The objective assessment of the effects on cognition functioning among military personnel exposed to hypobaric-hypoxia: A pilot fMRI study

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ABSTRACT

Objective: To identify regions of the brain affected during cognitive working memory during tasks to assess attention, planning and decision making among military aviation personnel who have chronic intermittent exposure to high altitude environment.

Method: A case-control study was conducted in the Universiti Putra Malaysia among eight military personnel, four of whom had chronic intermittent exposure to high altitude training. They were divided into two groups, chronic intermittent exposure group (CE) (n=4) and a control group (n=4). They underwent a task-based functional magnetic resonance imaging (fMRI) that utilised spatial working memory task to objectively evaluate the neural activation in response to the Tower of London paradigm. Each correct answer was given a score of one and the maximum achievable score was 100%.

Results: A consecutive dichotomised group of CE (4/8) and control (4/8) of age-matched military aviation personnel with a mean age of 37.23±5.52 years; showed significant activation in the right middle frontal gyrus (MFG). This in turn was positively correlated with response accuracy. A significant difference in the response accuracy was noted among both the groups at $p<0.05$.

Conclusion: At the minimum results of power analysis of this preliminary fMRI study, our group of aviation personnel who had chronic intermittent exposure to hypobaric hypoxic environment, did not have any significant decrease in cognitive function namely attention, decision-making and problem solving compared to controls during a working memory task.

KEY WORDS:
Aviation training; fMRI; chronic exposure; high altitude; cognition

INTRODUCTION

Chronic exposure to high altitude has been known to cause a physiological condition i.e., 'Hypobaric Hypoxia' (HH), which is predominantly observed among people who live at high altitudes.[1] This is due to the lack of oxygen supply to the brain tissues and is directly associated with cognitive dysfunction.[2] Adequate blood oxygen level is a key indicator of normal cell functioning in the human body. At certain extremes of environmental conditions i.e., at high altitudes; this function is often disrupted due to low ambient barometric pressure that results in reduced oxygen uptake by the tissues.[3] This leads to impairment of cognitive function, mood and behavioural changes, hormonal imbalance, decreased quality of sleep and adverse effects on reproduction.[4,5] Furthermore, there are several physiological adaptations that occur in people who are chronically exposed to high altitudes. Hypoglycaemia has been reported among high altitude residents as a result of low ambient barometric pressure.[6] However, this condition is reversible and increased glycaemia among high altitude residents may occur upon moving to a lower altitude.[7] Additionally, an increased number of red blood cells may also affect the level of glucose due to the mechanical impairment of diffusion of extracellular glucose into the cell membranes.[7] Increased haematocrit level has been noted among long term intermittent exposure to high altitude.[8] Measurement of blood glucose and haematocrit levels are frequently conducted among people exposed to high altitude as these parameters may confound functional magnetic resonance imaging (fMRI) signal and were previously reported to be affected by high altitude.[2,9]

In particular, many studies have implicated HH to cause impairment of working memory (WM). WM is defined as the ability to keep and process short-term information long enough to sustain attention to perform a cognitive task.[10] During exposure to HH, there are some physiological changes that occur in the brain, which can affect WM task.[11] Demonstrated WM deterioration is seen in subjects with acute exposure to HH, i.e., tested within one hour to not exceeding 24 hours after exposure.[12] Conversely, chronic or prolonged exposure to HH has also been noted to cause impairment in WM.[9,13] The pathophysiology of HH is a multisystem mechanism that is attributed to both low oxygen and low barometric pressure which leads to a cascade of autonomic

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and neuronal regulations that ultimately affect cognitive function.[14-19] The effects of acute and chronic HH upon WM and cognitive function can be illustrated by a flowchart as shown in Figure 1.

