VOL. 10, NO. 20, NOVEMBER 2015 ISSN 1819-6608
ARPN Journal of Engineering and Applied Sciences


www.arpnjournals.com

THE EFFECT OF WORKING MEMORY LOAD ON PREFRONTAL CORTEX ACTIVATION: AN OPTICAL TOPOGRAPHY STUDY

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ABSTRACT

Working memory (WM) is a theoretical concept that represents the system responsible for cognitive brain functions such as language, planning and problem solving. Studies have suggested that negative mood states impair the WM system, which can be reflected through changes in WM task performance and in activation of specific parts of the brain such as the prefrontal cortex (PFC). In this study, the relationship between working memory load and the PFC activation is investigated without biasing of mood using an optical topography (OT) system. Three levels of N-back tasks were carried out on 14 healthy male university students. It is found that the OT modality as a less-constrained neuroimaging tool can effectively measure the haemodynamic changes at PFC, confirming a significant increase of PFC activation is associated with increase of WM load from 0-back to 1-back task.

Keywords: working memory, optical topography, haemodynamic, prefrontal cortex.

INTRODUCTION

Working memory (WM) acts as a temporary buffer that keeps a limited amount of information for immediate manipulation or processing (Baddeley, 2000; D'Esposito *et al.* 2000; Fletcher & Henson, 2001). In 1974, Baddeley and Hitch proposed a multi-component model of working memory, which is managed by a central executive (CE) that directs attention to relevant information and actions, and coordinates cognitive processes. The CE is assisted by a 2-slave system; the phonological loop for verbal information and visuospatial sketchpad (VSSP) for non-verbal information (Baddeley, 2000). Thus, WM is closely engaged with the higher cognitive functions of the brain such as language, planning and problem solving (Cohen *et al.* 1997; Conway *et al.* 2005; D'Esposito *et al.* 2000).

N-back task is one of the known WM memory tasks which demands continuous retention and manipulation of information, where new stimuli are perceived and old information are discarded throughout the task (Purves, 2008). Sustained activation in the prefrontal cortex (PFC) with respect to increased WM load was reported in a study of functional magnetic resonance imaging (fMRI) using English characters as stimuli (Cohen *et al.* 1997). This finding was also supported by studies which described lateral PFC facilitates WM and it is anatomically organized with respect to cognitive functions (D'Esposito *et al.* 2000), maintenance of information, and also it influences all types of information rehearsal (Curtis & D'Esposito, 2003).

Studies have been carried out to map the neuro-anatomical brain functions using N-back and reordering tasks. The mapping with fMRI suggests that frontal cortex (FC) engaged with WM function in general, with the ventrolateral frontal cortex (VLFC) focusing on updating and maintaining information while the dorsolateral frontal cortex (DLFC) in monitoring and manipulation (Fletcher & Henson, 2001). A Similar study using Sternberg's task and n-back task have found that the VLPFC is engaged with maintenance efforts such as storing, rehearsal and matching; whereas the DLPFC responds more towards the manipulation functions such as reordering and updating of information (Veltman *et al.* 2003). Thus, the study suggests that the PFC region would engage with WM tasks with no clear differences between specified brain functions.

FMRI studies have reported that negative moods affect cognitive functions which that are related to working memory in the prefrontal cortex (PFC) region (Fales *et al.* 2008; Gray *et al.* 2002; Qin *et al.* 2009; Schoofs *et al.* 2008). Moreover, negative mood such as chronic stress will trigger the body stress response in the Hypothalamic-pituitary-adrenal axis (HPA) and anatomic nervous system (ANS) leading to the secretion of stress hormone, gluco-cortisol (Tsigos & Chrousos, 2002). Uncontrolled and prolonged psychosocial stress such as chronic stress will caused WM impairment that may lead to prefrontal cortex (PFC) dysfunction (Mizoguchi *et al.* 2000). Thus, studies were to examine the relationship of mood states and cognitive functions with WM tasks are important.

