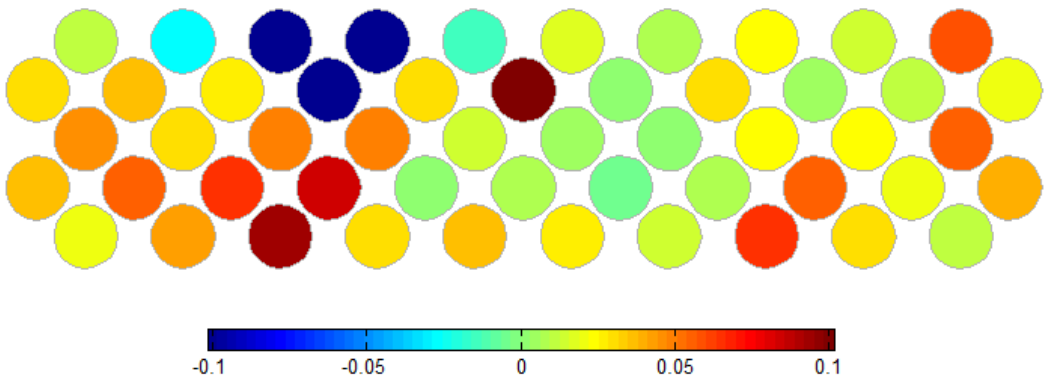
(b)

Fig. 15. Signal analysis: (a) blocked signal (b) baseline-fitted blocked signal

With accordance to Fig. 16(a), 5 s after the beginning of the task, the task-associated activation should be stable and can be observed clearly. The reason the duration for the activation to be stable is in the middle of task is that fNIRS data are delayed because changes of blood flow take time. The results or hemodynamic responses are shown in a channel layout, as illustrated in Fig. 16(b). The darker the shade of red is, the higher the activation is. From this layout, regions that are activated during the tasks can be seen vividly.



(a)



Concentration change of oxy-Hb (mM·mm)

(b)

Fig. 16. Signal analysis: (a) the duration for the activation to be stable (b) the hemodynamic responses in a channel layout

3.6 KEY MILESTONES

Table 6. Key milestones for FYP 1.

No.	Item/Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Title Confirmation	◆													
2	Completion of Protocol														◆
3	Ethics Approval of Research														◆

Table 7. Key milestones for FYP 2.

No.	Item/Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Trial run of experimental protocol	◆														
2	Finished recruiting subjects						◆									
3	Completion of data collection (MMSE)										◆					
4	Completion of data collection (CDR)										◆					
5	Completion of data collection (protocol)										◆					
6	Assessment of the effectiveness of fNIRS in differentiating NC from ED														◆	
7	Validation of the role of fNIRS in dementia diagnosis														◆	

3.7 GANTT CHART

Table 8. Gantt chart for FYP 1.

No.	Item/Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Select project														
2	Research and review														
3	Design, develop and test protocol														
4	Apply for ethics approval of research														

Table 9. Gantt chart for FYP 2.

No.	Item/Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Final test of protocol															
2	Identify and recruit subjects															
3	Data collection (MMSE)															
4	Data collection (CDR)															
5	Data collection (protocol)															
6	Data processing and analysis															
7	Statistical analysis															

CHAPTER 4
RESULTS AND DISCUSSION

4.1 SEQUENCING TASKS

It is reported that patients with Alzheimer's disease show broad impairment in the capacity for new learning [27]. Their WM deficits cause difficulties in retaining short-term memory, making them hard to consolidate memory items during the learning process [28]. Therefore, this study focused on the hemodynamic responses of each subject during the consolidation period of the sequencing tasks (see Fig. 10) and throughout the VFT.

4.1.1 Hemodynamic responses

The hemodynamic response of both subject groups during each level was assessed. Fig. 17 shows the comparisons between the averaged hemodynamic responses of healthy controls and ED patients during each level of sequencing task.

