COMPARISON OF BRIAN ACTIVITY IN THE PREFRONTAL CORTEX DURING DIGIT SPAN TASK BETWEEN STUDENT VETERANS WITH POST TRAUMATIC STRESS DISORDER AND CONTROLS USING FUNCTIONAL NEAR INFRARED SPECTROSCOPY

By

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ABSTRACT

COMPARISON OF BRIAN ACTIVITY IN THE PREFRONTAL CORTEX DURING DIGIT SPAN TASK BETWEEN STUDENT VETERANS WITH POST TRAUMATIC STRESS DISORDER AND CONTROLS USING FUNCTIONAL NEAR INFRARED SPECTROSCOPY

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Near Infrared Spectroscopy (NIRS) is a non-invasive optical imaging technique which makes use of near infrared light at particular wavelengths to measure the changes in concentrations of oxygenated haemoglobin (HbO) as well as the deoxygenated haemoglobin (HbR). Making use of this technique to acquire measurements during different functional activities subcategorises it into the novel and fast developing field of Functional Near Infrared Spectroscopy (fNIRS). In my study, I have made use of this novel imaging technique to study the pre-frontal cortex, while the subject performs the functional task of “digit span” consisting of the forward digit span and the backward digit span.

The Digit span task requires the subject to recall a set of digits that was flashed on the screen one after the other for one second each. In forward task, the subject recalls the flashed digits in the order it was shown; in the backward task, the subject recalls the digits in the reverse order. This test was done on two different groups of subjects, one being the control consisting of male students with good mental and learning abilities and the other being veteran students identified with Post Traumatic Stress Disorder(PTSD). The subjects were simultaneously imaged with fNIRS in their prefrontal cortices while doing the task.

A series of comparison mechanisms were used to analyze the HbO concentration changes happening in the prefrontal brain between the controls and the PTSD veterans while performing this cognitive task. It was found that in forward digit task the PTSD group showed significant deactivation compared to the controls in the frontopolar prefrontal cortex (PFC) regions of the brain. Higher levels of activation were found during the backward digit task, but a significant difference was not observed between the control group and the PTSD veteran group.

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CHAPTER 1

INTRODUCTION

1.1 Principle of Near Infrared Spectroscopy

Near Infrared spectroscopy makes use of near infrared light to detect and measure the changes in the concentrations of oxygenated (HbO) as well as the deoxygenated (HbR) hemoglobin. It makes possible the use of this principle to record measurements and assesses the brain activation from the human cortex.

1.1.1 Functional Near Infrared Spectroscopy

Functional optical imaging is usually related to the assessment of physiological changes associated with brain activity. It makes use of the changing optical properties of body tissues by using light in the near-infrared range (700–900 nm) to measure physiological changes.

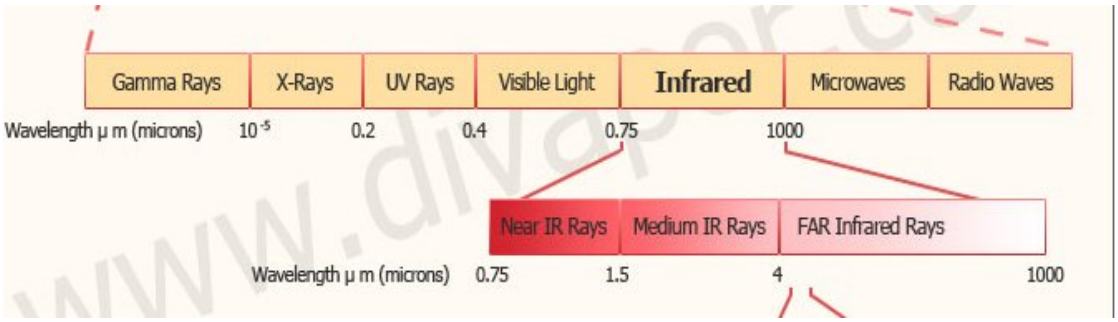

Figure 1.1 The electromagnetic spectrum with infrared region explained [7]

Human brain undergoes a lot of physiological changes relative to the different environmental stimuli available around, and these physiological changes are mainly the changes in blood level and other electrochemical activities which in turn affect the optical properties in that brain area. It is this change in optical properties, that the functional optical imaging makes use of, to measure the physiological changes.

1.1.2 Light in tissue

For understanding how the functional optical imaging of brain activity is done, we have to understand the interactions of photons with brain tissue and also the physiological events which are associated with brain activity and the relationship between optical and physiological parameters. Biological tissue is relatively transparent to light in the near-infrared range between 700–1000 nm. The main absorbers of light in tissue, water and the chromospheres are oxy- and deoxy- haemoglobin; their absorptions are relatively small but in fair amounts within this wavelength region (Fig. 1.2). Therefore, this wavelength range represents an 'optical window' for the non-invasive assessment of brain tissue [3][18].

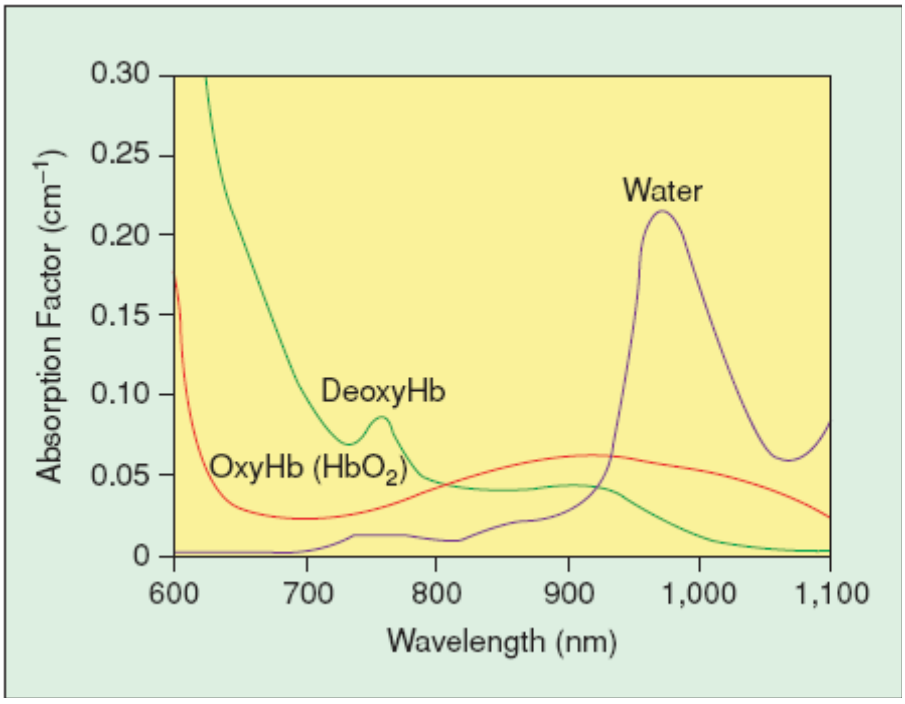

Figure 1.2 Absorption spectrum of Oxygenated hemoglobin, deoxygenated hemoglobin and water in the near infrared wavelength region [3].

During optical imaging of the brain, light sources are coupled to the subject's head via fibre-optical bundles (optodes). Photons entering the scalp and passing through most of the tissue are either scattered or absorbed. Since there are a relatively measurable amount of

photons that follow a banana shape path through the brain cortex to emerge back to the surface of the skin, a second optode receiver is placed 2–5 cm away from the first source optode to collect this light coming out, as shown in figure 1.3. The light-receiving optode is connected to a light detecting system to make a quantitative measurement of the received light [3].

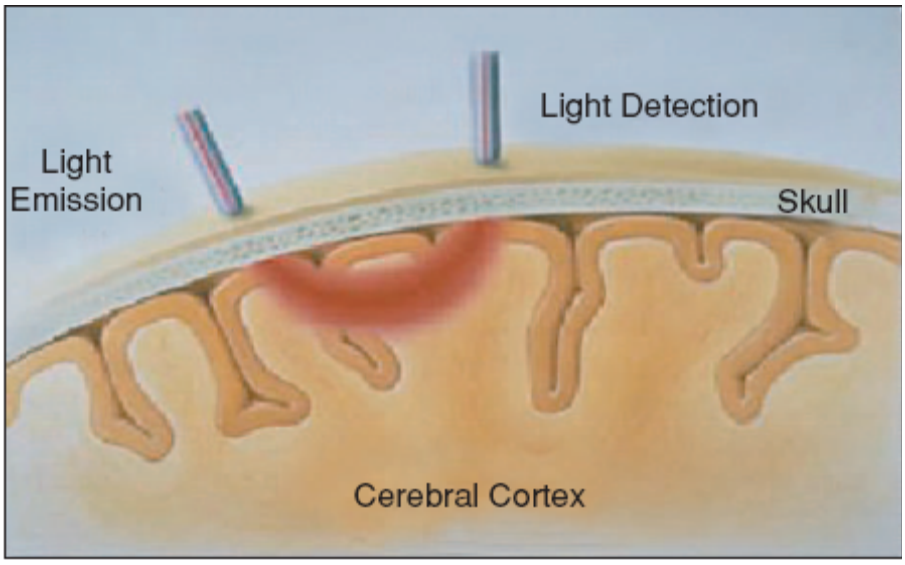

Figure 1.3 Dispersion of near infrared light through the cortex of brain in a banana shape [3].

The concentration of a light-absorbing chromophore in tissues is determined similar to that done to identify a substance concentration by a photometer. Light scattering is considered negligible by assuming infinitesimal substance concentrations. In such a condition, the concentration of a substance can be determined according to the modified Lambert–Beer law

$$\Delta OD = \log (I_o/I) = \varepsilon cL \quad \text{..... (1.1)}$$

where ΔOD is the change in optical density, I_o is incident light intensity, I is light intensity of transmitted light through tissue, ε is the extinction coefficient of the absorber, c is the concentration of the absorber. L is the path length through the tissue which is a function of the absorption and scattering coefficients μ_a and μ_s'. μa is defined as the number of absorption

events occurring per unit length, thus providing us with most of the hemodynamic information; μ_s' is defined as the number of scattering events occurring per unit length [18].

Since our imaging consists of the mixture of chromophores, namely, oxy-haemoglobin and deoxy-haemoglobin, the above equation can be further expanded to equation 1.2 for imaging done at a specific wavelength λ.

$$\Delta OD(\lambda) = \{\varepsilon_{Hbo}(\lambda)\,[HbO] + \varepsilon_{HbR}(\lambda)\,[HbR]\}\,L \quad \ldots\ldots\ldots\ldots\ldots\ldots (1.2)$$

$\varepsilon_{Hbo}(\lambda)$ and $\varepsilon_{HbR}(\lambda)$ represents the molar extinction coefficient, respectively, for the wavelength λ. [HbO] and [HbR] represent the molar concentrations of Oxy and Deoxy haemoglobin, respectively.

Making use of the above mentioned modified Beer-Lambert law and making use of two distinct wavelengths of light, it is possible for us to calculate the delta concentration of oxyheamoglobin (ΔHbO) and deoxyheamoglobin (ΔHbR) from equations 1.3 and 1.4. Knowledge of $\varepsilon_{Hbo}(\lambda)$ and $\varepsilon_{HbR}(\lambda)$ for the respective wavelengths is also a requirement; those values are already been calculated for the near infrared region by various researchers and is publicly available. ΔOD(λ) represents the change in optical density for the wavelength λ.

$$\Delta[HbO] = \frac{\varepsilon_{HbR}(\lambda_2)\Delta OD(\lambda_1) - \varepsilon_{HbR}(\lambda_1)\Delta OD(\lambda_2)}{L\times\{\varepsilon_{HbR}(\lambda_2)\varepsilon_{HbO}(\lambda_1) - \varepsilon_{HbR}(\lambda_1)\varepsilon_{HbO}(\lambda_2)\}} \quad \ldots\ldots\ldots\ldots\ldots\ldots 1.3$$

$$\Delta[HbR] = \frac{\varepsilon_{HbO}(\lambda_2)\Delta OD(\lambda_1) - \varepsilon_{HbO}(\lambda_1)\Delta OD(\lambda_2)}{L\times\{\varepsilon_{HbR}(\lambda_2)\varepsilon_{HbO}(\lambda_1) - \varepsilon_{HbR}(\lambda_1)\varepsilon_{HbO}(\lambda_2)\}} \quad \ldots\ldots\ldots\ldots\ldots\ldots 1.4$$

$$\Delta[HbT] = \Delta[HbO] + \Delta[HbR] \quad \ldots\ldots\ldots\ldots\ldots\ldots 1.5$$

1.2 Brain Physiology

Functional Near infrared spectroscopy is predominantly used to image the brain under different cognitive environments. For different kinds of tasks the brain responds in different patterns. These responses can be the changes in the HbO levels at particular areas as well as

the changes in the electrochemical activity at that area. All this contributes to the change in optical properties helping us to identify those changes using FNIRS.

1.2.1 Neurovascular coupling

Brain is a complex matrix of nerve cells and brain activity is basically the interaction of these nerve cells. This neuronal activities required energy, which is generated from glucose metabolism as it is in every other cells of human body. An increase in brain activity means an increase in glucose metabolism. Glucose metabolisms in our body are of two types: anaerobic, without the requirement of oxygen, and aerobic, requiring oxygen. In the brain, 90% of glucose metabolism is aerobic and this requires glucose and oxygen. This major requirement is met by the vast vasculature of cerebral blood vessels. Increased neural activity calls for an increased requirement of glucose and oxygen which stimulates the local arteriolar vasodilatation and increase of local cerebral blood flow (CBF) and cerebral blood volume (CBV), a mechanism known as “neurovascular coupling”. This process continues for a few seconds in the area being populated with oxy-haemoglobin. The increased oxygen concentration transported to the area typically exceeds the local neuronal rate of oxygen utilization, also known as the cerebral metabolic rate of oxygen consumption ($CMRO_2$), resulting in an overabundance of cerebral blood oxygenation in active areas [1][3]. Figure 1.4 shows this process.

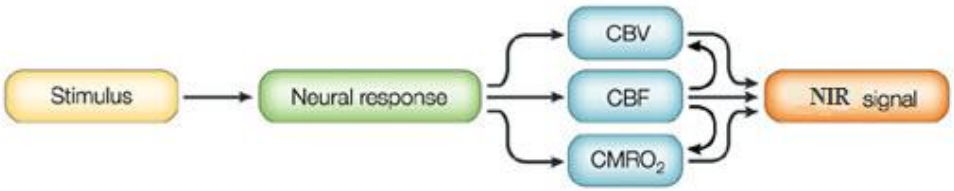

Figure 1.4 Schematic representation of the transformation of neural activity, starting from a stimulus to a hemodynamic response and resulting in a blood-oxygen-level-dependent change that can be measured by NIR signals. [4]

1.2.2 The Prefrontal Cortex

The prefrontal cortex (PFC) can be defined as the anterior portion of the frontal lobe lying in front of the motor and pre-motor areas of the human brain. A lot of researchers over time have shown the relation of this brain region to complex cognitive behaviours, personality expression, decision making and moderating correct social behaviour [19][23].