The utility of fMRI has been gaining popularity for research regarding WM tasks that evaluate cognitive function.[20] Relevant brain regions that are activated during a particular task can be quantitatively measured using Blood Oxygen Level Dependent (BOLD) sequence on fMRI, which detects the oxygen concentrations at activated brain regions as an internal contrast due to the magnetic susceptibility effect.[21,22] Previous studies using fMRI have shown that prolonged stay at high altitudes can have an effect on the parietal lobe, prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) of the brain which are associated with cognitive function.[23,24] Objective ways to assess cognitive function include evaluating the process involved in WM task during attention, decision-making and problem solving. Fundamentally, the PFC plays an important role in the processing of cognitive tasks, and it is made up of the superior frontal gyrus (SFG), middle frontal gyrus (MFG) and inferior frontal gyrus (IFG).[25] Specifically, spatial attention can be impaired due to high altitude exposures and is associated with a slowdown of reaction times during WM tasks.[26] Furthermore, experiments using WM tasks to assess cognitive function among people living in the highlands, have noted that there is a significant reduction in the attentional resources among those who are chronically exposed to high altitudes.[23,27,28] fMRI has also detected a significant decrease in activation of the cingulate cortex among those chronically exposed to high altitude.[29]

In recent years, there have been concerns regarding cognitive impairment among pilots who have undergone aviation training and who were exposed to high altitudes. It is known that acute exposures to extreme altitudes of 25,000 feet above sea level can lead to an adverse hemodynamic response. Furthermore, a review by Neuhaus and Hinkelbein in 2014 had implicated pilots who underwent exposure to HH in hypobaric chambers have experienced increased reaction time i.e., deterioration of attention, concentration and decision-making; which can adversely affect their ability to fly an aircraft.[30] However, there are few studies that assess the long term effects on cognitive function among aviation personnel who are intermittently exposed to high altitudes.

This study is a pilot study among military aviation personnel who had undergone a task-based, fMRI study to assess the WM function particularly related to attention, decision-making and problem solving; to determine the effects of chronic intermittent exposure to HH.

MATERIALS AND METHODS

Participants

Based on the Helsinki Declaration and the research centre's local committee approval, a task based fMRI study was conducted among eight right-handed, military personnel from the Malaysian Royal Aviation Research Facility; four military personnel (three males, one female) who underwent intermittent flight training at high altitude for a duration at least five years., i.e., chronic intermittent exposure (CE); and four age-matched (one male, three females) ground military staff (control group) at the Centre for Diagnostic Nuclear Imaging in the Universiti Putra Malaysia (UPM). Both the control and CE were considered homogeneous in their age group, IQ levels and cognitive function based on the normal range scores obtained from neuropsychiatric tests, i.e., Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The subjects had undergone high altitude exposures at 25,000 feet above sea level for an average duration ranging from 10 to 15 hours per annum (mean 10.5 hours/annum) at a frequency of about six training sessions in one year. They had regular routine medical examinations and were certified to be fit, having no known medical illnesses. Their recent glucose levels and haematocrits were within normal limits. The subjects were selected based on the time duration of three months between their last intermittent high altitude exposure and the time when fMRI scan was performed as suggested by Rimoldi et al., that stated any impairment pertaining to neuropsychological functions which were caused by acute short-term exposure to high altitude were no longer traceable three months following return to low altitude.[31] Prior to fMRI scanning, physiological parameters such as blood pressure and pulse rate were examined and noted to be in the normal range for all subjects.

Protocol for fMRI paradigm and data acquisition:

A task-based fMRI paradigm was created to assess WM in the two groups. Tower of London (TOL) paradigm was first designed to study cognitive function with clinical importance in the field of neuropsychology and to help assess executive planning and problem-solving tasks.[32] TOL depends on visuospatial WM task, which is able to assess several domains at once; because one must concentrate on the different arrangements of beads for each new task (paying attention), then temporarily having to hold several moves in mind while planning for the next move (decision-making and problem solving).[33,34] We used a modified TOL paradigm to perform the problem solving task among CE and control groups as shown in Figure 2a and Figure 2b. Nordic Activa software (Aerobe Pte Ltd, Singapore) was used to design a block design paradigm with 13 blocks, i.e., seven blocks with the task and six blocks with rest, alternatively. Each block was made up of 10 volumes and each task block consisted of one or two pictures depending on the level of difficulty and was displayed for 30 sec followed by fixation (rest) for 30 sec. Subjects were instructed to mentally calculate the number of moves required to arrange the coloured beads to obtain a certain arrangement on a platform having three pillars and then respond using a joystick. They had to decide whether it took 2, 3, 4 or 5 moves to achieve a certain beads arrangement pattern on the pillars. Firstly, the subjects were given simple tasks that required fewer moves as shown in Figure 2a followed by more complex tasks that required multiple moves (Figure 2b). Each correct answer was given a score of 1; and the maximum score achievable was calculated as 100%.

