

**NATIONAL UNIVERSITY OF
PUBLIC SERVICE**

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**Impact of organic sleep disorders on cognitive functions among military applicants and
active duty military members.**

**Preliminary results of cerebrovascular functional imaging to scan underlying
pathomechanism.**

PhD thesis

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Budapest
2014

Identification of the scientific problem

Adequate sleep is essential for general healthy functioning.

Restricting sleep can cause a range of cognitive and behavioral deficits, including lapses of attention, slowed working memory, reduced cognitive throughput. Behavioral researches have documented that disrupted sleep is accompanied by significant daytime cognitive and behavioral dysfunction that seems to extend beyond that is associated with simple sleepiness. Under emerging network-centric warfighting human error attributed to failures of cognitive performance becomes a critical issue.

Since network-centric, effects and information-based warfare, along with Joint Operations Concepts (JOpsC) requires sustained cognitive performance, U.S. Army Medical Research and Materiel Command keeps seeking prompt effective measures to minimize human errors and catastrophic failures.

Restriction of sleep can be consequence of primary or secondary sleep-wake disorders. On the one hand secondary sleep-wake disorders (jet lag, overnight flight, night shift work, sustained operations) are thoroughly investigated, and a number of programs, teams and research projects are operating in order to develop neurocognitive monitors and neurophysiological contra measures.

On the other hand the role of primary organic sleep-wake disorders contributing to failures of cognitive performance has not been fully elucidated.

In my present work I intended to bring these primary disorders into the focus of interest. My study was aimed at investigating their prevalence in military population, and to establish the underlying pathology. To the best of my knowledge my work is the first one to investigate the occurrence and the neuropsychological consequences of primary sleep disorders among active-duty military and military applicants, with extended imaging of regional cerebral brain functioning, and also estimating cerebral functional reserve capacity.

The primary reason of the choice of my subject was to overcome this scientific deficit.

Aims of research

During my work prevalence of primary sleep-wake disorder in military population was investigated to assess cognitive deficits and disclose underlying regional cerebral dysfunction, and find effective treatment. In keeping with this primary objective I determined the following research aims:

- to screen attention, memory and concentration deficit and fatigue among military applicants, with or without subjective symptoms of sleepiness;
- to analyse with objective measures psychomotor vigilance and attention and the quality of flexible thinking, thus validating the reliability of the questionnaire based screening results;
- .to reveal the different kinds of organic sleep disorders in the background, possibly contributing to the attention, cognitive and executive dysfunctions;
- to investigate regional cerebral blood flow and reserve capacity changes accompanying the different subtypes of organic sleep disorders;

- to carry out follow up control investigations to estimate the effect of the treatment started in our laboratory;
- to review the international scientific literature, paying special attention to former results of questionnaire based studies and focusing on the available results of functional investigations, also with special respect for the studies organized and carried out in sleep laboratories of military hospitals.

Determination of research problem

During my work, when seeking settlements for the above issues the following questions had to be answered.

1. In a special active military duty and military applicant population, is there any difference between the way the participants feel and the way they react to questions inquiring subjective symptoms of sleepiness, attention and memory deficit, mood changes and presence of fatigue?
2. Did monitoring by polysomnography justify any kind of abnormality in the background among subjects suspected of having organic sleep disorder, based on high questionnaire scores?
3. Does neuropsychological testing reveal altered psychomotor vigilance or mental flexibility among subjects enrolled with positive questionnaire results?
4. Do we have the capacity to provide adequate treatment for those affected by sleep disorders? (Especially with regard to gain back military capability, that is cost saving and logistic issue of crucial importance.)
5. Was my simplified questionnaire appropriate to screen for organic sleep disorders?
6. Can we expect further insight into the pathophysiology of day time dysfunction due to disordered sleep by applying regional cerebral blood flow and special reserve capacity investigations?

Hypothesis

1. It would be of practical use to apply my simplified questionnaire when selecting applicants for military service, since sleep disorders may occur in young healthy individuals, regardless of age or body mass index, or health state. The range and distributions of sleep disorders emerging in military applicants can be similar to that in the civilian population.