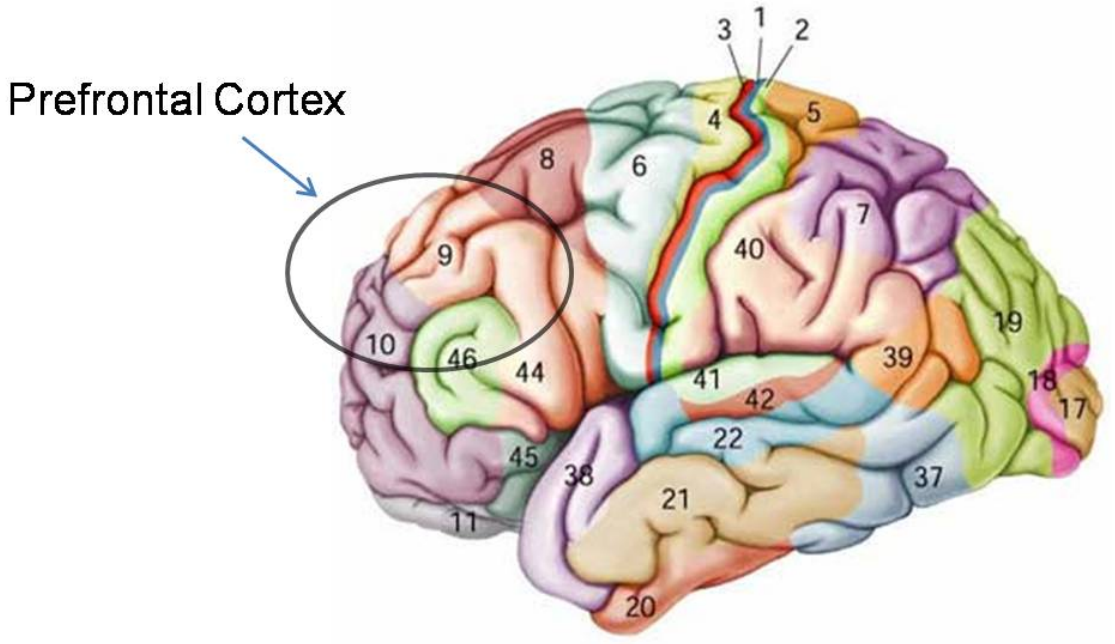

Figure 1.5 Human brain is divided and marked according to each Brodmann area; the prefrontal cortex is marked out [5].

Brodmann area (BA) is a numbered map of the human cortex with each number representing a physiologically and behaviorally relevant area as shown in above figure 1.5. The prefrontal area primarily includes most part of BA 9, 10, and parts of 8, 44, 46, and 47. The prefrontal cortex has a complex network of connections with other regions of the brain including the cortical regions as well as subcortical areas [19]. Based on the homogeneity of activations or responses to similar kind of stimuli, the whole prefrontal area is divided into smaller

subdivisions, namely dorsolateral PFC, ventrolateral PFC, orbitofrontal PFC, ventromedial PFC, and frontopolar PFC. There are even smaller portions and subdivisions for these too.

In our study, the main focus will be mostly on BA 9 and 10 and parts of 46 and 44 as well. The area in prefrontal cortex that includes BA 9 and 46 is named as the dorsolateral prefrontal cortex. This area is assumed to be important for working memory and executive function. Dorsolateral PFC is also acclaimed to be critically involved in executive function, formulating refining and manufacturing goals to regulate behavior and to solve problems. This area has connections to many primary and secondary areas of the cortex as well as the thalamus and hippocampus [24]. The rostral part of dorsolateral PFC is called the frontopolar PFC. Frontopolar can be in liberal terms mentioned as the lateral portion of BA 10. Also the borderline area including small parts of BA 46 and 9 are also included in frontopolar PFC. This area is believed to be the center for active processing such as evaluation, monitoring or manipulation, performed on internally generated data [2].

1.3 Post Traumatic Stress Disorder

Post-traumatic stress disorder is a neuropsychological anxiety disorder affecting tens of thousands of people each year, and only a fraction of those affected receive treatment. It is still unknown the actual causes of PTSD as any physiological, genetic, physical or social factors are involved in its cause. But it is almost certain that a person who had a traumatic experience involving threat of injury or death is prone to develop PTSD. Other life-threatening experiences may be from a natural disaster such as a flood or fire, or events like assault, domestic abuse, prison stay, rape, terrorism or war.

The National Institute of Health (NIH), a medical research agency under the United States Department of Health and Human Services, categorises the symptoms of PTSD into 3 groups, namely “relieving event”, “avoidance” and “arousal”. Under “relieving events” comes the symptoms of flash back about the traumatizing event, upsetting memories repeated nightmares

and strong and uncomfortable reactions to these situations. Under the avoidance group comes the symptoms of emotional numbness, detached feelings, lack of interests to normal activities, loss of mood anticipation of social events that might remind of the traumatic event. Finally, the symptoms such as difficulty in concentrating, startling easily and showing an exaggerated response, hyper vigilance, irritability and sudden outbursts of anger and trouble in sleeping pattern fall under the “arousal” group.

All trauma cases do not end up in PTSD. Most of us might have gone through some type of trauma at some point of our lives but only a small percentage of people develop PTSD. According to the United States Department for Veteran Affairs (USDVA), in the US, about 7-8% of the population at some point in their lives will have PTSD; about 5.2 million adults have PTSD during a given year, which is only a small portion of those who have gone through some form of trauma. It also says that women are more prone to develop PTSD in a 2:1 ratio compared to their male counterparts.

1.3.1 Student Veterans and PTSD

It was reported that more than 270,000 veterans from those served in Operation Enduring Freedom in Afghanistan and Operation Iraqi Freedom had enrolled in colleges in 2009 on the G.I. Bill, according to U.S. Army data, and likely more will attend college in the coming years [8]. At UT Arlington, veteran enrollment reached 1,128 in spring 2011, more than double the number two years ago [25]. According to USDVA, nearly 20% of the returning forces are likely to suffer from PTSD or depression. With the high level of PTSD cases present among veterans, it is important that efforts to send veterans to college should be coupled with programs that cater to their special behavioral health needs. For this purpose, we need to have a better understanding about PTSD and its effects on these student veterans.

Veterans that we studied in this project are having trouble in learning and complained about not able to do well in their studies. Some of the cognitive difficulties associated with

PTSD, which may affect academic performance, are difficulty in attention and concentration, information processing challenges, learning and memory deficits, sluggish abstract reasoning, and slowed executive functions (e.g., problem solving, planning, insight/awareness, and sequencing). Other challenges associated with difficulty in classroom performance also include the effects of additional stress factors such as assignments, exams, lack of sleep, and difficulty with time management between work and school, and panic attacks [9].

1.4 Post Traumatic Stress Disorder and Neuroimaging: a review

A variety of functional neuroimaging studies have been done so far on PTSD patients using a variety of tasks. Most of the studies have been based on symptom provocation and negative emotional response tasks, and fewer used cognitive tasks. A very few have been done using FNIRS, while most of the studies have been done using Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET). Though these individual study results vary greatly, reviewing them gives us a better understanding of the relations between PTSD and neuroimaging, helping us better conduct our study.

Some of the major PET-based cognitive studies done on PTSD patients have shown decreased activity in different prefrontal regions of the brain for PTSD groups. A (PET) study on child sex abused women compared those with PTSD and without PTSD by Bremner et al (2002). It found that significant deactivations were observed for the PTSD group in medial prefrontal cortex (MPC), though no detectable activation differences happened in the anterior cingulated cortex (ACC) [47]. Another such PET study by the group of Semple et al. (2000) on drug abused patients with PTSD and control group also showed a significant deactivation for the PTSD group in lower frontal cortex [48]. This group imaged the subjects while doing an auditory attention task. Similarly, Shaw et al. (2001) did a working memory task study in a PTSD vs control group and observed significant deactivations for the PTSD group in the inferior MPC [49]. Clark et al (2003) did a similar PET study for a similar PTSD vs control group while doing a

visual verbal cognitive task and observed deactivations in the dorsolateral prefrontal cortex [50]. These studies mentioned above summarized the PET-based studies on PTSD patients while doing a cognitive task.

A lot of fMRI studies also have been done on PTSD patients, most of which have performed the measurements while doing a symptom provocation task. The only two cognitive studies on PTSD patients using fMRI are by the groups of Shin et al (2007) [51] and Bryant et al (2005) [52]. Shin et al studied a group of trauma undergone men without PTSD compared to a group of trauma undergone men with PTSD. They studied the group while doing a counting Stroop task and increased activity for control group; significantly decreased activity for PTSD group was observed in the dorsal ACC. They also observed that the greater the symptom severity the lower was the activation in ACC. Bryant et al compared a PTSD group to a control group of 14 subjects each while doing an auditory odd ball cognitive paradigm. They investigated the dorsolateral PFC and medial frontal gyrus and found no significantly different activations between the groups.

FNIRS studies on PTSD patients in general have been very few. There was only one related study that could be found, which was done on a PTSD patient group while doing a cognitive task. Matuso et al (2003) did a comparative study between 8 PTSD subjects and 26 control subjects while doing a verbal cognitive task [53]. They found significant hypo activation in the PFC for the PTSD group. This study also did symptom provocative task on a PTSD vs control group to see deactivations in the PFC for the PTSD group [54]. These above mentioned studies were the only fNIRS reports so far conducted on a PTSD patient group and compared with a control subject group.

To summarize the review I described above, there is a high level of variability in the results published within a very limited number of studies available. The variability differs from the type of subject groups used for each study, the kind of studies used, the age group of the

subjects, and so on. In case of fNIRS, there was only one cognitive study found and it is not enough to offer a good comparison with my study. Majority of studies in this area have analyzed symptom provocation task and provided us with very little to learn about the cognitive impairments in PTSD (Racuh et al(1996), Liberzon et al (1996), Bremmer et al (1999), Osuchet al(2001)). Similarly, most of the symptom provocation tasks have been studied using fMRI and PET. Overall, most of the symptom provocation task studies have shown a good repeatable result of having hypo activation in the frontal cortical areas of PTSD subjects.

CHAPTER 2

DIGIT SPAN COMPARATIVE STUDY

2.1 Aim of Study

Veterans coming back to school have often complained about their inability to perform in studies compared to their counterparts in the class. These student veterans were the ones already or later diagnosed with PTSD or have gone through different levels of traumatic events in their service life. The majority of these students had most trouble studying the engineering related subjects, which require a relatively good level of math skills. So these student veterans, majority still in their 20-30's, had to either drop out of these demanding courses or change their field of study, as it became hard for them to perform well in their studies. These learning difficulties could be associated with PTSD and other comorbid syndromes. To ascertain this assumption, a comprehensive cognitive and educational comparative study has to be done between normal control students and veteran students with PTSD; such a study may help the student veterans select more effective learning strategies or even choose a better career path. A better understanding of the neurobiology of their brain can also lead them to a better treatment.

The digit span task has been used in neuropsychological research for long time. It is listed in the working memory index of the Wechsler Adult Intelligence Scale (WAIS), a test used for clinical evaluation of adult as well as adolescent intelligence [10]. Several studies have researched on brain activation while doing the digit span task mainly using PET [11][12] and fMRI [13]. Two studies were done using fNIRS investigating the PFC during the digit span task [14][15]. A lot of other functional neuroimaging studies have reported PFC activity while

performing working memory and problem solving tasks like mental arithmetics [16][17]. But to my knowledge, there has never been a comparative fNIRS study between controls and student veterans with PTSD making use of the digit span task to compare and assess the cognitive activity in the PFC. Thus the goal of my study includes:

i. to differentiate the hemodynamic activities in the PFC of controls as well as the student veterans, in response to the forward digit span and backward digit span task;

ii. to assess and compare the brain activation in different regions of the PFC between the controls and student veterans with PTSD during each of the digit span tasks.

2.2 Materials and Methods

2.2.1. Subjects

In this study we had 2 different groups of subjects, the control group and the student veteran group diagnosed with PTSD under DSM IV. The control group consisted of 11 healthy male students from the UTA community. None of the 11 control subjects had a prior neurological disorder. The veteran student subjects (from here on mentioned as the “veteran group”) consisted of 6 veterans enrolled in UTA and all diagnosed with symptoms of PTSD. All of the veterans were recruited as part of the Student Veteran Project from the social work department of UT Arlington. A signed inform consent form was obtained from all the subjects once the study objectives, equipment details, technology used and task details were all explained to them.

2.2.2. Instruments

2.2.2.1 Cephalogics High Density Optical Imager

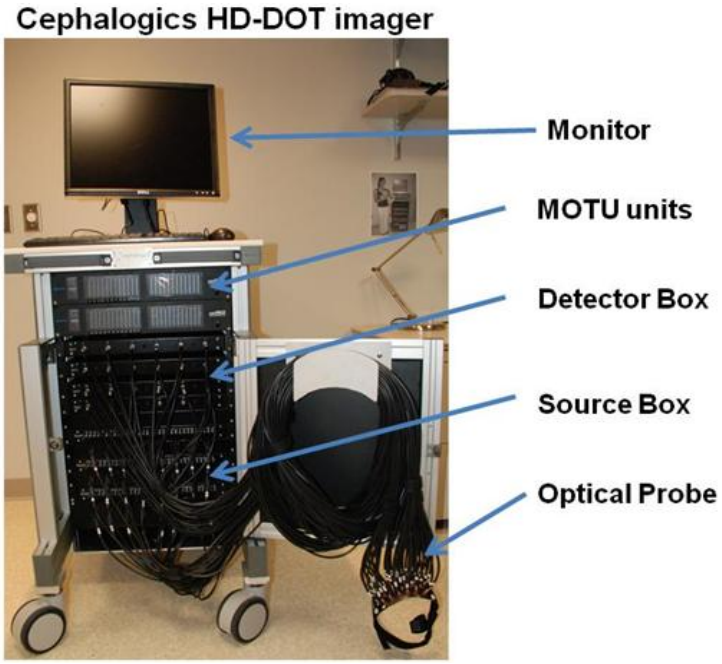

Figure 2.1 The Cephalogics high density diffuse optical tomography imager with individual components named [21].

The optical imager used in this functional brain imaging study was Cephalogics (Cephalogics LLC,MA) High Density diffuse optical tomography (HD-DOT) system. The Cephalogics HD-DOT has two source wavelengths of 750 nm and 850 nm, supplied by three 750 nm LEDs and one 850 nm LED, respectively. The 750 nm LEDs and 850 nm LED have a power of 1.2 mW and 1.6 mW each, respectively. These sources with two different wavelengths are modulated at different frequencies. The detectors used in the Cephalogics HD-DOT are Hamamatsu APDs (Avalanche Photo Diode). Figure 2.1 shows the whole equipment set-up with the source and detector box. The “MOTU unit” consists of a set of 24 bit analog-to-digital converters (ADCs). All the detector channels are digitized with dedicated 24-bit ADCs and the

sources are encoded (frequency-, time-, spatial-encoded). The ADC has a sampling frequency of 96 KHz which provides high instantaneous dynamic range and better cross-talk rejection [6].

2.2.2.2 Probe geometry

The probe geometry that was used for my study is as shown in the figure 2.2. The probes are made of fiber optical cables with a connector at the equipment side and a holder head at the other end. I have used a total of 12 sources and 16 detectors placed as intermitted lines with a gap width of 3 cm each. The sources as well as detectors were placed 2.5 cm apart to each other in each line. All together these 12 sources and 16 detectors form a combination of 36 source-detector pairs within a source-detector separation range of 3.25 cm. The distance between a line of detectors to the next line of detectors is 6 cm and the same for sources too. The total area this probe geometry covers on the forehead of a subject is 9X17.5 cm^2.

