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Université de Montréal

THE INFLUENCE OF SLEEP ON MEMORY

par

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Cette thèse intitulée :  
L'INFLUENCE DU SOMMEIL SUR LA MÉMOIRE:

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## AVANT-PROPOS

Cette thèse de Doctorat est présentée sous forme d'articles et a été autorisée par le vice doyen de la faculté des études supérieures. Trois articles scientifiques composent cette thèse, deux sont publiés et le 3<sup>ème</sup> a été soumis. L'auteur de cette thèse est également le premier auteur des 3 articles. (Appendix 6: Déclaration des co-auteurs).

Le premier article intitulé « The ERP Old/New effect: a useful indicator in studying the effects of sleep on memory retrieval processes » est *accepté* dans le journal Sleep 2006; 29(11) 1401-1500.

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Le troisième article intitulé « The effects of sleep deprivation on memory retrieval processes: An event-related potential study » est *soumis*.

"Sleep appears to be ubiquitous and necessary...It is difficult to believe that it does not have an important function" (Empson, 1993)

"The existence of forgetting has never been proved: we only know that some things don't come to mind when we want them to." (Neitzsche)

"I learned this, at least, by my experiment; that if one advances confidently in the direction of his dreams, and endeavors to live the life which he has imagined, he will meet with a success, unexpected in the common hours."  
(Henry David Thoreau, Walden)

## Résumé

Les études de cette thèse visent à déterminer l'influence du sommeil sur la mémoire de reconnaissance. Lors de ces études comportant trois volets, l'effet du sommeil sur la mémoire a été déterminé à l'aide de la technique des potentiels évoqués cognitifs (PEC), en comparant une nuit de sommeil, à une journée de l'éveil ou une nuit de privation totale de sommeil (TSD). Lors de la première expérience, les résultats comportementaux ont démontré une performance accrue après le sommeil comparativement à la veille. Les données PECs ont établi que l'effet de mémoire *Ancienne/Récente* (Old/New effect), le déplacement positif qui se produit quand les stimuli sont répétés, est obtenu après un long délai, de façon identique à ce qui a été démontré par d'autres chercheurs après de plus courts délais, et la magnitude de l'effet de mémoire était plus grande après le sommeil qu'après la veille, ce qui indique un rôle du sommeil dans la consolidation.

La deuxième expérience approfondit davantage autour de cette découverte à l'aide d'un montage plus élaboré afin de mieux caractériser les effets frontaux associés au traitement de la mémoire par le sommeil. Les PEC ont été analysés pendant les sessions d'études afin de vérifier les effets possibles confondants qui résulteraient de la différence entre les moments d'études des deux sessions. Les résultats comportementaux ont démontré que le sommeil favorise ou agit davantage sur la précision que sur les temps de réaction, ce qui est en accord avec l'idée que la consolidation consiste en une réorganisation des associations faibles visant à renforcer les liens associatifs. L'analyse des PEC de la session d'étude a démontré que la qualité de l'apprentissage ne varie pas selon le moment de l'encodage, ce qui suggère que ce qui influence les composantes tardives ne peut être attribué aux variations cycliques au moment de l'encodage. Pour ce qui est de la session d'évaluation, les données PECs ont révélé que le sommeil influence non seulement l'intégration contextuelle mais aussi un processus frontal d'interférence.

La dernière étude compare la TSD au sommeil normal afin d'établir les effets de l'absence de la nuit de sommeil sur les processus de la mémoire. Contrairement aux études précédentes, nous avons contrôlé pour la vigilance dans un modèle

ANCOVA avec l'amplitude N100 (reflète la vigilance). Nos données comportementales ont démontré que la TSD résulte en une performance moins précise avec les nouveaux items, ce qui suggère une incapacité de discriminer ce qui est et ce qui n'est pas en mémoire. Nous avons découvert une différence significative dans les réponses entre les items étudiés versus les nouveaux, mais aucune différence entre les sessions. Les résultats PEC ont révélé que les différences significatives reliées à l'effet *Ancien/Récent* étaient amoindries suite à la TSD. La TSD a affecté un processus postérieur hâtif de catégorisation et une composante frontale plus tardive représentant le traitement contextuel; cependant les deux étaient reliés à la vigilance amoindrie. Deux phénomènes inattendus, indépendants de la vigilance, ont été observés après TSD; 1) une amplitude N200 antérieure réduite de façon bilatérale et 2) une amplitude N200 postérieure réduite. Prises ensembles, les données suggèrent que la TSD résulte en un traitement moins structuré, amoindrit les processus alloués à l'indentification de détails et n'affecte pas l'accès à l'information sémantique. Cependant, l'information récupérée était moins élaborée, ce qui est cohérent avec un rôle du sommeil dans la consolidation.

**Mots-clé:** Sommeil, lent sommeil, PS, mémoire déclarative, épisodique, sémantique, reconnaissance, privation de sommeil, potentiels évoqués cognitif, PEC.

## **Abstract**

The aim of this thesis was to determine the influence of sleep on memory with an emphasis on recognition memory. These studies assess, using event-related potentials (ERPs), the influence of normal sleep compared to daytime wake and compared to one night of sleep deprivation (TSD) on memory in three experiments, without recording sleep. In the first experiment, the behavioral results demonstrated enhanced performance after sleep compared to wake. The electrophysiological data established that the "Old/New" memory effect (i.e.; positive shift that occurs when stimuli are repeated) was elicited after a long delay in the same way other researchers have shown this effect with shorter delays, which validates our protocol from an ERP perspective. More importantly, results revealed differences in the memory effect whereby the magnitude was larger after sleeping compared to wake, indicating a role for sleep in consolidation.

The second experiment expands on these findings by employing an extended montage to better characterize the frontal effects associated with memory processing by sleep. As a control for the possible confounding effects of the differences in the time of learning across the two sessions, the ERPs during the study session were analyzed. Our behavioral results showed that sleep favors or acts more on accuracy versus RTs, which is in agreement with the idea that consolidation consists in restructuring or re-organizing weak associations in order to strengthen associative links. The analysis on the study session ERPs showed that the quality of learning does not differ as a function of the time of encoding, suggesting that any effect on the later components cannot be attributed to cyclic variations at time of encoding. As for the test session, the electrophysiological data revealed that sleep influences not only contextual integration but also an early frontal process of interference inhibition.

The last study employs a TSD compared to normal sleep design to assess the effects of loss of a night of sleep on memory processes. Unlike previous studies, we controlled for vigilance across session in an ANCOVA model with the N100 amplitude whose functional significance is thought to reflect vigilance. Our behavioral data showed that TSD resulted in less accurate performance of the new

items, suggesting an inability to discriminate what is and is not in memory. We found a significant difference in the responses to the studied vs. new items but no difference across session. Electrophysiological results revealed significant differences related to the Old/New effect that were reduced following TSD. Deprivation of sleep affected an early posterior process of categorization and a later frontal component representing contextual processing, however both were related to lower vigilance. Two unexpected findings following TSD independent of vigilance were; 1) a reduced anterior N200 amplitude seen bilaterally, and 2) a reduced posterior N200 amplitude. Taken together the data suggests that TSD results in less structural processing, reduces processes allocated in identifying details, and does not affect access to semantic information. However, information retrieved was less elaborated, consistent with role of sleep in consolidation.

**Keywords:** Sleep, NonREM, REM, Memory, declarative memory, episodic, semantic, recognition, sleep deprivation, event related potentials, ERPs.

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**List of Abbreviations/Liste des Abreviations**

|         |                                       |
|---------|---------------------------------------|
| Ach     | Acetylcholine                         |
| ANOVA   | Analysis of Variance                  |
| ANCOVA  | Analysis of Covariate                 |
| ARAS    | Ascending Reticular Activating System |
| DR      | Dorsal Raphe                          |
| EEG     | Electroencephalogram                  |
| EMG     | Electromyogram                        |
| EOG     | Electro-oculogram                     |
| ERP     | Cognitive Event Related Potentials    |
| fMRI    | functional Magnetic Resonance Imaging |
| LC      | Locus Coeuleus                        |
| LDT     | Lateral Dorsal Tegmental nucleus      |
| $\mu$ V | Microvolts                            |
| NE      | Norepinephrine                        |
| NonREM  | Non-Rapid Eye Movement Sleep          |
| PPT     | Pedunculopontine nucleus              |
| REM     | Rapid Eye Movement Sleep              |
| 5HT     | Serotonin                             |
| SD      | Sleep Deprivation                     |
| TSD     | Total Sleep Deprivation               |
| VLPO    | Ventrolateral Preoptic area           |

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## Foreword

Previously considered a passive state, sleep is now considered an active process. During the sleep, the brain continues to show a certain activity, although different from that during wakefulness. To understand this complex behavioral state, this thesis focuses on examining the influence of sleep on long-term episodic memory processes in humans. In the text that follows, I will present briefly the various memory systems and structures of sleep, as well as the neuropsychological and neurophysiological support for the dissociation between memory systems and the distinction between the major sleep states. Following this, I shall describe in detail the results of research utilizing different experimental approaches (e.g. behavioral, total sleep deprivation and selective sleep deprivation) to study the relationship between the sleep and long-term memory. Two approaches were used for this investigation. The first approach measured cognitive event potentials and behavioral performance of a group of subjects following a night of normal sleep and after an equivalent period of daytime wake. The second approach measured the ERP neural activity and performance of another group of subjects after a sleepless night and after a period of nocturnal sleep.

## INTRODUCTION

In 1885, Ebbinghaus performed a series of experiments of what are generally acknowledged to be the first study of human memory. In his studies, Ebbinghaus learned 169 separate lists of nonsense syllables, and charted the rate of forgetting. The final result of these investigations was the classic curve of forgetting. Ebbinghaus' forgetting curve revealed that most forgetting occurs within the first hour, after which forgetting slowed dramatically between the 8 to 24 hour interval. Although sleep occupied a large part of this interval, Ebbinghaus did not mention the possibility that sleep may somehow be responsible for the observed results. Subsequently, other investigators attempted to isolate the effects of sleep on memory.

Currently, memory is conceived as multiple interacting systems and processes represented by diverse networks of brain structures. In the same way that memory cannot be considered homogeneous, both sleep and memory consolidation are complex phenomena that appear equally diverse. Even the term consolidation originally referred to as the process of trace stabilization through which the representation become resistant to interference has been redefined. More recent studies suggest that upon recall of previous consolidated information, the memory or representation returns to an unstable state, once more requiring consolidation, or re-consolidation.

Following the discovery of discrete sleep stages in the 1950s, sleep was no longer considered a homogeneous state, and research investigating the influence of sleep on memory has become gradually more complex. Many experiments looked at specific effects of the newly described sleep stages on memory. Initially, most of the

research effort was on rapid-eye movement sleep (REM) sleep deprivation. Many of the animal studies supported the idea that post-training REM sleep was important for memory consolidation; however, negative results in humans were simultaneously published. Further, it was argued that the deleterious effect of sleep deprivation was due to nonspecific effects of the experimental design. Moving away from sleep deprivation paradigms, in the early 70s, a novel approach was employed where four-hour periods of undisturbed sleep covering either the first or the second half of the nighttime sleep cycle was used. The studies that followed looking at the specific effect of sleep stages on memory sometimes resulted in mixed and contradictory conclusions. Some that was in favor of sleep dependent memory processing, and others against it. Results seemed to suggest that each stage of sleep contribute to different memory processes. In addition, several studies indicated that the more difficult the task, the less convincing its sleep-dependent consolidation.

Beginning about the 1980s, there was a marked reduction in the number of studies devoted to this area. The main reason for this decline was that a series of studies failed to convincingly demonstrate a relationship between sleep and declarative memory. In contrast, there has been robust support for the conclusion that REM sleep enhanced performance on tasks of procedural memory. As a consequence, procedural memory has been exclusively studied due to the consistent and strong support for sleep dependent processing. A comprehensive role of sleep in declarative memory and its subsystems remains to be established and represents a future challenge to researchers in the area of sleep and memory.

## CHAPTER 1. LONG-TERM MEMORY (LTM) SYSTEMS

The term *memory* implies the capacity to encode, store and retrieve information. Acquisition is a learning process that takes place at the time of exposure to the information and involves the encoding (i.e. analysis, classification of information and links it to past learning). Storage is the maintenance of the information across intervals of time between encoding and retrieval. Retrieval is the ability to recall or recognize the information following a delay (Reeves & Wedding, 1994). Memory is defined as the retention of the learnt material. It should be highlighted, how well information is encoded and stored in memory determines how likely it is to be accessed or retrieved.

Memory lasting anywhere from an hour to lifetime is called long-term memory (LTM). The LTM represents a system of storage of events, facts, procedures and skills that we accumulated over the years. The long-term system has an unlimited capacity and a relatively slow rate of acquisition of new material (Waugh & Norman, 1965). Research has given important insights on the nature of LTM. The most important is that LTM is made up multiple, interactive memory systems that are functionally independent (Squire, 1992)

### 1.1. The Principle of Double Dissociation: Partitioning LTM

The development of neuropsychological methods in the patients with cerebral lesions contributed to the reports of a distinction between different memory systems. The major argument of cognitive neuropsychologists in favor of a distinction between different memory systems, rested on revealing "functional dissociations" (McCarthy

& Warrington, 1990). In the mid-60s to early-70s, this logic was employed by cognitive psychologists to fractionate memory into separate systems (Glanzer & Cunitz, 1966). In this context, "functional dissociations" were used to support divisions of memory function but not necessarily to localize these functions in the brain. There are two main types of dissociations, single and double. A single dissociation corresponds to the observation that a localized brain lesion ( $X$ ) comes along with a disturbance of a memory system  $A$ , without distorting another  $B$  system. Much stronger evidence for comes from double dissociations. First introduced in the mid-50s, a double dissociation is observed when in the single dissociation comes to add to the fact that  $B$  system is disrupted by another insult ( $Y$ ), which does not affect  $A$  system (Figure 1) (Teuber, 1955). For example, individuals with brain-lesions who do well on task  $A$  but poorly on task  $B$ , with another group showing the opposite pattern. This suggests that two tasks involve different processing mechanisms and implies that there is a memory system required by  $B$  but not  $A$ . A double dissociation allows one to infer that  $A$  and  $B$  systems are functionally independent.

In the 1990s, some suggested that dissociations were not well supported by the data but instead due to lack of statistical power to detect such impairments (Ostergaard, 1992). Stochastic or statistical dissociations involving the administration of one study (learning) test and subsequently two retrieval tests to the same subject were found to be more compelling. An item-by-item analysis is used to evaluate the probability that performance of a given item in one test is statistically unrelated to performance on the same item in another test, i.e., stochastic independence. And each task is thought to rely on a different memory system. Nevertheless, if different types

or multiple functional dissociations across different aspects of memory all point to the same set of systems, then most likely that pattern of data is reliable (Schacter, 1992).

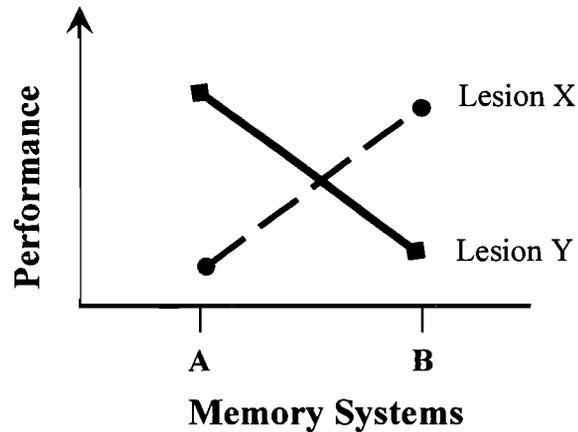


Figure 1. Schematic representation of memory deficits corresponding to a double dissociation.

#### 1.1.1. Dissociating Procedural vs. Declarative LTM

As early as 1970 a distinction was made that dissociates LTM into two systems (Squire, 2004). Subsequently, Squire (1987) proposes a model that dissociates LTM into procedural versus declarative memory systems (Squire, 1987). Procedural memory refers to skills or sequences of behavior and, is implicitly (unconsciously) learned and executed. Procedural learning of perceptual and motor skills is usually achieved through periods of performance repetition. Declarative memory, instead, consists of events that are usually explicitly (consciously) and intentionally learned and retrieved (Cohen & Squire, 1980). Research has provided ample evidence that performance on tests of procedural memory and declarative memory can be dissociated (Schacter, 1992; Roediger, 1990).

Perhaps the most compelling evidence for dissociation between procedural and declarative memories is provided by studies of patients with amnesia after bilateral resection of the medial temporal region (including the hippocampus and the amygdale) to relieve severe epilepsy. First described by Scoville and Milner (1957) was a memory change in a patient (H.M.) and later eight other cases, with profound amnesia that were unable to form any new memories after surgery (anterograde amnesia). These authors, however, found that patient H.M. exhibited daily improvements in procedures and skills, suggesting that his procedural memory was intact (Scoville & Milner, 1957). A similar observation was confirmed in another study that indicated localized lesions in the hippocampus were sufficient to lead to this type of amnesia in humans. Along the same lines, Cermak and *colleagues* (1973) presented alcoholic Korsakoff patients to show the distinction between declarative and procedural memory (Cermak & Butters, 1973). Their study examined the learning performance on a declarative task (finger maze<sup>1</sup>) vs. a procedural task (pursuit rotor<sup>2</sup>). The results showed that Korsakoff patients were able to learn the procedural task but were unable to learn the declarative task as well as the normal control group. Neuroimaging studies in the Korsakoff syndrome reveal general atrophy involving the frontal lobes (Shimamura, Jernigan, & Squire, 1988; Jacobson & Lishman, 1990) and diencephalic structures (Jernigan, Schafer, Butters, & Cermak, 1991) including the medial thalamus and/or mamillary bodies (Colchester et al., 2001).