2. In case of positive answers sleep laboratory tests are mandatory to unveil possible underlying organic sleep disorders. Sleep laboratory findings should be compared with that of the control group of patients referred to the centrum due to their symptoms suggesting organic sleep disorders in the background.

3. Military members and civilians - referred to the sleep laboratory with salient symptoms of attention and memory deficit- should also fill in the simplified screening questionnaire.

4. Elaborating the results of the questionnaires and the sleep investigations in both study groups gives rise to disclose potential pitfalls of my specified questions and to compare notably different subgroups of patients.

5. To clear the possible impact of the sleep disorders on the regional brain functions in special subgroups of the subjects included in my work, functional imaging of the regional cerebral blood flow was also effected. I hypothesized that these additional examinations could provide further pieces of information regarding the severity of the organic sleep disorders and could further extend our knowledge about the underlying pathological events.

Along with the diagnostic procedures longterm follow up investigations should be entertained to monitor the effect of the appropriate treatments.

6. Along with the sleep laboratory investigations neuropsychological testing should be performed in order to validate the result of my simplified questionnaire. Comparing the maps of the regional cerebral blood flow investigations to the neuropsychological test results in different subgroups of participants may give rise to new insight into the mechanism of day time dysfunctioning in cases of organic sleep disorders.

Research methods

Before planning the study I reviewed the scientific literature to analyse the latest results, developments and achievements on field of the matter. I put emphasize to focus on unresolved conflicting questions, to have the capacity to carry out a pioneer work.

Considering the selection criteria my work is a non randomised, prospective cohort study.

From points of clinical questions the study was crosssectional and in two subgroups long term follow up made basis for checking treatment effectivity.

The methods applied ranged from simple questionnaires on computer assisted neuropsychological testing to special sleep laboratory and nuclear medicine investigations. Data were visually analyzed and when necessary statistical methods, including paired and unpaired T tests and Fisher's probe were applied.

The whole work was aimed at gaining new results with practical use to develop neurocognitive monitors.

The roots of my special investigations date back to the sophisticated and committed work of Zoltán Szakács and Péter Köves. They have outlined the framework of our sleep laboratory and established a creative workshop, always meeting the actual need of the Hungarian Army.

Their cooperation with the Hungarian Army created the opportunity to bring about a sleep laboratory equipped at the level compatible with the requirements of the American and European Sleep Society. Zoltán Szakács in his thesis for the doctor's degree made a pioneer work when emphasized the urgent need for screening sleep-wake disorders in the military population. Nora Szternák was also a forerunner of my work. Her thesis for the doctor's degree was a questionnaire-based survey carried out over civilians age matched to potential military applicants. She concluded that both active duty military members and military applicants should undergo questionnaire based screening and in positive cases sleep investigations within the confines of the Hungarian Army.

My study is in concert with their prior achievements and is the continuation of their work.

Concerning the practical points, working in the Sleep Center of the Hungarian Army allowed to perform hundreds of special polysomnography investigations and thus forming appropriate control groups. Concerning the investigation and development the Sleep Center of

the Hungarian Army gives unique opportunity to analyze the range and distribution of sleep disorders in the military and the civilian population.

Structure and brief summary of the dissertation

My work consists of eleven chapters, in brief they read as follows.

Chapter one surveys the NATO summit meetings, and summarizes the decision-making processes, the introduced new policies, and the launching of major new initiatives leading to a growing capability of NATO forces to conduct network-centric and effect-based operations. At the same time I give a detailed review of the organic sleep disorders giving rise to a range of cognitive and behaviour deficits, that could have a profound impact on the planning and conduct of war, since network-centric doctrine requires sustained cognitive performance.

Chapter two reviews NATO medical doctrine and policy and addresses the special problems emerging due to restricted sleep.