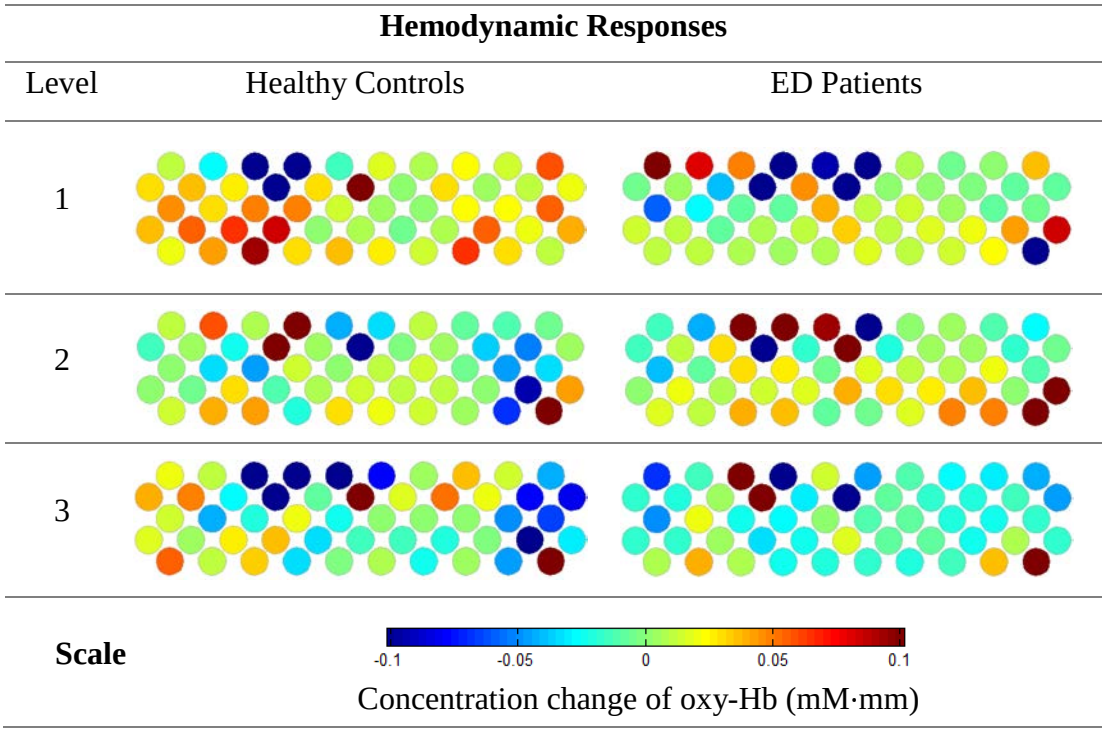


Fig. 17. The averaged hemodynamic responses during each level of sequencing task.

Referring to Fig. 17, the overall activation level of healthy controls was higher than ED patients regardless of level (level 1: 0.08 vs 0.04 mM·mm; level 2: 0.07 vs 0.06 mM·mm; level 3: 0.05 vs 0.04 mM·mm). During level 1 and 3, the activated regions of healthy controls were larger and more concentred on the right prefrontal cortex compared to ED patients. Other than that, for healthy controls, the right prefrontal cortex was more active in level 1 than in level 2 and 3.

As mentioned previously, the overall activation level of healthy controls was higher than ED patients regardless of level. Previous research has reported similar finding [32]. This may be due to the fact that some ED patients may be suffering from declined dilatory ability of cerebral vessels and compensatory ability of cerebral arterioles under hypoxic conditions. Both of these declines were reported to be associated with normal aging [39]. For healthy controls, the right prefrontal cortex was more active, suggesting that the right prefrontal cortex is more involved in short-term (working) memory [40].

4.1.2 Performance

The performance of both subject groups under each level was assessed by comparing the response time, which is the time taken for each subject to complete each task correctly. Fig. 18 shows the comparisons between the average response times of both subject groups in each level. Two-sample t-tests was deployed to show if there was a significant difference between the response time of healthy controls and ED patients. The t-test showed that there were significant differences in level 1 (p = 0.0073), 2 (p = 0.0069) and 3 (p = 0.0286).

The response time of healthy controls was found to be significantly shorter than that of ED patients in all three levels. This was expected as WM deficits are a recognised feature of ED. These deficits may cause them having difficulties in retaining short-term memory [28], deeply affecting their performances in the tasks.

