Details of the Project on Sleep and route learning

Origin of the proposal: The proposal originates from reports in humans and mice that sleep (especially stage 2 sleep spindles) ([1,2]Peigneux, et.al., 2004, 2006) helps in improvement of route learning. Research done in humans establish that humans use at least two main strategies governed by wither the hippocampus or caudate nucleus ([3]Bohbot, et.al., 2003) for the learning of navigational routes

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[1] Peigneux, P., et.al., *Neuron*, **2004**, 535-545; [2]Peigneux, P., et.al., *PNAS,* **2006**, 7124-7129; [3]Bohbot, V., et.al. *Journal of Neurosci*, **2003,** 5945-5952; [4]Evans, A et.al., *PNAS,* **1996***,* 9212-9217

Objectives of the proposal project:

a) To evaluate the role of sleep in consolidation of route learning in a virtual environments in humans

b) To evaluate the role of sleep in the use of hippocampal vs. straitum guided strategies for navigation of routes in virtual environments

c) Comparison of male vs. female performance on route learning tasks in virtual environments

Review of research & development in proposed area:

The idea that memory was consolidated during sleep lies on the assumption that sleep allows for a slow recovery of "learned synapses" i.e. new contacts between neurons are formed. This assumption was forwarded in 1966 by Moruzzi ([1]Moruzzi, 1966) and has been verified in recent years by many branches of life science for e.g. molecular genetics, neurophysiological and behavioral studies in humans and animals ([2]Maquet, 2003). Memories that can be consciously and symbolically expressed belong to the declarative memory system. At the neuroanatomical level the initial maintenance of these memory traces, rely on the medial temporal lobe with the hippocampus being a central component. Personal experiences of events in spatiotemporal context are episodic memories of the declarative type. Evidences from human and animal studies suggest very strongly that hippocampus is involved in spatiotemporal learning as encodings of these learning traces involve a flexible knowledge of relationships between environmental cues. Hippocampus dependent spatial memory in animals is thus phylogenetically viewed as a homologue of human (episodic) declarative memory Spatial navigation in well learned environments is also mediated by the straitum through the expression of stimulus-response associations ([3]Burgees, 2003). Recent research with rodents and humans navigation on spatial memory tasks suggests that initially the hippocampus is involved in spatial learning but after repeated practice a straitum dependent strategies comes into play during such route navigation. The involvement of multiple brain areas represent the different strategies used while navigating in a virtual environment. With humans it was found that navigation to a target location can involve the use of the cognitive map of the environment by thinking about the landmarks and their spatial relationships. Alternatively, one can use the distance from a single landmark as a reference or make choices with respect to body motion, independent of the landmarks available in the environment. These strategies depend on the practice in the navigating environment and rely on different brain areas.

Studies on humans involving hippocampal dependent memories clearly outlines non rapid eye movement sleep (NREM), which includes slow wave sleep (SWS) and stage II sleep, to play a major role in consolidation of such memories. Deprivation of slow wave sleep (SWS) ([4,5]Born, 1997, 2004) and administration of the cholinergic agonist physostigmine during SWS impairs retention for sleep dependent memories of lists of word pairs, where as transcrainal direct stimulation during SWS improves the retention of such lists. Recognition memory performance for landscapes correlates with amounts of SWS gained during post a post learning nap. Also, extensive navigation in a virtual maze increases stage II sleep duration on the first post training night. In a positron emission tomography (PET) study it was found that hippocampal activity associated with place learning in a large scale virtual town during wakefulness increases during SWS (and stage II sleep) on the first post training night and more than reported on procedural memory tasks.

The above literature tends to solve most of the mysteries behind the role of sleep in the consolidation of spatial memories during navigation of routes in a virtual environment. However the following questions remain to be explained:

a) Navigation of routes in a virtual environment during wakefulness leads to encodings of hippocampal traces of such spatial memories. However during post training sleep which of the two regions (the hippocampus/ straitum) are most involved in the maintenance and consolidation of such traces
b) At recall during post training sleep, which of the two strategies (hippocampal /starital) do subjects utilize for route navigation
c) How do subjects perform and what strategies do subjects involve for route navigation in novel vs. well learned environments during post sleep retest

d) How do males and females perform on such virtual navigation of route tasks? Is there a significant difference in the choice of navigation strategies in males and females on such virtual route during post training sleep retest

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[1]Moruzzi, G., *Brain and Conscious Experience*, **1996**; [2]Maquet, P., *Sleep and Brain Plasticity,* **2003;** [3]Burgees, N, *Neuron,* **2002,** 625-641 [4]Born, J., *Journal of Cog Neurosci*, **1997**, 534-547; [5]Born,J., et.al., *PNAS*, **2004**, 2140-2144