In psychiatry, the current challenge is the lack of objective diagnosis approaches, which limits clinical validity (Stephan & Mathys, 2014). A recent paper on using functional near-infrared (fNIR) neuroimaging-guided diagnosis of psychiatric disorder such as depressive disorder has been a breakthrough (Takizawa *et al.* 2014). Hence, it is hypothesised that fNIR can be effective in probing the mood state of a healthy individual.

Optical Topography (OT) is a non-invasive fNIR based neuroimaging modality, which acts as an alternative to fMRI for the study of haemodynamic responses in the brain grey matter level (Sato *et al.* 2013). More importantly, the modality imposes less constraint (Aoki *et al.* 2011; Koike *et al.* 2013) on subjects during the study, as well as having low noise performance and minimum space

occupancy (Maki *et al.* 1995). Hence, in the present study, the haemodynamic responses on the PFC region are measured using OT modality without any bias to the subject's mood states. This work is vital to validate the working memory experiment design protocol as well as development of OT measurement and analysis techniques.

MATERIALS AND METHODS

Participants

Fourteen healthy and right-handed university male students (age: 21.8 +/-1.4 years) participated in this study. None of them reported to have any family history of neurological or psychiatric illnesses. Subjects with a smoking habit, on any form of medication, having less than 6 hours of sleep or those who consumed any caffeinated products on the day of participation were all excluded from this study.

Experiment protocol

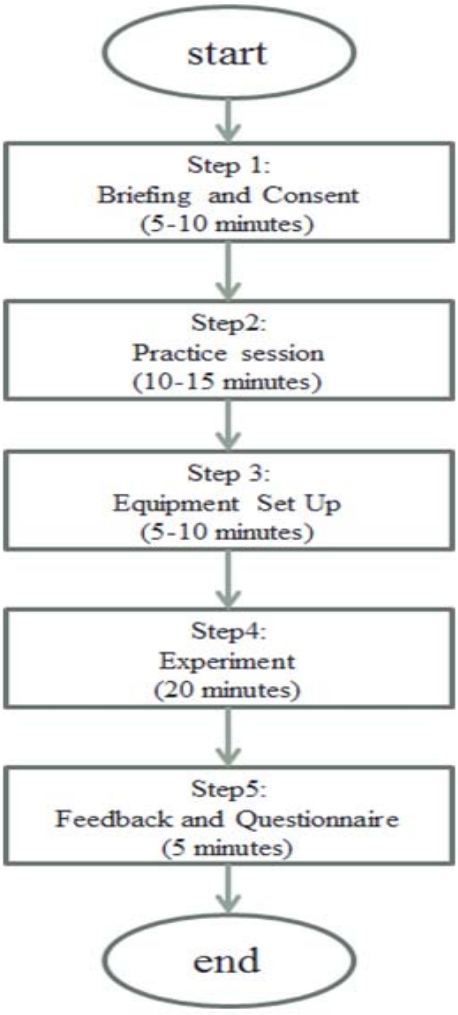

Figure-1. Study flow diagram.

The flow of study with the estimated times of completion for each step is shown in Figure-1. Upon arrival, each subject is seated for a briefing on the purpose and what to be expected from the study. The subject is given an ample amount of time to read through the research information. Once the subject reaches an understanding of what to be expected and is still willing to participate in the study, the subject is given a consent form to sign.

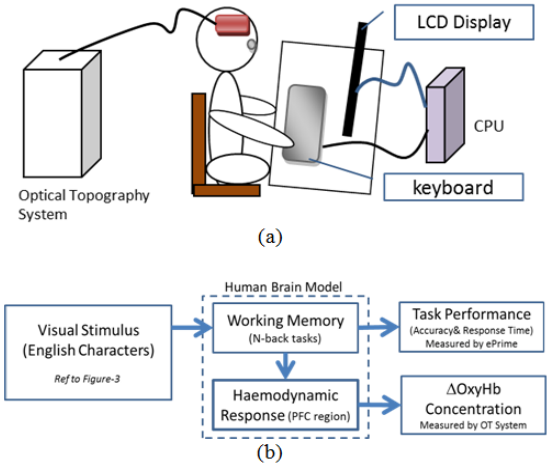

Figure-2. (a) Illustration of study setup; (b) Overall system block diagram.

