Conference organized by Itzhak Fried (UCLA / Tel-Aviv University) as part of the Paris IAS Brain, Culture & Society Program

From an interdisciplinary perspective including neuroscience, medicine, the humanities and art, the meeting aims at (1) advancing and disseminating scientific knowledge on how specific sleep processes aid memory consolidation (2) inspiring science and arts to adopt new approaches to the importance of sleep and dreams (3) benefiting society by promoting awareness for good sleep habits and their effect on cognitive well-being.

Cognition during Sleep

Unsuspected cognition in the sleeping brain
Sid Kouider (CNRS - ENS)

Sleep has been argued to be the price to pay for neural plasticity: it allows optimising memory consolidation at the price of rendering organisms vulnerable to external threats. Yet, recent research reveals that the sleeping brain is actually not fully shut down from the environment, as it continues registering and integrating external events to some extent. This raises the questions of why would sleepers continue processing external information and why do they remain unresponsive at the behavioural level? Here I will argue that the sleeping brain attempts to finely balance the need to turn inward in order to optimise memory consolidation with the ability to rapidly revert to wakefulness when necessary. This leads to the hypothesis that sleepers enter a "standby mode" in which neural mechanisms aimed at tracking relevant signals in the environment remain functional. I will present several studies using neural markers of cognitive processing to show that the human brain, even after falling asleep, continues to 1) classify auditory events in a task-dependent manner, 2) rely on selective attention to resolve the cocktail party phenomenon, and 3) even form new memory contents on perpetual learning tasks. I will describe how the sleeping brain continued connection with the external world is restricted to specific sleep stages, though, and that the presence or absence of neural responsiveness can be traced back to specific sleep rhythms (e.g., slow-waves, K-complexes, spindles).

Sensory disconnection across sleep and anesthesia
Yuval Nir (Tel-Aviv University)

During sleep, although some information processing persists, by and large external sensory events do not reliably affect behavior or subjective experience. Such sensory disconnection is a defining feature of sleep, and similar processes occur during light anesthesia or during cognitive lapses. What are the changes in brain activity that mediate such disconnection from the external world?

Traditionally, it was believed that sensory disconnection is due to "thalamic gating", in other words that signals from sensory organs such as the ears or skin "stop" at the level of the thalamus and do not trigger robust responses

in the cerebral cortex. However, we find that in the auditory system of both rodents and humans, responses in sleep and light anesthesia are relatively preserved in primary auditory cortex (A1), challenging the dominant dogma. Instead, robust attenuation occurs later in high-level cortical regions, where sensory signals create perceptions and interface with memory systems. In addition, sleep affects more strongly responses that require integration over long time intervals such as speech grammar, and responses to high-frequency content that allow to follow the precise details of external stimuli.

What is it about sleep that prevents sensory signals from effectively driving activity in high-level regions and reliably influence behavior and perception? In other words, what are the underlying mechanisms? we are testing the hypothesis that reduced locus coeruleus-noradrenaline (LC-NE) signaling during sleep plays a key role in mediating sensory disconnection. Using single-neuron electrophysiology, behavioral, pharmacological, and optogenetic techniques alongside auditory stimulation and sleep monitoring in freely behaving rats, we show that NE signaling affects the probability of sound-evoked awakening from sleep. In other words, it is a key factor in determining how deeply we sleep and may change in periods of stress or in pathological conditions of hyper-arousal and sleep disorders. Along this line, we predicted that reduced NE signaling during wakefulness will show some "sleep-like-disconnection". We tested the effects of NE levels on perception and sensory-evoked activity (EEG, fMRI) in awake humans using pharmacological manipulation of NE levels in double-blind placebo-controlled experiments. We find that NE modulates visual perception and boosts late visual responses. Together, our results suggest that NE is a key factor causally linking sensory awareness to external world events.