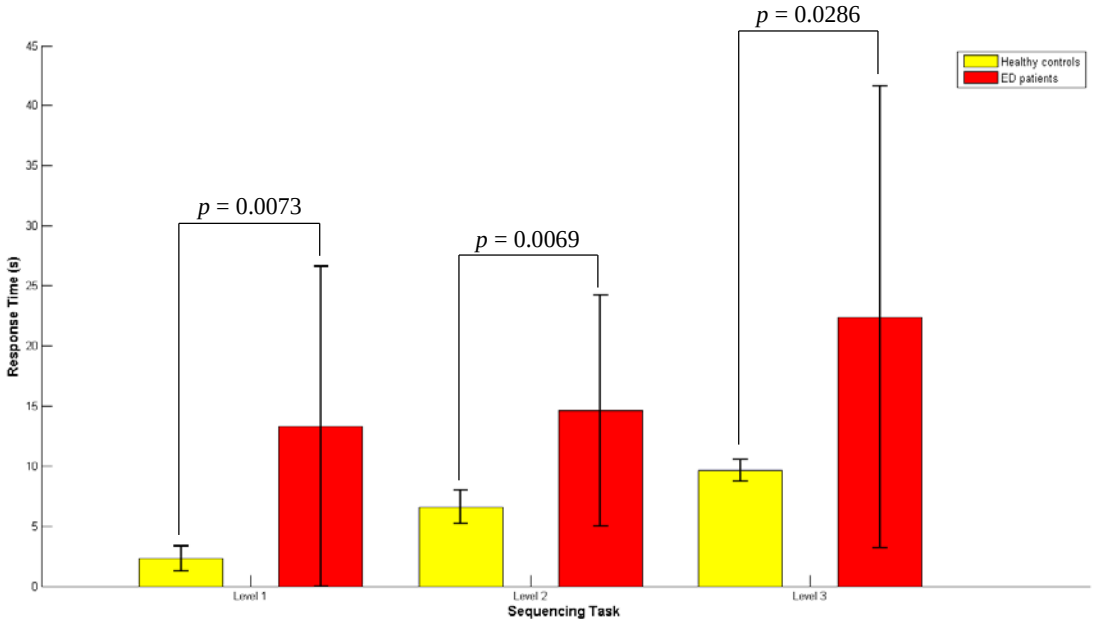


Fig. 18. The response time of both subject groups in each level of sequencing task.

4.2 VFT

4.2.1 Hemodynamic responses

The hemodynamic response of both subject groups during VFT was assessed. Fig. 19 shows the comparisons between the averaged hemodynamic responses of healthy controls and ED patients during VFT. With accordance to Fig. 19, the overall activation level of healthy controls was higher than ED patients (0.2 vs 0.1 mM·mm). More complicated activations were observed during VFT as it tests not only working memory but also verbal and executive control abilities. It was also found that activated regions of healthy controls were more concentred on the left and right prefrontal cortex compared to ED patients. Other than that, ED patients showed increases in oxy-Hb in the left prefrontal cortex during VFT. These findings clearly indicate that the VFT activated the left and right prefrontal cortex of healthy controls but only the right prefrontal cortex of ED patients.

The overall activation level of healthy controls was higher than ED patients regardless of level. Previous research has reported similar finding [32]. This may be due to the fact that some ED patients may be suffering from declined dilatory ability of cerebral vessels and compensatory ability of cerebral arterioles under hypoxic conditions. Both of these declines were reported to be associated with normal aging [39].

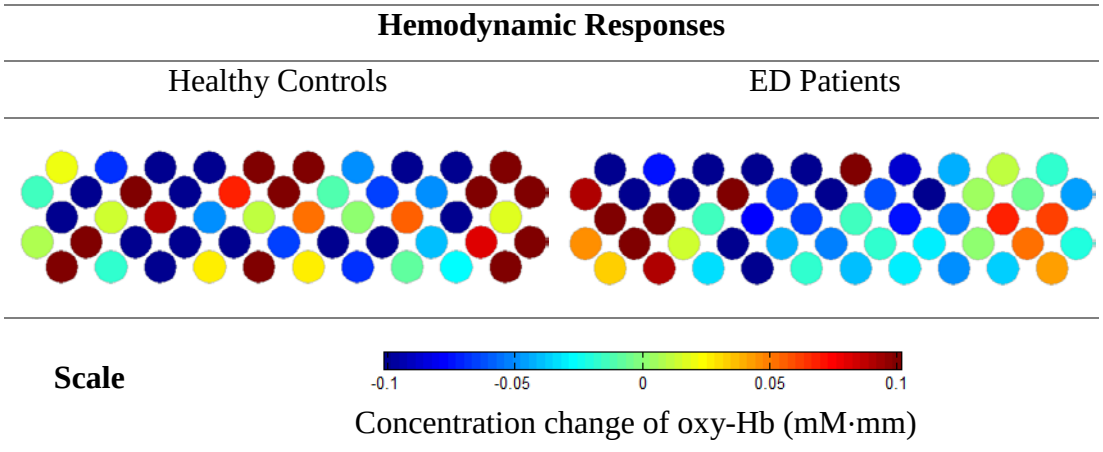


Fig. 19. The averaged hemodynamic responses during VFT.