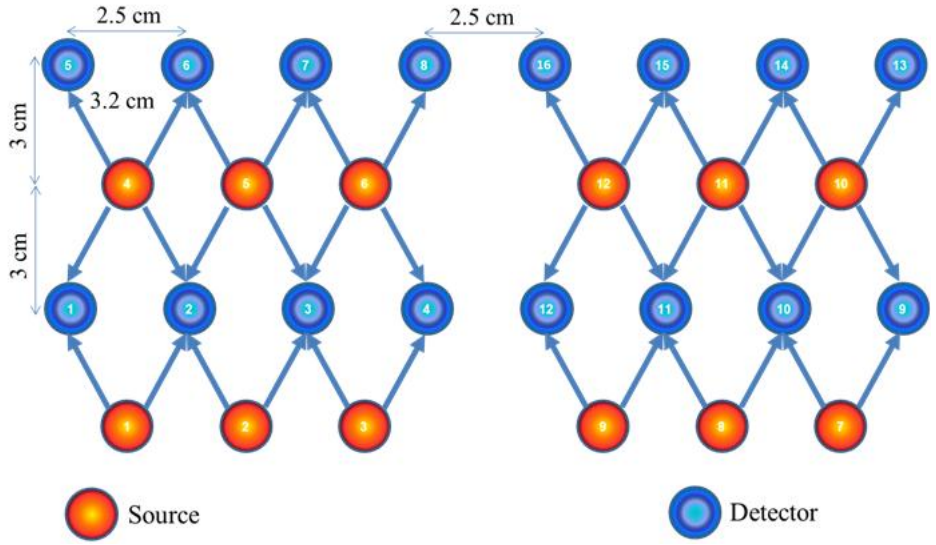

Figure 2.2 Probe geometry

2.2.3. Experimental Paradigm

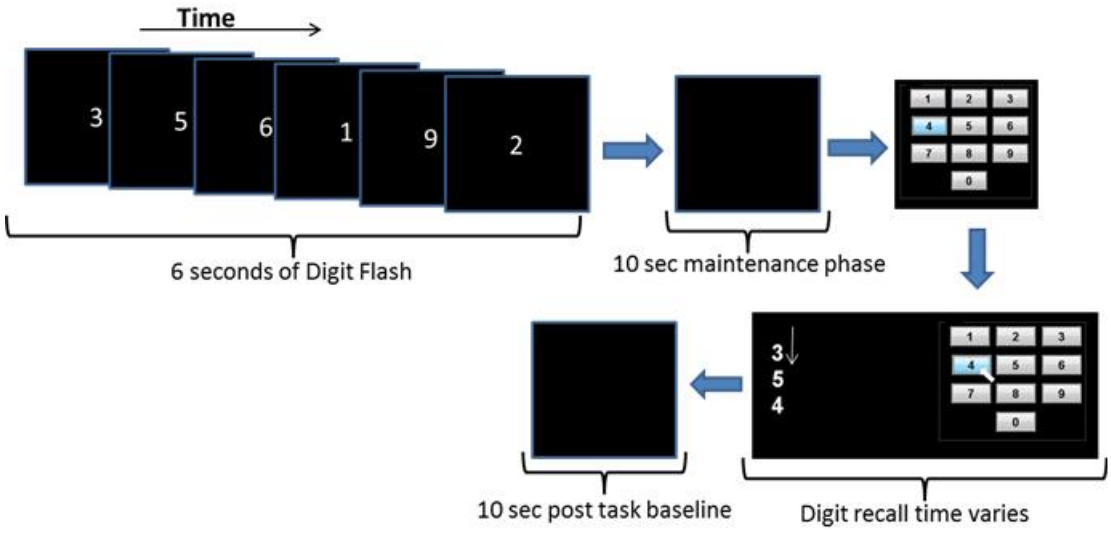

Figure 2.3 Pictorial representation of the structural flow of digit span task.

In digit span task, we have 2 sessions, the forward digit span task (FRWTSK) and the backward digit span task (BKWTSK). In the FRWTSK, the subject is shown a series of 6 digits one after the other on the computer screen with a black background. A Matlab based program chooses these 6 digits at random from 0 to 9 and makes it flash on the screen one after the other. Each digit is visible on the screen for 1 second thus summing up to the 6 seconds of “digit flash time”. These 6 seconds is followed by a 10-second “maintenance phase”, where there is a black blank screen in front of the subject and the subject uses this time to recollect and memorize the 6 digits that were shown to him. The 10-second maintenance phase is followed by a number pad screen on the computer and the subject has to input the 6 digits one after the other, in the same order as it appeared in front of him at the digit flash time. This phase is called the “Digit recall time”. Once the subject enters all 6 digits, a 10 second post task baseline time is

allowed where a black screen appears. In case the subject forgets any of the digits during the digit recall time, he was instructed to enter a random number which will be recorded as a wrong input. This makes up one block of the FRWTSK and the subject is made to repeat this task 8 times, thus a total of 8 blocks in the full FRWTSK session. Figure 2.4 shows clearly this 3-phase experiment paradigm. The BKWTSK, which is the second session of the digit span task, follows the same procedure until the “Digit recall phase” where the subject has to input the numbers on to the number pad in the reverse order with respect to that it appeared during the digit flash time. Thus the only difference between the FRWTSK and the BKWTSK is in the “digit recall time” where the subjects have to recall in the reverse order for the BKWTSK.

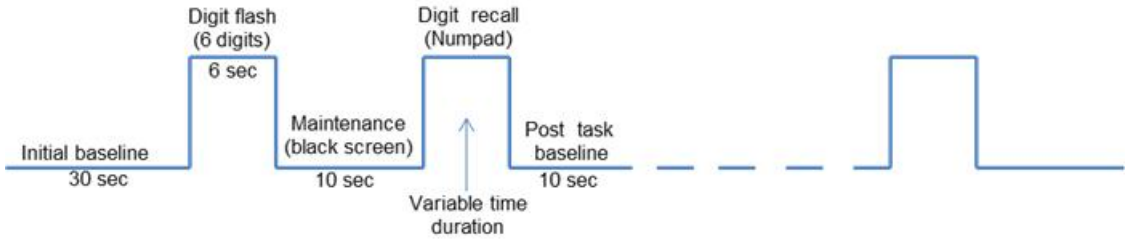

Figure 2.4 Experimental paradigm

2.2.4. Experimental Set-up and procedure

Once the entire digit span protocol was explained to the subjects, they were asked to sit comfortably on a chair. The subjects were allowed to do a practice of the whole task before the probes were placed on the head. After the practice, the nasion(Nz), inion(In), left ear (AL) and right ear (AR) locations were marked on the head, as representations in co-ordination with the 10-20 international system of electrode placement [20]. Then the probe holders with the probe were placed on the forehead area, covering the PFC. The lowest line of probes being 3-5 mm above the eye brows (see Fig. 2.5). The probe holders were tightly held on to the subject’s head using Velcro; any hair between the optodes and the scalp were carefully removed to make sure good contact. Finally an elastic bandage was tied over the probe set to hold it tight in position as

well as to block any ambient light, as shown in Fig. 2.5. The chair was pushed to a comfortable distance from the screen where the subject could clearly see the computer screen as well as reach the mouse to respond to the task. The room was kept dark and silent throughout the task period; the subject was asked not to talk and keep his body movements as less as possible while performing the task, to reduce the motion artifacts as much as possible. Once the task started, fNIRS signals were acquired continuously. A 10-minute break was given between the 2 sessions of FRWTSK and BKWTSK.

Figure 2.5 Experimental set-up.

2.2.5. Optode co-registration

A 3D digitizer from the Polhemus Inc, PATRIOT^{TM} Digitizer was used to record the neuro-anatomical positions of the probes on the subject's head. The system consists of a stylus, source and a system electronics unit. The system makes use of the electromagnetic sensing and positioning technique. The source contains electromagnetic coils and generates magnetic fields, which serves as the reference frame for positioning the stylus. The system electronics unit has the hardware to compute the position of the stylus and interfaces with the host computer through an RS-232 or an USB interface[26]. So using the stylus we first measure the co-ordinates of nasion (NZ), inion (IN), left ear (AL), right ear (AR) and center point (CZ). CZ is the central point between NZ-IN and AL-AR. After that, we recorded the co-ordinates of each of the optodes one after the other. Later with the help of a Matlab-based free software package NIRS-SPM [27][28], the co-ordinates are represented as spatial locations of optodes on a

human brain template, as shown in figure 2.6 below. The figure shows the probe geometry overlaid on the PFC, and we can infer that the areas covered by the optodes correspond to BA 10, BA 9 and smaller region of BA 46.

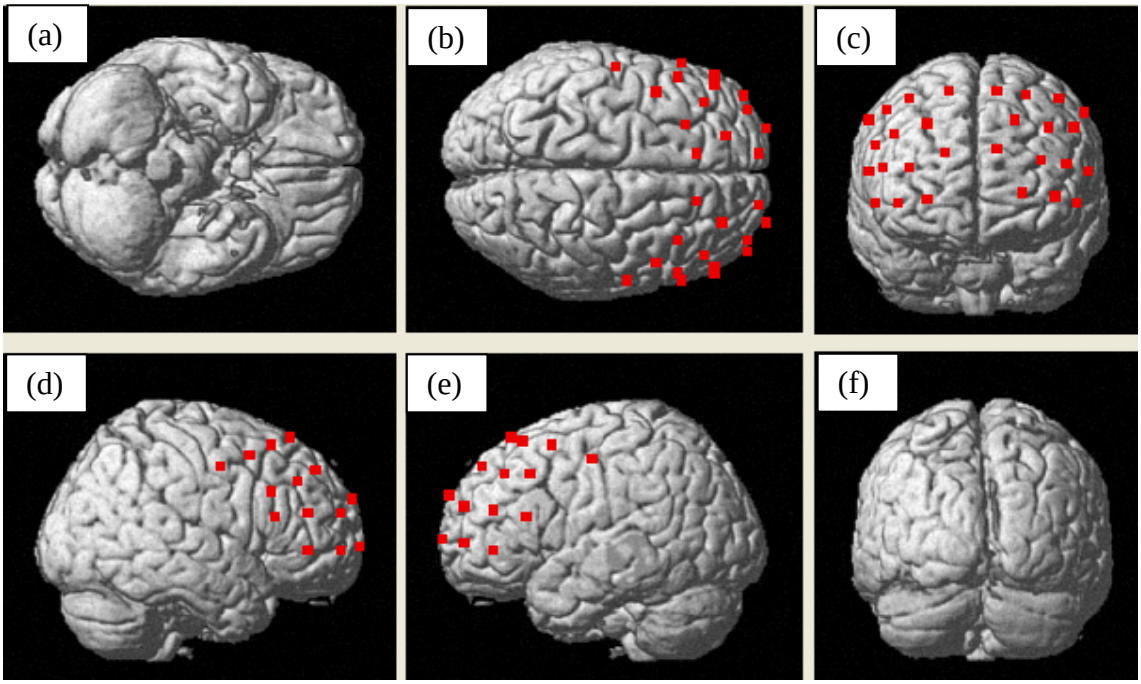

Figure 2.6 Optodes co-registered on a human brain template: (a) Bottom view, (b) Top view, (c) Frontal view, (d) Right Lateral view, (e) Left Lateral view and (f) Occipital view.

2.2.6. Data processing

The acquired fNIRS raw data is downloaded from the Cephalogics system and processed through a Matlab based free software called HomER (Hemodynamic Evoked Response). HomER is being extensively in use for the processing of fNIRS data [29][30]. Once the data is imported to HomER, the raw optical intensities are scrutinized channel wise for extremely noisy or faulty signals to be removed from further analyzing. The power spectral density feature also helps to identify faulty or noisy channels by identifying the characteristic frequency presence like the heart beat frequency or respiration frequency.

The second step filtering does a band pass filtering of the data through a range of 0.01 to 0.2 Hz. This is done to eliminate the unwanted systemic physiological noises like cardiac pulsation, respiratory signal and vasomotion [31]. Instrumental noises can also be eliminated using this filter. The block averaging step follows this. The whole 1 session data consists of 8 blocks. The stimulation time points of each of these blocks (which were saved while the subject performed the task) are fed in to HomER, and it is block averaged to get an averaged block for approximately 30 seconds as the digit recall time varies from subject to subject. This process considerably enhances the signal to noise ratio. At this point, temporal data can be extracted from HomER for further evaluation purpose. For a spatial response, HomER does an image reconstruction using the regular back-projection method to generate a two dimensional spatial activation map for a selected temporal window.

2.3 Experimental Results

The data acquired from fNIRS imager and processed through HomER were then used for further analysis. Both temporal as well as spatial analysis were performed among the control subjects and the veteran subjects, separately, to do a comparative study.

2.3.1. Digit span behavioral analysis

The digit task containing 2 sessions, the FRWTSK and BKWTSK, was conducted one following the other on each subject in a single day, with a time gap of 10 minutes between sessions. All test conditions were the same for both the control subject group as well as the veteran group. The response of each subject was recorded using a Matlab software during the task (e.g., the number of digits the subject got correct as well as the total time it took in the digit recall phase). Later this data was used to calculate the mean reaction time and the average correct responses of each group in each task. The results obtained are as shown in the figures 2.7 and 2.8.

Figure 2.7 shows the number of correct responses averaged across the group, for each task. For the FRWTSK, the control group's mean of number of correct answers was 47.36±1.29

and the veteran group's being 43.67±5.39. A paired t-test was conducted between these groups and a p-value = 0.16 was obtained, showing a minimal significant difference between these groups. This implies that in the forward task overall the controls had no significant difference from the veterans in obtaining correct answers. In BKWTSK, the control group's mean of number of correct answers was 43.18±6.03 and the veteran group's being 45.17±3.19. A paired t-test was conducted between these groups and a p-value = 0.47 was obtained, again showing no significant difference between the results of these groups. A paired t-test was also done between the means of number of correct answers in FRWTSK vs BKWTSK in each group, and a significant difference with p=0.03 was obtained for the control group, showing that the controls had significantly more correct answers in the FRWTSK compared to BKWTSK. However, a similar result was not seen in the veteran group with p-value being 0.57.

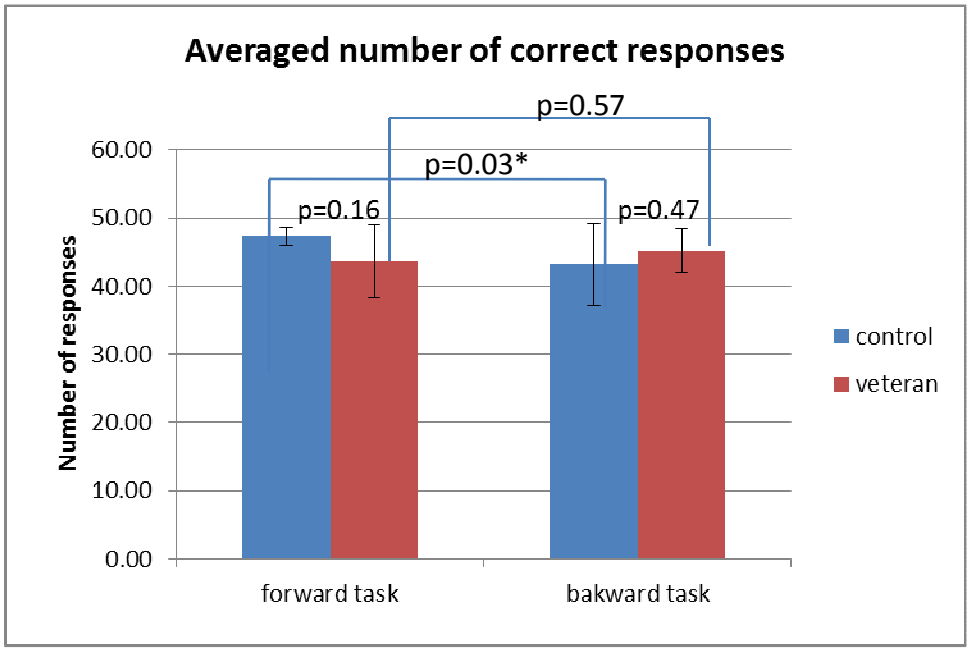

Figure 2.7 Group averaged number of correct responses with standard deviations for control group (n=11) and veteran group (n=6) at both FRWTSK and BKWTSK, with each between group p-values displayed

Similarly, Figure 2.8 shows the reaction time in recall phase averaged across the each group for each task. In the FRWTSK, the control group's mean reaction time in recall phase was

5.12±0.45 seconds (secs) and the veteran group's being 5.70±1.12 secs. A paired t-test was conducted between these groups and a p-value = 0.26 was obtained showing not much significant difference between these groups. This implies that the evidence is not enough to prove that in the FRWTSK, the average time taken by the controls to recall and input all answers was not much different from that by the veterans. In the BKWTSK, the control group's mean reaction time in recall phase was 7.38±1.73 seconds (secs), and the veteran group's being 7.70±3.14 secs. A paired t-test was conducted between these groups, and a p-value = 0.82 was obtained showing there being no significant difference at all between these groups. This implies that in the BKWTSK, the mean time taken by the controls to recall and input all answers were almost the same as the veterans'. A paired t-test was done between the mean reaction times in recall phase in FRWTSK vs BKWTSK in each group, and a significance difference of p=0.002 was obtained for the control group, showing the controls took significantly less time recalling the digits in the FRWTSK as compared to the BKWTSK. A similar result was not seen in the veteran group with p-value being 0.17.