Enhancement and Inception (Part I: Rodents)

Brain dynamics of memory consolidation during sleep

Michael Zugaro (CNRS - Collège de France)

Most modern theories of memory formation and consolidation posit that initially labile memory traces are formed in the hippocampus, then stabilized in neocortex for long-term storage. A seminal mechanistic model proposed that hippocampal endogenous activity during high frequency oscillations ('ripples') played a key role in this process. This idea received striking correlative support with the discovery of sleep replay in rats, whereby neural activity patterns experienced during exploration of a maze are endogenously reactivated during sleep ripples, as if the rats were 'dreaming' of their exploration.

Yet, direct causal evidence that these patterns were involved in memory consolidation remained elusive for the following 20 years. Using a real-time, closed-loop perturbation approach, we first demonstrated that selective ripple suppression during sleep significantly impaired memory consolidation on a spatial reference memory task. In a subsequent study, we trained rats to learn but not remember a spatial reference memory task, and showed that boosting during subsequent sleep the precise temporal coupling between ripples, cortical delta waves and thalamo-cortical spindles, triggered functional changes in neocortical subnetworks which induced memory consolidation and resulted in perfect performance upon recall on the next day. This provided direct and causal evidence for the long-hypothesized hippocampo-cortical dialogue underlying memory consolidation. Finally, we have recently shown that the emergence of sleep replay requires a delicate, fine timescale organization of hippocampal activity during previous behavior. This activity takes the form of fast sequences paced by ongoing theta oscillations, and are thus known as 'theta sequences'. Our results show that theta sequences mediate the initial learning phase during behavior. In summary, hippocampal sequences emerge during behavior, then endogenously reactivate during sleep ripples, finely coordinated with cortical rhythms. These network events mediate the formation and consolidation of memory.

Changing the mind of mice : Inception of memories during sleep

Marie Lacroix (CNRS - ESPCI Paris Tech - Cog'X)

Sleep is now recognized to be crucial for the consolidation of preexisting memory traces. One important model to study memory in rodent is the spatial memory, as hippocampal neurons have been shown to code for spatial location

of the animal. This correlate between animal behavior and hippocampal neuronal activity is so strong that those « place cells » assemblies are believed to support the « cognitive map », which is the mental representation of space in the animal brain. During sleep, those place cells assemblies show reactivations of recent waking experience, and this replay would be instrumental in the process of memory consolidation.
Here we show that neuronal reactivations can be used to induce a new artificial place/reward association during sleep. We designed a protocol where intracranial rewarding stimulations were triggered by a hippocampal place cell during sleep. We were able to induce an explicit memory trace, leading to a goal-directed behavior toward the place field artificially associated to reward.
These results show first that it is possible to create an artificial explicit memory during sleep that is used during subsequent waking period to drive a goal directed behavior. But more importantly, it demonstrates the causal role of place cells on the mental representation of space, and that hippocampal cell assemblies still conveyed the same spatial information during sleep as it did during wakefulness.

Enhancement and Inception (Part II: Humans)

Elucidating the role of REM sleep and dreams in cognitive functions
Delphine Oudiette (ICM)

Why do we dream ? Artists and Nobel laureates often report that dreams inspired their greatest discoveries. Are dreams involved in the creative process? Sleep plays a major role in memory consolidation, via the reactivation, at the neuronal level, of newly acquired information. Does mental content (i.e. dreams) accompany these neuronal reactivations? It is difficult to scientifically study dreams because we cannot access dreamers' mental content at the very moment dreams occur. Researchers have to rely on retrospective dream reports , which have numerous biases such as forgetting, censure, verbalization difficulty, lack of correlation between the dream report and physiological features in the absence of temporal marker, etc. Another approach consists in studying rapid eye movement (REM) sleep, which is the sleep stage during with the most vivid and bizarre dreams happen.
In this talk, I will show how a neurological sleep disorder that directly impacts REM sleep, -narcolepsy-, can help to shed light into the role of REM sleep and dreams in cognitive functions.

