INFORMATION PAPER
DARPA'S PREVENTING SLEEP DEPRIVATION PROGRAM

The goal of the DARPA Preventing Sleep Deprivation Program is to research and develop technologies that will assist in maintaining the cognitive performance of warfighters despite short-term sleep-deprivation. DARPA's Preventing Sleep Deprivation program is in its final year.

Short-term sleep-deprivation is a fact of modern combat operations, and indeed has been a problem faced by warfighters historically. Typical operational scenarios might include lack of sleep for 24 to 36 hours; or short sleep (four hours per night) experienced for several days. This has led DARPA to focus on developing short-term approaches to maintaining cognitive performance.

Sleep deprivation interferes with the ability to do higher order mental processing, such as complex problem-solving. It also slows psychomotor responses to changing situations.

DARPA's Preventing Sleep Deprivation program is seeking technologies that precisely restore the biochemical deficits associated with cognitive dysfunction following sleep deprivation. In general, these approaches are NOT general stimulants and have none of the non-specific effects typical of stimulants such as caffeine (shakiness, blood pressure changes, heart palpitations, etc.). DARPA's program seeks methods that are much more effective at maintaining cognitive function than current interventions.

The program is taking a very broad look at mechanisms to safely maintain cognitive function following sleep deprivation. This broad look includes investigations aimed at understanding the basic biochemistry of neural transmission following sleep deprivation, non-invasive imaging of neural networks, and lessons from the animal kingdom. There is also research being performed that investigates the utility of natural compounds found in foods to support the memory structures in the brain; these nutrients and vitamins may have the potential to maintain performance in the sleep deprived state. Some of these compounds are found in chocolate, as well as leafy green vegetables. These approaches are still in the basic research stage.

The DARPA-funded research for the preventing sleep deprivation program has focused on the fundamental pathways involved sleep from several different perspectives.

Research included investigations of model systems that occur in the natural world (flies, rodents, cetaceans, birds) that allow us a window into the regulation of sleep across species. These animal systems enabled researchers to investigate in detail how exposure to sleep deprivation affects normal physiologic function and the corresponding behavioral and molecular changes. Some species, like migratory birds, are naturally resistant to the performance decrements seen in other species after sleep deprivation. Birds must maintain vigilance while they migrate in order to avoid predation.

The fruit fly research project is the most widely published of all the work in the program. Flies are often used as a model system to study human physiology, because they are an extremely

useful biological system for experimental purposes. Working with flies allows researchers the opportunity to study specific behavioral or physiologic characteristics that would be very difficult to study in humans due to complexity in human physiology. The researchers examined families of fruit flies with unique sleep/wake characteristics in their experimental paradigm. They discovered flies that did not require as much sleep, but that still were able to perform normally on a task. These were simple behavioral tasks (for flies) like danger avoidance. These "sleep deprivation resistant flies" were used to identify the specific biochemical mechanisms of sleep deprivation resistance in flies.[1] Some of these mechanisms have been verified in rodents. The group also investigated migrating birds to try to deduce how and why birds can function with limit amounts of sleep, without performance degradation.

The results of these studies have been scientifically important. Investigators have discovered the detailed biochemistry of what happens to brain cells after sleep deprivation. Similar changes may also occur in forms of dementia.

Another researcher used functional Magnetic Resonance Imaging (fMRI) to image the brain of human subjects while performing a standard memory task. Researchers were able to identify differences in brain regions that were activated during the task and the individual variations in the degree of activation. After baseline imaging, the same subjects were then sleep deprived asked to perform the same memory task. The people that performed poorly on the in the task had a lower degree of activation in the brain regions used in the task after sleep deprivation. Investigators demonstrated that some subjects were able to maintain their level of performance while others could not perform as well after a lower amount of sleep. These differences in performance could be explained by differences in the use of brain "neural networks" as documented by non-invasive neuroimaging (fMRI). Transcranial magnetic stimulation may provide the ability to non-pharmacologically maintain function of these neural networks that are altered by sleep-deprivation.[2]