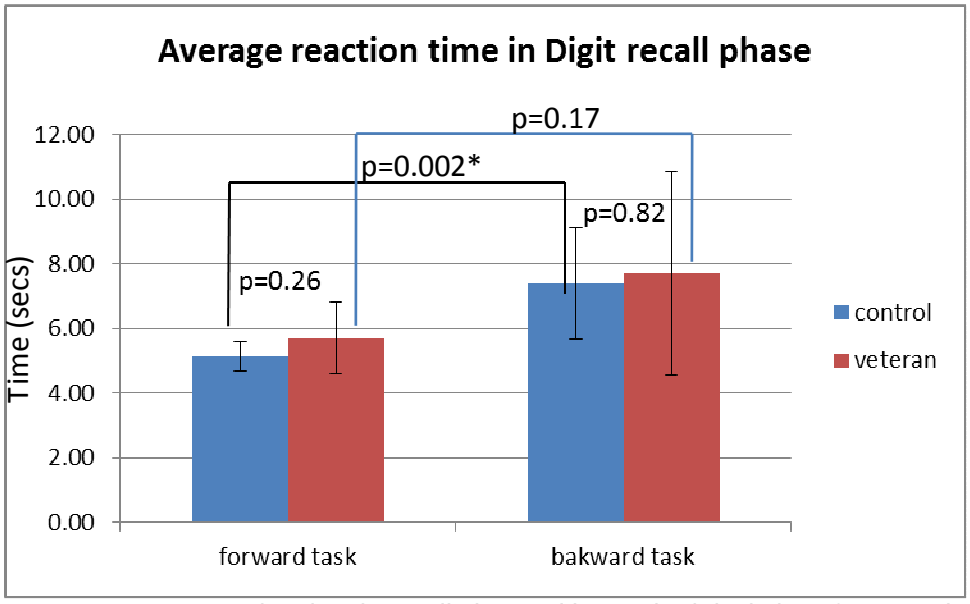

Figure 2.8 Group mean reaction time in recall phase with standard deviations for control group n=11 and veteran group n=6 at both FRWTSK and BKWTSK, with each between group p-values displayed

2.3.2. Cluster Analysis

As we saw in section 2.2.2.2 we have 36 source-detector pairs each called as a channel providing us with data from that particular location. Together these 36 channels cover 9X17.5 cm^2 of area on the forehead. So for a more localized activation analysis we chose do a cluster analysis. Two type of cluster analysis were done primarily focusing on BA 9/46 in each right and left hemispheres as well as BA 10 in right and left hemispheres. For temporal analyses 30 seconds from the stimulation point was considered, with the stimulation point being the start of digit flash.

2.3.2.1 Twelve cluster region analysis.

Twelve regions were selected as shown in figure 2.9. U1 to U6 primarily cover the upper PFC region including the BA9 and BA 46, and the regions L1 to L6 cover the lower PFC region of BA10. Each region consists of 2 channels, and the output from the region is the block-averaged HbO signals from the 2 channels present in that region. These block-averaged values at each region were averaged across the subject group to obtain a group averaged temporal pattern as shown below, from Figures 2.10 to 2.13.

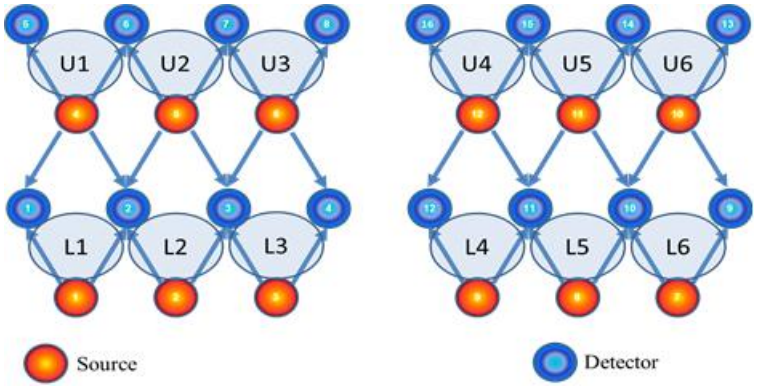

Figure 2.9 Probe geometry with the 12 selected clusters

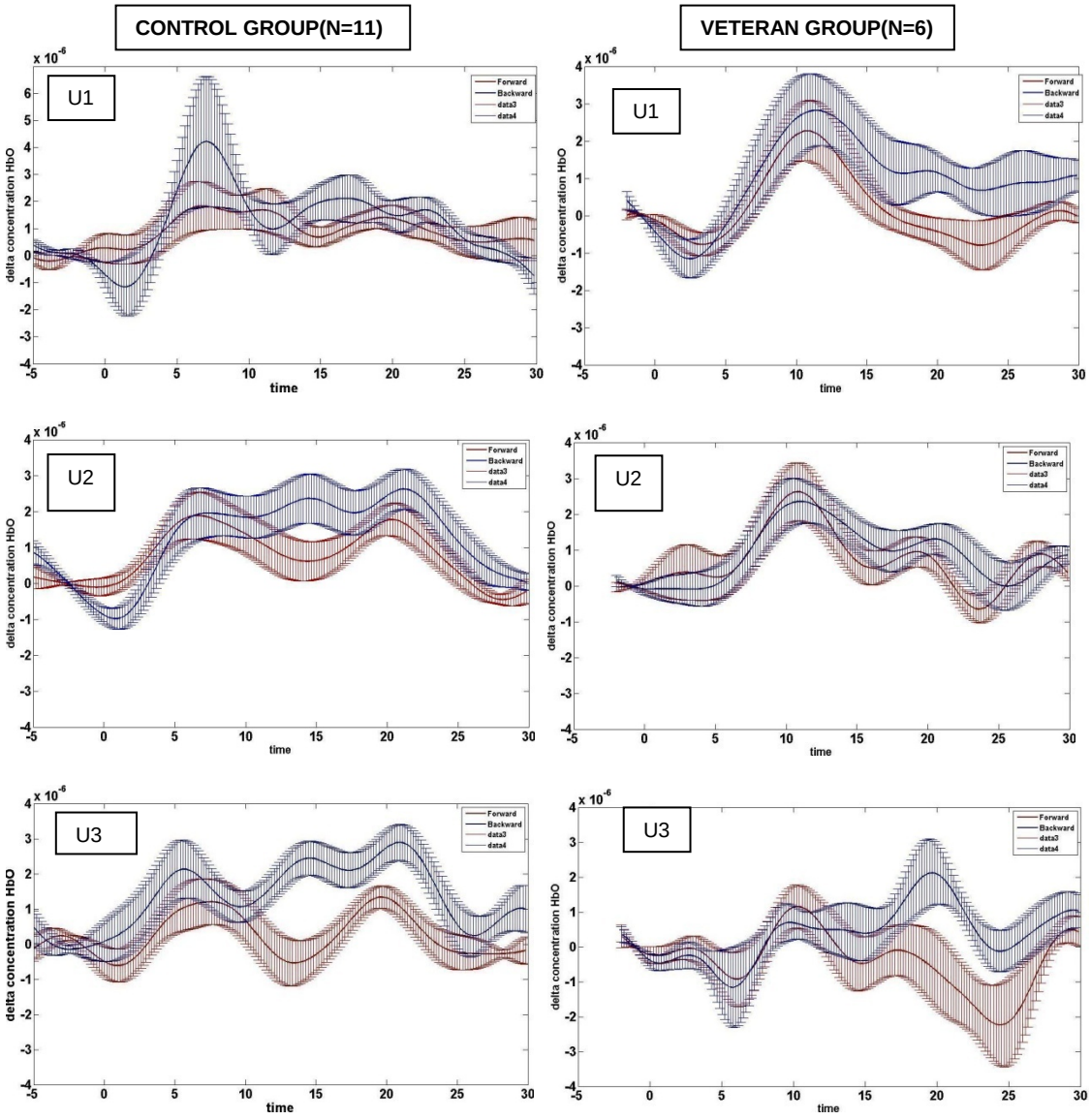

Figure 2.10 Group averaged temporal plots for control group and veteran group from regions U1, U2 and U3 of the 12 selected clusters. Red line indicates FRWTSK with error bars indicating standard error of means (SEM) and the blue line indicates BKWTSK with SEM. x-axis: time in seconds and y-axis: mean delta concentration (HbO) in M.

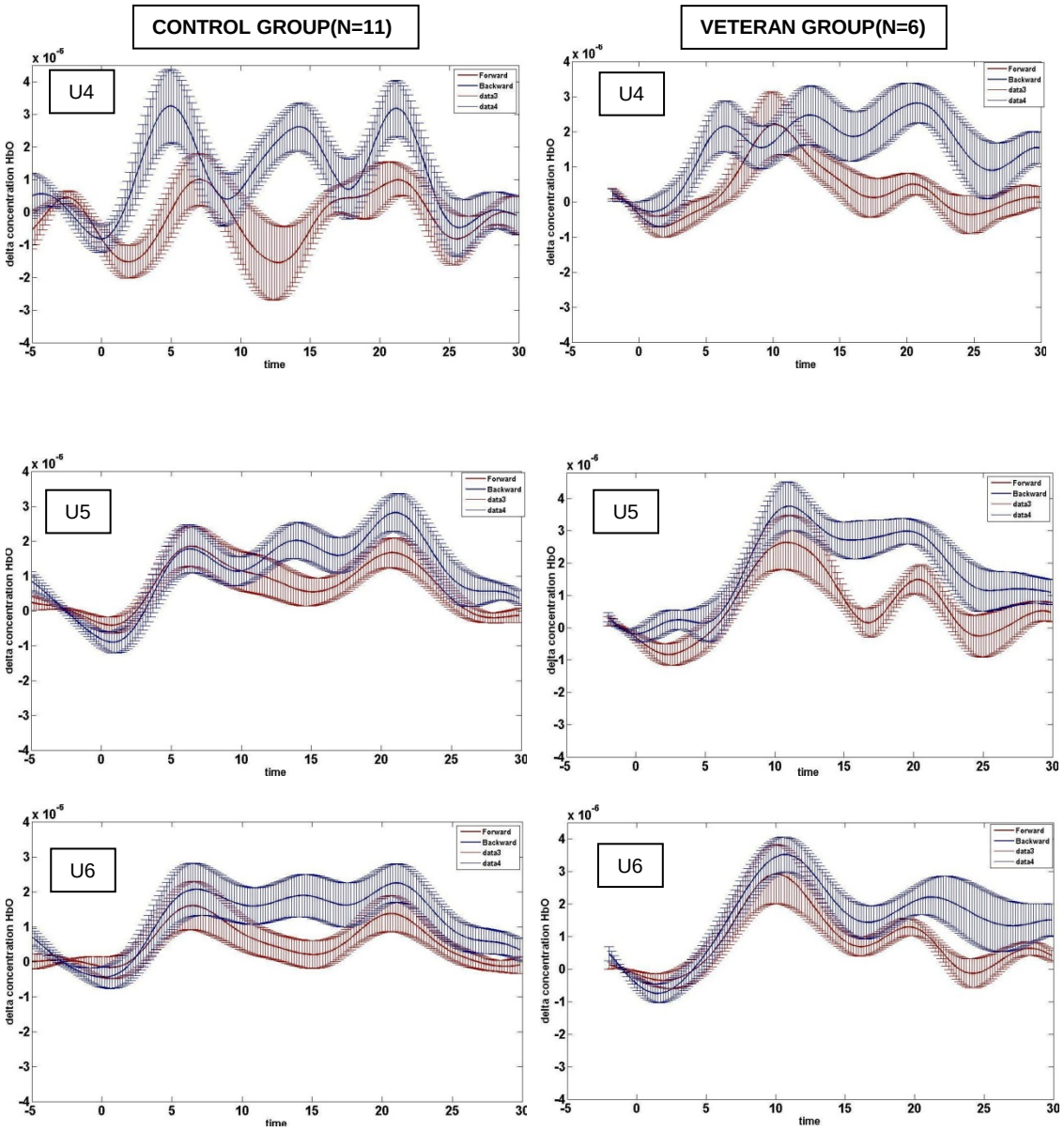

Figure 2.11 Group averaged temporal plots for control group and veteran group from the U4, U5 and U6 regions of the 12 selected clusters. Red line indicates FRWTSK with error bars indicating standard error of means (SEM) and the blue line indicates BKWTSK with SEM. x-axis: time in seconds and y-axis: mean delta concentration (HbO) in M.

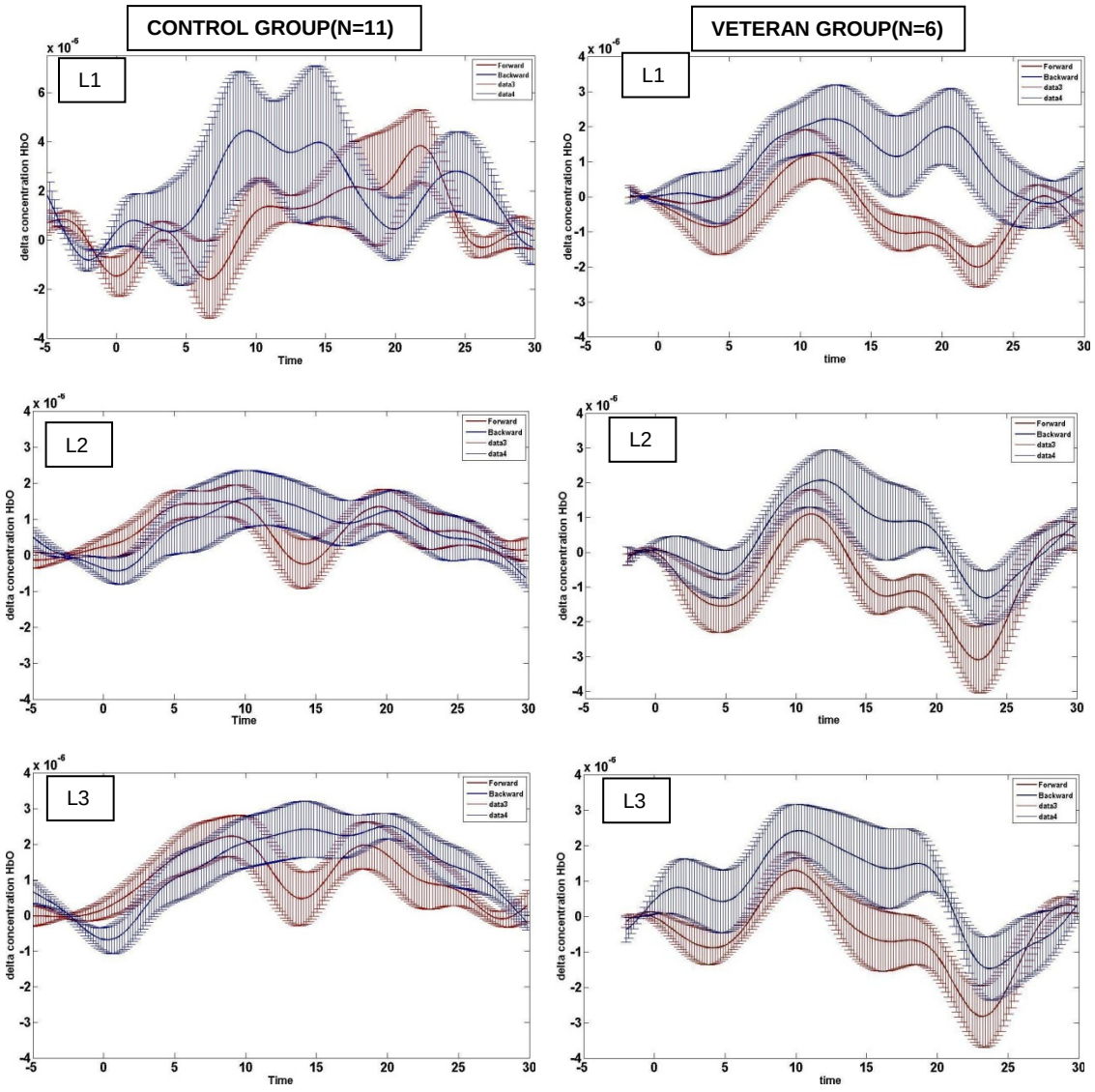

Figure 2.12 Group averaged temporal plots for control group and veteran group from the 12 selected clusters. Red line indicates FRWTSK with error bars indicating standard error of means (SEM) and the blue line indicates BKWTSK with SEM. x-axis: time in seconds and y-axis: mean delta concentration (HbO) in M.