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<sup>1</sup> Finger maze task – (declarative task) the task consists of trial learning by tracing finger mazes while blindfolded.

The second part of the evidence of a double dissociation between declarative and procedural memory is found in neurological patients with Huntington's chorea characterized by the degeneration of cells in the basal ganglia (Martone, Butters, Payne, Becker, & Sax, 1984). The patients with Huntington's chorea are unimpaired on tasks of declarative memory but are often impaired in procedural skill learning. A study by Martone *et al.* demonstrated impairments on procedural nonmotor skills task (i.e. mirror reading<sup>3</sup>) on which patients with temporal lobe lesions are unimpaired (Martone, Butters, Payne, Becker, & Sax, 1984). Neuroimaging studies using positron emission topography (PET) have provided evidence for the involvement of the basal ganglia in procedural skill learning in normal individuals, e.g. (Grafton, Hazeltine, & Ivry, 1998). Yet another distinction proposed within LTM is between subsystems of declarative memory.

#### 1.1.2. Dissociating Episodic vs. Semantic LTM.

A previous distinction made by Tulving (1972) have been integrated into the long-term declarative memory model of Squire (1987). In his model Tulving (1972) argues that declarative memory is made of two different, nonetheless, interacting systems: semantic memory and episodic memory (Tulving, 1972). Others envisioned a similar distinction earlier, for example, Broad (1925) and Furlong (1948) distinguished "recollective" or episodic memory from what they referred to as "propositional" or semantic memory (Furlong, 1948; Broad, 1925).

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<sup>2</sup> Pursuit rotor task – (procedural task) the subject learns to track a metal dot on a turntable platter with a flexible metal rod.

Semantic memory relates to general world knowledge, concepts and facts (Tulving, 1972) not temporally dated. A concept is associated with the attributes for example, its function (a kitchen chair, office chair) or its form (round, square). Information is stored as semantic "nodes" which are interconnected to form a network of knowledge (Collin & Loftus, 1975; Quillian, 2007) such as, knowledge about the meaning of words (a chair is a type of furniture), the properties of objects (chairs have four legs) and facts (we sit in chairs). This organization explains semantic associations (table, chair), categorizations (furniture) (Morton, 1969; Anderson, 1983) and the implicit (i.e. unintentional) retrieval of information such as semantic priming (e.g. cue learning) (Squire & Zola-Morgan, 1991).

In addition, semantic memory is also affiliated with non-verbal knowledge (e.g. objects, faces). Early models of face recognition (Bruce & Young, 1986) propose that the identity of faces provides access to semantic knowledge and other identity information. Several different kinds of identity information exist and are clustered according to type (biographic details, physical features, name), and may only be accessed in a particular order due to its proximity see Figure 2, below (Zeineh, Engel, Thompson, & Bookheimer, 2003). In addition, there are two entry points. One is the recovery of biographic details about a person without recognizing their face. A second entry point is via global information; an example of this would be when we vaguely recognize a face as familiar but are unable to recollect the biographic details (when, where) of the person.

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<sup>3</sup> Mirror reading task- (procedural memory) – in this task, words are presented in a mirror-reversed

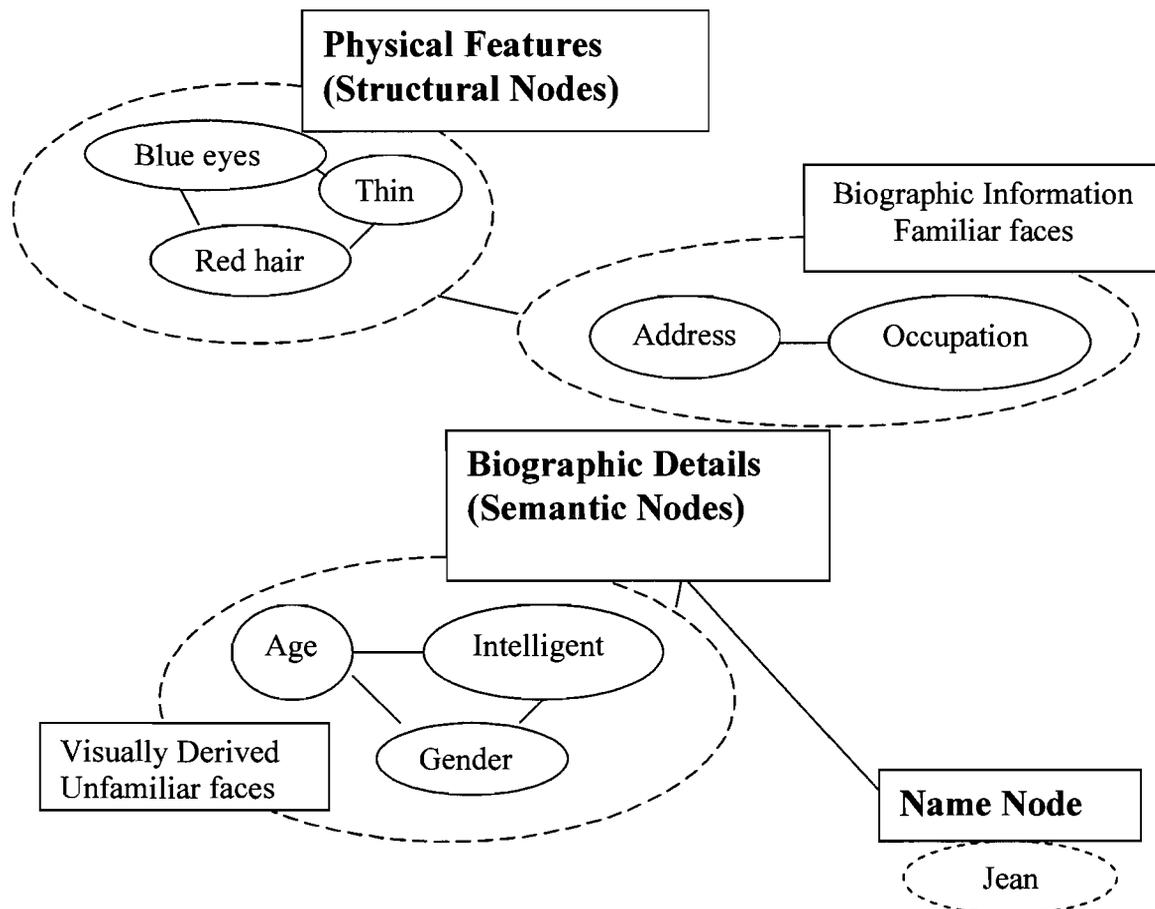


Figure 2. Example of the hierarchical representation of information in semantic memory network during familiar and unfamiliar face recognition

On the other hand, episodic memory is memory for personal autobiographic events, and is usually acquired with relatively few exposures to the information. In episodic memory, information is encoded in relationship to their temporal and spatial context (i.e. when and where) (Clayton & Dickinson, 1998; Nyberg et al., 1996).

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manner for the subjects to read.

According to Tulving (1972), every time we learn a piece of information, a new episode is stored with its new context. Subsequently, every rehearsal strengthens the trace of the episode. Thus, episodic memory "feeds" semantic memory, in that with iteration, the item and contextual association progressively consolidates as a semantic trace (Tulving, 1972).

Another distinction reminiscent to episodic and semantic memory is the relationship to the subjective experience of retrieval rather than on the type of information. Some have argued that recognition memory is not a unitary but is composed of two different processes (Yonelinas & Levy, 2002; Tulving, 1983; Mandler, 1980). One is an automatically or implicitly induced process (i.e. familiarity) at the re-exposure of an event, in the absence of any conscious knowledge about the context in which the event occurred (Jacoby, 1999; Knowlton & Squire, 1995). The other process refers to a conscious or explicit process of recollection, and involves the retrieval of contextual details (Knowlton & Squire, 1995; Jacoby, 1999). Research has shown that familiarity occurs earlier than recollecting detail in retrieval (Hintzman & Curran, 1995) and depends on the frontal structures (Rugg et al., 1998).

Evidence for dissociation between semantic and episodic memory comes from the study of individuals with circumscribed amnesia, neurological problems and normal aging. Semantic dementia is characterized by a progressive disorder of semantic knowledge while at the same time recalling a specific episode is relatively preserved (Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Nery, 1989). In this type of amnesia there is impaired ability to name objects, define words or in describing famous people. On imaging studies, semantic dementia

characteristically shows damage to the inferior and lateral temporal cortex (Hodges, Patterson, Oxbury, & Funnell, 1992b; Snowden et al., 1989).

Neurological patients with Alzheimer's disease show an initial impairment of episodic memory and, as the disease progresses, they become increasingly impaired on semantic memory tasks. This suggests that semantic memory is not dependent on the same MTL structures that are damaged in anterograde amnesia and believed to underlie the episodic memory deficits (Squire, Shimamura, & Graf, 1987) but rather may be stored in association areas<sup>4</sup> presumed to be impaired in the later stages of Alzheimer's disease. These observations imply that lesions at the level of the association area of the posterior cerebral cortex provoke disturbances of the storage or the access of semantic knowledge.

In dementia patients with Alzheimer's disease (Warrington, 1975); (Martin & Fedio, 1983), symptoms consist of a change in semantic knowledge (e.g. word knowledge and meaning of the objects). There are often selective deficits in stimulus modality (visual / verbal), of a specific category (concrete / abstracted) (Shallice & Warrington, 1975) or from a domain (language / face) (Peretz, Belleville, & Fontaine, 1997). Similarly, Warrington and Shallice (1984) demonstrated that in herpes encephalitis, patient's identification of living things and foods was severely impaired relative to their ability to identify inanimate objects, and that this was independent of modality of presentation (Warrington & Shallice, 1984). There is disagreement about the interpretation of these category specific impairments. One explanation for these

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<sup>4</sup> Association Areas: Parieto-temporal-occipital cortex receives input from the sensory modalities and relays the information to the frontal association area that also receives input from the limbic association area.

selective deficits is that living things may be processed in terms of their sensory properties, whereas inanimate objects are processed for the most part in terms of their function (e.g. (Warrington & Shallice, 1984; Borgo & Shallice, 2001). Other dissociations have been found in the processes involved in treatment (e.g. understanding words, identification of objects) versus those involved in the organization (e.g. reasoning, syntax) (Shallice, 1988).

In contrast, normal aging typically shows a mild gradual impairment of episodic memory accompanied by a relative sparing of semantic memory ( Craik, Anderson, Kerr, & Li, 1995). Jelacic *et al.* (1995) tested young and old adults on a cued recall task<sup>5</sup> under two different conditions: the first condition was to name the first word that comes to mind, the other condition, was to recall a word from the word list (Jelacic, Craik, & Moscovitch, 1996). They reported that the younger participants performance was equal on each task, while the older participants found the word list task more difficult, providing support for the existence of separate memory subsystems. Some have attributed this age-related decline in memory to a decline in fronto-striatal function (Gabrieli, 1995). This idea is supported by neuroimaging studies that showed age-related differences in frontal but not medial temporal regions during episodic retrieval (Schacter, Savage, Alpert, Rauch, & Albert, 1996). More compelling evidence for double dissociation comes from KC, a patient who lacked the ability to retrieve any specific personal events, who was able to learn semantic facts (Rosenbaum *et al.*, 2000) due to bilateral MTL damage from a motorbike

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<sup>5</sup> Cued recall task - (declarative memory) subjects are shown a word list and following a delay are presented with a cue (e.g. first few letters of a word or related word). The task is to recall a word from the studied list that matches the cue.

accident. When KC was presented with a series of pictures, with a short sentence, and then tested, he successfully completed the sentences in response to a cue. This occurred despite the fact that KC had no recollection of any specific episode on why he knew these facts.

Conversely, as mentioned above, patient HM initially demonstrated deficits in episodic and also in semantic memory (Gabrieli, Cohen, & Corkin, 1988; Postle & Corkin, 1998). More recently it has been shown that HM was able to acquire new semantic but not episodic knowledge that suggests a distinction between episodic and semantic memory (O'Kane, Kensinger, & Corkin, 2004). In addition, it indicates that semantic memory is supported by structures beyond the MTL.

## 1.2 Neuroanatomical Basis for Multiple LTM Systems.

The observed dissociations in the memory performance of clinical and nonclinical populations support the functional dissociations of multiple memory processes. Further, the lesion studies and related selective deficits have prompted speculation about the cortical and the anatomical support for distinct brain regions associated with different types of LTM.

### 1.2.1. Procedural Memory: Basal ganglia, Cerebellum & Motor Cortex

Procedural memory is often intact in patients with declarative memory problems either due to amnesia (e.g. HM) or in the early stages of Alzheimer's disease (Gabrieli, Corkin, Mickel, & Growdon, 1993). Procedural skills learning is often impaired in patients with basal ganglia diseases such as Huntington's disease

(Martone, Butters, Payne, Becker, & Sax, 1984). Grafton & coworkers scanned the brains of normal individuals during a procedural task (motor pursuit task) and found increases in cerebral blood flow in the motor cortex, basal ganglia and cerebellum, whereas the acquisition of the skill included a subset of structures (e.g. primary motor cortex, supplementary motor cortex and the pulvinar nucleus of the thalamus) (Grafton, Hazeltine, & Ivry, 1998). It appears that the neural structures involved in procedural learning are diverse, involving both cortical and subcortical networks. While different perceptual-motor skills may share some anatomical commonalities, the networks modulating specific kinds of procedural learning are defined by the sensory (input) and motor (output) demands of the task (Grafton, Hazeltine, & Ivry, 1998); (Jancke, Gaab, Wustenberg, Scheich, & Heinze, 2001; Karni et al., 1995; Schwartz, Maquet, & Frith, 2002).

### 1.2.2. Episodic Memory: Medial Temporal Regions

As mentioned above, the first lesions to appear in most cases of Alzheimer's disease occur in the medial temporal region (Hyman, Van Hoesen, & Damasio, 1987). However, Alzheimer patients also have early damage to cholinergic neurons in the basal forebrain (Arendt, Bigl, & Teanstedt, 1983), and lesions in this area cause impairments in declarative memory. Therefore, it is difficult to say that the deficits seen in Alzheimer's disease are exclusively to medial temporal injuries. Medial temporal lesions (as in the case of HM) resulting from a bilateral lobectomy implicate the hippocampus and/or the amygdala in episodic memory. Later, studies showed that hippocampal damage alone was sufficient to lead to amnesia (Squire, 1992).

Further evidences come from numerous neuroimaging studies reporting medial temporal activations during memory retrieval (Squire et al., 1992; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Schacter et al., 1995). One hypothesis regarding MTL lobe region is that it allows for the retrieval of contextual, spatial and temporal information with the relevant information in memory (Winocur, 1982; Hirsh, 1974). Thus, the hippocampus appears to be the key structure in the episodic system.

The amygdala is located in the MTL lobe near the hippocampus, and patient HM underwent resection to both structures. By virtue of its location, the amygdala was thought to have a role in the formation of declarative memories. However, the role of the amygdala has been found to be separate from the "medial temporal lobe memory system" that comprises the hippocampus and adjacent cortex (Zola-Morgan, Squire, & Amaral, 1986; Squire & Zola-Morgan, 1991). This structure plays a more specific role in processing emotional context. Evidence for this comes from numerous studies in normal individuals, where emotionally arousing stimuli are consistently remembered better than neutral stimuli (Heuer & Reisberg, 1990; Buchanan, Brechtel, Sollers, & Lovallo, 2001). In a recent fMRI study, Canli *et al.* showed that pictures rated as "extremely emotionally intense" led to increased amygdala activation on first exposure. In addition, these same authors reported better memory for the "extremely emotionally intense" compared to "less emotionally intense" rated pictures, indicating a role of the amygdala in the enhancement of memory by emotion (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000).

### 1.2.2.1. Subcortical Structures

Diencephalic lesions seen in Korsakoff's syndrome involve damage to the medial thalamus and often mammillary body. Press *et al.* (1989) reported that damage to these regions is sufficient to produce memory impairment even when the medial temporal regions are anatomically intact. However, these authors found the medial thalamic lesions to have a greater effect than the mammillary body lesions on declarative memory (Press, Amaral, & Squire, 1989). At present, it is unclear what specific aspect of the thalamic lesions account for this type of amnesia.

### 1.2.2.2. Frontal Structures (Inferior Frontal & Superior Frontal)

Lesions of frontal structures do not dramatically impair episodic memory, in contrast with damage to the medial temporal regions (Janowsky, Shimamura, Kritchevsky, & Squire, 1989; Millner, Corsi, & Leonard, 1991). This indicates that the frontal region is not necessary for episodic memory *per se* but helps in the processing of contextual information.

Studies in primates, where lesions are more precise, suggest that the prefrontal cortex can be divided into two main regions: the dorsolateral area (superior frontal) and the orbitofrontal area (inferior frontal) located on the medial and ventral surface of the brain. The superior frontal region is recruited when active manipulation or monitoring of information is required (Petrides, 1994). Evidence for this idea comes from recent study by Petrides (2000) reporting that lesioning the superior frontal region resulted in a mild impairment in the monitoring of information (Petrides, 2000). Similarly, functional neuroimaging studies have provided data showing

increased activity in the superior frontal region when information is monitored (Tremblay & Schultz, 2000). There is some controversy whether the superior frontal region is involved in the maintenance, e.g. the process of keeping information in mind (Cohen, Porjesz, Begleiter, & Wang, 1997; Cohen, Porjesz, Begleiter, & Wang, 1997) or in the manipulation, e.g. the reorganization of the information that is being maintained (D'Esposito, Ballard, Aguirre, & Zarahn, 1998; Smith & Jonides, 1999) processes during retrieval. One explanation for the disagreement may be that with more complex tasks, the more likely it is to involve manipulation, and manipulation of the information probably requires increased maintenance (Raye, Johnson, Mitchell, Reeder, & Greene, 2002).