Subjects were instructed to remain still and rest during fixation. The total duration of the task with 130 volumes was six minutes and 30 seconds. Using a 3.0 Tesla magnetic

Table I: fMRI problem-solving task data: Response time for CE and control group

GROUP	NO.	SIMPLE TASK (n=5) Response Time (seconds) Max: 15 sec						COMPLEX TASK (4) (n=5) Response time (seconds) Max: 30 Sec				
		Qn1	Qn2	Qn3	Qn4	Qn5	Mean±SD	Qn6	Qn7	Qn8	Qn9	Mean±SD
CE	1	7.37	5.34	9.72	8.17	10.4	8.2±2.00	7.64	9.43	11.27	10.97	9.82±1.67
	2	12	10.45	7.57	8.51	7.22	9.15±2.03	8.06	30	10.78	27.19	19.00±11.19
	3	9.21	12.43	12.31	9.27	11.69	10.98±1.61	11.65	25.37	14.39	17.70	17.27±5.94
	4	10.62	15	15	9.58	15	13.04±2.71	3.34	30	14.44	14.56	15.58±10.96
	Total						10.34±2.14					15.42±3.98
CONTROL	1	5.37	13.61	11.54	8.76	9.23	9.70±3.10	30	25.53	21.16	33.58	27.56±5.39
	2	12.79	12.58	14.15	15	15	13.90±1.17	11.13	30	18.40	5.28	16.20±10.65
	3	7.28	15	13.56	13.15	11.92	12.18±2.95	8.68	22.09	12.67	12.84	14.07±5.68
	4	9.01	15	14.62	1.71	13.06	10.68±5.55	12.67	30.57	11.99	19.48	18.67±8.62
	Total						11.61±1.83					19.12±5.93

Table II: fMRI problem-solving task data: Response accuracy for CE and control group

	Response Accuracy										
	CE group					Control group					
	1	2	3	4	Mean ± SD	1	2	3	4	Mean±SD	p-value
SIMPLE TASK	60%	80%	40%	40%	55±19.15	0%	60%	20%	20%	25±25.17	0.110
COMPLEX TASK	25%	25%	25%	25%	25±0.0	25%	0%	0%	25%	14.43±7.22	0.182
TOTAL	44%	55.5%	33.3%	33.3%	41.52±10.59	11.1%	33.3%	11.1%	22%	19.37±10.61	0.025*

* Two-Independent-Samples t-test is significant at the p<0.05 value

Table III: Percentage signal change (PSC) at selected ROI in CE and control group during problem-solving task

Group	No.	Intensity of BOLD at ROIs									
		LIFG	RIFG	LMOG	RMOG	LT	RT	LSTG	RSTG	LMFG	RMFG
CE	1	0.192	0.469	1.355	0.872	-0.152	-0.312	-0.050	-0.163	0.289	-1.025
	2	0.958	0.981	1.155	0.946	0.074	0.000	0.413	0.456	0.897	0.131
	3	0.623	0.469	0.731	1.057	0.231	0.220	0.266	0.098	0.200	-0.107
	4	0.826	0.740	0.845	1.104	0.323	0.217	0.391	0.208	0.687	-0.101
	Group	0.65	0.665	1.022	0.995	0.119	0.077	0.255	0.15	0.518	-0.276
Control	1	0.358	0.278	1.325	1.303	0.000	0.000	-0.064	0.00	0.625	0.523
	2	0.540	0.39	1.053	0.474	0.000	0.000	0.040	0.00	0.527	0.531
	3	0.636	0.681	1.395	2.024	0.000	0.000	-0.075	0.00	0.509	0.781
	4	0.427	0.816	0.919	1.173	0.000	0.000	0.093	0.00	0.559	0.638
	Group	0.490	0.541	1.173	1.244	0.000	0.000	-0.001	0.00	0.555	0.618
p-value		0.486	0.486	0.486	0.343	0.343	0.686	0.114	0.343	1.000	0.029*