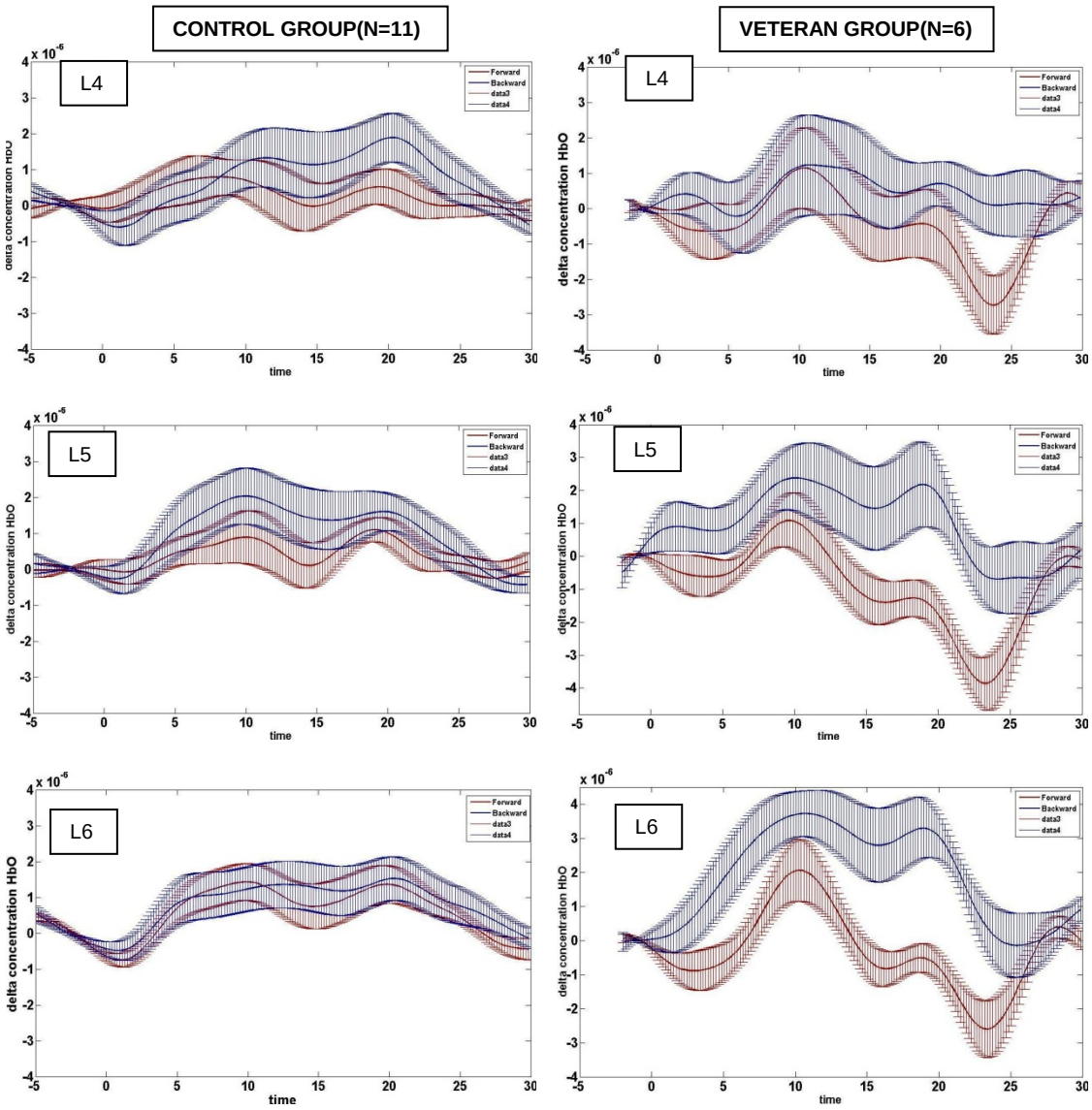

Figure 2.13 Group averaged temporal plots for control group and veteran group from the 12 selected clusters. Red line indicates FRWTSK with error bars indicating standard error of means (SEM) and the blue line indicates BKWTSK with SEM. x-axis: time in seconds and y-axis: mean delta concentration (HbO) in M.

To better characterize and evaluate these temporal plots and do a comparative study between the pattern changes in control group vs veteran group, 3 evaluation time intervals were chosen. Considering a hemodynamic response delay of 4 seconds [32][33], the first interval being the “digit flash time” was selected from 0 to 10 seconds, 2nd interval “maintenance time”

was selected from 10 to 20 seconds, and the final “digit recall time” was from 20 to 30 seconds. Areas under the curve (AUC) in these 3 intervals were calculated for each subject separately, and group-averaged AUC was found in each cluster and used for a comparative analysis of the brain activations at these 3 psychologically different phases (digit flash, maintenance and digit recall) between the control group and veteran group. The results obtained are displayed below, from Figures 2.14 to 2.19.

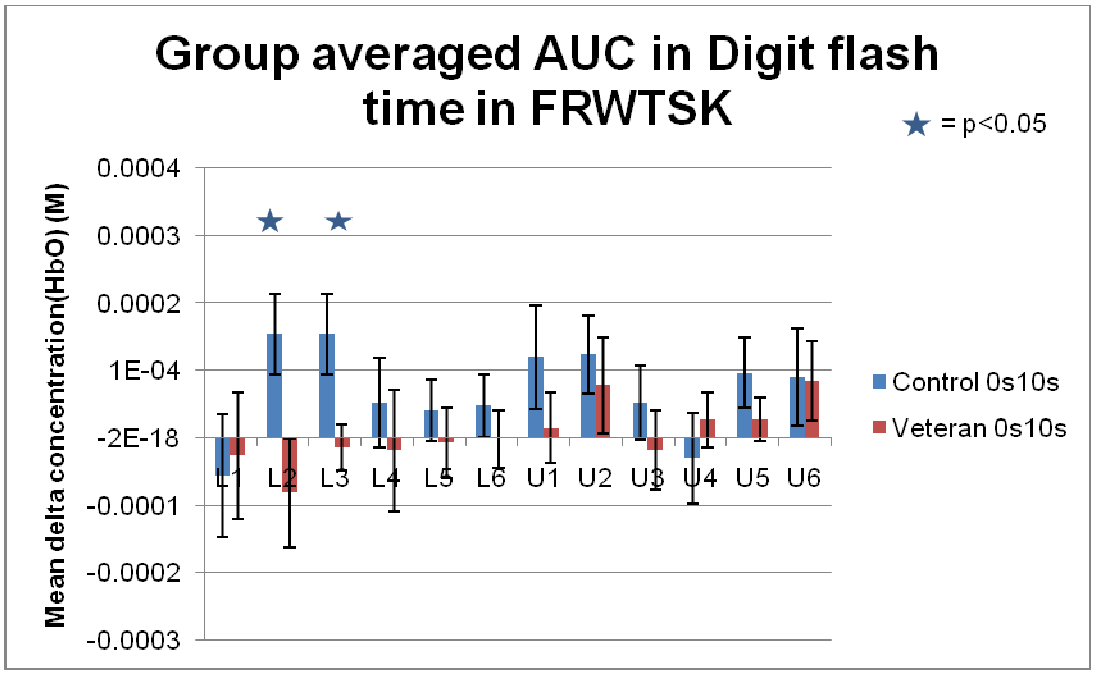

Figure 2.14 Group averaged AUC with SEM at the 12 clusters during the digit flash time with comparison between control group and veteran group in FRWTSK. Error bars represent standard error of means.

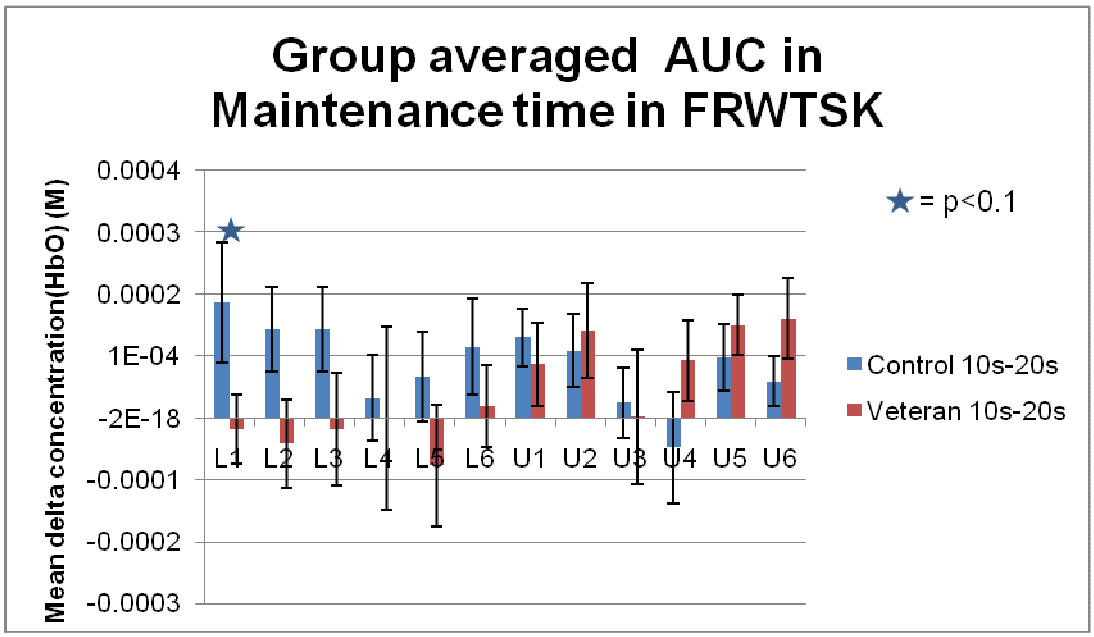

Figure 2.15 Group averaged AUC with SEM at the 12 clusters during the Maintenance time with comparison between control group and veteran group in FRWTSK. Error bars represent standard error of means.

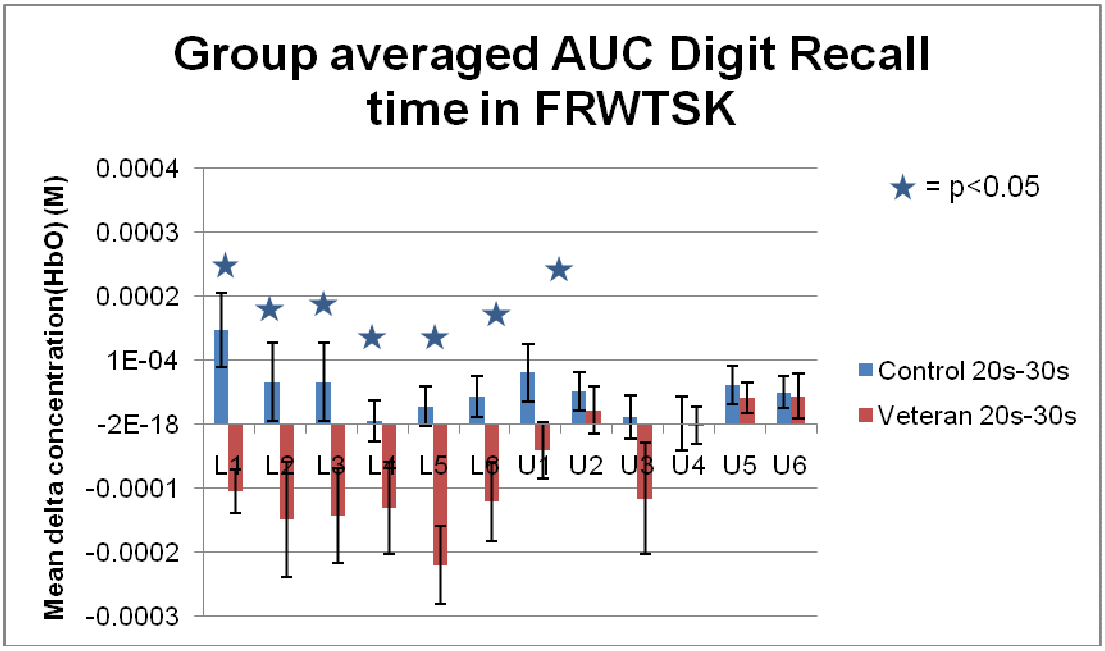

Figure 2.16 Group averaged AUC with SEM at the 12 clusters during the digit recall time with comparison between control group and veteran group in FRWTSK. Error bars represent standard error of means.

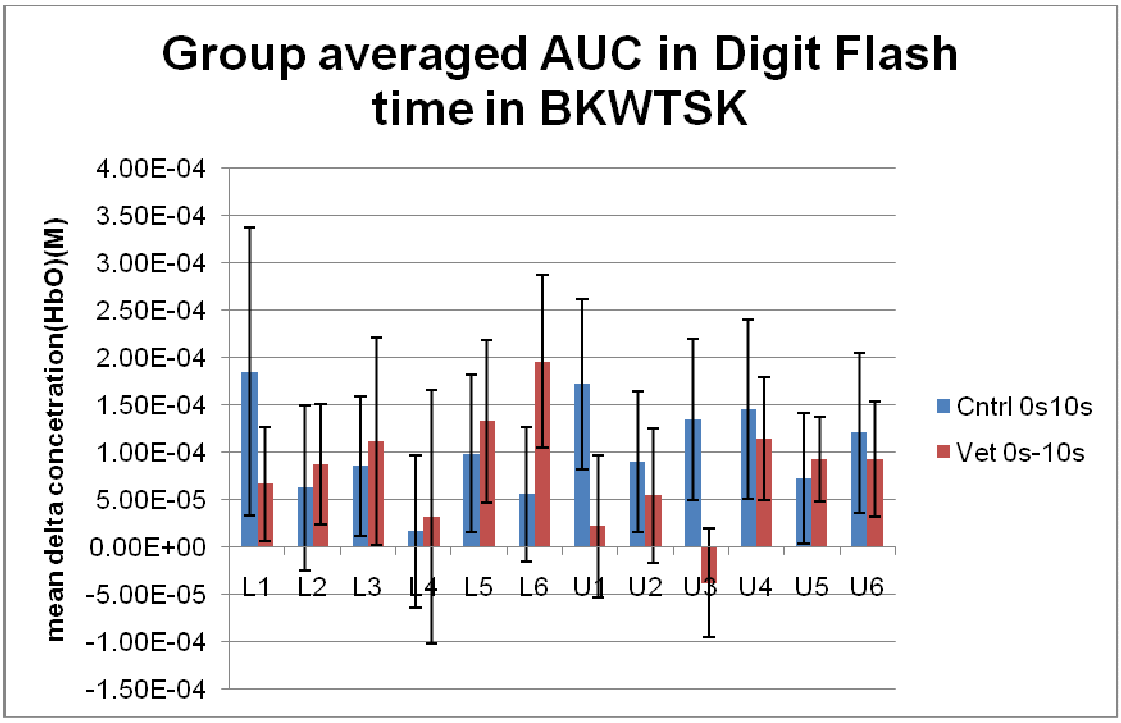

Figure 2.17 Group averaged AUC with SEM at the 12 clusters during the digit flash time with comparison between control group and veteran group in BKWTSK. Error bars represent standard error of means.