Neuropsychological investigations of individuals presenting with inferior frontal brain damage implicate the orbital frontal cortex in episodic memory (Wallesch, Kornhuber, Kollner, Haas, & Hufnagl, 1983). Since the famous case of Phineas Gage, it has been known that lesions of the inferior frontal cortex produce dramatic changes of personality (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Patients with inferior frontal damage exhibit impulsive and disinhibited behaviors and fail to withstand interference from distraction. Recent work suggests that the inferior frontal region has a specific role in strategic control and/or inhibition of interfering information (Stuss et al., 1982; Fuster, 1980).

### 1.2.3 Semantic Memory: Association Areas

Around the mid-70's, data obtained in patients with focal cerebral lesions began to be analyzed within the theoretical framework of the semantic memory. This

was about the same time this subsystem was introduced by Tulving (1972). As mentioned previously, semantic memory is severely affected in disorders such as Alzheimer disease, herpes encephalitis and also semantic dementia. The first neuropsychological case study was applied by Warrington (1975) in dementia patients with Alzheimer's disease (Warrington, 1975) and shortly afterwards by others (Schwartz et al. 1980; Martin & Fedio, 1983).

#### 1.2.3.1. Posterior Cerebral Cortex: Temporal, Parietal Regions

Semantic memory is strongly language-based and describes memory for general knowledge of facts, concepts and words. Language-related areas in the human brain are located in the left hemisphere. The processing of language involves a complex network of interacting brain regions. "Aphasia" is the term used to describe an acquired loss of language function, and manifest itself as impaired expression, comprehension, or both. For example, a common manifestation of aphasia is when a patient cannot find the right word. Snowden *et al.* (1989) coined the term "semantic dementia", a progressive disorder in naming and word comprehension (semantic knowledge) (for review see Murre, Graham, Hodges, 2001). Imagery studies in patients with semantic dementia show severe atrophy of the inferior temporal lobe (Hodges, Patterson, Oxbury & Funnell, 1992; Snowden, Goulding & Neary, 1989). Along the same lines, other studies show that the type of aphasia identified in 1873 by Karl Wernicke also affects the understanding of semantic contents. In this type of aphasia there is damage to the left, superior temporal gyrus that extends

into the inferior parietal region (Coughan & Warrington, 1978; Basso et al. 1985).

Many similar examples can be derived from neurological disorders of apraxia, i.e. disorders of skilled movements and agnosia, i.e. inability to recognize or identify objects despite intact sensory function. Jakobson *et al* (1991) observed a patient, V.K., with damage to the posterior parietal lobe that exhibited a deficit in her ability in how to reach for objects but was able to recognize and name objects (Jakobson, Archibald, Carey, & Goodale, 1991). V.K. was unable to coordinate reaching and hand postures for different objects that could not be ascribed to either motor or visual deficits.

On the other hand, visual agnosia is characterized by the inability to recognize familiar objects (Farah, 1994) and is confined to the visual modality. Object recognition is the ability to place an object in a category of meaning. There are many subcategories of visual agnosia. Some patients lose their ability to recognize faces of friends and family members (Milner & Goodale, 1995) but are able to see and can recognize objects, while others retain only face recognition. In patients with facial agnosia, the anterior region of the temporal lobe (specifically the right fusiform gyrus) responsible for recognition and categorization of faces is damaged. Patients with this type of agnosia, referred to as prosopagnosia, often identify a person by other cues such as their voice, clothing, gait or their shape.

#### 1.2.3.2. Frontal Structures: Hemispheric Lateralization

Neuroimaging studies distinguish separate roles of the right and left frontal cortex during retrieval. One proposal is that the function of the left frontal cortex is

involved in semantic processing (Cabeza, Locantore, & Anderson, 2003; Poldrack et al., 1999) such as, the meaning of words. Others have shown that the function of the right frontal cortex is associated with monitoring during retrieval (Allan, Dolan, Fletcher, & Rugg, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Rugg, Fletcher, Chua, & Dolan, 1999). On the other hand, results from imaging studies using simple, memory retrieval tasks report a right frontal activation (Nolde et al., 1989) but more demanding tasks produce bilateral or left frontal activation (Rugg, Fletcher, Chua, & Dolan, 1999; Henson, Rugg, Shallice, Josephs, & Dolan, 1999). This is consistent with the idea that frontal activation reflects the degree of retrieval effort with increased activation when retrieval is difficult (Schacter, Alpert, Savage, Rauch, & Albert, 1996).

In summary, there is evidence for several dissociations that suggests a distinction between the various types of memory systems. It should be mentioned that the above examples do not comprise a comprehensive list of the disorders that give rise to amnesia since it is beyond the scope of this thesis. What they do conclude, however, is a dysfunction or damage in medial temporal/diencephalic circuitry (or in the frontal regions) produces amnesia with a selective deficit in declarative memory and sparing of procedural memory. On the other hand, lesions of the association areas appear to have a greater impact on semantic memory processes. In the same way that memory cannot be considered unitary, the spectrum of sleep stages in the human brain, and the processes that create and sustain sleep, appear equally diverse.

## Multiple Memory Systems

*Explicit, Implicit (Graf & Schacter, 1985)*

*Procedural, Declarative (Squire, 1987)*

*Episodic, Semantic (Tulving, 1972, 1983)*

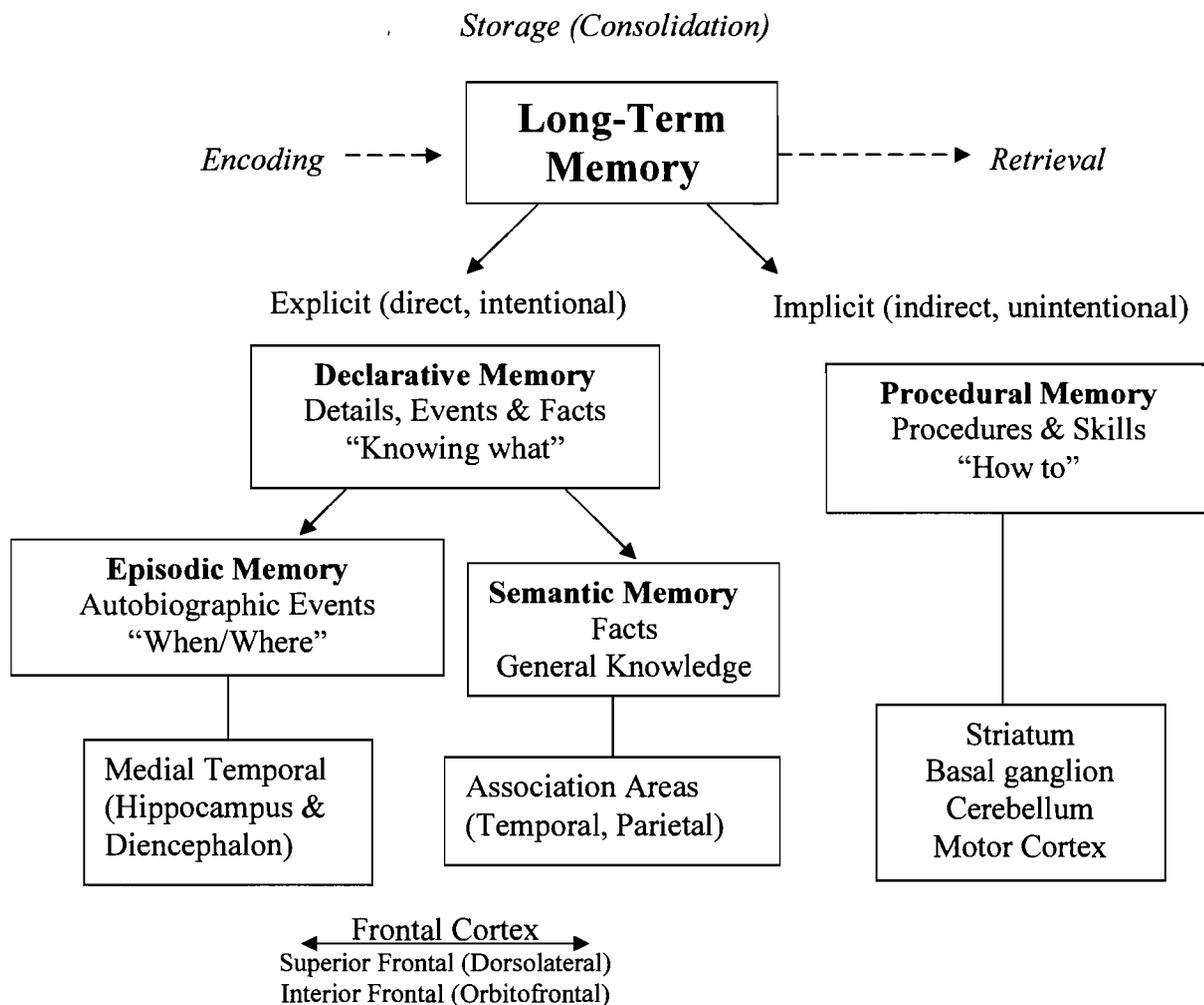


Figure 3. This figure shows the multiple memory systems associated with the brain regions and subcortical regions involved in long-term memory.

## **Chapter 2: NORMAL SLEEP: The Structure**

For centuries, sleep was defined as an inactive or passive behavioral state.

Prior to electroencephalography in 1929 by Hans Berger, it was impossible to demonstrate differences in the brain's electrical activity between sleep and wakefulness. Much of what is known today about brain activity during human sleep is due to the discovery of electroencephalography, a method by which electrical activity in the cortex can be recorded by scalp electrodes.

### **2.1. Electroencephalography, EEG**

The EEG displays fluctuations of electrical fields recorded at the scalp electrodes from neurotransmitter release and thalamocortical synapses. It is produced by the summation of transient excitatory (or depolarizing) and inhibitory (or hyperpolarizing) postsynaptic potentials in the pyramidal layer of the cortex (Lopes da Silva, Storm van Leeuwen, & Remond, 1986; Niedermeyer & Lopes da Silva, 1987). The brainwave patterns reflect voltage and time whereby the frequency, amplitude and waveform can be quantified. In addition to the EEG, sleep researchers also rely on electrophysiological muscle and eye potentials to determine sleep stages.

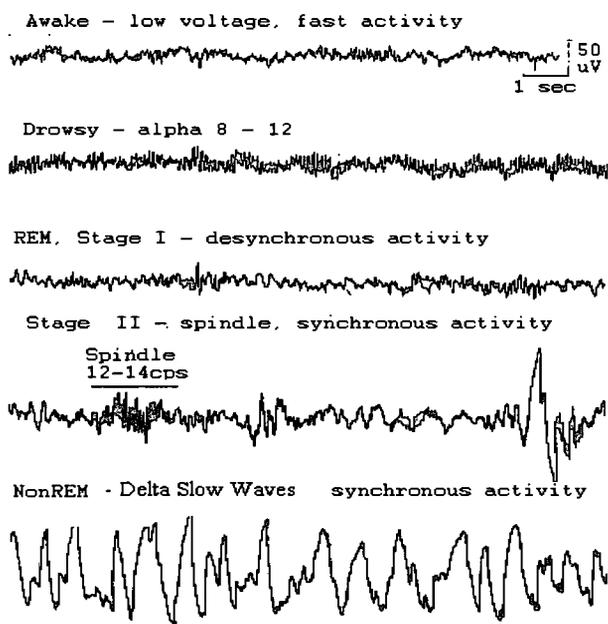
In 1937, sleep was classified into different stages (Loomis, Harvey, & Hobart, 1937). It was not, however, until the landmark 1953 discovery of REM sleep (Aserinsky & Kleitman, 1953), that sleep was considered as an active process. A few years later, it was discovered that REM sleep is associated with dreaming. Subsequently, the cyclic organization of sleep was described (Dement & Kleitman,

1957) and broadly defined as an alternation between distinctly different stages: Non-Rapid Eye Movement (NonREM) sleep and REM sleep.

## 2.2. Sleep Stages: NonREM & REM sleep

NonREM sleep consists of several stages of light sleep (Stages I, II) and deep, slow wave sleep, SWS (Stages III, IV) (Rechtschaffen & Kales, 1968). The EEG during NonREM sleep begins with a dominance of theta activity (4-8 Hz) in the early stages that progresses to synchronous intermittent spindling (12 to 14 Hz) to a predominance of high-voltage  $> .75 \mu\text{v}$ , low frequency Delta slow activity (.5-3 Hz) (Figure 4), which provide a neural substrate to cognitive activity during sleep.

### Human Sleep Stages



**Figure 4.** EEG Patterns associated with the stages of sleep in humans. [Adapted from Hauri, P & Orr, W. C (1982) *The Sleep Disorders, Current concepts*, UpJohn Company.]

A rapid, low-voltage desynchronous theta, atonia of postural muscles and bursts of rapid eye movements characterize REM sleep. The different EEG activity during NonREM and REM sleep stages suggests that the two stages are governed by two different networks, each possibly associated with different cognitive functions involved in consolidation of memory.

### 2.2.1. NonREM and REM Sleep Cycles

Sleep cycles show a periodicity of approximately 90 minutes in normal adults (see Figure 5). Overnight sleep often is divided into three time periods: the first third of the night, consisting of the highest percentage of deep NonREM sleep; the middle third of the night; and the last third of the night, the majority of which is made up of REM sleep. The cycle repeats itself 4 to 6 times during a normal nights sleep (Kleitman, 1939). Knowing this provides a useful approach to study the interaction between sleep and memory by taking advantage of the naturally occurring fluctuations in REM and NonREM sleep stages that will be discuss in later chapters.

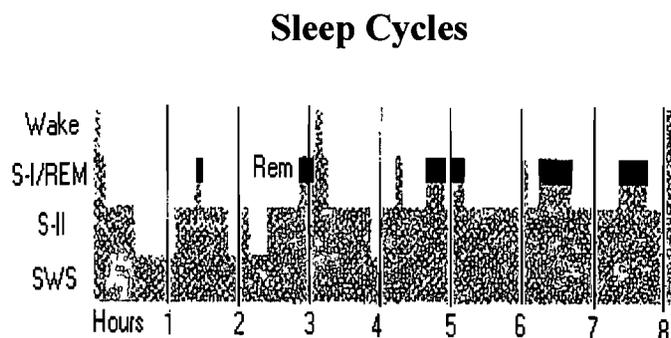


Figure 5. Example of the time course of sleep cycles across a night of normal sleep in adults. [Adapted from Hauri, P & Orr, W. C (1982) *The Sleep Disorders, Current concepts*, UpJohn Company.]

## 2.3 Neural Substrates & Pathways of Sleep & Wake

As mentioned above, the electrical activity at the surface of the scalp picked up by the EEG reflects the firing patterns in the thalamocortical system. These firing patterns differentiate between wakefulness, NonREM and REM sleep. The thalamic neurons have two distinct stages (e.g. transmission mode and burst mode), which will be discussed below along with the neurotransmitters and neurocircuitry involved in sleep and wake. It is beyond the scope of this thesis to review the numerous neurotransmitter and neuropeptide systems implicated in sleep other than the basic regulatory role of aminergic and cholinergic systems in wake, NonREM and REM sleep.

### 2.3.1 Wakefulness: Ascending Reticular Activating System

The first evidence of specific brain regions responsible for the maintenance of wakefulness was by von Economo (1923) in patients with encephalitis resulting in coma and subsequent death. He reported a loss of cells in the posterior mesencephalic reticular formation and posterior hypothalamus (von Economo, 1923). A later study by von Economo performed in rats, demonstrated that lesions to the preoptic basal forebrain caused insomnia (von Economo, 1930). Following this was the classic study by Moruzzi & Magoun (1949) who showed that electrical stimulation of the mesencephalic reticular formation of the brainstem produced arousal (Moruzzi & Magoun, 1949). The conclusion of these early studies was that the reticular formation in the rostral region of the brainstem and the ascending neuronal pathways were critical for maintaining wakefulness and arousal. Subsequently, this region and

its associated projections become known as the Ascending Reticular Activating System (Seigel, 2004).

There are two pathways implicated in arousal when the reticular formation is activated (Jones, 1990; Jones, 2000). One is the *dorsal pathway* that begins in the reticular formation projects to the thalamus, and then to the cortex. The second is the *ventral pathway* also beginning in the reticular formation but projects to hypothalamus, the basal ganglia and then to the basal forebrain region and cortex. The neurons then project to the hippocampus and to the cerebral cortex (Jones, 1993; Jones, 1990).

During wake the thalamic neurons are in a depolarized state, incoming excitatory potentials produce single action potentials, and this state is called *transmission mode*. In this mode, incoming excitatory postsynaptic potentials can sustain wakefulness. The thalamus is kept in the transmission mode by the action of acetylcholine from the rostral pons and basal forebrain. The cholinergic cells stimulate the sensory thalamic nucleus and inhibit the reticular nucleus. As a result, the thalamus lets all sensory information through, and the cortex is now highly active. The resulting EEG pattern that reflects this ongoing sensory stimuli is fast, low-voltage brain waves termed *desynchronized*.

### 2.3.2 NonREM Sleep

For NonREM sleep is to occur, there is decreased firing rate in the reticular formation cells (Lineberry & Siegel, 1971; Siegel & Lineberry, 1971) and the reticular nucleus of the thalamus inhibits the sensory nucleus with gamma-

aminobutyric acid (GABA) an inhibitory amino acid, thus reducing sensory input to the cortex (Table 1). It has been shown that GABA is released from the cerebral cortex in high concentrations during NonREM sleep (Nitz & Siegel, 1997). When the thalamic neurons are hyperpolarized, they respond to incoming depolarization with bursts of action potentials. Neurons in this state are in the *burst mode*, and produce a pattern of *synchronized* activity.