4.2.2 Performance

The performance of both subject groups under each category of VFT was assessed by comparing the number of words given. Fig. 20 shows the comparisons between the numbers of words given by both subject groups in each category. Two-sample t-tests was deployed to show if there was a significant difference between the number of words given by healthy controls and ED patients. The t-test showed that there were significant differences in category fruits (p = 0.0021), food (p = 0.0174) and animals (p = 0.0018).

The number of words given by healthy controls was found to be significantly higher than that of ED patients in all three categories. This was expected as semantic memory impairment is very prominent in of ED. This impairment may cause the ED patients difficulties in retrieving semantic information [27], deeply affecting their performances in the tasks.

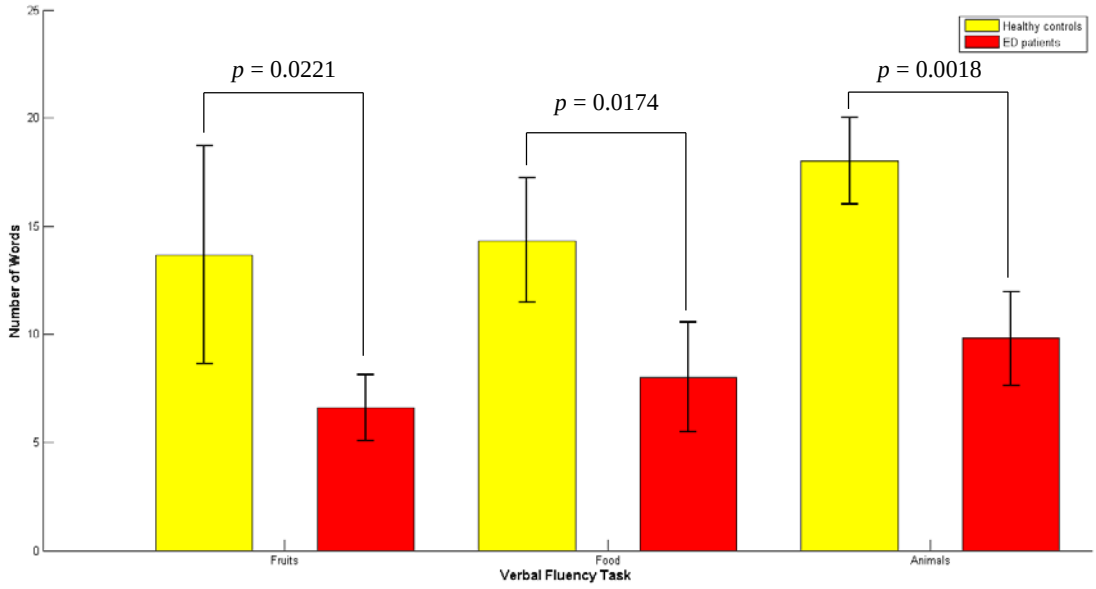


Fig. 20. The number of words given by both subject groups in each category of VFT.

CHAPTER 5
CONCLUSION AND RECOMMENDATION

As of now, there is no cure for dementia and it cannot be stopped from progressing. Dementia may involve deficits in memory, language, attention, praxis, visuospatial skills and executive functions. With these deficits, it is difficult for dementia patients to carry out activities of daily living without any interference.

To date, only pen-and-paper tests are used to screen for dementia. These tests can be time consuming, not economical in the sense that the services of psychiatrist or psychologist don't come cheap, and are just behaviour assessments. Thus, this study tested the effectiveness of fNIRS in clinical diagnosis of dementia by differentiating normal cognition and early dementia.