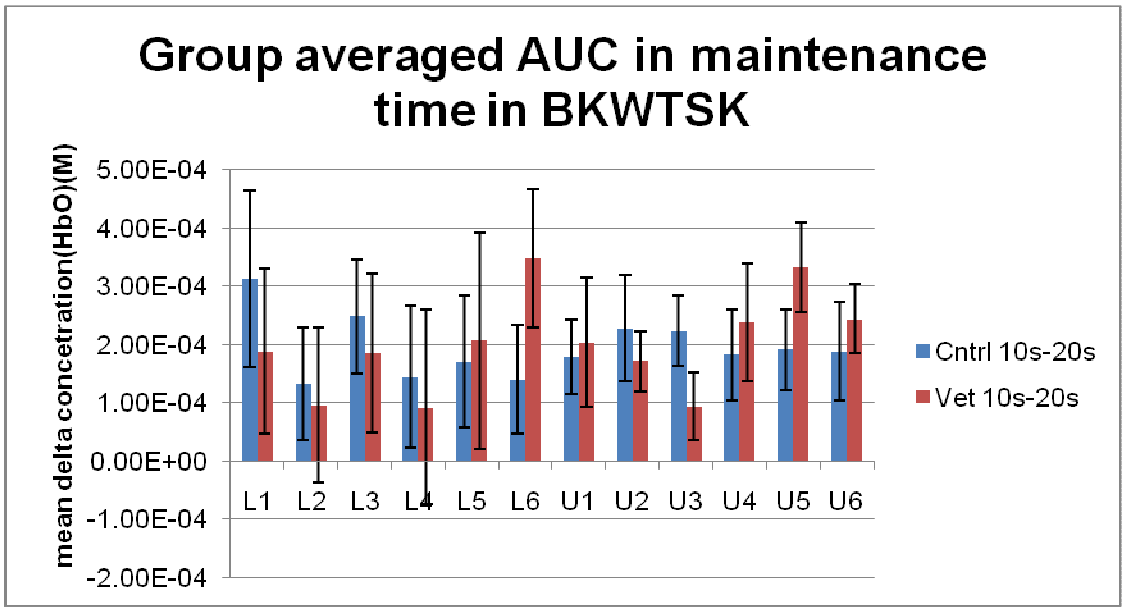

Figure 2.18 Group averaged AUC with SEM at the 12 clusters during the maintenance time with comparison between control group and veteran group in BKWTSK. Error bars represent standard error of means.

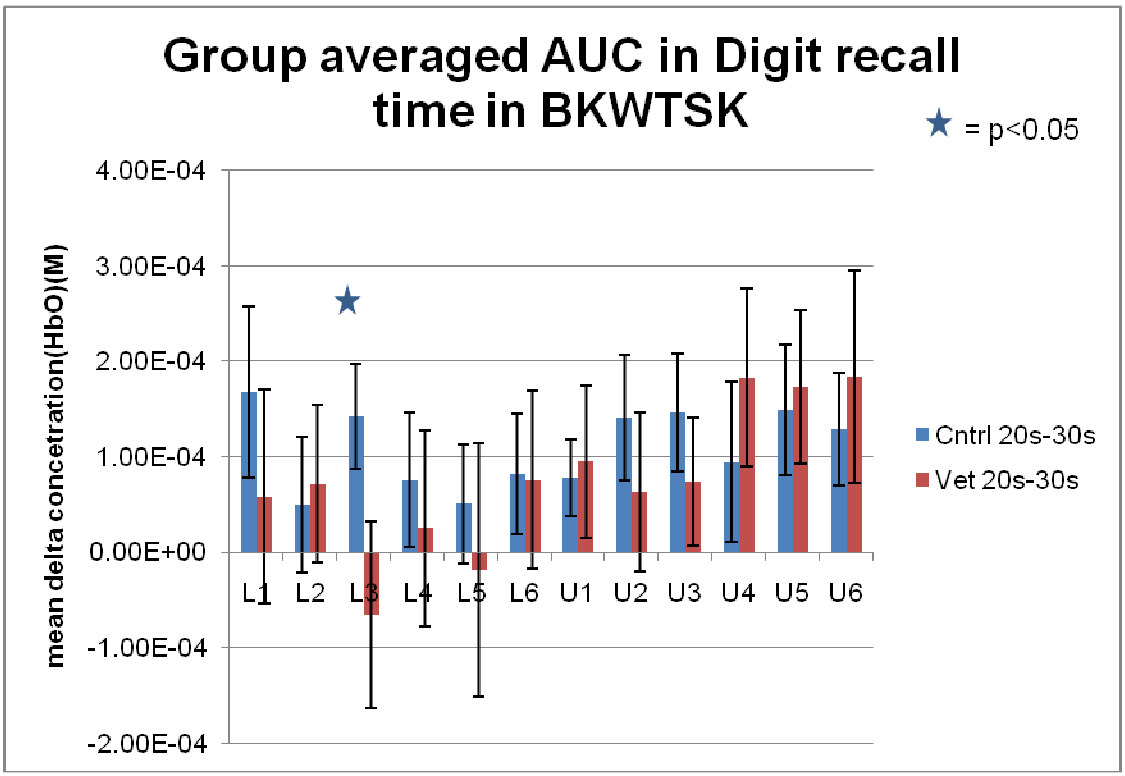

Figure 2.19 Group averaged AUC with SEM at the 12 clusters during the Digit recall time comparison with control group and veteran group in BKWTSK. Error bars represent standard error of means.

From the above results, we could see evident deactivation in FRWTSK for the veterans in the whole lower cluster L1 to L6, all showing a significant difference in deactivations from the control group (figure 2.16), during digit recall time. In digit flash time, only clusters L2 and L3 showed significant difference between the control and veteran groups. In digit maintenance time, only cluster L3 showed a possible significant difference with p-value=0.089. For BKWTSK, a significant difference between the activities in control group vs veteran group was found only in cluster L3 in the digit recall time.

2.3.2.2 Four cluster region analysis.

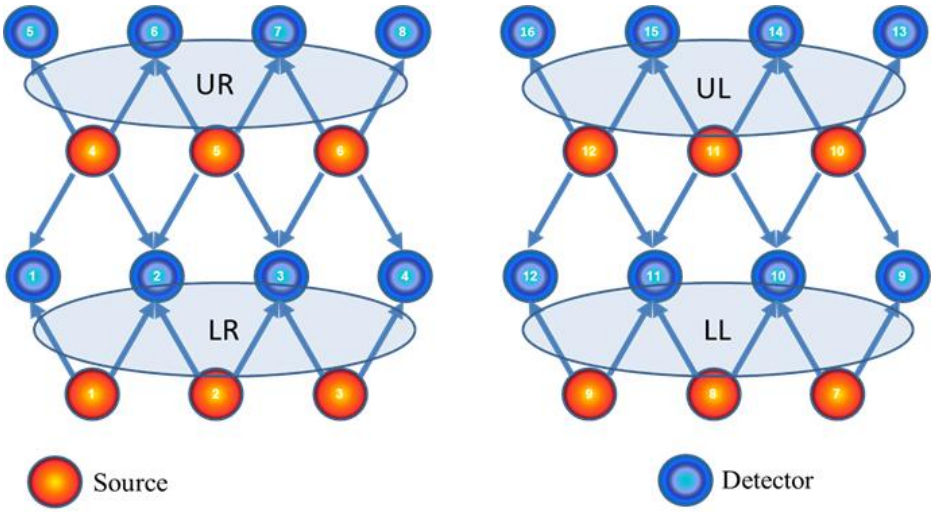

Figure 2.20 Probe geometry with the 4 selected clusters

Four regions were selected as shown in figure 2.20. UR represents Upper Right, UL represents Upper Left, LR represents Lower Left and LL represents Lower Left. By choosing these four clusters, I believe we can analyze and compare the right hemisphere BA9/46, left hemisphere BA9/46, right hemisphere BA10, and left hemisphere BA10. HbO signals from the 6 channels present in each cluster region were block averaged, and then grand averaged across the subject group to obtain a group-averaged temporal pattern, as shown below, in Figure 2.21.

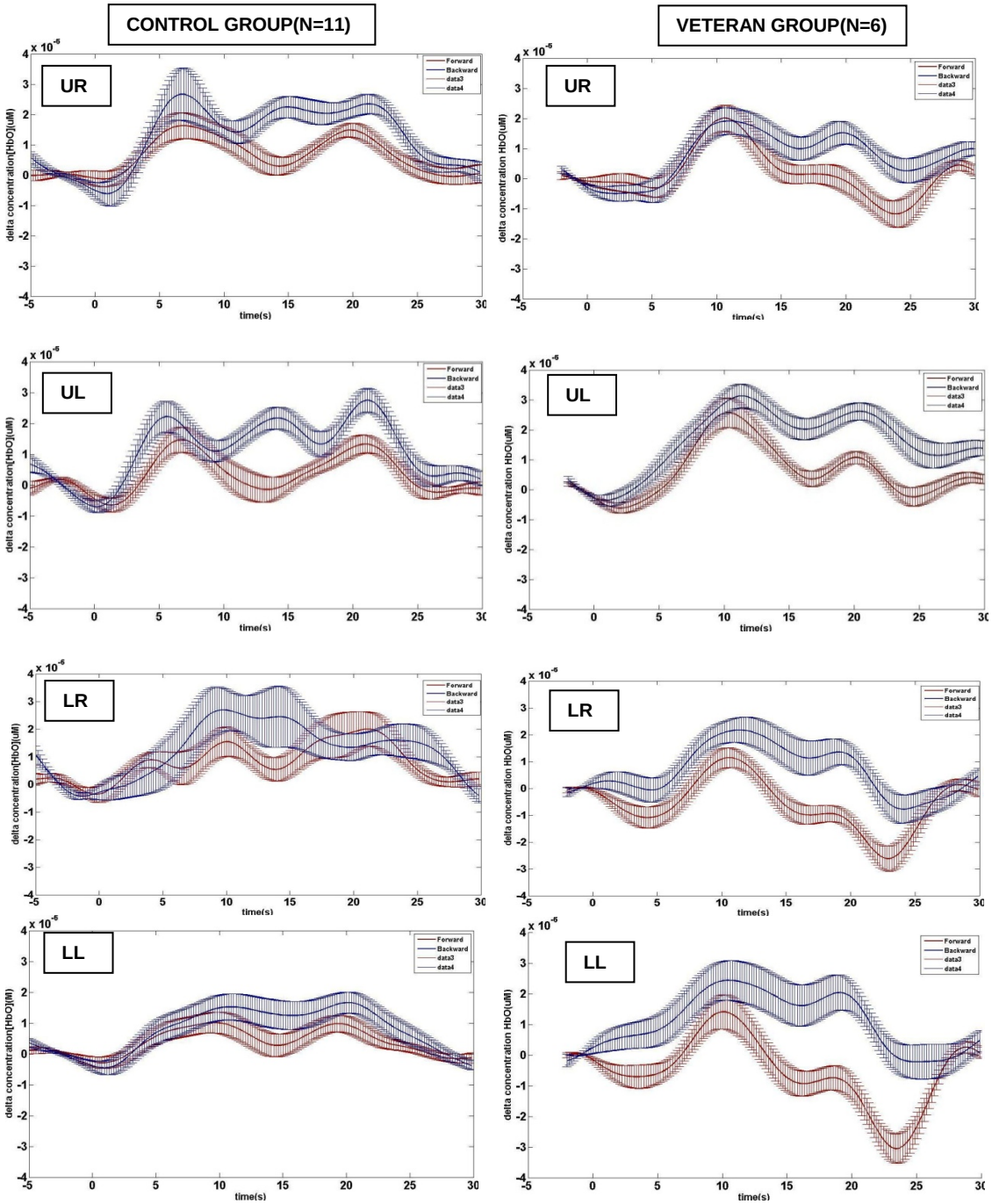

Figure 2.21 Group-averaged temporal plots for control group and veteran group from the 4 selected clusters. Red line indicates FRWTSK with error bars indicating standard error of means (SEM), and the blue line indicates BKWTSK with SEM. x-axis is time in seconds and y-axis reprents mean delta concentration (HbO) in M.

Areas under the curve (AUC) in the 3 phases or intervals (digit flash, maintenance and digit recall) were calculated for each subject separately; then a group-averaged AUC was found in each cluster for a comparative analysis of the brain activations between the control group and veteran group, for each of the 3 psychologically different phases. The results obtained are displayed below, from Figures 2.22 to 2.27.

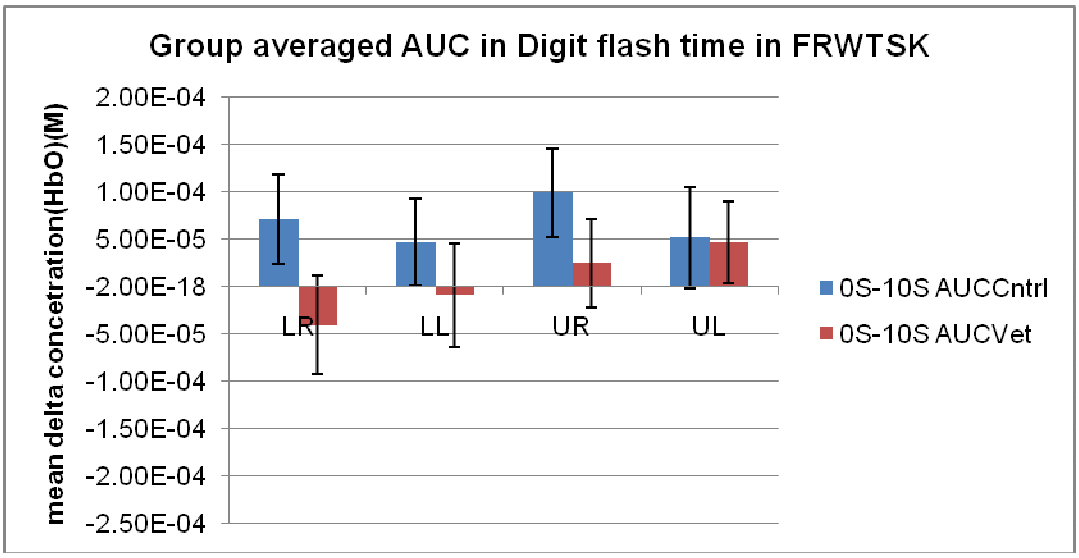

Figure 2.22 Group averaged AUC with SEM at the 4 clusters during the Digit flash time with comparison between control group (Cntrl) and veteran group (Vet) in FRWTSK. Error bars represent standard error of means.