The generation of synchronous oscillations (e.g. sleep spindles or slow wave) depends on the degree of hyperpolarization of thalamocortical cells (Amzica & Steriade, 1998a; Amzica & Steriade, 1998b). Two factors account for the appearance of NonREM synchronous waveforms. The first consists of intrinsic properties that allow the thalamic cells to oscillate and synchronize the synaptic networks that include the reticular thalamic nucleus. The second is the dampening of the activity in the ascending cholinergic brainstem reticular projections that normally act to prevent or block these oscillations. As mentioned above, GABAergic projections from the reticular nuclei to sensory nuclei of the thalamus results in inhibition of thalamocortical projections, a process believed to mediate NonREM oscillations and synchronization. Thus, the NonREM synchronous waveforms (e.g. spindles, slow waves) depend on the reticular-thalamocortical-corticothalamic pathways.

In concordance with von Economo's early work (1930) demonstrating that forebrain lesions caused insomnia in rats, more recently it has been shown that there are sleep active-neurons of the ventrolateral preoptic nucleus (VLPO) that also contain GABA and galanin (Szymusiak, Alam, Steininger, & McGinty, 1998; Sherin, Shiromani, McCarley, & Saper, 1996). Neurons of the VLPO innervate multiple

Table 1. MECHANISMS OF WAKEFULNESS AND SLEEP:

|                 | WAKE  | NonREM  | REM   |
|-----------------|---|---|---|
| <b>CORTEX</b>   | Ach (+)<br>5-HT, NE (-) (+)<br>Histamine (+)                              | GABA (-)  | Ach (+)   |
| <b>Thalamus</b> | Sensory n. (+)<br>Reticular n. (-)<br>Transmission<br>EEG - desynchronous | Sensory n. (-)<br>Reticular n. (+)<br>Burst Mode<br>EEG - synchronous | Sensory n. (+)<br>Reticular n. (-)<br>Transmission<br>EEG - desynchronous |
| <b>VLPO</b>     |   | GABA &<br>Galanine (-)<br>↓<br>Histamine (+)                          |   |
| <b>TMN</b>      | Histamine (+)   | Histamine (+)   | Histamine (-)   |
| <b>BF</b>       | Ach (+)   |   | GABA (-)  |
| <b>Midbrain</b> |   |   |   |
| <b>RF</b>       | Glutamate (+)   |   |   |
| <b>PONS</b>     |   |   |   |
| <b>DRN</b>      | 5-HT(-)<br>NE(+)  |   | REM-OFF (-)   |
| <b>LC</b>       |   |   |   |
| <b>PPT/LDT</b>  | ACh (+)   |   | REM-ON (+)  |

Wake/Arousal: Ascending Arousal System of the reticular formation (RF) modulates the forebrain via neurotransmitters (Serotonin (5-HT) from Dorsal Raphe (DRN); nor epinephrine (NE) from locus coeruleus (LC) of the pons. Inhibitory (-); Excitatory or facilitation (+)

NonREM Sleep (GABAergic inhibition): Ventrolateral Preoptic area (VLPO) contains sleep-active neurons. VLPO neurons inhibit wake/arousal systems (e.g. tuberomammillary nucleus (TMN); LC; DR; pedunclopontine (PPT); lateral dorsal tegmentum (LDT) during sleep.

REM Sleep (cholinergic activated): Cholinergic (ACh) stimulation from PPT/LDT nuclei regulates REM sleep. PPT/LDT nuclei project to the thalamus (TH), basal forebrain (BF) and cortex.

arousal-promoting regions, e.g. locus coeruleus, LC, tuberomammillary nucleus (TMN), dorsal raphe, DR<sup>6</sup> (Sherin, Elmquist, Torrealba, & Saper, 1998) (Table 1). These sleep-active VLPO neurons may regulate sleep by inhibition of these arousal systems (Sherin, Elmquist, Torrealba, & Saper, 1998). Support of this idea comes from a study by Lu *et al* (2000) who has shown that lesioning VLPO neurons correlates with the loss of NonREM sleep (Lu, Greco, Shiromani, & Saper, 2000) .

### 2.3.3 REM Sleep

In the early 60s, transection studies performed in cats by Jouvet established the critical structures for the generation of REM sleep located within the pontine regions (Jouvet, 1962; Jouvet, 1963; Jouvet, 1965). Following this work, others were able to further establish that the critical areas for REM sleep generations were within the lateral portion of the pontine tegmentum.

During REM sleep the thalamic neurons are in a depolarized state and excitatory potentials produce single action potentials referred to as *transmission mode*. Although the desynchronous activity is similar in wake and REM sleep, during REM sleep it is derived from cholinergic input to the thalamic-cortical circuitry (Table 1, above). REM sleep is mediated by mesencephalic and pontine cholinergic neurons. As REM sleep initiates, norepinephrine from the LC and serotonergic raphe neurons become inactive. Projections from the lateral dorsal tegmental (LDT) and pedunculopontine (PPT) regions to the thalamus, basal forebrain and cortex produce

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<sup>6</sup> Initially it was suggested that 5-HT raphe nuclei increased sleep, however, recently it has been suggested that these 5-HT neurons of the dorsal raphe have wake-promoting properties.

the characteristic EEG desynchronization of REM sleep (Semba & Fibiger, 1992) (Table 1, above).

#### 2.3.4. Reciprocal Interaction Model

One early model explaining the NonREM-REM sleep cycling hypothesizes that REM sleep is the result from activity in the medial pontine reticular formation using acetylcholine (ACh) as the neurotransmitter (REM-On cells) and/or a decrease in the activity in the DR nuclei and LC using serotonin (5-HT) and norepinephrine, respectively (REM-Off cells) (Hobson & McCarley, 1977; McCarley & Hobson, 1975; Rye, 1997; Hobson, McCarley, & Wyzinski, 1975).

This early model of Hobson & McCarley has been altered and extended. More recently, it has been shown that the principal sources of subcortical ACh are the PPT and LDT nuclei, not the medial pontine reticular formation. The release of 5-HT from the DR nuclei in turns controls the PPT cells by hyperpolarizing them during wake. During REM sleep when the dorsal raphe cells do not fire, the inhibition is lifted and ACh is released (Siegel, 2000; Rye, 1997). Once REM sleep is turned on, aminergic REM Off- cells will reinstate their activity up to a threshold beyond which they can inhibit cholinergic REM On-cells activity again (i.e. after 90-minutes).

#### 2.4 Neuroimagery Studies *during* Sleep

In recent years, the relationship between sleep and memory processes has benefited from a variety of imagery studies. Neuroimaging techniques have revealed distinct regional patterns of neuronal activity during different stages, i.e. wakefulness, NonREM and REM sleep (Maquet, 2004; Maquet et al., 2000; Maquet et al., 1997;

Maquet et al., 2003; Nofzinger, 2005; Nofzinger et al., 2002; Braun et al., 1997; Braun et al., 1998) which is discussed below.

#### 2.4.1 NonREM Sleep

The process of falling asleep compared to wake is characterized by relative decreases in metabolism in the brainstem, forebrain and the fronto-parieto-temporal association areas (Nofzinger et al., 2002; Nofzinger, 2005). During NonREM sleep, studies using imaging techniques demonstrate reductions in the association areas (Braun et al., 1997) as well as the thalamus relative to waking (Maquet et al., 1997). Regional deactivation during NonREM sleep is also seen in the pons, mesencephalon, orbito-frontal/inferior frontal cortex and MTLlobe (Braun et al., 1997; Maquet et al., 1997). This decline in cerebral activation during NonREM sleep is thought to reflect the progressive deactivation of the reticular activating system as well as the GABAergic inhibition by thalamic neurons which accompanies the progressive deepening of this sleep stage (Steriade, 1997; Steriade, 1999).

#### 2.4.2 REM sleep

Compared to wake, REM sleep imaging studies indicate activation of the limbic and paralimbic regions (e.g. basal ganglion, anterior cingulate, medial prefrontal cortex) (Braun et al., 1998; Nofzinger, 2005) with simultaneous deactivation of the orbital/inferior frontal and dorsolateral/superior frontal cortex (Braun et al., 1998). During REM compared to NonREM sleep, Braun *et al.* (1997) also noted relative activation in the limbic, medial prefrontal and inferior temporal cortices along with decreases in frontoparietal association cortices. Figure 6 summarizes the neuroimaging data for NonREM and REM sleep.

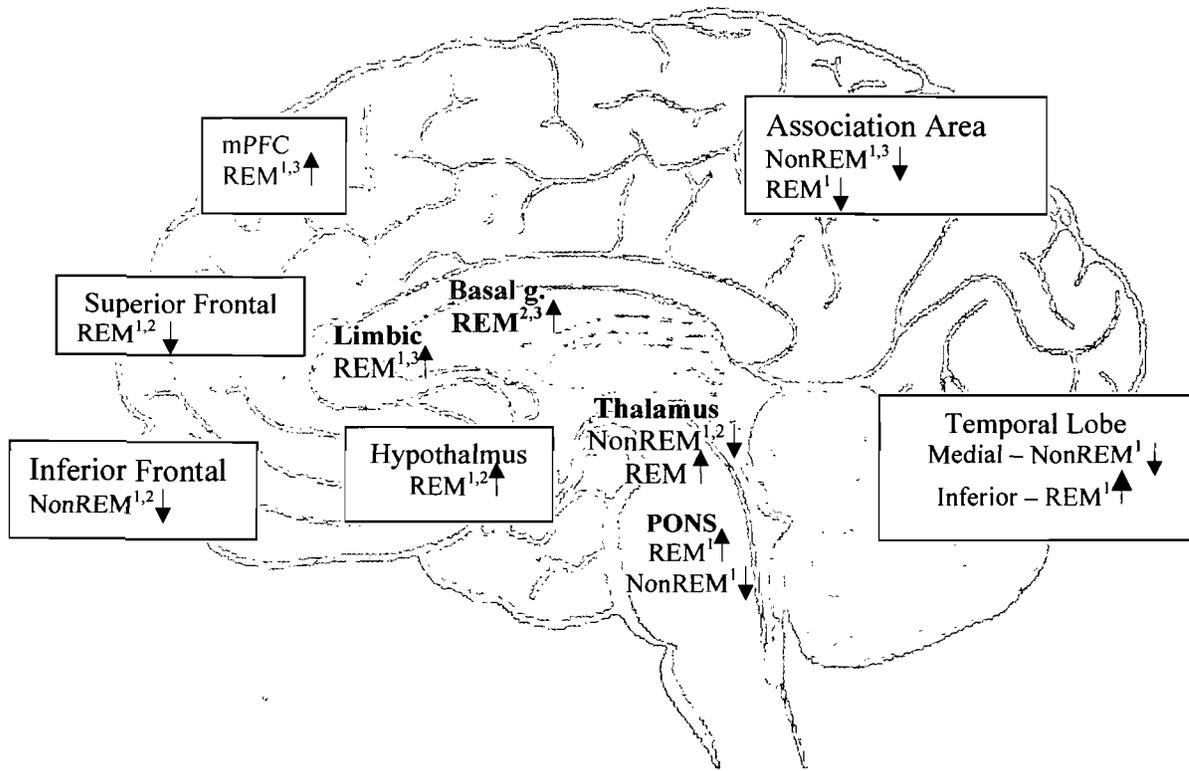


Figure 6: A schematic sagittal view of convergent findings in relative regional brain activation and deactivation. REM compared to NonREM (red). REM and NonREM compared to Waking (black) (<sup>1</sup>Braum et al., 1997, 1998; <sup>2</sup>Maquet et al., 1997; <sup>3</sup>Nofzinger, 2005).

Taken from above, diverse changes in cerebral neurochemistry electrophysiology and functional neuroanatomy are connected with NonREM and REM sleep stages, making them dissociable from one another (Hobson & Pace-Schott, 2002). Additionally, these sleep stages are distinct from the waking brain. Thus, sleep similar to memory cannot be treated as a homogeneous state. Instead, each sleep stage possesses a set of mechanisms and processes that may contribute uniquely to memory consolidation. Likewise, different classes of memory formation appear to be processed by distinct memory systems (Cohen & Squire, 1980; Gabrieli, Brewer, & Poldrack, 1998).

There has been much progress concerning our understanding of the the mechanisms of sleep but this tells us nothing about the actual function. The above imagery studies have reported changes during sleep in many of the brain regions involved in memory suggesting that sleep is somehow involved.

### **Chapter 3: STUDIES INVESTIGATING SLEEP & MEMORY**

There is strong evidence in both humans and animals to support the hypothesis that sleep plays an important role in the consolidation of memory (Peigneux, Laureys, Delbeuck, & Maquet, 2001; Smith, 2001; Stickgold, Hobson, Fosse, & Fosse, 2001; Stickgold & Walker, 2005; Walker & Stickgold, 2006). A variety of studies using different approaches and methodologies has shown the existence of a relationship between sleep and memory. One approach exposes the subjects to a learning task, and then measures the impact on sleep the following night. Another approach looks at the effect sleep deprivation has on learning and behavioral performance. Some researchers study the interaction between sleep and memory using imaging techniques and electrophysiological techniques.

#### **3.1 Learning Dependent Modification on Sleep**

The idea that a specific sleep stage should be modified by prior exposure to learning material is based on the premise that increased learning will require increased off-line processing/consolidation and thus more time spent in a specific sleep stage. Sleep and learning studies in animals using a variety of protocols and test paradigms have demonstrated increase in the percentage of REM sleep (Fishbein, Kastaniotis, & Chattman, 1974; Hennevin, Hars, Maho, & Bloch, 1995; Smith & Rose, 1997; Datta, 2000) or the number of REM sleep periods after training (Hennevin and Leconte, 1977). A review by Horne & McGrath (1984) highlights that in some of these early animal studies, the increase in REM sleep duration may have been due to increases in total sleep time (Horne & McGrath, 1984).

Previous studies in humans involving the effects of learning on sleep have focused primarily on REM sleep (Smith, 1996). Those early studies that trained subjects on a variety of tasks and subsequently recorded the changes in the sleep, showed evidence that REM sleep is important in learning. Intensive language learning (De Koninck J., Lorrain, Christ, Proulx, & Coulombe, 1989), learning Morse code (Mandai, Guerrien, Sockeel, Dujardin, & Leconte, 1989) and academic course work (Smith & Lapp, 1991) all have been reported to increase aspects of REM sleep; such as, REM sleep percentage or the number of rapid eye movements.

In the late 70s several researchers reported that REM sleep may not be important for declarative memory (Smith, 2001). However, this would exclude REM sleep from having any type of role in the learning of language or course work since these are declarative memory tasks and makes the above results difficult to reconcile. Studies on the role of REM sleep on a procedural memory task using prism glasses, where the subjects must relearn their visual perception and motor procedures have showed mixed results. Initially, there were reported increases in REM sleep on such tasks (De Koninck & Prevost, 1991; Zimmerman, Stoyva, & Metcalf, 1970). Later, others were not able to replicate the results when controlling for confounding factors (Allen, Oswald, Lewis, & Tagney, 1972; Horne & McGrath, 1984; Zimmerman, Stoyva, & Reite, 1978). It may be that the tasks are not purely procedural, and require both NonREM and REM sleep stages for processing.

Research assessing the role of NonREM sleep in learning is less clear and few in number (Siegel, 2001), yet there have been reports of increases in deep NonREM sleep secondary to REM deprivation (Hennevin, Hars, & Maho, 1995). More

recently, light NonREM sleep has also been reported to be important for consolidation of certain kinds of procedural tasks (Gais, Molle, Helms, & Born, 2002; Fogel & Smith, 2006; Schabus et al., 2006) and increased theta activity during REM sleep have been reported in tasks of declarative memory (Fogel, Smith & Cote, 2007). This suggests that both sleep stages may be important in memory consolidation (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Ambrosini & Giuditta, 2001; Giuditta et al., 1995).

Lastly, in intensive learning situations changes in EEG spindle activity during NonREM sleep have been shown to be important. Researchers have reported increases in spindle density following the learning in a variety of declarative and procedural tasks (Fogel & Smith, 2006; Fogel, Smith & Cote, 2007; Clemens, Fabo, & Halasz, 2005; Gais, Molle, Helms, & Born, 2002). A recent study by Gais *et al.* (2002) looked at the changes in EEG activity during nocturnal sleep after training on a declarative learning task. These authors reported that the density of sleep spindles was significantly higher after a declarative learning task but not after the non-learning control task. Furthermore, recall performance was correlated with spindle density, indicating that spindle activity during NonREM sleep is sensitive to acquisition of information or previous learning experiences (Gais, Molle, Helms, & Born, 2002). Along the same lines, Clemens, Fabo & Halasz (2005, 2006) have demonstrated that the number of automatically detected sleep spindles in left fronto-central regions is correlated with recall of verbal material, while sleep spindles in centro-parietal regions are correlated with visual spatial memory performance. Another study reported an increase in spindle density following learning in a procedural task (Fogel

& Smith, 2006). Specifically, they found that motor skills learning increased the duration of light Stage II sleep, spindle density (spindles/minute), and that the increase in the number of spindles was correlated with performance improvement. Alternatively, sleep spindle activity has also been related to attentional processes. Forest *et al* (2005) reported a negative correlation between reaction time on a selective attention task and NonREM spindle density (Forest & Godbout, 2005). When attention was low, the subject used controlled processes, which require greater effort. In contrast, with high levels of attention, there was a shift from controlled processes to automatic processes, i.e. quick, effortless processing. These authors proposed the idea that sleep spindle activity is associated with automatic attentional processing.