Enhancing human memory: From single neurons to neuromodulation
Itzhak Fried (UCLA / Tel-Aviv University)

Loss of memory is one of the most dreaded afflictions of the human condition. With the increase in population age and subsequent striking increase in number of patients with memory impairments, we are facing a social calamity of alarming dimensions
The medial temporal lobe (MTL) is central to the transformation of percepts into lasting memories that can be consciously recollected in the future. Yet the neuronal code underlying this transformation in humans remains unclear. Recordings from neurons within the brain and focal brain stimulation in patients implanted with electrodes for clinical reasons provide a rare opportunity to bridge physiology with cognition.
During sleep these recordings provide insight into the orchestration of several brain rhythms- slow waves, spindles and ripples- that are thought to be critical to the consolidation of memories during non-REM sleep. These recordings point to the local nature of slow waves and spindles, and to the propagation of slow waves through the human cortical- hippocampal circuitry. Still demonstration of neuronal replay related to human episodic memory and the study of hippocampal-neocortical dialogue remains a formidable challenge.
Electrical stimulation provides an exciting tool to study causal mechanisms of memory encoding and consolidation. During encoding, of new information, electrical stimulation applied at the entorhinal region appear to enhance subsequent performance on memory retrieval of that information. During slow wave sleep electrical stimulation locked to hippocampal slow waves applied at frontal lobe sites, results in enhancement of slow wave power as well as improvement in memory performance. These results may lead to development of closed loop neuro-prosthetic devices- memory aids- providing stimulation based on sensing of local brain activity in order to enhance memory encoding during waking periods and memory consolidation during sleep.

Dreaming (Part I)

The relation of dreaming to memory consolidation during sleep

Mark Blagrove (Swansea University)

There is considerable research on how REM sleep and Slow Wave Sleep are related to memory consolidation. These consolidation processes prioritize emotional and salient memories. Dreaming also incorporates emotional memories from waking life, and so it has been proposed that dreaming reflects functional neural processes during sleep. Arguments in favor, and against this possibility will be explored. That dreams refer to waking life experiences in an associative or metaphorical manner has been seen to be a result of processes of linking new memories to established memories, guided by emotions common to each. That we are embodied in the dream, in a simulation of the waking world, may be required for full processing of emotions, or may have another, practice-based virtual reality function. Separate from the debate on dream function is the debate on whether the consideration of dreams by the dreamer when awake, can elicit insight. This possibility is supported by the finding that dreams preferentially incorporate emotional experiences, and refer to them metaphorically. Designs for testing this against the null hypothesis, that dreams do not tell us anything new, will be discussed, and will include recent studies on whether the sharing and discussion of dreams can increase empathy towards the dream sharer.

Dream appreciation and revisiting dreams by artwork

Mark Blagrove, Julia Lockheart (Swansea University)

Dream Appreciation session will be conducted following the group technique described by psychiatrist and psychoanalyst Montague Ullman (1996, Appreciating Dreams: a Group Approach, Sage books). The stages of the technique are: recall and clarification of the dream; groups members' projections about the dream; dreamer describes their recent waking life; dream is read back; connections between dream and dreamer's waking life are suggested by the group. The Gains from Dream Interpretation questionnaire will be completed. As a separate activity, during the session, artist Dr Julia Lockheart will create a painting of the dream onto a page taken (with publisher's permission) from Freud's book The Interpretation of Dreams, incorporating into the artwork the text format and keywords. A gallery of these artworks, and rationale for this art science collaboration, including hypothesized empathy changes, can be seen at http://DreamsID.com. An enlarged print of the artwork is sent to the dreamer after the event and can be used to revisit the dream with friends and family.