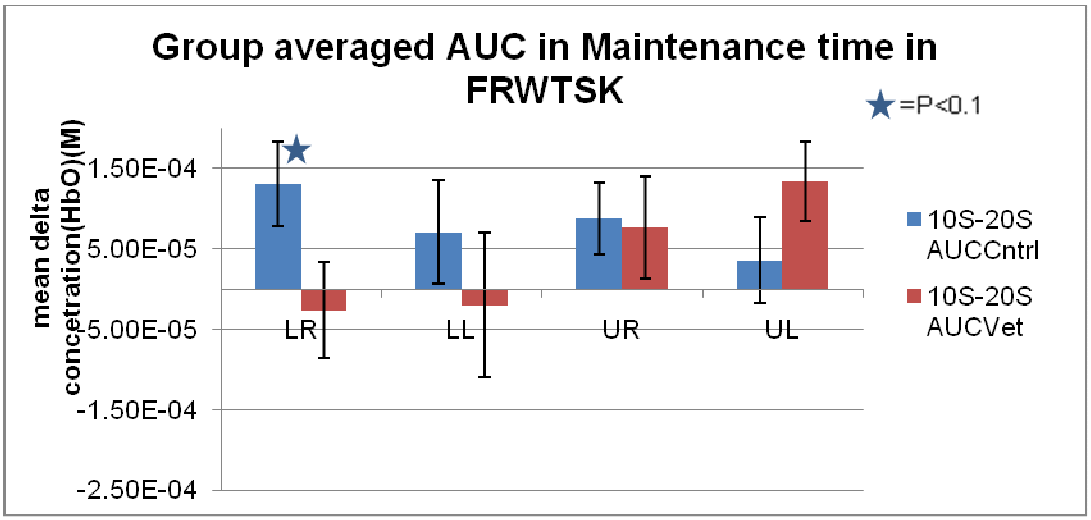

Figure 2.23 Group averaged AUC with SEM at the 4 clusters during the Maintenance time with comparison between control group (Cntrl) and veteran group(Vet) in FRWTSK. Error bars represent standard error of means.

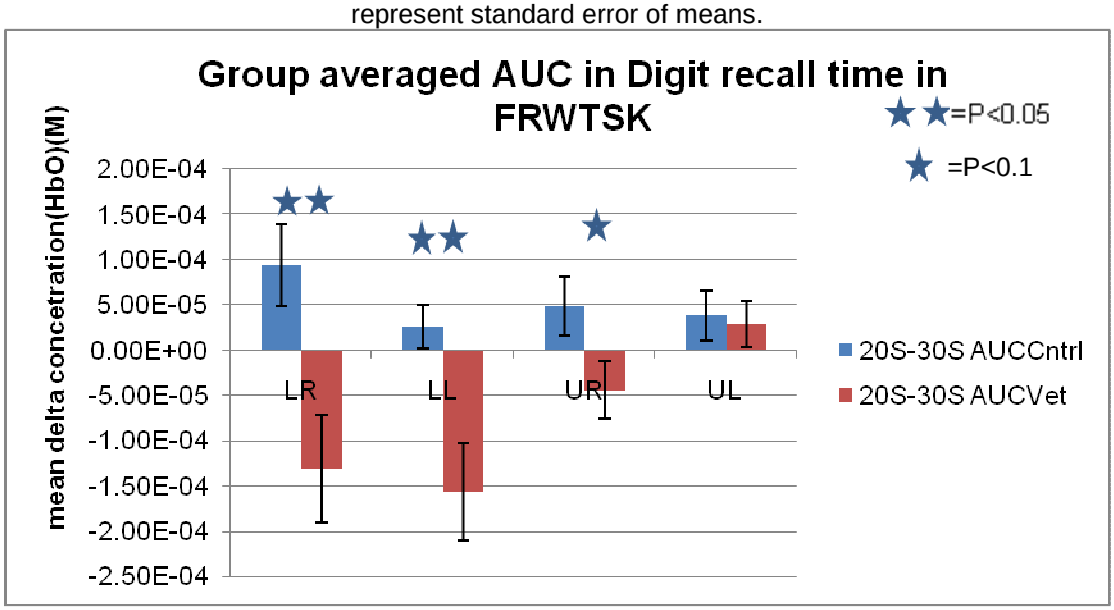

Figure 2.24 Group averaged AUC with SEM at the 4 clusters during the Digit recall time with comparison between control group (Cntrl) and veteran group(Vet) in FRWTSK. Error bars represent standard error of means.

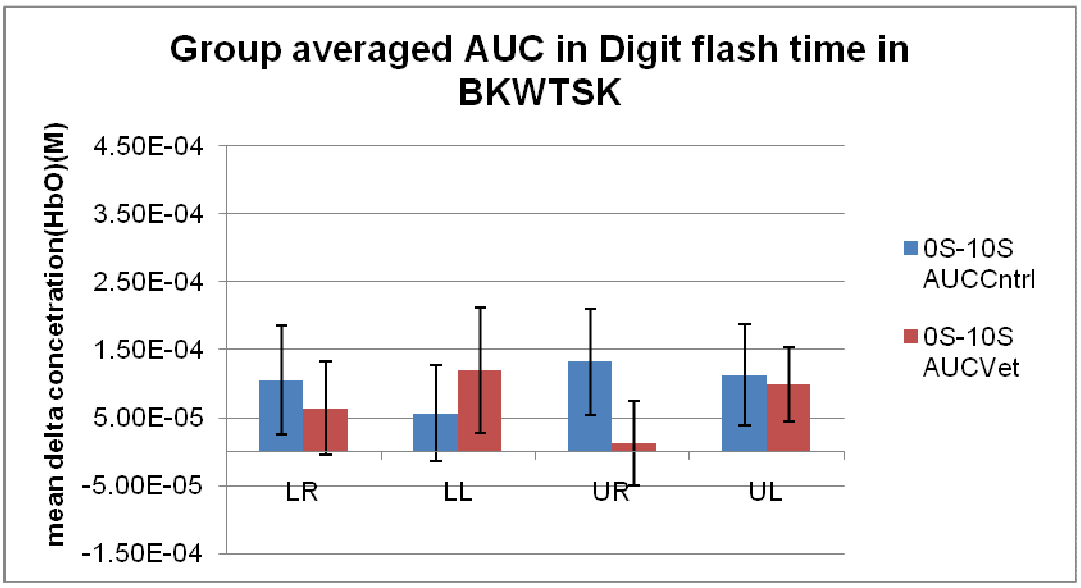

Figure 2.25 Group averaged AUC with SEM at the 4 clusters during the Digit flash time with comparison between control group (Cntrl) and veteran group(Vet) in BKWTSK. Error bars represent standard error of means.

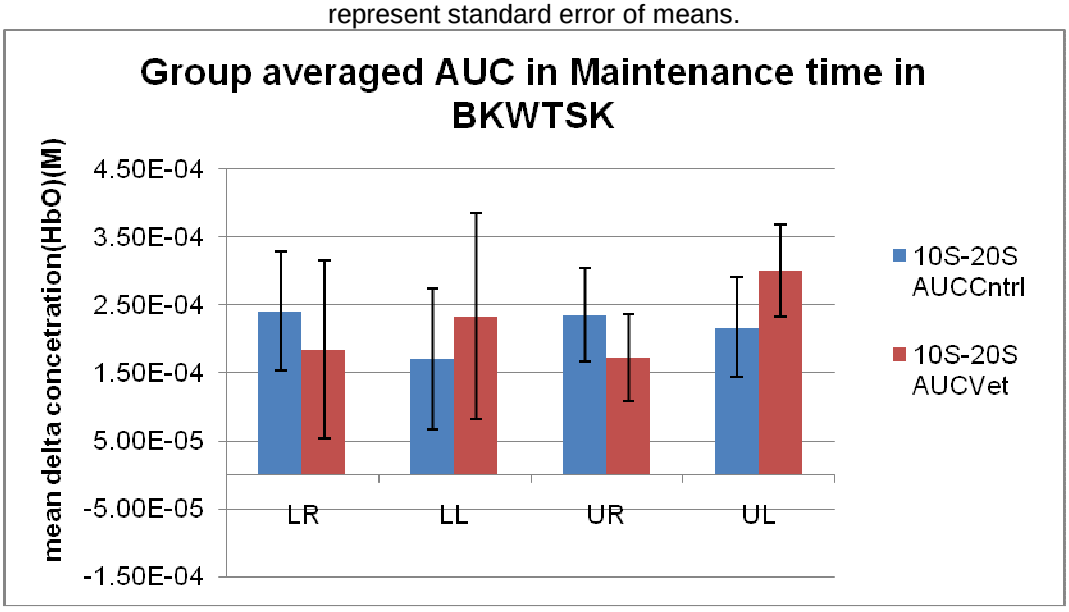

Figure 2.26 Group averaged AUC with SEM at the 4 clusters during the maintenance time with comparison between control group (Cntrl) and veteran group(Vet) in BKWTSK Error bars represent standard error of means.

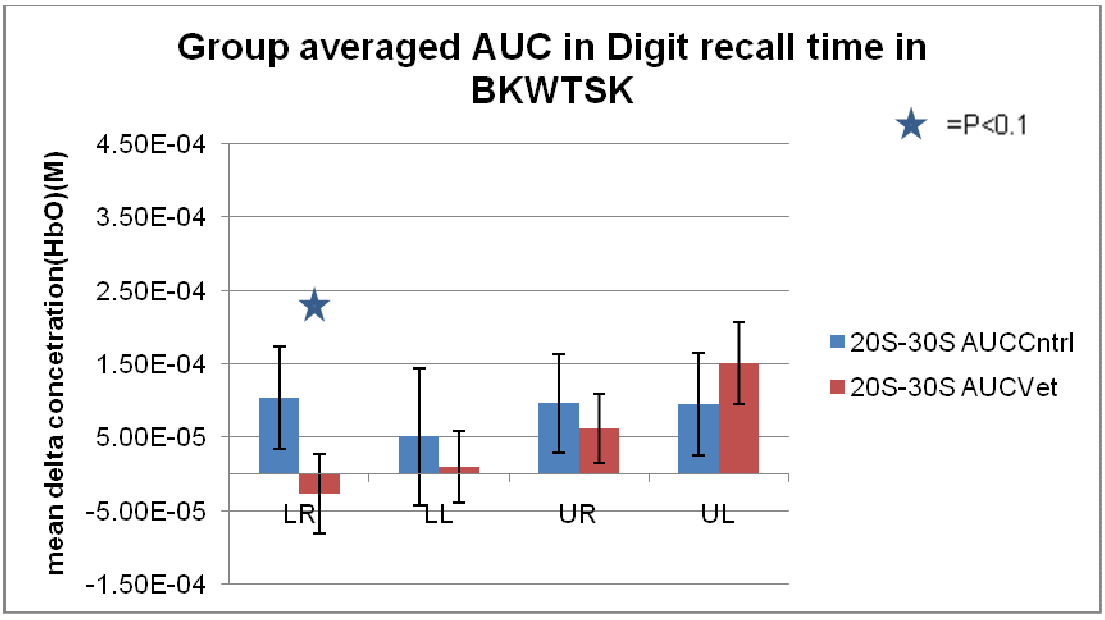

Figure 2.27 Group averaged AUC with SEM at the 4 clusters during the Digit recall time with comparison between control group (Cntrl) and veteran group (Vet) in BKWTSK. Error bars represent standard error of means.

The above results suggest that there were significant differences of the activations in LR and LL (p=0.012 and p=0.016) regions, respectively, between the control group and veteran group during the digit recall time of FRWTSK, with evident deactivation shown by the veteran group. Almost significantly different activation was observed in UR with p=0.06 during the recall time and also in LR region (p=0.077) during the maintenance time with a mean deactivation for the veterans in the FRWTASK. During BKWTSK, a significance of p=0.083 was found in the LR region during the digit recall time. None of the regions showed a significant difference in activation in the other 2 time intervals of digit flash and maintenance. From these results, it is evident that veterans have a significant deactivation in FRWTSK in BA 10 bilaterally, which corresponds to the frontopolar PFC, and that the major changes happen during the digit recall time. In BKWTSK as well as FRWTSK, we can see activation happening in both veterans and controls during the maintenance time in the UR and UL regions, corresponding to dorsolateral PFC.

2.3.2.2.1 Task correlation assessment

A subject-wise correlation analysis was done between the BKWTSK and FRWTSK for the whole temporal profiles. After each subject's correlation coefficient (R) was obtained, a group mean and standard deviation were calculated for each group. The results obtained are shown in table 2.1. A two sample t-test was performed between the correlation coefficients of the control group and veteran group, and the results are also shown. Comparatively the veteran group showed better mean R values than the control group, showing there might be lesser activation variations between the tasks for the veterans when compared to the control group.

Table 2.1 Correlation (R) analysis

	Control	Veteran	T-test(p)
UR BKWTSK VS FRWTSK	0.37± 0.36	0.49±0.31	0.52
UL BKWTSK VS FRWTSK	0.32±0.38	0.63±0.36	0.14
LR BKWTSK VS FRWTSK	0.31±0.43	0.49±0.18	0.28
LL BKWTSK VS FRWTSK	0.41±0.33	0.39±0.38	0.93

2.3.3 Hemodynamic response map comparison

HomER generates a 2D spatial activation map, the averaged functional activation for a selected time window which we choose. This time window can be chosen based on the characteristic of our task. The block-averaged temporal plot can be viewed in HomER and the time window can be chosen from it. HomER generates a light-sensitive matrix based on the probe geometry we utilized to match a semi-infinite diffusion model [22], which allows calculating the absorption changes across the spatial distribution. Through this method with the data available from the fNIRS measurements, as well as using the modified Beer-Lambert law, HomER can generate an activation map for HbO, HbR and HbT concentration changes. Here in my study, I am considering only the HbO changes. So, all the activation maps displayed are from HbO activation. The temporal windows chosen are the same 3 time intervals or phases as

those we used in temporal analysis in previous sections, namely, digit flash, maintenance, and digit recall. Based on each temporal window, I have plotted the group mean activation maps for the control group and veteran group, respectively, in each FRWTSK and BKWTSK as wells as the difference maps between BKWTSK and FRWTSK (i.e., BKWTSK-FRWTSK) for a visual comparison, in Figures 2.28- 2.30.