One hypothesis to these results is that spindle activity occurring in NonREM, may play a role in sleep-dependent plasticity and memory processing (Sejnowski & Destexhe, 2000; Steriade & Timofeev, 1997; Steriade, 1999). NonREM sleep oscillations (i.e. slow waves, spindles) may be related to a stage during which newly acquired information, which are temporarily stored in the hippocampus, are later transferred to the neocortex for integration into memory (Buzsaki, 1998; Sutherland & McNaughton, 2000; Hasselmo, 1999).

### 3.2 Neuroimaging Studies involving Sleep & Memory

A recent imaging study investigated in how consolidation affects the neural correlates of memory retrieval over short and long retention periods (Takashima *et al.*, 2006). The results indicated that the pattern of brain activation was dramatically

different at the different retention intervals. For example, recognition of previously study items was associated with hippocampal activation at 1-2 day intervals; whereas, longer retention delays were associated with activation of medial prefrontal cortex. Furthermore, the duration of NonREM sleep one day after learning positively correlated with recognition memory performance on subsequent testing, indicating that sleep-dependent processes may play a role in memory. Another neuroimaging study, using a spatial episodic memory task, revealed that hippocampal areas activated during route learning were reactivated during subsequent NonREM sleep (Peigneux et al., 2004). In addition, the hippocampal re-activation was positively correlated with improved retrieval performance the following day. Taken together this indicates that sleep plays a role in memory replay and consolidation, and that the neural circuits supporting recognition memories undergo synaptic re-organization over time.

Evidence supporting a role of REM sleep in memory comes from functional imagery studies showing that brain areas (e.g. bilateral cuneus, left supplementary motor areas) involved in the learning of procedural skills (serial reaction time task<sup>7</sup>) are reactivated during subsequent REM sleep (Maquet et al., 2000) but not during NonREM sleep. Subsequently, these same authors looked at the functional connectivity of the reactive areas (Laureys et al., 2001). They reported a larger correlation between that the left posterior parietal regions and bilateral supplementary

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<sup>7</sup> Serial Reaction Time task (SRT) is a procedural skills task involving sequence learning through repetitions. A target appears on 1 of 4 locations on a computer screen and the subjects task is to indicate as quickly as possible the spatially matched location of the target.

motor area during REM sleep in the trained subjects compared to the untrained subjects on a serial reaction task.

Other functional studies have shown that medial temporal activation and transient rhinal-hippocampal interactions are associated with successful formation of declarative memory (Fell et al., 2001, 2003). The rhinal cortex is the major interface between the hippocampus and the neocortex. As mentioned above, consolidation is associated with replay and the transfer of information from the MTL to the neocortex during sleep, more specifically REM sleep. There have been reports that differences in rhinal-hippocampal and intrahippocampal connectivity is associated with the ability to recall dreams during REM sleep and determines successful formation of declarative memories (Fell, et al., 2007).

Recent findings challenge the idea that memory consolidation or the transfer to the neocortex occurs only during sleep. Functional investigations have shown that memory consolidation originally thought to occur during sleep may also occur during wake in some memory tasks (Peigneux et al., 2006; Axmacher et al., 2007).

One approach to determine the role of sleep in learning and memory has been to use different types of sleep deprivation techniques. Several different types of sleep deprivation techniques are used experimentally to investigate the effects of sleep loss on memory processes and behavioral performance. Two types of sleep deprivation paradigms will be covered: total sleep deprivation and selective sleep deprivation. Both of these methods have brought to light the importance of sleep on memory consolidation (Sutherland & McNaughton, 2000; Smith, 2001).

### 3.3 Sleep Deprivation Experiments

#### 3.3.1. Total Sleep Deprivation (TSD)

In the late 1800s, Patrick and Gilbert (1896) published the first sleep deprivation study in humans. In their study, subjects remained awake for 90 hours and were subsequently submitted to a variety of physiological and psychological tests. They reported decreases in sensory acuity, reaction times, temperature and memorizing ability. At the end of the deprivation experiment, 12 hours of sleep completely restored all of the functions to baseline levels (Patrick & Gilbert, 1896).

##### 3.3.1.1. General Effect on Cognition

Much of the early research on the effects of sleep deprivation on learning shows many inconsistencies that may depend on the number of hours of sleep loss, the specific task (Colrain & Campbell, 2007) and/or testing procedures utilized. In fact, short, simple tasks are relatively unaffected by total sleep deprivation (Dinges & Kribbs, 1991), whereas interesting complex tasks are more vulnerable and require shorter periods of sleep loss to show performance decrements (Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Angus, Heslegrave, & Myles, 1985). The effects of sleep deprivation may reflect failure to maintain sustained attention (vigilance) or momentary performance lapses (Dinges & Kribbs, 1991) leading to increased variability in RTs in longer and/or uninteresting tasks.

More recent studies in the literature indicate that cognitive behavioral performance is adversely affected under conditions of sleep deprivation (Horne, 1978; Horne, 1985; McCarthy & Waters, 1997; Killgore, Balkin, & Wesensten, 2006;

Dinges et al., 1991). Consistently, sleep deprivation produces impairment of attention (Drummond, Gillin, & Brown, 2001; Drummond et al., 2005; Durmer & Dinges, 2005). In addition, TSD results in a variety of impairments in higher order cognitive processing; for example, cognitive inflexibility, impaired decision making, impaired temporal memory (Harrison & Horne, 2000; Harrison & Horne, 2000), decreased divergent thinking (Horne, 1988; Wimmer, Hoffmann, Bonato, & Moffitt, 1992), deficient error detection (Nilsson et al., 2005) and the inability to inhibit a response (Drummond & Brown, 2001; Drummond, Paulus, & Tapert, 2006). These complex cognitive processes often referred to as 'executive functions' largely rely on the prefrontal cortex (Harrison & Horne, 2000).

#### 3.3.1.2 TSD *Before* Learning (encoding) Studies

The effect of TSD before learning depends on the specific type of learning task and memory testing procedure utilized. Several investigators have reported memory deficits with one night of TSD when employing nonsense syllables, pairs of letters or digits (Idzikowski, 1984; Polzella, 1975), memory for stories (Blagrove, Cole-Morgan, & Lambe, 1994) and an arithmetic task of working memory (Drummond et al., 1999). Williams *et al.* (1966) found that recognition memory for faces presented after 24 hours of sleep deprivation was significantly impaired (Williams, Giesecking, & Lubin, 1966). Of interest is a more recent study reporting that subjects deprived of sleep remembered the previously presented faces, but they had difficulty remembering in which of two sets of photos the faces had appeared

(Harrison & Horne, 2000). This study suggests that TSD affects more the contextual organization of memory than the trace of information itself.

On the other hand, Hu *et al* (2006) investigated the impact of 36 hours of sleep deprivation on declarative memory encoding of emotional and non-emotional picture stimuli (Hu, Stylos-Allan, & Walker, 2006). Subjects were sleep deprived or allowed to sleep before learning sets of negative, positive, and neutral stimuli. Twelve hours later, the subjects performed a recognition test. Overall, the sleep-deprived subjects exhibited a 40% reduction in retention relative to subjects who had slept. When these data were separated into three emotional categories (positive, negative, or neutral), the magnitude of the effect differed across the categories. There was severe disruption of retention for neutral and positive emotional memory in the sleep-deprived group. Within the sleep control group, both positive and negative stimuli were associated with superior retention compared to the neutral condition. This concurs with the idea that emotional stimuli facilitate memory encoding (Phelps, 2004).

Animal studies reported no effect of TSD *before* learning either on encoding of information or retrieval processes (Smith, 1985). This is inconsistent with other studies showing that sleep deprivation can disrupt learning for tasks that require hippocampal involvement (Smith, 1985; Guan, Peng, & Fang, 2004). Recently, it was demonstrated that selective REM deprivation prior to training is sufficient to impair encoding on a task of spatial memory (Beaulieu & Godbout, 2000). These authors reported that with increasing task complexity, there was increased frontal

cortex involvement. This indicates that with increasing complexity, spatial learning requires additional frontal lobe involvement.

#### 3.3.1.3. TSD *After* Learning

More relevant to this proposal are studies investigating memory consolidation processes when TSD *follows* learning of a task. According to the consolidation hypothesis, the memory trace stays in a fragile state until exposure of a subsequent sleep period occurs. In humans, TSD after learning has been shown to interfere with recognition memory (Nesca & Koulack, 1994; Idzikowski, 1984). However, the exact role that sleep and sleep loss play in memory consolidation and on which cognitive processes they act remains unclear (Nesca & Koulack, 1994; Idzikowski, 1984; Rotenberg, 1992). Similarly, studies in animals has shown that sleep deprivation *following* task acquisition can result in impairments at later testing (Smith & Kelly, 1988; Smith & Lapp, 1986).

TSD induces nonspecific disturbances in sleep patterns that could affect behavioral performance and mask any real effects of the technique (Horne & McGrath, 1984). Further, the acquisition of information preceding or following deprivation is a matter of lower vigilance (fatigue) that subsequently affects memory performance during recognition. This makes it difficult to know to what extent these impairments in memory are due to either learning (encoding) or retrieval processes.

#### 3.3.1.4. Neuroimaging Studies during and after TSD

Neuroimaging studies using functional magnetic resonance imaging, fMRI have shown changes in cerebral activation occurring as a function of sleep

deprivation, and that these changes are associated with changes in performance (Drummond et al., 1999; Drummond et al., 2000; Drummond & Brown, 2001). Using fMRI, Drummond *et al.* (1999) scanned the brains of sleep-deprived and rested participants while performing an arithmetic task. They observed bilateral activation of the prefrontal cortex, parietal regions and motor areas following a night of sleep. After sleep deprivation, participants not only performed worse on this, but the fMRI scan confirmed a decrease in activity in all of these regions, particularly in the PFC after TSD. In contrast, when testing verbal learning performance in participants who underwent 35 hours of TSD compared to rested controls, the inverse was found i.e. increase in the parietal region and enhanced activity in the prefrontal cortex, and, greater activation of the bilateral parietal lobe was associated with better task performance (Drummond & Brown, 2001). As to why sleep deprivation resulted in an increased activity in certain regions when confronted with verbal exercises, but in general shows less activity when confronted with arithmetic problems, is not entirely clear. These authors interpreted their findings as compensatory changes in other brain areas not typically used in performing such a task that attempts to take over cognitive functions (Drummond & Brown, 2001; Drummond, Meloy, Yanagi, Orff, & Brown, 2005). As mentioned earlier, other researchers (Harrison & Horne, 1999; Harrison & Horne, 2000; Harrison & Horne, 2000) have reported problems associated with the frontal cortex in sleep-deprived subjects. In addition, there are similar impairments in remembering contextual information in patients with frontal lobe lesions indicating a possible role of the frontal cortex (Millner et al., 1991; Shimamura & Squire, 1987).

### 3.3.2. Selective Sleep Deprivation

Ekstrand *et al.* were the first to use a selective sleep stage deprivation contrast paradigm where four-hour periods of undisturbed sleep covering either the first or the second half of the night was used (Barrett & Ekstrand, 1972; Ekstrand, 1967; Ekstrand, 1977; Fowler, Sullivan, & Ekstrand, 1973; Yaroush, Sullivan, & Ekstrand, 1971). The advantage of such a paradigm is that it allows for the dissociation of the effects of NonREM sleep and REM sleep because the first half of the night is characterized by a high percentage of slow waves, whereas REM sleep prevails in the second half.

Many studies have shown robust support for REM or late sleep on procedural memory and priming (Smith & Rose, 1997; Smith, 2001; Gais, Plihal, Wagner, & Born, 2000; Plihal & Born, 1999; Walker *et al.*, 2003; Walker & Stickgold, 2004; Plihal & Born, 1997). On the other hand, deprivation of early SWS has been shown to be more deleterious than REM sleep deprivation for tasks involving episodic memory (Ekstrand, 1967; Fowler, Sullivan, & Ekstrand, 1973; Yaroush, Sullivan, & Ekstrand, 1971; Gais, Lucas, & Born, 2006; Drosopoulos, Wagner, & Born, 2005) but does not affect procedural memory, (Plihal *et al.*, 1997). This is in contrast to other researchers who reported no effect of SWS deprivation on episodic memory (Ekstrand, 1977; Ekstrand, Sullivan, Parker, & West, 1971; Smith, 1995). Similarly, Tilley & Empson (1978) showed that episodic memory tasks (e.g. paired association) were not vulnerable to REM sleep deprivation, but REM deprivation does have an impact on episodic tasks involving more complex material, unrelated word pairs and nonverbal,

emotional stimuli (Tilley & Empson, 1978; Empson & Clarke, 1970; Wagner, Fischer, & Born, 2002; Wagner, Gais, & Born, 2001).

The relationship between sleep and memory is complicated; it varies with different types of memory (i.e. episodic, semantic, procedural), task complexity and different sleep stages (Peigneux, Laureys, Delbeuck, & Maquet, 2001) (Table 2). What is clear from the above research is that there are substantial differences between NonREM and REM sleep and, it is likely that each sleep stage contributes in a differential manner to memory processing.

Table 2. Summary Table: Relationship among Memory Systems, Sleep Studies & NonREM (light Stage II, deep SWS) and REM Sleep Stages.

| <b>MEMORY SYSTEM</b>   | <b>REM SLEEP</b>   | <b>NonREM SLEEP</b>  |
|--|--|--|
| Procedural Memory<br><br><i>Visual discrimination</i><br><br><i>Motor skills</i> | Gais et al., 2000<br>Karni et al., 1995<br>Stickgold et al., 2000<br><br>Plihal & Born, 1997<br>Fischer et al., 2002<br>Maquet et al., 2000<br>Laurey et al., 2000   | <u><i>SWS, Deep Sleep</i></u><br>Gais et al., 2000<br>Stickgold et al., 2000<br><br><u><i>S-II Light Sleep</i></u><br>Fogel et al., 2001; 07<br>Smith & McNeil, 1994<br>Walker et al., 2002 ;03  |
| Episodic Memory  | <u><i>Emotional Material</i></u><br>Wagner et al., 2001<br><br><u><i>Unrelated words</i></u><br>Gais et al., 2002<br>Fogel, Smith & Cote, 2007<br><br><u><i>Difficult Tasks</i></u><br>Empson & Clark, 1970<br>Tilley & Empson, 1978<br>Tilley, 1981 | <u><i>SWS, Deep Sleep</i></u><br>Barrett & Ekstrand, 1972<br>Born et al., 2006<br>Dosopoulos et al., 2005 ; 07<br>Ekstrand et al., 1977<br>Fowler et al., 1973<br>Gais & Born, 2004<br>Gais et al., 2002; 06<br>Huber et al., 2004<br>Lee & Wilson, 2002<br>Peigneux et al., 2004<br>Plihal & Born, 1997; 99<br>Yaroush et al., 1971 |
| Semantic Memory<br>or<br>Priming   | ?DeKornick et al., 1989<br>?Mandai et al., 1998<br>Plihal & Born, 1999<br>Stickgold et al., 1999<br>Wagner et al., 2002  |  |

Both NonREM sleep and REM sleep may be needed when tasks are more complex or involve semantic aspects. It may be that the effects of sleep on memory depend on the temporal sequence of NonREM sleep and REM sleep phases. Currently, we lack a comprehensive understanding of the respective role of NonREM and REM sleep stages in memory processing and consolidation (Smith, 2001). There

are still many questions in this area of the effects of sleep on memory, including the exact nature of memory deficits involved and the mechanism(s) underlying the deficits or resilience of some but not all of these processes.

### 3.4. The Functions of Sleep in Memory

Many theories have been put forth in hopes to elucidate the possible connections between sleep, learning and memory. Below is a discussion of general theories under the umbrella of neuronal plasticity. It is not meant to be an exhaustive list and only theories relevant to this thesis are discussed.

Sleep varies and undergoes changes across lifespan. In infants approximately 50% of the time spent sleeping consists of REM sleep and this percentage decreases with age. The increase in REM during developmental periods is thought to provide evidence that synaptic circuits are modified during sleep. This led Roffwarg *et al.* (1966) to suggest that the function of REM sleep during development might be to provide the developing brain with endogenous stimulation (Roffwarg, Muzio, & Dement, 1966). Of interest, is a theory by Crick & Mitchison that also utilizes the idea of neuronal plasticity, but suggests the opposite. They posit that the oscillating depolarization and hyperpolarizations in the brain induce reverse learning in order to remove redundant or excess synapses (Crick & Mitchison, 1995). Furthermore, that the purpose of REM sleep is to fine tune and clear up the system by means of random neuronal firings that eliminate spurious connections, and thus consolidating 'real' memories. An obvious problem with Crick & Mitchison's theory is that directly testing it is difficult. Nevertheless, many of the ideas they proposed have been

influential in formulating current theories about sleep, learning and memory; such as, the idea that sleep is an opportune time for memories to be strengthened.