After the consent form is signed, the subject is asked to be seated for a practice session with 3 difficulty levels of n-back tasks (i.e. 0-back, 1-back and 2-back). A liquid-crystal-display (LCD) is used for visual stimulus presentation and the subject is required to respond by typing in a numeric input (number "1" - target or "2" – not a target) using a standard keyboard. Once the subject achieves the accuracy of 80% or a higher for each task, he is then allowed to proceed with OT data acquisition setup as illustrated in Figure-2 (a).

With the necessary assistance, the subject is required to put on the OT headgear (refer to Figure-5) to perform the same tasks as in the practice sessions. The overall system block diagram is shown in Figure-2 (b) where the visual stimulus (Figure-3) activates the brain WM functions resulting in haemodynamic responses in the PFC. Task performances and changes in Hb concentration are measured concurrently using the ePrime software and OT system respectively. Three measurement sessions (Figure-4) are carried out for each respective task (from '0-back task' followed by '1-back task' and lastly '2-back task'). Sufficient rest time is given to the subject after each task is completed. Once the tasks are completed, the OT headgear is then removed from the subject. The study ends with a feedback session, where the subject is encouraged to share their experience during the study.

N-back tasks

The N-back task was designed using the e-Prime 2.0 software (Psychology Software Tools Inc.). In this study, English characters (i.e. A, B, C, D, E and X) were used as visual stimuli to excite the subject's verbal working memory. For each n-back task, 20 random visual stimuli are shown sequentially within a 40s duration (2s per frame with stimuli fading after 1s). The subject is required to respond with either number "1" – target or "2" – not a target, for each stimulus as fast as possible, within the duration of 2s.

In 0-back task, the subject is required specifically to look for the target (character 'X'). Upon seeing the target, the subject is required to type in "1" as the response within the duration of 2 seconds before the stimuli fades. For other characters, the subject has to reject these non-targets by typing in "2" as the response.

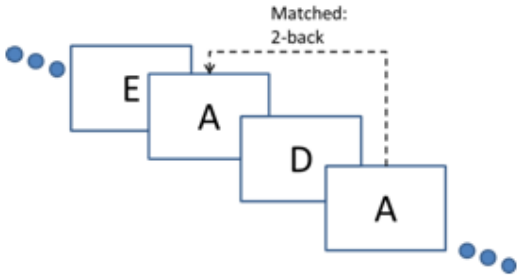

Figure-3. Visual stimulus presentation for n-back task.

For 1-back and 2-back tasks, the character "X" is not included as visual stimulus. These two tasks differ from 0-back task; instead of finding a specific target, the subject is expected to compare the previous characters as targets. For instance, the target in 1-back task refers to the subsequent repeated stimulus, where the current character matches with the previous. As for 2-back task, the subject has to match the current character with the character following the subsequent character i.e. two characters earlier as shown in Figure-3.

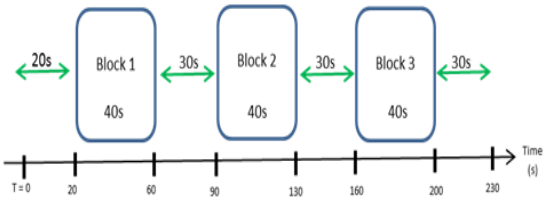

Figure-4. N-back task blocks (repetition).

For each n-back task, it is obligatory for the subject to complete 3 repetitions (blocks) with a 30s rest interval. After the rest interval, the subject is prompted to get ready for the task through an on-screen instruction (5s before the starting of the each block). The expected duration taken to complete each task is 3 minutes and 50 seconds as shown in Figure-4.

Behavioural data such as accuracy and response times are measured for each subject throughout the study using the e-Prime software. The data from all subjects are merged and pre-analysed using e-DataAid in the e-Prime software. The data is then exported into Statistical Package for the Social Sciences (SPSS software, IBM Co.) for statistical analysis.

Optical topography data acquisition

The OT-R40 Optical Topography system (Hitachi Medical System) is used to measure the haemodynamic responses. The system operates based on dual-wavelength near-infrared spectroscopy (NIRS: 695nm and 830nm), at a sampling rate of 10Hz.