Dreaming (Part II)

The dreaming brain

Francesca Siclari (UNIL - CHUV)

Dreaming is a form of consciousness that occurs during sleep, while we are functionally disconnected from the environment. Traditionally, it has been linked to rapid eye movement (REM) sleep, a behavioral state characterized by fast, desynchronized electroencephalographic activity similar to wakefulness. In recent years however, it has become clear that dreaming can also occur in Non-REM sleep, a stage of sleep dominated by EEG slow waves and spindles. This has challenged the understanding of the neural correlates of conscious experiences in sleep. In the present talk I will outline characteristic features of dreaming that distinguish this state from waking cognition. I will then present a series of studies investigating the neural correlates of dreaming using a serial awakening paradigms and high-density EEG recordings. More specifically I will show how local EEG features, including spectral power in different frequency bands, slow waves and spindles relate to the presence and absence of dreaming, and to specific dream contents. These results suggest that local EEG correlates may account for the presence of conscious experiences in behavioral states with radically different global EEG signatures.

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In Search of Lost Sleep

Genius, Memory and Sleep : the Cases of M. Proust and F. Kafka

Antonio Perciaccante (Goriza Hospital)

The cases of the writers Marcel Proust and Franz Kafka are examples of the relationship among genius, memory and sleep.
The interest of Marcel Proust on involuntary memory may be related to his medical history. The novelist suffered from bronchial asthma and insomnia. At that time, asthma was considered a "nervous habitus", and a diagnosis of "neurasthenia" was performed. Proust was admitted to Paul Sollier's Clinic in Paris, to try to treating his neurasthenia and insomnia. Sollier studied several aspects of the memory, and used the surges of involuntary memory to treat his patients. So, Proust experienced the surges of involuntary memory, which himself cited in the famous episode of "les Madeleines" in his masterpiece "In search of lost time".
If the memory is a central element in Proust's work, the sleep plays a pivotal role in Kafka. Insomnia affected Kafka's life and literary work. He considered the sleep as the most innocent creature, and the insomnia as a rejection of the natural. At the same time, he was afraid of sleep, because it represented an area where the consciousness was lost. Insomnia allowed him to write and to refuge into literature. So, Franz Kafka, «used» the insomnia for their creative processes. He wrote in a sleep-deprived state, because it provided access to otherwise inaccessible thoughts. In his diaries he wrote: « it was the power of my dreams, shining forth into wakefulness even before I fall asleep, which did not let me sleep.» It seems to be a description of an hypnagogic hallucination. Many references to the importance of the sleep may be found in the brief story "Metamorphosis".

Insomnia and Emotional Memory

Eus Van Someren (Netherland Institute for Neuroscience)

Insomnia is the second-most prevalent mental disorder and the primary modifiable risk factor for depression, anxiety disorders and PTSD [1]. In search of brain mechanisms, circadian and a homeostatic processes seem surprisingly intact. The hyperalert insomniac brain differs strongly from the hardly awake sleep-deprived brain [2,3]. Big data psychometrics (sleepregistry.org) showed different insomnia types, all involving distributed deviations in brain circuits underlying stable characteristics of affect [4].

HD-EEG, MRI and animal model studies converge to suggest that the core issue causing insomnia is a deficiency in overnight processing of memories of distressing experiences [5-7]. Rapid Eye Movement (REM) sleep plays an important role in the reorganization of emotional memory circuits. Uniquely during the transition to REM sleep, and throughout REM sleep, the Locus Coeruleus (LC) is inhibited [8]. This time window of low noradrenaline release facilitates synaptic depotentiation [8,9]. Meanwhile, increased activity occurs in (para)limbic regions including amygdalae and anterior cingulate cortex, which is selectivly activated by the claustrum during REM sleep [10].
However, in insomnia and related mental disorders, abundant EEG arousals during sleep indicate insufficient inhibition of LC activity. Abiding LC activity during sleep abolishes the only noradrenaline-free time window available to the brain including its unique balance between synaptic potentiation and depotentiation during nocturnal replay and neuronal network adaptation. We posit that this in particular interferes with overnight processing of emotional distress [5-7], resulting in daytime hyperactivation of salience- and emotional- circuits. This new model of circuits involved in insomnia is supported by GWAS [11]: risk genes for insomnia turn out to be expressed in cell types and brain areas identified with neuroimaging, including the claustrum and anterior cingulate cortex that activate during REM sleep [3,6,10,12].