The research showed that people that seem to enlist more areas of their brain to perform a task before sleep deprivation seem to do better on that same task after sleep deprivation. The hypothesis is that when individuals are sleep-deprived it decreases the appropriate enlistment of task specific regions in the brain. People who are more "naturally" sleep-resistant have more available brain activation "in reserve" that they can utilize to perform a task well even in sleep-deprived conditions. People that have lower overall activation at baseline on a task fared more poorly on task performance after sleep deprivation. This work adds to the mounting evidence that function after sleep deprivation varies widely based on individual differences. The work suggests that individual differences are significant when designing any sleep deprivation countermeasure.

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[1] Cirelli C, Bushey D, Hill S, Huber R, Kreber R, Ganetzky B, Tononi G. Reduced sleep in Drosophila Shaker mutants. *Nature*, 434: 1087-1092, 2005a. See also http://ntp.neuroscience.wisc.edu/faculty/cirelli.html and http://ntp.neuroscience.wisc.edu/faculty/tononi.html for additional publications.

[2] Habeck C, Rakitin B, Moeller J, Scarmeas N, Zarahn E, Brown T, Stern Y. An event-related fMRI study of the neurobehavioral impact of sleep deprivation on performance of a delayed-match-to-sample task. *Cognitive Brain Research*, 18 (2004) 306-321.
http://www.cumc.columbia.edu/dept/sergievsky/cnd/pdfs/AnEventRelatedfMRIStudy.pdf

DARPA also investigated how ampakines impact sleep deprivation. Ampakines are a compound that interact with AMPA receptors in the brain. Ampakines are of interest for preventing sleep deprivation because they seem to have a very specific effect on select regions of the brain that are affected by sleep deprivation, rather than the very general effect that current stimulants such as caffeine and amphetamines have on the entire nervous system. Researchers compared performance at baseline, and after sleep deprivation in a "delayed match to sample" memory task (DMS). Efficacy of ampakines was compared to currently used fatigue countermeasures such as caffeine, modafinil and ephedra in animal models. In preliminary animal studies, an ampakine known as CX717 was shown to restore one of the major biochemical changes associated with sleep deprivation, without having any typical stimulant side-effects.[3] DARPA and the Army next sponsored a study looking at the effect ampakines have on humans in a shift-work paradigm. In the study, CX717 did not reverse the effects of degraded performance and alertness from the simulated night shifts.[4]

Any therapeutic with investigations sponsored by DARPA must meet the same rigorous safety and efficacy standards, and FDA approval, as any civilian medication. These include studies which prove safety in animals after both short-term and long-term administration, and in doses orders of magnitude higher than those to be given to humans. The developer company must also prove safety in human studies to the satisfaction of the FDA and study investigators before compounds are even considered for DARPA clinical trials. All human clinical trials must also be approved by the local Institutional Review Board. Studies in Preventing Sleep Deprivation must also undergo a second level of review by an Army Human Studies Review Board. DoD Directives mandate that all studies adhere to the Common Rule.

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[3] Facilitation of Task Performance and Removal of the Effects of Sleep Deprivation by an Ampakine (CX717) in Nonhuman Primates, by Porrino LJ, Daunais JB, Rogers GA, Hampson RE, Deadwyler SA, Department of Physiology and Pharmacology, Wake Forest University Health Sciences, Winston-Salem, North Carolina, United States of America. PLoS Biol. 2005 Aug 23;3(9). http://nootropics.com/ampakines/cx717.htm

[4] Ampakine (CX717) Effects on Performance and Alertness During Simulated Night Shift Work, by Wesensten, Nancy J.; Reichardt, Rebecca M.; Balkin, Thomas J. Aviation, Space, and Environmental Medicine, Volume 78, Number 10, October , 2007 , pp. 937-943(7).
http://www.ingentaconnect.com/content/asma/asem/2007/00000078/00000010/art00004