Muller and Pilzecker (1900) were the first to suggest that sleep consolidates memories (McGaugh, 2000). In a now classical study, Jenkins & Dallenbach (1924) compared the rate of forgetting during sleep and wake in order to determine failures in memory (Jenkins & Dallenbach, 1924). The subjects learned a list of nonsense syllables and then were asked to recall the list at four intervals (1, 2, 4, and 8 hrs) of sleep or daytime waking activity. Figure 7 shows that during the wake condition there was a steady decline, however, recall for the first two hours in the sleep condition decreased and then stabilized in the middle and later parts of the night. They interpreted their results in terms of Interference theory (McGeoch, 1935) that is the processing of other items that interferes with the processing of the relevant

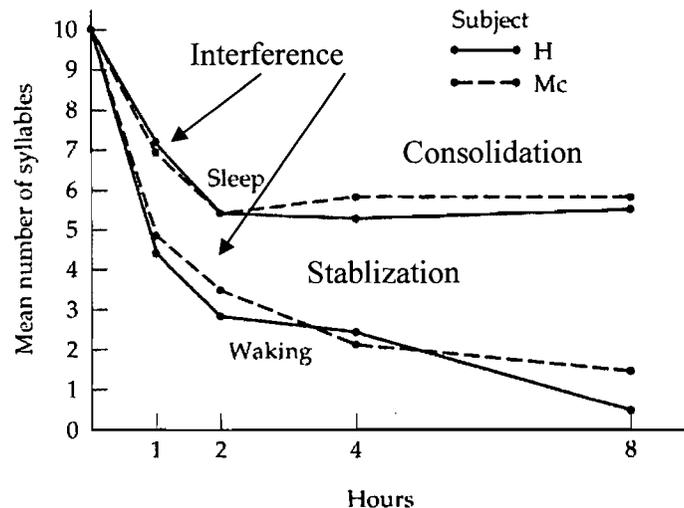


Figure 7. Number of items recalled as a function of hours awake and sleep. (Adapted from Jenkins & Dallenbach, 1924).

information (Keppel & Underwood, 1962). However, Interference theory is unable to explain why forgetting progresses normally during the first few hours and then stops

or stabilizes after sleep. One explanation for the higher recall levels after sleep versus wake, is consolidation theory, i.e. the processing of memory traces during which the labile trace is reactivated, analyzed and gradually incorporated into LTM (McGaugh, 2000; Sutherland & McNaughton, 2000).

Initially, consolidation theory assumed that new memories are initially fragile and sensitive to disruption before undergoing a series of neural plastic changes that result in a stronger and more stable trace. Furthermore, that memory consolidates only once and with time becomes stronger and more stable. Nearly 55 years after, consolidation and the role of sleep has evolved. The reconsolidation hypothesis implies that every time a memory is reactivated it must again undergo the consolidation process (Stickgold & Walker, 2005; Walker, Brakefield, Hobson, & Stickgold, 2003; Walker et al., 2006). This is in stark contrast with the classical view that a memory consolidates only once and over time it becomes stronger. The reconsolidation hypothesis posits at least two specific forms of consolidation one of stabilization and the other re-consolidation (i.e. enhancement). In the first stage, stabilization appears to take up to 4 to 6 hours. During this period, the memory seems particularly fragile. The second stage of memory processing is consolidation that occurs *during* sleep. This type of consolidation after a night of sleep has been found to improve the subject's performance the following day. Finally, a later retrieval process referred to as reconsolidation when the information is re-activated at retrieval. This third stage is re-accessing the memory to be edited. Re-consolidation would occur repeatedly every time the memory representation is activated, suggesting that

retrieval is a dynamic process during which new information modifies the original representation.

### 3.5. Theoretical Models: Dual vs. Sequential Hypotheses of Sleep Stages

Several studies investigating the role of sleep in memory have provided arguments in favor of two theoretical frameworks. Some have suggested a dual-process whereby early NonREM sleep is mainly involved in processing of declarative types of memories (Smith, 1995; Plihal et al., 1997; Gais, Plihal, Wagner, & Born, 2000) and late REM sleep facilitates procedural or nondeclarative memories (Plihal et al., 1997). Procedural skills memory improvements in performance has been reported to be related to time spent in REM sleep (Fischer et al., 2002) or in late Stage II, NonREM sleep (Walker et al., 2002), which support this idea.

Giuditta *et al.* (1995) and subsequently Stickgold *et al.* (2000) propose the sequential hypothesis or serial processing of the sleep (Giuditta et al., 1995; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). In this theoretical model it is suggested that orderly succession of sleep stages are needed whereby first NonREM sleep and then REM is essential for data processing during the sleep. Accordingly, NonREM sleep would be first stage of data processing. During NonREM sleep it is suggested that there is elimination of useless or superfluous memory traces and/or a strengthening of those that are relevant and adapted (process of discrimination). Subsequently, the memory traces would then pass to a second stage during REM sleep. During this sleep stage the memory trace is stored in the neuronal circuit, i.e. consolidation process. Thus, the disruption or removal of one or the other sleep

stage, would significantly alter memory performance by breaking the natural NonREM-REM cycle sequence. Accordingly, it is believed that both sleep stages reflect different neuronal processes and act in a complimentary manner to transform the labile trace into a more permanent form.

Along the same lines, Ficca *et al* (2000) have shown reduced performance on morning recall in young adults when a night of disturbed sleep cycles occurred but not if the sleep-cycle organization remained preserved (Ficca, Lombardo, Rossi, & Salzarulo, 2000). This indicates the importance of NonREM-REM sleep cycle organization in some memory tasks. Similarly, a nap improves performance on a visual discrimination task when both REM & NonREM occur during sleep (Mednick, Nakayama, & Stickgold, 2003). Thus, it is not just being asleep that is associated with performance improvements, it is a particular type or combination of sleep stages that is needed.

It has been argued that these two theories are not necessarily mutually exclusive. For example, most of the human studies support the hypothesis that deep NonREM sleep is more critical for consolidation of hippocampal dependent declarative (episodic memories) tasks. On the other hand, procedural memory involving skills require light NonREM sleep. At the same time, it has been shown that performance improvements on visual discrimination task correlates with the amount of early NonREM sleep in the first quarter of the night and the amount of REM sleep in the last quarter of the sleep cycle (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). The available data on the partial sleep deprivation studies suggest

that each sleep stage may facilitate different components of consolidation process and may contribute more or less to the consolidation based on the type of task.

The results of the various studies outlined above provide evidence of in favor of both dual and sequential theories. The nature of the relationship between sleep and cognitive processes needs to be better clarified. There is evidence that sleep plays a significant role in declarative and procedural memory functions. However, much of the presented research does not utilize systematic approaches. For example, studies are needed to control for the effects of learning on subsequent memory retrieval and control for the effects of vigilance during sleep deprivation procedures on memory and behavioral performance. On the other hand, the above review does not allow to determine with certainty the respective roles of the various the stages of sleep on memory processes and because of this, in this thesis total sleep deprivation is used while at the same time, vigilance was controlled for.

Many of the above of sleep studies require responses during a task and that the participant be skilled in motor or verbal domains. A typical behavioral reaction-time experiment consists of a stimulus followed by a response, without being able to observe the processing that occurs between them. Event related potentials (ERPs) reflect neurophysiological activity elicited by the stimulus independent of behavioral response requirements. Additional knowledge may be gained from merging information about the behavioral performance and non-invasive electrocortical activity such as ERPs that will allow for the characterization of memory processes after sleep, wake and following deprivation of sleep.

#### **Chapter 4: EEG, EVOKED POTENTIALS & ERPs**

In stark contrast to the passive EEG activity demonstrated initially by Hans Berger in the 1920s or that seen with simple sensory stimulations (i.e. sensory evoked potentials), the later ERP components (after 200 ms) are independent of the sensory modality and dependent on the task demand (Sutton, Braren, Zubin, & John, 1965; Lesevre, 1988; Donchin, 1979). In the mid-1960s, several researchers showed evidence of an electrical phenomenon directly related to the cognitive treatment of the information (Sutton, Braren, Zubin, & John, 1965; Walter, 1964). In these studies, they observed fluctuation in voltage additional to the stimulation during a cognitive task. These fluctuations associated with the processing of information were referred to as cognitive evoked potentials or event-related potentials.

Today, cognitive psychologists investigate the stages of information processing of the brain using ERPs. Similar to the EEG, ERPs reflect postsynaptic potentials generated during neurotransmission. These electrical potentials travel through the brain to the surface of the scalp, where they contribute to the overall scalp recorded activity. During a cognitive task, participants are repeatedly presented with a series of stimuli while the EEG is recorded before and following stimulus and the behavioral response. Time-locked averaging techniques are used to extract the small ERPs ( $\mu\text{V}$ ) from the EEG (mV). ERPs are described as a series of components that are identified according to their polarity (P or N), latency (in ms) within a specific time window after a stimulus is presented and scalp topography (Smith, Donchin, Cohen, & Starr, 1970; Ritter, Simson, Vaughan, Jr., & Friedman, 1979) The resulting

averaged ERP waveform consists of several positive (P) and negative (N) deflections that are called ‘peaks,’ ‘waves,’ or ‘components.’

The sequence of components following a stimulus reflects the sequence of cognitive processes triggered by the stimulus, beginning with early sensory processes and proceeding through decision- and response-related processes (Picton, 1988; Walter, 1964; Sutton, Braren, Zubin & John, 1965; Picton et al., 2000). In addition to peak naming, the functional approach defines the peaks in terms of information processing operations or cognitive functions (Donchin, 1979). Thus, the ERP distribution allows identifying certain functions associated to certain specific components. By varying the task parameters and/or the subject’s instructions, each component has been associated with specific information processing operations. It should be mentioned that ERPs do not allow identifying with certainty the exact location of the neural generator. This method does, however, allow perceiving in which sensory modality the stimuli are presented. In addition, the topographic distribution enables one to study the solicitation of certain brain regions involved and the cognitive demands associated to it. With the use of an expanded montage, a more detailed view of neural activity can be obtained, which has been found to be consistent with neuropsychological assessment in individuals with brain lesions, patients with neurological problems and studies with functional imaging.

#### 4.1 ERPs In Simple Tasks During Wake & Sleep

##### 4.1.1 N100 & P200 components: Fatigue, Arousal & Vigilance

The N100 is a negative deflection, peaking at approximately 80 – 100 ms (Naatanen & Picton, 1987) and is often followed by a positive peak (P200) at

approximately 175-200 ms. Early ERP studies have linked changes in N100 with states such as arousal (Naatanen & Picton, 1987) fatigue, vigilance (Haider, Spong, & Lindsley, 1964) and sleepiness (Harsh, Voss, Hull, Schrepfer, & Badia, 1994). In concordance with the electrophysiological findings, behavioral performance (RTs) is positively correlated with the latency of the N100-P200 components (Naatanen & Picton, 1987; Ritter, Simson, Vaughan, Jr., & Friedman, 1979).

The influence of sleepiness generally results in lower amplitudes and/or longer latencies of these potentials (Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Campbell & Colrain, 2002; Campbell & Colrain, 2002). During NonREM light sleep, the amplitude of N100 is reduced or near baseline (Cote, Epps, & Campbell, 2000). The attenuation of the amplitude of the N100 component reflects the brain's hypoarousal state (Cote, Epps, & Campbell, 2000) or decrease in cortical excitation known to occur around sleep onset. In REM sleep the N100-P200 complex is almost similar to that obtained during wakefulness (Campbell, McGarry, & Bell, 1988). Recently, Ferrara *et al.* (2002) reported that the changes in the N100-P200 amplitudes relates to greater effort under periods of increased homeostatic drive for sleep (Ferrara *et al.*, 2002). For the later components, sleep deprivation has also been shown to decrease the amplitude and increase the latency.

#### 4.1.2. N200-P250 components: Discrimination and Selection.

First reported by Squires *et al.* (Squires, Squires, & Hillyard, 1975), the N200 component has multiple functional interpretations, including orientation response, stimulus discrimination/classification (Ritter, Simson, & Vaughan, Jr., 1983) and

target selection (Donchin, Ritter, & McCallum, 1978). The N200 has been shown to vary depending on the stimulus type (e.g. words, pictures, faces) and the type of task (semantic vs. physical discrimination) (Ritter, Simson, & Vaughan, Jr., 1983), suggesting that it is a family of responses (the N2s) that differ based on the features of the stimuli, (Donchin et al., 1978). The N200 component is followed by the P250, a positive going component with a peak latency that varies from 150 to 275 ms, and is less well studied than the other ERP components. The P250 has been associated with selective detection (Hackley, Woldorff, & Hillyard, 1990) feature detection processes (Luck & Hillyard, 1994) and stimulus saliency (Potts & Tucker, 2001). The processes of stimulus discrimination, categorization and interference inhibition (N200) are helped by making relevant stimuli more salient (P250) and thus easier to detect.

Recent studies suggest that sleep affects a variety of negative components. At sleep onset the amplitude and latency of the N200 component is increased. As such, the term N200 is interchanged with N300 and N350. In fact, the predominant NonREM components are negativities approximately 300-400 ms (N350) and 500-700 ms (N550). These sleep "N2s" have been reported to be elevated in response to infrequent or target stimuli before sleep onset (Harsh, Voss, Hull, Schrepfer, & Badia, 1994c; Hull & Harsh, 2001; Bastien & Campbell, 1994; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991).

The emergence of a N350 component at the Cz site is seen when falling asleep (Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Colrain, Webster, Hirst, & Campbell, 2000). It is larger close to sleep onset (Ornitz, Ritvo, Carr, La, & Walter, 1967) and larger during light NonREM sleep (Kallai, Harsh, & Voss, 2003). More recently it

has been associated with the emergence of alpha-to-theta activity during the transition to sleep (Colrain, DiParsia, & Gora, 2000; Gora, Colrain, & Trinder, 1999).

On the other hand, during light NonREM sleep the N550 has been shown to be absent or reduced due to K-complexes a phenomenon of NonREM Stage II sleep (Bastien & Campbell, 1992; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Gora, Colrain, & Trinder, 2001). Unlike the N350, the N550 component is not seen until the later stages of sleep (Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Webster & Colrain, 1998; Harsh, Voss, Hull, Schrepfer, & Badia, 1994) and fully develops during deeper NonREM sleep (Cote, de Lugt, Langley, & Campbell, 1999). The N550 has a fronto-central topographic distribution (Cote, de Lugt, Langley, & Campbell, 1999). Lastly, these sleep "N2s" are often separated by a small positivity. The actual relationship of the sleep "N2s" with the N200 is still unclear. For some authors, the fact that they cannot be recorded during wake with the same latency and topography indicates that these components are distinctly a sleep phenomenon (Ogilvie, Simons, Kuderian, MacDonald, & Rustenburg, 1991).

Previous studies on ERP changes during sleep have also shown an enhancement of P2s associated with falling asleep (Atienza & Cantero, 2001; Crowley & Colrain, 2004). Because the changes during the transition to sleep have been suggest to be a sleep-protecting process that inhibits the cortex from responding to stimuli during sleep (Peszka & Harsh, 2002), the enhancement may reflect a decrease in cortical excitability and increased inhibitory process around sleep onset (Bastuji & Garcia-Larrea, 1999).

#### 4.1.3. P300 Component: Stimulus Evaluation

In contrast to the scarcity of information about the preceding positivities, P200 and P100, there is a large quantity of data about the P300 (for review Polich, 2007). This is partly due to the ease at which it can be elicited and its large amplitude. The P300 was first observed and reported in 1965 (Desmedt, Debecker, & Manil, 1965; Sutton, Tueting, Zubin, & John, 1967) in an ‘oddball’ task design, where the subject detects the rare stimuli among distracters, and the subject’s response to the rare target stimuli elicits a P300 component. Its amplitude is related to stimulus probability, stimulus significance and task-relevance, and is more prominent in the centro-parietal sites. P300 latency has been reported to vary with stimulus complexity (McCarthy & Donchin, 1981), and is assumed to reflect the duration of stimulus evaluation (Polich & Donchin, 1988). To date, all P300 theories (see Polich, 2007) agree that this component reflects a comparison between sensory input and the subjects’ expectancies along with closing (e.g. confirmation/disconfirmation) (Pritchard, 1981; Johnson, Jr., 1988; Verleger, 1988; Donchin, 1981).

Studies have shown that the discrimination of significant stimuli persists during sleep. There are reports of P300 in REM and NonREM sleep (Bastuji, Garcia-Larrea, Franc, & Mauguiere, 1995; Cote & Campbell, 1999). In line with these findings, several others report that a P300 was elicited in light NonREM sleep (Salisbury, Squires, Ibel, & Maloney, 1992; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Pratt, Berlad, & Lavie, 1999; Voss & Harsh, 1998). Harsh *et al.* (1994) studied the behavioral responsiveness and P300 during the transition from wakefulness to NonREM sleep as subjects performed an auditory oddball task (Harsh, Voss, Hull, Schrepfer, & Badia, 1994). Their data indicated that the P300 disappeared during later NonREM sleep in association with diminished behavioral responding. As to why

the P300 is seen in early, but not late NonREM sleep is unclear. It may simply be that with a deepening of sleep, the stimuli is not sufficiently salient (Salisbury, 1994) due to oscillations in the thalamus associated with synaptic inhibition and reduced sensory transmission (Amzica & Steriade, 1998).

#### 4.1.4. Effect of TSD in Simple ERPs Tasks

The latency of the N100 has been reported to increase during sleep deprivation (Gauthier & Gottesmann, 1983) and when sleep is fragmented (Cote, Milner, Osip, Ray, & Baxter, 2003). A study by Peeke, *et al.* (1980) reported an increased latency of the P200 in sleep-deprived subjects (Peeke, Callaway, Jones, Stone, & Doyle, 1980). The prolonged latency is in accordance with early researchers reporting findings of a reduction N100-P200 amplitude with decreasing vigilance before sleep onset (Weitzman & Kremenn, 1965), during sleep-wake transitions (Ferrara *et al.*, 2001b) and after taking sedatives, e.g. benzodiazepines (Noldy, Neiman, el-Nesr, & Carlen, 1990).