In conclusion, the differences between normal cognition and early dementia can be observed clearly during the sequencing and verbal fluency tasks. In early dementia a reduction of blood flow and oxygenated haemoglobin may occur during activation of brain function, probably mainly in the degenerating brain regions, namely left and right prefrontal cortex. However, as of now, the sample size is not sufficient enough to conclude this study. The data collection is still on-going and by then more detailed statistical analysis can be done. Once the data collection are completed and the sample size is large enough, the role of fNIRS in dementia diagnosis can be validated.

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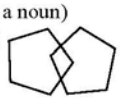
APPENDICES

APPENDIX A – MINI MENTAL STATUS 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.

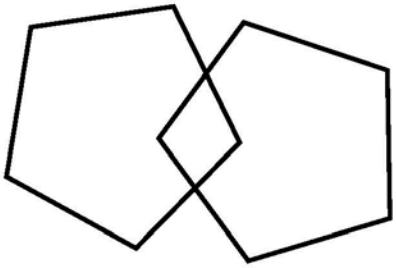
RN	
Name	
DOB	
Sex	
Unit	

Read and obey:

CLOSE YOUR EYES

Write a complete sentence:

Copy this design:



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

APPENDIX B – CLINICAL DEMENTIA RATING (CDR) WORKSHEET

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.

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?
If not, please probe further.

Community Affairs: 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.**

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	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 1 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.

APPENDIX C – SUBJECT INFORMATION FORM

Participant Information Form

First name:		**Last name:**	
Email:		**Assigned ID:**	

Personal Information			
Nationality:		NRIC/Passport No.:	
Phone No.:		Emergency	Name & Relationship
Alternative No.:		Contact:	Contact Number
Mailing Address:			

Research Related Information			
Date of Birth:	__(dd) __ (mm) __ (yy) Age: ( )	First Language:	
Gender:		Past Occupation:	
Ethnicity		Highest Education Level:	
Dominant Hand:	Hand used for writing / mouse control	CDR Score:	
Smoking?	No: ☐ Yes:☐ (Hours:___) ago	MMSE Score:	
Caffeine Intake?	No: ☐ Yes:☐ (Hours:___) ago	English Proficiency Test:	Eg. IELTS, TOEFL, Cambridge
Vision:		Movement:	

Health Condition – Interview Log (To be filled by researcher)					
Physical Condition: Are you feeling well? Hungry? 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?					
Information completed?	**Yes**	**No**	**Suitable for Experiment?**	**Yes**	**No**
Date of Experiment	(Day:)		Start and End Time	start	end

VFT Results		
Fruits	Foods	Animals

Yellow Channels	**Order of Level**

1

Remarks:

2

APPENDIX D – INFORMED CONSENT FORM

Informed Consent Form

Purpose and Procedures: This study is intended to validate the functional near-infrared spectroscopy (fNIRS) in differentiating normal cognition from Early Dementia. If you agree to take part in this research, you will be asked to undergo series of computer games. Your memory will be assessed using Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) Scale. You are required to wear the fNIRS while performing the computer games in order to measure your brain activity. This will take about 30 minutes.

Voluntariness: Your participation in this research is voluntary. You may refuse to participate, discontinue participation, or skip any questions you do not wish to answer at any time without penalty or loss of the benefits to which you are otherwise entitled.

Risks and Benefits: You may experience some mild, temporary discomfort relating to taking the tests and your performance on the test. You will receive travelling remuneration for RM100 per visit in the study. Furthermore, your participation may help researchers and clinicians understand the underlying mechanism of the study.

Confidentiality: Only the principal research will have access to research results associated with your identity. In the event of publication of this research, no personally identifying information will be disclosed. To make sure your participation is confidential, and your personal identity will not 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 of risk.

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:

Dr. Esther Gunaseli: +6013 – 5201220 / esthergunamy@yahoo.com

Dr. Tang Tong Boon: +6012 – 7336653 / tongboon.tang@petronas.com.my

Yap Kah Hui +6016 – 5536721 / kahhui@hotmail.com

Consent form

I certify that I have read this form and volunteer to participate in this research study. I hereby grant permission to Dr. Esther Ebenezer, Dr Tang Tong Boon, and co-researchers to utilize my demographic data and my test results without identifying personal information for research and educational purposes. Only aggregate results will be used and individual information will not be retrievable. I understand that my anonymity and confidentiality be protected.

(Print) Name of Subject	I/C number of Subject
Signature of Subject	Date

.....

(Print) Name of Investigator	I/C number of Investigator
Signature of Investigator	Date