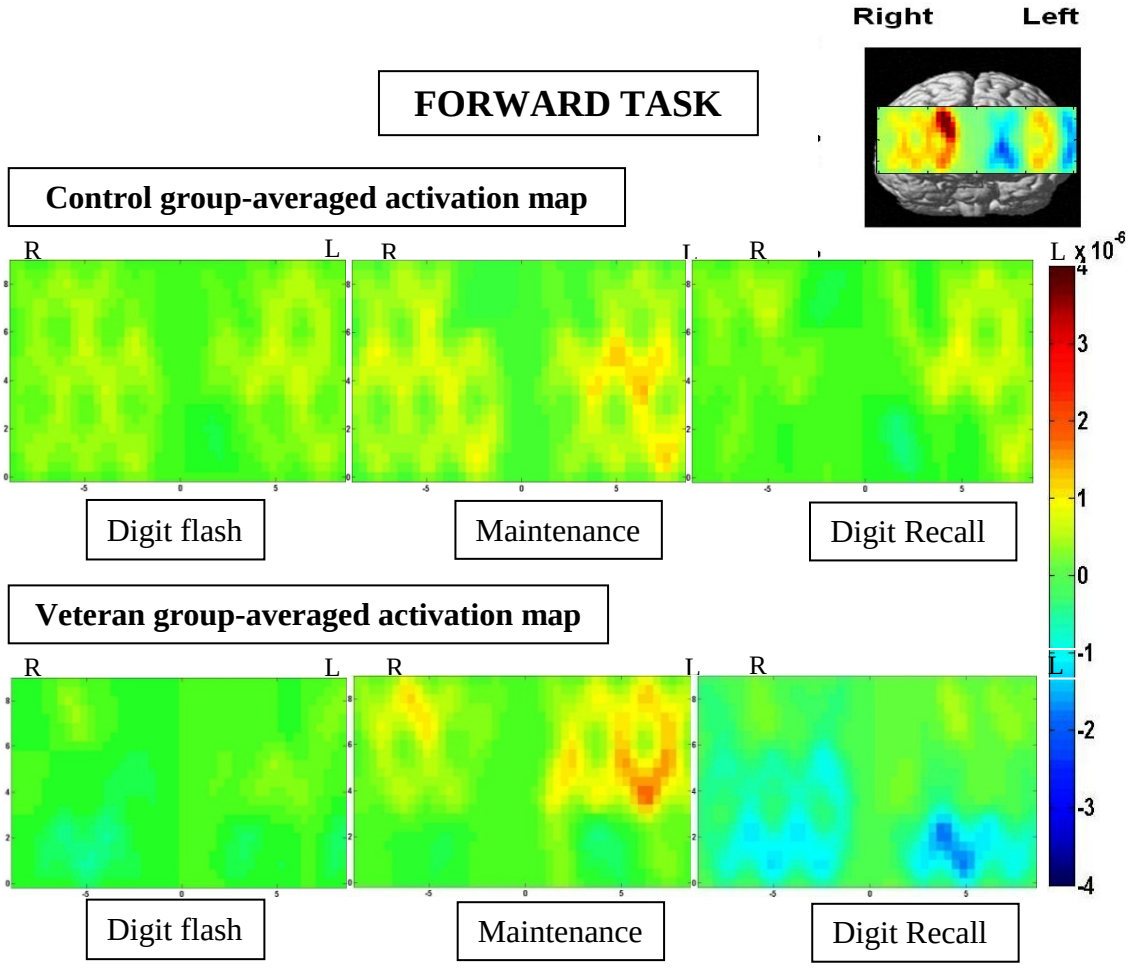

Figure 2.28. Mean 2D hemodynamic activation maps for control and veteran groups performing the FRWTSK at the three different intervals: Digit flash time, Maintenance time, and Digit recall time, listed one after the other. 'R' and 'L' indicate the right and left hemispheres of the brain. The unit for the color bar is M.

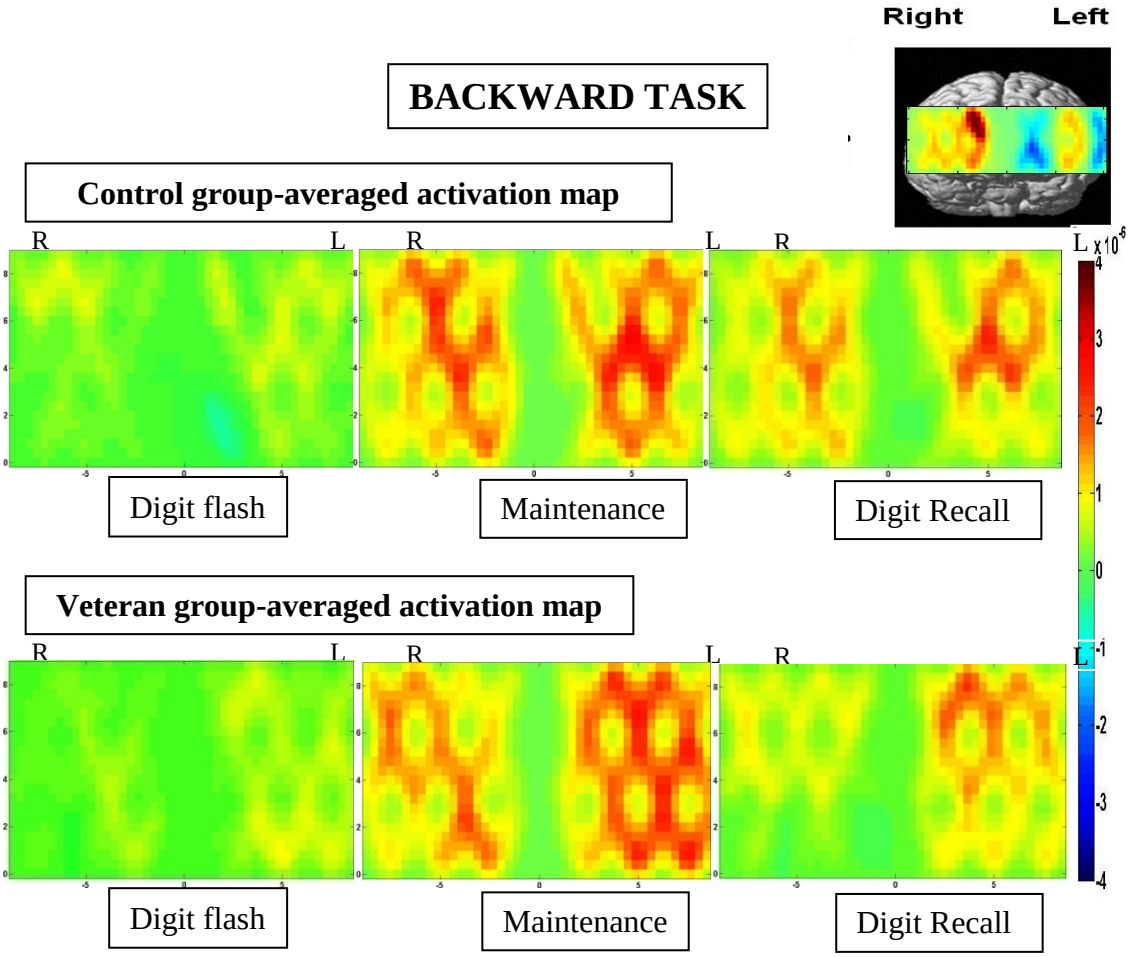

Figure 2.29 Mean 2D hemodynamic activation maps for control and veteran groups performing the BKWTSK at the three different time intervals: Digit flash time, Maintenance time, and Digit recall time, listed one after the other. 'R' and 'L' indicate the right and left side of the brain. The unit for the color bar is M.

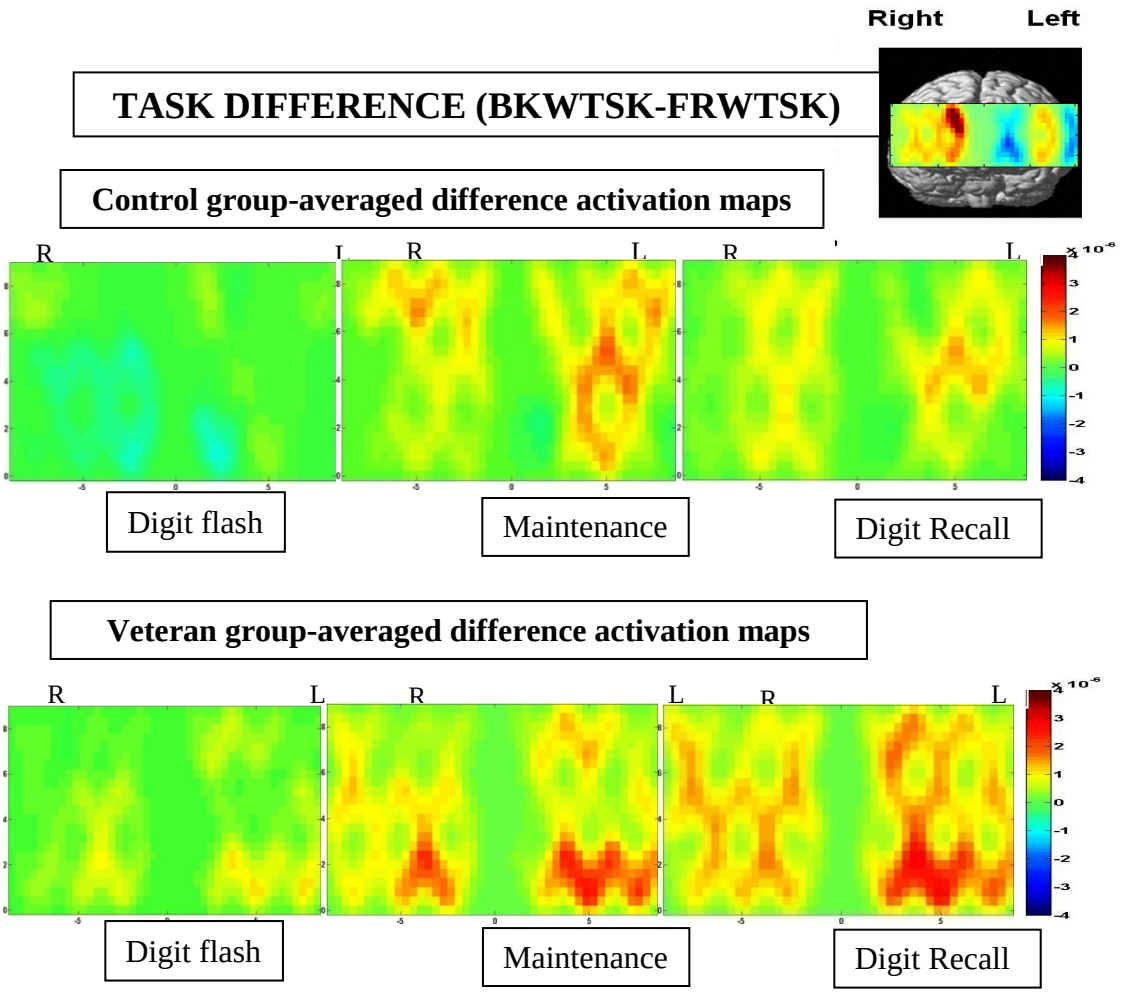

Figure 2.30. Mean 2D hemodynamic difference activation maps for controls and veterans induced by the difference of BKWTSK-FRWTSK at the three different intervals: Digit flash time, Maintenance time, and Digit recall time. 'R' and 'L' indicate the right and left side of the brain.

From the spatial activation maps, we can see that significant activation and deactivation patterns exist during each of the three temporal phases, which are in good agreement with the temporal curve analyses, given in section 2.3.2. It is evident from these activation maps that significant cognitive activations and deactivations happen on the prefrontal cortex induced by the forward digit span task and backward digit span task. We can also see significant activation

pattern differences between the tasks as well as between the subject groups. As the temporal plot analysis showed, significant deactivation in veterans in the LR and LL regions is clearly evident during the digit recall time of FRWTSK, as seen in Figure 2.28 with the blue color showing deactivation. Moreover, Fig. 2.30 clearly illustrates that veterans surely have more brain activations in the LL region during the BKWTSK with respect to FRWTSK, as compared to the controls. Further studies are needed to better understand and interpret the activation/deactivation maps shown in these figures.

CHAPTER 3

DISCUSSION AND CONCLUSION

3.1 Digit span comparative study

In this comparative study between the veteran group with PTSD and normal control subjects, I used fNIRS to assess the brain activities in the PFC areas (BA 9/46 and BA 10) using the digit span task. The temporal responses were analyzed, dividing the whole prefrontal area of analysis into 12 clusters as well as 4 clusters, and dividing the entire temporal response into 3 intervals of digit flash time, maintenance time, and digit recall time. I also plotted the spatial response maps where we could see significant HbO activation and deactivation happening in the analyzed areas. From the temporal analysis, I was able to find significant deactivation happening in the lower PFC regions relative to BA 10 (i.e.,frontopolar PFC) during the FRWTSK for veterans, whereas the controls had activation.

This observation is consistent with the fMRI studies done on the PFC of patients with traumatic brain injury [34]. Few other studies also have supported the result of hypo-activation in the PFC [35][36][40]. On the contrary, there were also findings with hyperarousal/ hyperactivity in PFC observed in patients with PTSD while doing cognitive and memory tasks [37][38][41][42]. The BKWTSK showed considerable activation for both groups with no significant changes observed between the groups. Unlike FRWTSK, no hypo-activity in the recall phase was observed during BKWTSK. One reason for this could be the sealing effect due to the high levels of activation that happened during the maintenance and recall phase. From the temporal plots, it can be observed that the activation is decreasing as the time progresses. If we analyze the signals after a time delay, it might show the deactivation, similar to the FRWTSK, in the recall phase of BKWTSK too. Also in the 12 cluster analysis, we could see the

deactivation happening in the L3 region for BKWTSK, and the nearby areas showing a similar trend. The task correlation was better observed in veterans but that too showed a lot of variability within the group to make an inconclusive result. Since this study was the first few of its kind using fNIRS, there are a lot of improvements to be done to finally reach a definite conclusive result.

Numerous neuroimaging studies have been conducted on PTSD patients, and a variety of results have been published. However, there exists a broad range of variability, including the imaging techniques used, the tasks chosen for cognitive studies, the variability at different levels of PTSD, the different kinds of comorbit symptoms such as anxiety, stress, attention deficiency, hypervigilance, and so on. All of these add to the difficulty in obtaining a definite conclusion. For example, one neuroimaging study has published hypo-activation for patients with PTSD alone, whereas hyperactivity was observed for patients with both PTSD and anxiety together. The authors have also emphasized the importance of emotional regulation and emotional responses in PFC as most of the PTSD patients have emotion inhibition difficulties [40]. In my study, I did not classify the veteran group based on their level of PTSD or the comorbit symptoms they had, which might have affected in obtaining a more precise or conclusive result. Another factor that was not taken into consideration was the medication effects on the brain functions of these PTSD subjects as all of them were under medication. Another interesting MRI volume-based morphology study indicated significant reduction in the size of hippocampus, anterior cingulated cortex (which lies behind the dorsolateral PFC), as well as reduction in grey matter of insula [43][44][45][46]. This poses a new problem of changing the anatomy or shape of the brain in patients with PTSD and introduces extra variability to the comparative study between the veterans and controls. This was another factor that was not taken into consideration in this study and would have had a possible effect on the results of my study.

3.2 Limitations and Future study

As we discussed above, there were a lot of variability factors that were not taken into consideration. To better classify the veteran subjects based on different levels of PTSD and its comorbid symptom could be a better approach. To test reliability of the data, a test-retest approach could also be a good method to prove and validate the method and study. Since my study was the first of its kind, to my knowledge, done in fNIRS, a test-retest operation has to be done for better purifying the results and obtaining a definite conclusion. The group population was also a limitation to this study, as we had only 6 veterans to compare against 11 control subjects. For a firm statistical comparative analysis, we need to have a good number of subject populations. Also, we need to reduce the variants within the group like age, sex, PTSD level, different types of trauma, and right-handed or left-handed subjects. Another limitation factor in fNIRS is the environmental conditions and the repeatability of those conditions throughout the subject group as compared to fMRI where the subjects are all under a closed environment with minimal variability of the environmental factors. This proves to be important in PFC imaging as PFC is also known for its attention centre. Environmental distraction can cause error in the results, and becomes even more relevant in cases of PTSD patients with attention problems. The limitation of fNIRS with low spatial resolution has also been a factor to conduct good spatial analyses of the data.

Therefore, in the future study, I would like to perform repeated experiments with a higher patient population in better controlled environments, as well as better classifying the PTSD patients to reduce the variability within the group. Use of different analysis methods, such as feature identification and selection, to make up for the spatial analysis limitations of FNIRS, would be good. Also more complex statistical analysis with better flexibility to incorporate subject variation would be very useful. A longitudinal study of the same patients repeating the

tasks after undergoing therapy or other treatments would also be an interesting approach to see the variations that the therapeutic interventions may bring to the brain activities.

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BIOGRAPHICAL INFORMATION

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