Corsi-Cabrera and *colleagues* (1999) evaluated subjects' reaction times and ERPs in a visual discrimination task, every two hours during a period of 40 hours of TSD (Corsi-Cabrera, Arce, Del Rio-Portilla, Perez-Garci, & Guevara, 1999). They reported that TSD resulted in a progressive amplitude reduction and a longer latency in the sleep "N2s". The stronger effect was for the earlier negativity within the 300 – 400 ms time window with its amplitude reaching only approximately 40% of the original amplitude with TSD. This indicates that stimulus discrimination becomes impaired and requires a longer time after sleep loss. Given that TSD enhances sleep

propensity and increases the arousal threshold during subsequent sleep, an alternative view is that this component reflects a sleep protective process during sleep initiation such as inhibition of external stimuli during the process of falling asleep. However, several other researchers report increased amplitudes following sleep disruption or deprivation of the sleep N2s. More specifically, the amplitudes of the N350 during sleep and the N550 during wake to sleep transition increased following TSD (Nicholas, Trinder, & Colrain, 2002; Peszka & Harsh, 2002). Alternatively, the latency of the wake N200 has been reported to vary as a function of task difficulty (Morris, So, Lee, Lash, & Becker, 1992; Ritter, Simson, Vaughan, Jr., & Friedman, 1979; Ritter, Simson, & Vaughan, Jr., 1983), suggesting that the task becomes more difficult with TSD.

The relationship between the P300 component and sleep deprivation have also been investigated. Gosselin *et al.* reported regional differences in the amplitude of the P300 after sleep deprivation, whereby a reduced anterior and larger posterior P300 amplitude was seen in the sleep deprived group compared to the controls (Gosselin, De Koninck, & Campbell, 2005). In another study, after 18 hours of sleep deprivation, the P300 showed decreased amplitude and increased latency but there was no change in performance as measured in RTs (Morris, So, Lee, Lash, & Becker, 1992). The authors concluded that the P300 was more sensitive than the behavioral measure to sleep deprivation. These data are inconsistent with the results reported in another study by Humphrey, Kramer & Stanny (1994) who investigated the influence of TSD (i.e. extended wakefulness) in a visual search task. Similar to the study by Morris *et al.* (1992), the P300 showed an increased latency and a decrease in

amplitude, but they also reported a decline in performance (i.e. less accurate responding) with sleep deprivation (Humphrey, Kramer, & Stanny, 1994). Lee *et al.* (2003) showed that the impairments in the P300 during sleep deprivation reflect the decrement in vigilance resulting in longer RTs. Thus, the confounding effects of changes in vigilance across session may explain the discrepancies in the earlier research on the effects of sleep deprivation on behavioral performance.

Several other researchers have reported reduced amplitude in a later slow positive wave extending from 400 to 800ms or longer with TSD (Corsi-Cabrera, Arce, Del Rio-Portilla, Perez-Garci, & Guevara, 1999; Nicholas, Trinder, & Colrain, 2002; Peszka & Harsh, 2002). This late positivity has been associated with a deepening of sleep (Yang & Wu, 2007). Others have shown that following TSD, or disturbed sleep, its amplitude during recovery sleep increased (Peszka & Harsh, 2002; Nicholas, Trinder, & Colrain, 2002). In contrast, Corsi-Cabrera *et al.* (1999) reported that the latency of this component did not recover after one night of sleep, indicating that one night of recovery sleep was not enough to restore this component to baseline after sleep deprivation. These authors suggested that this positivity reflects the final evaluation of the decision process, i.e. post-decisional process associated with frontal lobe function, and its reduction in TSD might reflect deterioration at this processing stage (Corsi-Cabrera, Arce, Del Rio-Portilla, Perez-Garci, & Guevara, 1999).

To summarize, in spite of the discrepancies between studies, what can be retained from the above is the following: First, ERP components that can be elicited during sleep resembles those observed at wake, indicating that information is processed at some point during sleep. Second, that sleep deprivation affects all of the

ERP component latencies and amplitudes, indicating that nocturnal sleep may somehow influence the processes they reflect. Some of the observed effects are probably a consequence of lower vigilance and some may be due to sleep deprivation itself. A major criticism of the above sleep studies is that it was unclear as to the true effects of sleep deprivation. Finally, it is noteworthy that much of the ERP literature involved in the effects of sleep on information processing utilizes simple tasks and stimuli. Although useful to investigate how arousal and sleep affect perception, attention and classification processes, these tasks do not directly address memory. Researchers have started to use complex tasks that elicit components of interest to those who study memory.

## 4.2. ERPs in Complex Tasks during Wake & Sleep

### 4.2.1 N400 Component: Semantic Integration

The semantic analysis of verbal and nonverbal stimuli is indexed by the N400 (Kutas & Hillyard, 1980). It has been well established that during wakefulness, the N400 wave is enhanced in response to words that are semantically unrelated compared to related words (cat-house vs. cat-rat) or when a word is incongruent within a given context of a sentence. The amplitude of this effect is correlated to the degree of semantic incongruence (Kutas & Hillyard, 1980; Bentin, Kutas, & Hillyard, 1993). (see below). The relationship between sleep and semantic processing has been investigated using ERPs. Brualla, *et al.* (1998), reported a negative component peaking at 430 ms after stimulus onset (N400) during wake that persists during light sleep and REM sleep (Brualla, Romero, Serrano, & Valdizan, 1998). For the

semantically associated words, a decreased N400 response was obtained reflecting a semantic priming effect consistent with behavioral studies reporting a facilitatory effect of REM sleep on priming.

#### 4.2.2. Late Positive Component, LPC: Episodic Information

Typically, the N400 is followed by a late positive component, LPC (or P600), which begins around 400 to 500 ms post-stimuli often with a left-sided predominance. Many researchers have proposed that the LPC belongs to the family of P300 waves (Coulson, King & Kutas, 1998). The LPC has been attributed to elaboration or mnemonic binding that leads to formation or retrieval of an episodic trace consisting of the stimuli and its context. The modulation of this component is thought to reflect the reactivation of a memory representation, and to constitute the substrate of episodic information retrieval (McClelland, McNaughton, & O'Reilly, 1995).

Two studies report that during wake, REM and NonREM sleep a late positive component (400 to 600 ms) was selectively evoked by the subject's own name (Berlad & Pratt, 1995; Pratt, Berlad, & Lavie, 1999; Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999; Bastuji, Perrin, & Garcia-Larrea, 2002). Pratt *et al.* used the subject's own name against an irrelevant word, which acted as a 'non target' (Pratt, Berlad, & Lavie, 1999). They reported a significant effect of stimulus type (own name vs. irrelevant word) for various ERP components between 300 and 700 ms during light and deeper NonREM sleep. The authors concluded that there was evaluation of the auditory stimulus during NonREM sleep, which diminishes during

deep sleep and then is replaced by evaluation of stimulus context during REM. Another study used a paradigm where the subject's name was presented in an equiprobable approach, against several other first names (Perrin, Garcia-Larrea, Mauguier, & Bastuji, 1999). Auditory ERPs were recorded both during wakefulness and sleep but unfortunately SWS responses were not analyzed. The morphology of the ERPs during wakefulness and REM sleep were very similar where in both cases a late positive wave at 400–600 ms was selectively evoked by the subject's own name but with a maximal amplitude slightly more posterior in REM than during waking. To the extent that subjects own name conveys mostly autobiographic, episodic information, the findings of similar LPC/P600-like component during REM, NonREM and wakefulness stages are in general agreement with behavioral sleep deprivation studies suggesting that both REM and NonREM may be important for declarative memory processing.

The tasks used in the above studies likely address processes involved in memory processing. Since these processes are activated *during* sleep, they may represent a role for sleep in memory consolidation. However, memory consolidation is a process that occurs sometime during sleep and subsequently facilitates next-day performance at retrieval. In order to answer the question: "*How sleep influences memory?*" actual memory tasks need to be employed and tested during wake *after* a delay of sleep.

### 4.3 Cognitive Event-Related Potentials & Memory

Now that the components of the ERPs have been described and their sensitivity to sleep has been established, below I will summarize the relevant literature on ERPs involving complex memory tasks. Recently there has been a proliferation of ERP studies of memory encoding and retrieval operations in LTM (Friedman & Johnson, 2000). Generally, the protocol design includes a study phase (encoding), in which the participants are presented with a series of stimuli and told explicitly to study each item. During the test phase (recognition), participants are instructed to indicate, by pressing a key on the computer keyboard, the studied items (old) from the new items. An advantage of this type of ERPs protocol is that the data can be collected and analyzed during both the study and retrieval phases of an experiment.

#### 4.3.1. ERPs in Study Phase: Memory Encoding

An issue in memory research concerns the nature of the encoding processes that promote the formation of robust memories. The more remembered item at test depends on the depth of processing ( Craik, 2002): items processed to the level of their physical features are less likely to be remembered than those that are semantically processed. The ‘transfer appropriate processing’ principle suggests that the probability of retrieval is largely determined by the amount and details of the overlap between processing carried out at study and test.

Encoding processes, defined as the transformation of sensory input into a lasting representation, are associated with an increased positivity between 300 and

800 ms. In a seminal paper, Sanquist and colleagues (1980) describe neural differences during encoding as a function of subsequent retrieval (Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980). They reported that the items subsequently recognized elicited larger late positivity component, LPC (or P600, P3-like) over the midline parietal site than those items that were later forgotten (i.e. misses). This led to independent measures of learning and retrieval by recording ERPs both during the study and test phases. Subsequently, Paller *et al.* (1987) isolated this difference in activity by subtracting the study items, e.g. ERP subsequently recognized (hits) from the subsequently forgotten (miss) responses (Figure 8, below). These authors also found that the more deeply an item is analyzed, the more likely it is to be remembered and result in a greater positivity during encoding than those forgotten (Paller, Kutas, & Mayes, 1987). Paller *et al.* (1987) referred to this effect as the 'Dm' for Difference in subsequent Memory (Figure 8).

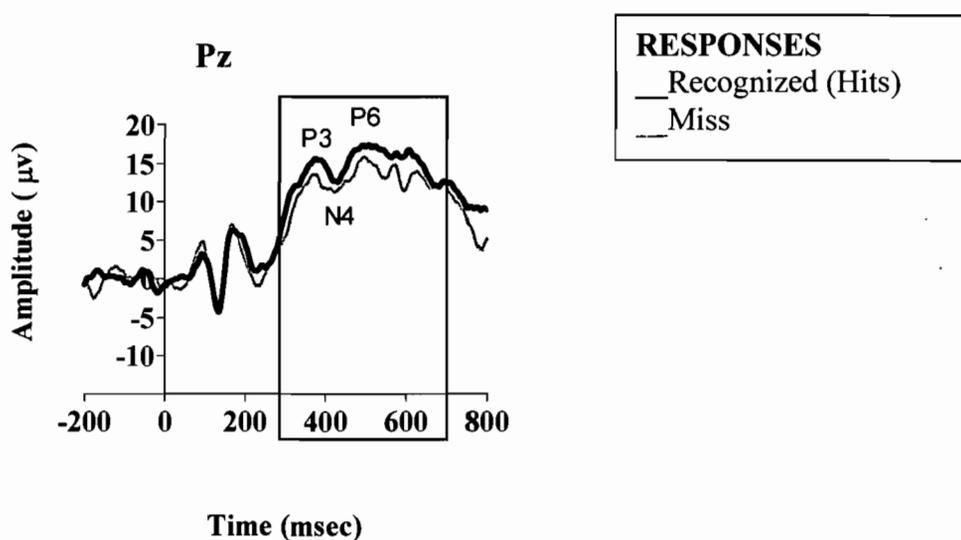


Figure 8. Grand average ERPs difference in memory (DM) effect elicited during the Study Session and processed according to whether or not they were correctly recognized (Hits) or not recognized (Miss) during the subsequent Test Session.

Similarly, others have shown DM effects during the encoding of verbal and nonverbal stimuli (Karis D, Fabiani, & Donchin, 1984; Johnson, Jr., Pfefferbaum, & Kopell, 1985; Neville, Kutas, Chesney, & Schmidt, 1986; Friedman & Johnson, Jr., 2000). DM effects are not seen for items that have no preexisting trace representation in LTM. However, the DM effect has been shown to change in amplitude, latency and scalp distribution by factors other than subsequently memory performance. A study by Fabiani, Karis & Donchin (1990) had subjects rehearse the study stimuli by rote (i.e. learning by repetition) vs. elaborations. In the rote condition, the effect was an early, posterior positivity, whereas in the elaborators the effect had a frontal maximum slow positive wave (Fabiani, Karis, & Donchin, 1990). It shows that the DM comprises several components; for example, a posterior LPC and when more complex treatment of the information is required, a frontal component.

#### 4.3.2. Memory Retrieval: The 'Old/New effect'

Neville and *colleagues* (1986) were the first to report the relationship between retrieval-related memory processes and ERPs. During wake, recognition tests have consistently shown that differential ERP responses to old (studied) and new items are useful for studying retrieval processes (Friedman et al., 2000; Johnson, Jr., Pfefferbaum, & Kopell, 1985; Karis et al., 1984; Paller, Kutas, & Mayes, 1987; Rugg & Nagy, 1989). These and other studies have consistently shown that correctly recognized (old) stimuli elicit more positive ERP compared to new stimuli (Friedman, Putnam, & Sutton, 1990; Barrett & Rugg, 1989; Rugg & Nagy, 1989; Rugg & Allan, 2000; Rugg & Wilding, 2000). This difference termed 'Old/New effect'(Allan, Wilding, & Rugg, 1998) begins approximately 250 ms post-stimulus onset and lasts until 800ms. Further, the effect has not been described in ERPs elicited by incorrectly

judged old as new items (misses) or by new items incorrectly judged as old (false alarms) (Allan, Wilding, & Rugg, 1998). It is typically observed whether the items to be recognized are pictures, faces or verbal material (Allan, Wilding, & Rugg, 1998; Jemel, George, Chaby, Fiori, & Renault, 1999).

The Old/New effect is not a unitary phenomenon. It is composed of distinct components that can be distinguished by their specific timing and scalp topography. Each of these effects reflect the contribution of a particular cognitive process to recognition (Friedman et al., 2000; Rugg et al., 1998) and there is both direct (from lesion and intracranial ERP studies) and indirect (from neuropsychological and imaging studies) evidence that each of these effects originate in separate brain system (Chao & Knight, 1996; Guillem, N'kaoua, Rougier, & Claverie, 1995). The main contribution to the ERP Old/New effect is provided by the modulation of two posterior components; namely, the N400 and LPC. More recently, certain authors (Donaldson & Rugg, 1999; Friedman, 2000; Curran, 1999) identified two frontally distributed components, a fronto-central component (or superior frontal) and the other a fronto-polar (or inferior frontal) component, which overlaps the N400 and LPC in time, but differ in their functional meaning.

#### 4.3.2.1. Early Posterior Component, N2b: Categorization

As mentioned previously (section 4.1.2), a number of distinct N200 components have been characterized (Naatanen & Picton, 1987; Patel & Azzam, 2005). Simson and *colleagues* (1976) found differences in scalp topography. For example, in the auditory modality, the N200 had a fronto-central distribution, however, the scalp topography of the visual N200 had two foci one central parietal and another more lateral, posterior, suggesting a modality specific effect (Simson, Vaughn, Jr., & Ritter, 1977; Simson, Vaughan, & Ritter, 1976). It has also been

found to be stimulus specific (e.g. N170 to faces, N200 to verbal stimuli). For instance, the N200 component elicited by face stimuli is known to vary with memory (Pfütze, Sommer, & Schweinberger, 2002; Schweinberger, Pickering, Jentsch, Burton, & Kaufmann, 2002; Schweinberger, Pickering, Burton, & Kaufmann, 2002) and is larger to familiar vs. unfamiliar faces over the inferior temporal sites (Schweinberger, Pickering, Jentsch, Burton, & Kaufmann, 2002). Despite the numerous distinct N200 components that have been characterized, the N200 with a posterior distribution is generally thought to index stimulus discrimination, identification (Renault, Ragot, Lesevre, & Remond, 1982) and classification (Naatanen & Picton, 1987). Said otherwise, it reflects the extraction of information necessary for the later information processing operations (Renault, Ragot, Lesevre, & Remond, 1982). Several researchers report correlations between the latency of "classification" N200 and behavioral reaction time performance (Ritter, Simson, Vaughan, Jr., & Friedman, 1979; Renault, Ragot, & Lesevre, 1980; Brecher, Porjesz, & Begleiter, 1987; Novak, Ritter, Vaughan, Jr., & Wiznitzer, 1990).

There is little data about the generators of the N200. Early work by Halgren *et al.* (1992) reported depth recorded ERP activity in the regions of Herschel's auditory gyrus corresponding in time with the scalp recorded N200. Allison *et al.* recorded ERPs sensitive to faces from lateral temporal cortex (Allison, Puce, Spencer, & McCarthy, 1999; Allison *et al.*, 1994) Puce, Allison, Spencer, Spencer & McCarthy, 1997). Similarly, studies have shown discrete foci of activation of a negative component to faces (N170) in lateral temporal cortex, particularly in the right hemisphere (Puce, Allison, Gore, & McCarthy, 1995; Puce, Allison, Asgari,

Gore, & McCarthy, 1996). More recently, a study by Anderer *et al.* (2004) employing low resolution electromagnetic tomography (LORETA) for the analysis of the source density of auditory ERPs implicated the superior temporal gyrus, precuneus and medial anterior cingulate gyrus as possible cortical generators of the N200 component (Anderer *et al.*, 2004).