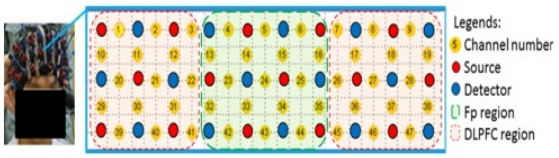

Figure-5. OT probe arrangement and set up(red-emitter, blue-receiver).

In the study, the measurement OT probe arrangement and set up is shown in Figure-5. The probes were configured in 10x3 arrangements, where the sources (red) to detectors (blue) separation were fixed at 30mm on a probe holder. These separations between sources and detectors provide sufficient coverage on the subject's PFC region with 47 measuring channels. The channels were sub-divided into Frontal Pole (FP) regions and Dorsolateral Prefrontal Cortex (DLPFC) region for analysis and discussion. The light attenuation (from the detectors of each channel) is converted into haemoglobin concentration by using modified Beer-Lambert Law (Maki *et al.* 1995). Thus, such dual wavelength OT system can measures both oxygenated haemoglobin (OxyHb) and deoxygenated haemoglobin (deOxyHb) levels, which expressed as the product of haemoglobin concentration changes and optical path length (mM.mm).

OT data analysis

Firstly, channels with detected low level of light are identified and eliminated from further analysis. The contributing factors for these 'bad' channels could be due to loose contact of probe during the task or the light is being blocked (i.e. hair, obstacles such as spectacles). These channels are identified when the total gain is more than 6667 times, which indicates the light reflected back to the detectors is less than 1pW for the particular measuring channel. Channels registering sudden and large haemodynamic responses (>0.4mM.mm) will be excluded as these haemodynamic changes are considered as motion artefacts (Aoki *et al.* 2011).

Next, the high frequency system noise and low frequency drift in the remaining channels are removed by using a digital Butterworth band-pass filter (0.012-

0.80Hz). Block averaging technique is then applied, where the signal in each channel is self-averaged across all blocks. Each block consists of 5s pre-task, 40s task (shaded in green) and 15s post-task period (Figure-6 middle). The OxyHb signal is then baseline-corrected with linear fitting method using the average value from pre-task and post-task period (Figure-6 right).

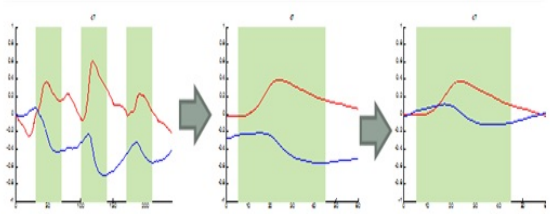

Figure-6. OT signal block averaging technique (middle) and baseline Fitting (right).

The OxyHb signal is focused for further analysis as significant WM task effect was reported (Aoki *et al.* 2011; Sato *et al.* 2011). Paired t-test is performed to identify the channels with significant OxyHb changes ($p \leq 0.1$) due to the n-back WM loads. The mean activation value in the OxyHb signal (10s after starting of task towards the end of task) are extracted with the consideration of the delay in haemodynamic response (Sato *et al.* 2013). OxyHb concentration change in the PFC regions (FP and DLPFC) are then tabulated in respect to WM loads.

RESULTS AND ANALYSIS

This section discusses the aspects of behavioural data (i.e., accuracy and response time) and PFC haemodynamic response during task activation. Table-1 below tabulates the grouped parameters for each task.

Table-1. Parameters for N-back tasks.

Parameters	Mean	±SD
0-back task		
Accuracy (%)	99.49	0.38
Response Time (msec)	538.71	57.44
DLPFC ΔOxyHb (mM.mm)	0.0258	0.0345
FP ΔOxyHb (mM.mm)	0.0180	0.0245
1-back task		
Accuracy (%)	97.31	1.20
Response Time (msec)	489.01	39.76
DLPFC ΔOxyHb (mM.mm)	0.0588	0.0426
FP ΔOxyHb (mM.mm)	0.0266	0.0272
2-back task		
Accuracy (%)	89.10	2.33
Response Time (msec)	570.60	65.40
DLPFC ΔOxyHb (mM.mm)	0.0505	0.0451
FP ΔOxyHb (mM.mm)	0.0422	0.0296