* Two-Independent-Samples t- test is significant at the p<0.05
LIFG/RIFG- left/ right inferior frontal gyrus, LMOG/RMOG- left/right middle occipital gyrus, LT/RT- left/right thalamus, LSTG/RSTG- left/right superior temporal gyrus, LMFG/RMFG- left/right middle frontal gyrus

resonance imaging scanner, Siemens MAGNETOM Prisma (Siemens, Erlagen, Germany), all the subjects underwent a structural T1-weighted imaging, followed by functional imaging utilising 2d echo planner BOLD imaging sequence that detected their response to the paradigm.

Data analysis
The fMRI data was analysed using the statistical parametric mapping (SPM12) software; (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Region of interest (ROI) analysis using WFU pick atlas (http://www.nitrc.org/projects/wfu_pickatlas/), was done and areas of activation in each individual, and according to CE and control groups were observed using a threshold value of 0.05(corrected for family wise error (FWE). Bilateral inferior frontal gyrus (IFG), bilateral middle occipital gyrus (MOG), bilateral thalamus, bilateral superior temporal gyrus (STG) and left middle frontal gyrus (MFG) were chosen as ROI from the previous study and the corresponding percentage signal change (PSC) was calculated.[9] Percentage signal change (PSC) at these regions among the 2 groups (CE and control) was measured using MARSeille Boite A region d'interest (MarsBar) (http://marsbar.sourceforge.net/).

Statistical Analysis
Behavioural data was analysed using IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp.). Parametric test such as Two-Independent-Samples t-test was performed to determine any significant brain activation in CE and control group in response to the task. Two-Independent-Samples t-test was also performed to determine any significant change in the response accuracy and response

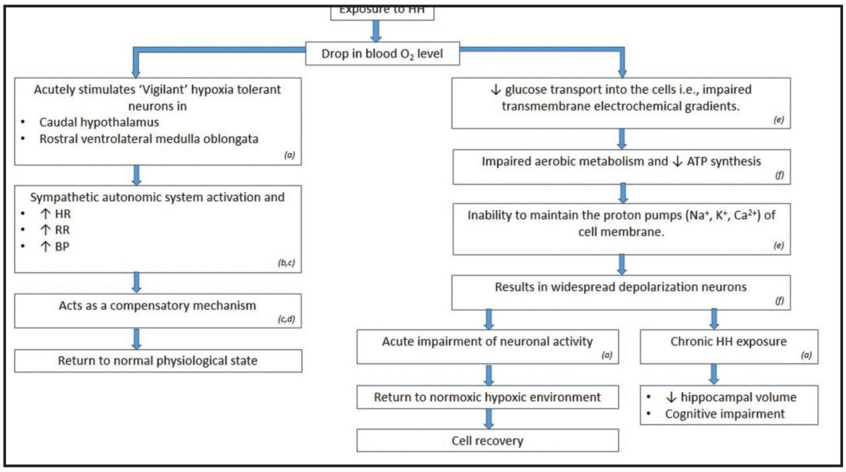

Fig. 1: The effects on WM and cognitive function upon exposure to acute and chronic hypobaric hypoxia
a: Goodall, Twomey, and Amann (2014); b: Dillon and Waldrop (1992); c: Horn and Waldrop (1998); d: Dillon and Waldrop (1993); e: Martin, Lloyd, and Cowan (1994); f: Papadelis, kourtidou-Papadeli, Bamidis, Maglaveras, and pappas (2007); HR: Heart Rate; RR: Respiratory Rate; BP: Blood Pressure; ATP: Adenosine Triphosphate; HH: Hypobaric Hypoxia