Chapter three deals with the role of Allied Command Transformation (ACT) that is primarily intended to lead military transformation of alliance forces and capabilities, using new concepts such as the NATO Response Force and new doctrines in order to improve the alliance's military effectiveness. Here I give details of the NATO Centres of Excellence for Military Medicine, with special emphasis on the fact that having been accredited by NATO on 12 October 2009, it is located in Budapest, Hungary, with a core task to facilitate interoperability between the military medical services in NATO. The capacity of our sleep laboratory may organically fit into that concept and could outline future cooperation with the MILMED COE.

Chapter four (along with appendix one) enlists the different organic sleep disorders leading to the syndrome of excessive daytime sleepiness, and deals with the adverse consequences.

Chapter five gives examples of concrete cases of friendly fire attacks during latest operations, calling attention how human error attributed to failures of cognitive performance becomes a critical issue.

Chapter six reviews the activity of U.S. Army Medical Research and Materiel Command when seeking prompt effective measures to minimize human errors and catastrophic failures. It gives insight into the activity of subordinated team works as for example the Neurophysiological Measures and Cognition Focus Team (NMCFT) and special preventive programs, like the Cognitive Performance, Judgement, Decision-making Research Program (CPJDRP).

Chapter seven refers to the data of the Defense Medical Surveillance System (DMSS) maintained by the Armed Forces Health Surveillance Center (AFHSC) to have a line of sight on the incidence and health care burdens of neurological disorders among active U.S. military members, during the period of 1998 to 2010. Analyses have indicated that the above incidence have risen dramatically, and majority of the increase is attributable to the introduction of the new International Classification of Diseases (ICD-9) where organic sleep disorders are classified under ICD-9 327. Prior to the introduction of the new code these

disorders would have been coded as ICD-9 780.57 and classified under the category of “Signs, Symptoms and Ill-Defined Conditions”, practically these cases would not have been considered as a neurological related encounter. These radical changes observed in the medical care of our NATO partner underlines the need for a more precise investigation of the prevalence of organic sleep disorders in our military population.

Chapter eight describes the domestic conditions of sleep investigations, paying tribute to the creative work of Péter Köves and Zoltán Szakács when establishing the Sleep Center of the Hungarian Army. Their effort was essential and a prerequisite to launch the special activity of the Sleep Center. My work could not have been carried out without the framework of this up to date, well equipped, validated laboratory.

Chapter nine deals with the recruiting process and presents the five different subgroups of the study population. My work compares subgroups of military personnel and civilians referred to our laboratory due to symptoms with daytime sleepiness and/or cognitive dysfunctioning with a group of healthy military applicants and active duty military members, suspected of having sleep disorder based on high questionnaire scores. This chapter also presents the special investigation tools and equipments allocated either in the Sleep laboratory or operating under special conditions in the Hospital of the Hungarian Army.

Chapter ten gives a detailed presentation of the procedure of polysomnography examinations, the regional cerebral blood flow single photon emission tomography investigations and the complementary computer based neuropsychological testing in the subjects enrolled into our study, based on their prior questionnaire result or the referral diagnosis.

Chapter eleven (along with appendix three) surveys the results of related international scientific studies and publications, with respect to their possible pitfalls and deficiencies and presents my original -and to my best knowledge- “first ever” findings.

New results

1. I have tested a new simplified questionnaire to screen over military applicants and active duty military members for the previously undiagnosed sleep disorders (with leading clinical symptom of executive dysfunctions with/or without sleepiness), a precursor to some serious consequences hampering to achieve operational or tactical objectives.
2. I have been the first in Hungarian scientific literature to compare active-duty military, civilians and military applicants to determine if age, body mass index and comorbidities correlate with sleep disorder severity.
3. By means of the professional and personal background of the Hungarian Army, I had the opportunity to investigate the impact of different subtypes of sleep disorders on regional cerebral blood flow and the integrity of the cerebrovascular reserve capacity. Considering prior international scientific publications, to the best of my knowledge my study is the first one to address this question.