Task performance

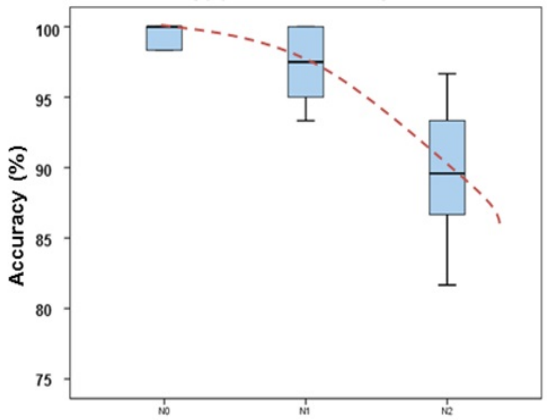

Figure-7. Task accuracy (%) vs. N-back task difficulty levels (WM load).

During 0-back task, the study group has no issues with the task achieving a mean accuracy up to 99.5%. From Figure-7, the task accuracy decreases as the WM load (difficulty level) increases from 0-back to 2-back task as expected. The spread of accuracy also broadens with increased task difficulty levels; this suggests that subjects are being challenged with increasing task difficulty. In all the n-back tasks, all subjects performed well (above 80%) as per requirement of the study. None of the subjects performed unexpectedly poor (no outliers in the box plot).

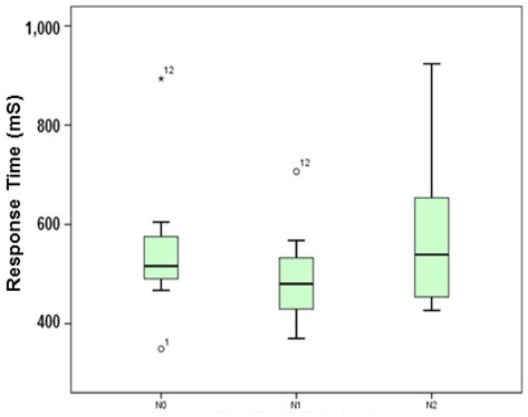

Figure-8.Response time (msec) vs. N-back task difficulty levels (WM load).

Increase in response times is expected with increase of WM load as longer duration is needed to manipulate and decode the information. From the plot in Figure-8, significant increase and spread (interquartile range, IQR) of the response time is observed going from 1-back to 2-back tasks. However, the response time shown from 0-back to 1-back task indicates most subjects performed faster in 1-back task as compared to 0-back task. This appeared to be unusual as the response time is hypothesized to be longer for an increase in WM load

based on previous study (Ayaz *et al.* 2012). It is speculated that the subjects experienced a delayed adoption on the task response mechanism (in 0-back task) with the set up of OT measurement. Hence, they are able to response slightly faster in 1-back as compared to 0-back task while the WM laod is still manageable.

Outliers are observed in both 0-back and 1-back tasks, where subject 12 took significantly longer time to respond (> 1.5 IQR + Q3) and Subject 1 was found to respond significantly fast (response time < Q1 – 1.5 IQR), with 100% task accuracy during 0-back task. None of these outliers is excluded from the study as these are valid responses which are well within the response duration and accuracy range.

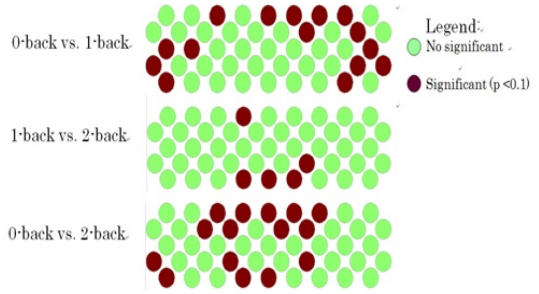

Figure-9.Channels with significant oxyhb change vs. N-back task difficulty levels

Figure-9 shows the tendency of activation region when the WM load changed from 0-back to 1-back, 1-back to 2-back and 0-back to 2-back respectively