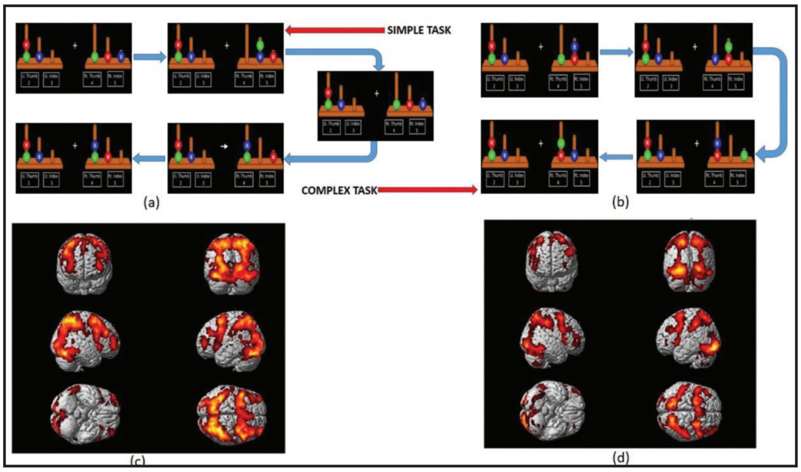

Fig. 2: Paradigm for working memory (WM) task involving problem solving Tower of London task and 3D rendered Brain maps to illustrate the impact of WM task on brain activations
(a) WM Paradigm for Simple task, (b) WM Paradigm for Complex task, (c) Brain activations in CE group (p< 0.05, FWE corrected), (d) Brain activations in Control group (p< 0.05, FWE corrected)

time among the two groups. Pearson's correlation analysis was performed to determine any correlation between the intensity of regional brain activation, response time and response accuracy and $p<0.05$ was taken to be significant.

RESULTS

A consecutive dichotomized group of CE (4/8) and control (4/8) of age matched military personnel having mean age of 37.23±5.52 years; underwent the fMRI study. No significant difference in the response time was observed between the two groups (CE=113.41±22.19, control group=134.6±17.61; p=0.188) (Table I). There was a significant difference in the response accuracy of the task-based fMRI study between the CE and the control group (mean percentage score: 41.52±10.59 vs 19.37±10.61; p=0.025) (Table II). Two-Independent-Samples t-test indicated that there was a significant difference in the PSC at the right MFG between the CE and the control group (mean: 0.27±0.51 vs. 0.62±0.12; $p<0.05$). Independent sample test revealed that CE group showed increased activation in bilateral IFG, bilateral thalamus and bilateral STG compared to the control group as shown in Figure 2c. The control group showed increased activation in bilateral MOG and bilateral MFG with deactivation in bilateral thalamus and right STG as shown in Figure 2d. Both the groups demonstrated various regional activations as described in Table III. Significant positive correlation was found between the response time and the BOLD PSC at the right MFG. No significant correlation between response accuracy and BOLD intensity change was observed.

DISCUSSION

The impact of long term or chronic exposure to high altitude on a healthy population has been studied exponentially. There is strong evidence to suggest that it leads to the development of cognitive impairment particularly causing WM deficit i.e., inability to sustain attention, verbal incompetence, prolonged reaction time and higher error rates in performing short term memory tasks.[9, 23, 35] In this study, it is important to note that there was no significant difference in the response time, but a significant difference in the accuracy of responses among the CE subjects. Chronically exposed subjects have been noted to have reduced response time, which is postulated to be caused by the body's regulatory response in preserving the oxygen utility in the brain.[9] This is likely to occur only when there is constant chronic exposure to HH. We noticed that both the groups took almost the same time to solve the simple questions, but when encountered with complex questions, both the CE and the control group took slightly longer to answer the complex questions. Our finding is similar to a previous electroencephalography (EEG) study that detected the accuracy of response decreased with increasing WM load or task complexity.[10] Another study by Malle et al., identified that exposure to hypoxia caused reduced performance in a questionnaire-based WM task.[13] However, to the best of our knowledge our study is the first ever fMRI study conducted among aviation personnel to study the effects of chronic intermittent HH upon WM function.