4. I have demonstrated, that the ratio of respondents to my questionnaire indicating a positive test (in practice the domain that my jeopardize the success of operations) reached 10 per cent of the military population.
5. I have revealed, that although symptom free military applicants were younger and less overweight than civilians or military personnel, referred to our sleep laboratory-suspected of having sleep disorder-, prevalence of sleep disorder did not differ between groups. Since cognitive or executive dysfunction due to disordered sleep will affect young, nonobese individuals to a similar extent, screening for sleep disorders should be a part of military aptitude test, regardless of age or BMI.
6. I have determined, that polysomnography investigations, initiated on the basis of positive questionnaire answers, in all cases disclosed organic sleep disorders that showed a distribution according to conventional proportion. The ratio of sleep related breathing disorders was approximately 80 % and that of the movement disorders and central hypersomnia was about 20%. However cases selected by screening questionnaire were characterized by normoxemia, while patients referred to the sleep center mostly featured the typical pattern of intermittent hypoxia-reoxygenization. All these findings underline that relying solely on oxygen measurements will be insufficient, and cooperation between the Hungarian Army and the sleep laboratory is a prerequisite for complete screening among military applicants.
7. I have been the first to demonstrate that both normoxemic and hypoxic cases had the capacity to give rise to regional cerebral blood flow alterations by SPECT. I have also unveiled that cases with normoxemia affected mostly the temporal lobe, while those with intermittent hypoxia mostly altered the function of the frontal lobe. Furthermore, by monitoring autoregulation in the human brain under vasodilatory stress, I have been the first to realize, that not fragmented sleep, but hypoxia is responsible for impaired cerebrovascular reserve capacity. I have also pointed out the relationship between failure on Wisconsin Card Sorting Test and altered reserve capacity.

Recommendations

Contrary to general practice, screening for sleep disorder related cognitive and executive dysfunction should be planned and scheduled early, when recruiting applicants for military service, or with active military members before deployment, or combat operation.

Cooperation between our Sleep Diagnostic Center and the Hungarian Army likely increases the availability of expert assessment of sleep disorders.

My work is intended to shed light on and to increase awareness of the matter, and should prompt an increased screening for the condition in among otherwise healthy applicants or service members.

When my simplified questionnaire raises the suspicion of undiagnosed sleep disorder, then the applicants should undergo a full night polysomnography testing in our laboratory.

When precision and tactical innovation are vital to the conduct of successful operations, we should not rely on the questionnaire alone, since a negative finding clearly doesn't exclude the possibility of the sleep disorder. Under these special circumstances, investigating the full military staff in the sleep laboratory could also be entertained.

My work is also in line with the increasing efforts on cost cutting in the military health care system by revealing a condition that, if treated and controlled, could significantly reduce both the health care costs and the burdens of military losses.

Further research directions

The limited number of control examinations does not allow to draw conclusions regarding the effectiveness of treatment, and the question of functional reversibility and clinical improvement cannot be answered either. As a preliminary result I mention that launching effective therapy in all cases ameliorated symptoms of sleepiness, but was associated only in limited number of cases with improvement on Wisconsin Card sorting Test or normalization of regional cerebral blood flow values on SPECT. The issue is of importance, because improving knowledge about the mechanism of regeneration could enhance our ability to rehabilitate military personnels having been previously trained at high-cost. Further studies are needed to settle the matter.

When dealing with cerebrovascular diseases sleep related breathing disorders are frequent comorbidities. SPECT alterations are frequent in both disease group, that may give rise to unintended misinterpretations. I recommend that in cases when choice of treatment is based on SPECT findings (for example indicating reconstruction of significant uni or bilateral asymptomatic carotis interna stenosis), we should make effort to exclude confounding effect of sleep related breathing disorder in the background. Contrary, when coming across positive SPECT findings during neurological evaluation without any identifiable cause, then effort should be made to rule out sleep related breathing disorder in the background.

Considering the different contribution of sleep disorders to functional imaging changes should be kept in mind when planning further studies. Proper selection of study subgroups at least according to normoxemia or intermittent hypoxia, and to the lack or presence of apnea and obstruction could improve reliability of future studies.

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From 1989 co-leader of acute stroke department and co- leader of neuro-SPECT laboratory.

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