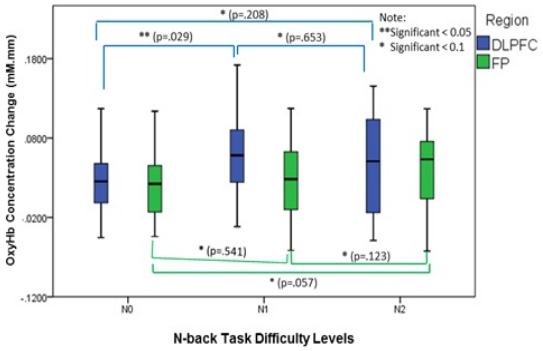

Figure-10. OxyHb response (mM.mm) vs. N-back task difficulty levels in DLPFC and FP region.

Based on the grouped data in all channels within the PFC region, significant increase of OxyHb concentration level was found when comparing 0-back with 1-back task (p=.036) and 2-back task (p=.030) respectively. No significant was observed between 1-back and 2-back task. From the regional analysis as shown in Figure-10, the OxyHb change around the DLPFC region significantly increased (p=.029) from 0-back to 1-back task. As in the FP region, significant increase of OxyHb level was found between 0-back and 2-back task (p=.057). No significant increase of OxyHb was found in both DLPFC and FC region when subject proceeding from 1-back to 2-back task.

Generally, OxyHb in DLPFC increases with N-back WM load as described in previous works using fMRI (Jansma *et al.* 2000) due to the increased demand of information manipulation (Fletcher & Henson, 2001). Significant increased of OxyHb in DLPFC from 0-back to 1-back task is reported in our study. It is known that a higher WM load (i.e., 1-back and 2-back) require maintenance of information of stimuli sequence, where 0-back task does not (Cohen *et al.* 1997). Thus, the increase load manipulation (greater n-back value) leads to a significant higher PFC activation as compared to load retention only WM task (Veltman *et al.* 2003).

However, our results were slightly differ from an established work using fMRI with 0,1,2,3-back tasks (Cohen *et al.* 1997), as significant increase of OxyHb is solely observed when proceeding from 0-back to 1-back task, but not from 1-back to 2-back task. From these findings, it is suggested that the task performance (i.e., accuracy) should be considered in the haemodynamic response analysis. Subjects with poor and good performance should be treated separately as the degree of attention and WM task engagement played an important role in PFC activation level (Jansma *et al.* 2000).

Furthermore, this study was conducted with the procedures known to the subjects, without randomizing the task order whilst performing the 0-back, 1-back and 2-back tasks. Hence, the expected brain haemodynamic response towards increasing WM load might be masked off (Koike *et al.* 2013), resulting in insignificant increase of OxyHb when proceeding from 1-back to 2-back task.

CONCLUSIONS

OT modality based on fNIRS has been developed to measure haemodynamic changes in the PFC region in particular. An analysis algorithm is developed to cater for repeated (blocks) measure of n-back tasks, to minimize accidental haemodynamic responses which are not related to WM task activation. Significant increase PFC activation is observed when proceeding to higher WM load, particularly from 0-back to 1-back task. This finding is at par with established studies that mainly uses fMRI modality, the gold standard for neuroimaging. The study also demonstrated the tendency of WM load effect on different PFC regions, particularly the FP and DLPFC.

Nonetheless, one of the limitations in this study is identified to be the habituation factor, where subjects become familiarized with the flow of the experiment session. It is suggested that the n-back task's sequence should be randomized, where the task instruction is presented right before the task is started. Besides that, the WM task performance from each subject should be used to rationalize the PFC activation level in future study. Hence, this study highlighted the importance of protocol design considerations, in order to improve the relationship of WM load on the PFC activation.

Therefore, the study protocol presented in this paper could be further developed to probe on the effect of psychological factors (i.e., mood states and stress) on the PFC activity during WM task, as proposed by earlier studies using various neuroimaging modalities (Aoki *et al.* 2011; Qin *et al.* 2009).

ACKNOWLEDGEMENTS

This research is supported by the National Higher Institution Centre of Excellence Grant (HiCOE, Malaysia). The authors acknowledge the collaborative work of the Centre for Exploratory Research, R&D Group of Hitachi Ltd. Japan.

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