Although the CE group took a longer time to respond, this difference was not statistically significant (p=0.182). Furthermore, we noticed that the response accuracy decreased when solving complex questions in both groups and was more prominent in the control group; with the overall response accuracy being significantly increased in the CE group. Previously, it has been suggested that the accuracy of cognitive responses increased with response time, whereby the process is of an upgrading nature; hence a slightly increased response time while answering complex questions was observed among the CE subjects. Among our control subjects the fast response rate was associated with reduced accuracy.[36]

The CE subjects demonstrated significantly decreased activation of the MFG portion of the PFC, which controls attention and concentration. Planning and problem solving depend on the cooperative achievement of other functions such as WM, decision-making ability, inhibitory control, mental flexibility, and sustained attention. A study by Vartanian et al., found that the decreased activation of PFC during WM task is associated with more efficient divergent thinking.[37] Similarly, we postulate that the decreased activation of MFG among the CE group is associated with improved fluid intelligence due to training, i.e., the simple questions prepared them to perform better in complex questions as compared to the control group. Thus, we postulate that CE subjects developed adaptive measures to overcome any cognitive deficits that they may have experienced. As a matter of fact, a study using a relatively small sample size of 10 subjects, applying a double blind randomized experimental control method to study the effect of acute exposure to normobaric hypoxia (fraction of inspired oxygen (FIO2) of ~14.1%) at a height of 3000m above sea level, and exposed for 45 minutes and had WM tested within two hours of exposure did not detect any significant WM impairment. They explained that this phenomenon occurred due to the short duration of exposure to such an environment may not cause any prolonged impairment to WM.[38] The difference of the former study with our study is that we studied the effects of cumulative acute exposures leading to chronic intermittent exposure, and we performed fMRI after three months of the last exposure, which we believe has given enough time for our subjects to recover from any potential long term effects of HH as advocated by Rimoldi et al.[31] Although the latter study did not detect any significant impairment to WM caused by acute exposure to hypoxic environment, we believe this may be due to lack of exposure to extreme environment of high altitude. Thus, the negative physiological changes to WM task may be only evident in the presence of both high altitude i.e. low atmospheric pressure and low oxygen.[9,12]

Additionally, Chen et al., hypothesized that there was a significant reduction in the functional connectivity between the putamen and the STG in subjects with HH.[39] Contradictorily, the CE subjects in this study showed increased activation of STG, which gives evidence of preserved cognitive functions related to audio-visual tasks. These results are encouraging and give an objective assessment of the cognitive function among our CE subjects. There is potentially no long-term detrimental effect on the cognitive function among the military aviation personnel who had intermittent exposure to HH. This observation is likely due to acclimatisation, which is responsible for a faster recovery of cognitive functions in the exposed group.[40] Furthermore, in the acute phase of exposure, aviation personnel have been noted to develop a drop in cognitive function, which was transient and reversible once the exposed group returned to sea level altitude.[30] It is apparent that there are no long term adverse effects on cognitive functioning among the intermittently exposed subjects. This is clearly observed among our CE subjects, who were assessed after three months following the most recent HH training, thus adaptation and return to baseline function would have occurred.

The limitation of the study is the small sample size. Nevertheless, it is the first of its kind to objectively assess the effects of CE to HH among military aviation personnel using fMRI. We recommend future research to increase the sample size and perform resting state fMRI to evaluate any potential impact on cortical functional connectivity among aviation personnel.

CONCLUSION

Preliminary findings suggest that chronic intermittent exposure to hypobaric-hypoxia does not lead to a significant drop in working memory performance among the observed military aviation personnel.

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DECLARATION OF CONFLICTING INTEREST

The authors declare that there is no conflict of interest.

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