People with insomnia have developed a brain optimally wired to stay alert, at the cost of suffering bad sleep.

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Sleep quality, Cognition and Aging

Geraldine Rauchs (Inserm - Caen University)

Sleep is essential for an efficient cognitive functioning. Recent evidence also suggest that poor sleep quality may increase the risk of cognitive decline and Alzheimer's disease (AD), notably by exacerbating amyloid deposition. But, sleep quality may also have an impact on brain structure and function.

We first investigated, in a group of cognitively normal older adults, the impact of subjective sleep quality on brain integrity and cognitive performance, focusing on executive functioning and episodic memory (Branger et al., 2016). Sleep quality was assessed using a questionnaire covering the last five years. We showed that older adults complaining of recurring difficulties falling asleep have greater amyloid burden in prefrontal areas, known to be early affected in AD. Furthermore, fragmented sleep was also associated with lower grey matter volume of the insula. Surprisingly, subjective sleep quality was not associated with cognitive performance nor brain metabolism. In a second study, we analyzed actigraphy data collected during one week and focused on indices of sleep fragmentation (mean intensity and night-to-night variability). In cognitively unimpaired elderly participants, we showed that the intensity of sleep fragmentation mediated the association between fronto-hippocampal hypometabolism and lower executive functioning. Moreover, a high night-to-night variability in sleep fragmentation was related to thalamic atrophy and, to a lesser extent, to amyloid burden in prefrontal areas. However, in patients with subjective cognitive decline and/or mild cognitive impairment, sleep fragmentation no longer contributed to the expression of cognitive deficits. These findings suggest that sleep fragmentation may directly contribute to lower cognitive performance in cognitively unimpaired elderly subjects. In addition, treating sleep disturbances before the onset of cognitive deficits may help to cope with brain alterations and maintain cognitive functioning (André et al., 2019).

Neuronal lapses during sleep deprivation

Itzhak Fried, Yuval Nir (Tel-Aviv University)

Chronic sleep deprivation or sleep restriction has long-term effects on health including increased risk for hypertension, diabetes, obesity, heart attack, and stroke, as well as aggregation of amyloid beta and other proteins and accelerating dementia. On the short term, it has been established that sleep deprivation slows down our behavioral reaction times, contributing to vehicle accidents and medical errors, and is therefore an important topic of investigation with major implications for society.

However, it has been unclear exactly how the lack of sleep affects brain activity in a way leading to degraded behavior and lapses. We had a unique opportunity to examine this issue in epilepsy patients implanted with depth electrode, recording single-neuron and LFP activities in as participants performed a face/non-face categorization psychomotor vigilance task (PVT) in multiple experimental sessions, including after staying awake all night (full-night sleep deprivation).

We find that just before cognitive lapses, selective spiking responses of individual neurons in the medial temporal lobe (MTL) are attenuated, delayed, and lengthened. These 'neuronal lapses' are evident on a trial-by-trial basis

comparing the trials with the slowest behavioral reaction times to the fastest. The “neuronal lapse”, or slowdown, affects the brain’s visual perception and memory associations.

Furthermore, during cognitive lapses the local electrical fields show in increase in sleep-like slow/theta activity that is correlated with degraded single-neuron responses. In other words, select circuits enter a sleep-like states while we are still awake but as the need for sleep rises.

Altogether, the results show that cognitive lapses involve local state-dependent changes in neuronal activity already in the visual-memory hubs in the human brain, and that these changes co-occur with sleep-like brain waves occurring during wakefulness.