#### 4.3.2.2. Early Inferior-Frontal Component: Inhibition & Saliency

The inferior frontal (IF) component is not well-known. An early, bilateral inferior frontal negativity is elicited between 250 and 350 ms (Barrett & Rugg, 1989) particularly in tasks involving inhibition of interfering stimuli during retrieval (Tendolkar & Rugg, 1998; Guillem, Bicu, & Debruille, 2001). From a functional standpoint, studies show that this component is unchanged or tends to increase amplitude when the number of interfering items between the study and the recognition phase increases (Guillem, Bicu, & Debruille, 2001; Guillem, Bicu, & Debruille, 2000). This lead some researchers to suggest that this early effect over the frontal lobe is associated with inhibition of interference (Guillem, Bicu, & Debruille, 2001; Guillem, Bicu, & Debruille, 2000; Goldstein, Spencer, & Donchin, 2002), whereby a reduced amplitude to old items (i.e. larger effect) means that these stimuli entailed less interference inhibition than the new items. Other researchers have found frontal components (frontal N2 and P2a) within the same latency modulated by stimulus salience (Breton, Ritter, Simson, & Vaughan, Jr., 1988; Potts, Liotti, Tucker, & Posner, 1996). The relationship of the N2 and anterior P2 has been suggested to represent the interaction between brain regions involved in interference inhibition and

stimulus saliency processing (Potts, Liotti, Tucker, & Posner, 1996) (see section 4.1.2).

In support of the above studies, intracranial ERPs studies suggest that the neural generator of this inferior frontal component is at the level of the orbital frontal cortex (Guillem, Rougier, & Claverie, 1999; Halgren, Marinkovic, & Chauvel, 1998). This region of the frontal cortex is known to play a role in maintaining information in the face of interference (D'Esposito, Postle, Jonides, & Smith, 1999; Fuster, 1980). ERP recordings in patients suffering from frontal lobe lesions lend support that the orbital and ventral medial origin of this frontal polar component (Chao & Knight, 1998).

#### 4.3.2.3. Posterior N400 Component: Semantic Processing

As already mentioned (section 4.2.1), Kutas and Hillyard (1980) were the first to demonstrate that the N400 is significantly reduced in sentences ending in words that are semantically congruous (e.g. I take cream in my coffee) compared to words that are incongruous (e.g. I take dog with my coffee) (Kutas & Hillyard, 1980). This indicates that it was sensitive to semantic processing of linguistic stimuli. Subsequent, research showed that a reduced N400 is elicited in tasks where a target word is semantically unrelated vs. related to a prior prime word (Holcomb, 1988; Bentin, McCarthy, & Wood, 1985).

The N400 component has been identified in a variety of visual priming tasks using nonverbal stimuli (Polich, 1985) and faces (Barrett et al., 1989), indicating that the N400 component may not be as specifically related to linguistic stimuli as was

initially suggested. It is larger for familiar faces vs. unfamiliar faces (Schweinberger, Klos, & Sommer, 1995). Meaningless items (e.g. distorted pictures, impossible objects or illegal non-words (Rugg & Doyle, 1994) do not elicit the N400 effect. Although there is no complete consensus, there is evidence to suggest that the N400 effect reflect the ease or difficulty of integrating the stimulus or concept with semantic knowledge (Rugg et al., 1994; Holcomb & Neville, 1990). A less negative N400 amplitude to the old items is thought to indicate easier integration as a result of pre-exposure to the stimulus, i.e. semantic priming. Semantic priming has been explained as due to the spread of activation, for example, from a prime word to related words in an associative network. When a related item is presented, its higher level of activation facilitates the behavioral response (Collins & Loftus, 1975). In such a case, access to the representation would require only a weak level of activation resulting in a reduced N400. In contrast, an unrelated item would not benefit from any facilitation, and would require larger (more negative) N400.

The posterior N400 possesses a centro-parietal distribution suggesting a contribution of the associative posterior region (Guillem, Bicu, & Debrulle, 2000g). Unilateral anterior temporal lobectomy (Smith & Halgren, 1987) attenuates the N400 component implicating the role of the temporal lobe in its generation. Moreover, the N400 amplitude has been reported attenuated in patients with the comprehensive type of aphasia, thus, involving the temporo-parietal structures (Swaab, Brown, & Hagoort, 1998; Hagoort, Brown, & Swaab, 1996). Intracranial ERPs have supported this conclusion (Smith & Halgren, 1989; McCarthy & Wood, 1985). Guillem *et al.* (1995) recorded steep voltage gradients and local polarity reversals within the

superior and inferior parts of the parietal lobe, indicating that the parietal lobe also contributes to the N400 activity at the scalp. Taken together these findings suggest that medial temporal structures (amygdala, hippocampus, parahippocampal gyrus and entorhinal cortex) and parietal regions may be involved in the generation of the N400 activity at the scalp (Guillem, N'kaoua, Rougier, & Claverie, 1995).

As previously mentioned (section 1.2.3.1.), neuropsychological studies of memory deficits in neurological patients and patients with lesions in this area have implicated these posterior regions in semantic memory. Further support for this idea comes from brain-imaging studies that report activation of the posterior parietal region in studies of semantic memory (Petrides, 1989; Schacter et al., 1999) .

#### 4.3.2.4. Superior Frontal Component, F-N400: Familiarity

The Superior Frontal component, also referred to as a frontal central or F-N400 component, overlaps temporally with the N400, but differs both in its topography and functional meaning. It has been demonstrated that the posterior and the frontal Old/New effects are functionally dissociable (Allan, Wilding, & Rugg, 1998). Different studies show that this component elicited between 300-500 ms or longer is related to familiarity assessment (Curran, 1999; Rugg et al., 1998). ERP research showed decreased amplitude in the superior frontal component when the interval between the acquisition of an item and its recognition increases (Guillem, Bicu, Semkowska, & Debrulle, 2002), indicating a greater amplitude with short delay intervals. However, recent evidence has supported that the F-N400 Old/New effect is maintained across one-day retention interval, indicating that familiarity of an item last

and contribute to memory retrieval after long periods (Curran & Friedman, 2004). The spatial distribution of the superior frontal component suggests that it is generated at the level of the dorsolateral frontal cerebral cortex (Rugg, Schloerscheidt, Doyle, Cox, & Patching, 1996; Allan, Doyle, & Rugg, 1996). Further support for this idea comes from intracranial ERP studies (Guillem, Rougier, & Claverie, 1999).

#### 4.3.2.5. Late Positive Component: LPC: Elaboration & Episodic Memory

Only during the last 10 years has the Late Positive Component (LPC) or P600 been studied. It is highly controversial how this positivity and the earlier positivity (P300) are related (VanPetten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). One line of thinking is that the LPCs recorded in tasks involving repetition of words in lists, sentences and text may contain overlapping contributions from the P300 along with other potentials. In one study, the LPC was observed only when elaborative and complicated processes were required, supporting the idea that the LPC and P300 reflect different processes (Smith, 1993).

The majority of studies report increased amplitude in the LPC during recognition that corresponds to the elaboration of an episodic representation integrating the item and its contextual attributes. More specifically, the LPC reflects a process of "memory synthesis" allowing regrouping the various aspects of the information, which were extracted from previous processes (e.g. N400, superior frontal, inferior frontal) to form a coherent memory representation of the event in LTM (Rugg et al., 1994). In regards to the sensitivity of this component, studies show a reduction of the LPC component with an increase in the time interval and/or the

number of intervening stimuli (Nagy & Rugg, 1989), or an instability for long intervals (Swick & Knight, 1997). However, other studies showed that in spite of a decrease with the increase of intervals, LPC remains present until 20 items inserted between presentations (Guillem et al., 2000) or even after one day (Curran & Friedman, 2004). Finally, the interpretation of the LPC component agrees with the fact that it is generated approximately at the level of the median temporal level (more specifically in the hippocampus). This observation has been confirmed by an intracranial ERP study (Smith & Halgren, 1989; Guillem, Rougier, & Claverie, 1999).

#### 4.3.2.6. Late Frontal Component, LFC: Strategic & Contextual Processing

In tests of recognition memory that require an explicit search for context, a late frontal component is seen. This superior frontal effect is elicited between 300 – 500 ms up to 1,500 ms post-stimulus and sometimes with a right predominance (Rugg & Wilding, 2000; Senkfor & VanPetten, 1998; Wilding & Rugg, 1996; Wilding, Doyle, & Rugg, 1995). Wilding & Rugg (1996) were the first to identify this late frontal component and suggested that the activity in the prefrontal region reflected successful recovery of contextual information because the amplitude is larger when the context of the items is correctly identified. Similarly, ERP effects in tasks employing source judgments (contextual information) have exhibited a late frontal component (Johnson, Jr., Kreiter, Russo, & Zhu, 1998; Senkfor & Van, 1998; Johnson, Jr., Kreiter, Russo, & Zhu, 1998). Frontal effects may also reflect the degree of retrieval effort (Schacter, Savage, Alpert, Rauch, & Albert, 1996). For

instance, when retrieval is complex and difficult there is a bilateral or left lateralized frontal contribution (Johnson, Raye, Mitchell, Greene, & Anderson, 2003). This broader distribution has been interpreted as reflecting additional retrieval of semantic information necessary to complete the task. In general, it can be said that the LFC reflects strategic monitoring processes (Allan, Wilding, & Rugg, 1998; Wilding & Rugg, 1997; Wilding, 1999). Its scalp distribution, interpretation and intracranial recording are consistent with this ERP effect in the dorsolateral prefrontal cortex (Guillem, N'kaoua, Rougier, & Claverie, 1996; Guillem, Rougier, & Claverie, 1999). This would suggest that the LFC originates in the frontal and right dorsolateral cerebral cortex, which is in agreement with PET and fMRI studies showing evidence of greater activity in this region in the search in memory (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). In addition, neuroimaging studies of human memory have shown right frontal activity related to recollection and strategic processes (Henson, Rugg, Shallice, Josephs, & Dolan, 1999) that pertain to information retrieved from episodic memory (Nolde, Johnson, & D'Esposito, 1998). This ends the section 4.3 ERPs & Memory, and Table 3 below shows a summary of the characteristics of the ERP components related to the Old/New effect.

## 4.3.3. Summary Table: Old/New ERP Components.

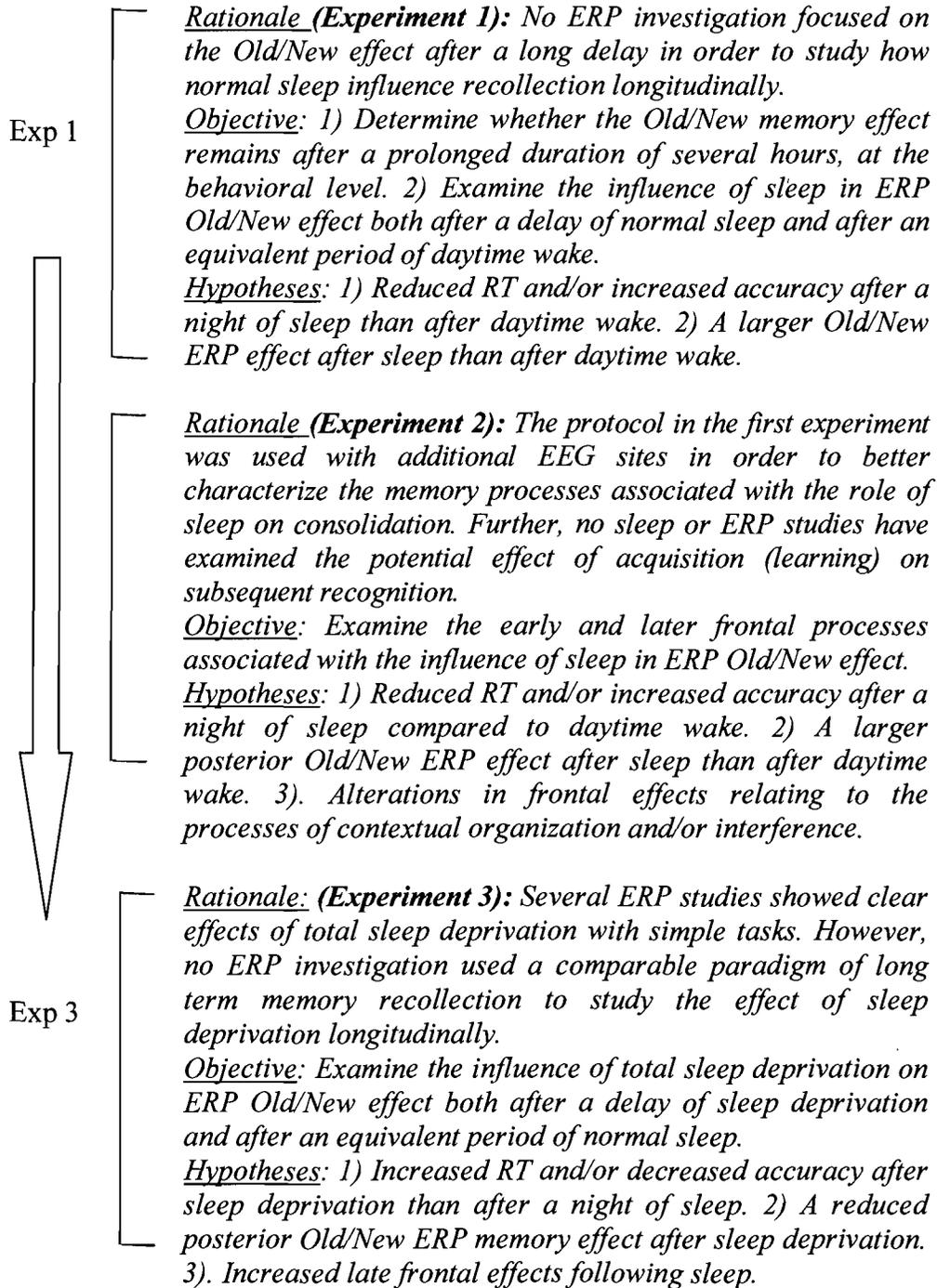
| <b>ERP Components</b>                              | <b>Anatomical Region(s)</b>                            | <b>Functional Interpretation</b>  |
|--|--|---|
| N200 (N2b)   | Posterior Cortex;<br>Association Areas                 | Stimulus Discrimination &<br>Categorization                                   |
| N2-P2a   | Frontal Polar; Inferior<br>Frontal, IF                 | Interference inhibition<br><br>Stimulus Saliency                              |
| Posterior N400                                     | Parietal Cortex;<br>Association Areas                  | Semantic knowledge; Trace<br>Assess; Semantic Priming                         |
| F-N400   | Fronto-central ; Superior<br>Frontal, SF; Dorsolateral | Familiarity (left-sided)  |
| Late Positive<br>Component (LPC)<br><br>P600 (P3b) | Medial Temporal Lobe,<br>MTL (hippocampus)             | Mnemonic binding; Episodic<br>Memory; Elaboration of a new<br>representation. |
| Late Frontal<br>Component (LFC)                    | Frontal Cortex;<br>Dorsolateral                        | Strategic or Contextual Processing;<br>Post-retrieval process.                |

## 5. OBJECTIVES OF THE THESIS

From the review of the literature, we can make the following assertions: 1) Early components (N100-P200) reflect vigilance and are influenced by sleep loss. 2) N400, which has been proposed to reflect semantic integration, is present during REM sleep and, 3) LPC (P600), thought to represent episodic processing and declarative memory, is present REM and/or NonREM sleep. There are, however, numerous inconsistencies in the literature likely reflecting the lack of tests specificity and difficulties separating the various memory processes involved. The results from ERP studies could provide a solution regarding these inconsistencies in the sleep and memory literature on declarative memory.

The general *objective* of the dissertation was to study *how sleep influences memory processing* with the aid of ERPs in a direct recognition memory task. This was done in three experiments (see below)

## 6. RATIONALE & HYPOTHESES:



## 7. GENERAL METHODOLOGY

### 7.1 Participants

All participants were screened initially by telephone interview in terms of motivation to attend, medical history, sleep history and meet with our inclusion/exclusion criteria (see Appendix 1 for more details). Participants were asked to keep regular sleep-wake schedules. Eligible participants underwent an interview in the laboratory and completed a standard questionnaire used to collect the socio-demographic characteristics before the experiment (Appendix 1), approximately ½ hour in duration. All participants were fully informed of the recording methods and signed a consent form before participating in this experiment (Appendix 2).

To determine the number of participants in each experiment, power was calculated on the mean amplitude of the LPC component taken at parietal location (Pz site). These results were based on a pilot study with a similar task of 10 subjects (see Appendix 6). We found that a minimum of 17 participants per experiment are required for significant results at  $p > .5$ , two tailed test with a power of .90, assuming a mean of 4.8  $\mu\text{v}$  (SD +/- 1.6  $\mu\text{v}$ ) after normal sleep and a mean of = 6.7  $\mu\text{v}$  (SD +/- 1.5  $\mu\text{v}$ ) after sleep deprivation. A total of 40 participants (20 per experiment tested twice in a repeated measure design) was recruited in order to enhance statistical power and compensate for experimental loss associated with drop out or technical difficulties.

## 7.2 Experimental Design

The general protocol was built as a classical study-test design. The study (learning) phase and the test (recognition) phase, each lasting about 15 minutes, were separated either by a delay of a night's sleep (SLP session), daytime wake (Wake session, Experiments 1 & 2) or one night of sleep deprivation (TSD session, Experiment 3) (see Table 4.). All conditions were counterbalanced to control the effects of practice and, participants were randomly assigned to either condition. To limit the possible confounding effects of cognitive variations throughout the day, time of testing was kept constant (Table 4, below). All nights were spent in the sleep laboratory under the supervision of at least two other staff members. Participants were tested twice in a counterbalanced fashion to control the effects of practice.

### a) Protocol for Sleep vs. Wake Experiments 1 & 2

|                              |       |                       |              |                            |     |                         |
|------------------------------|-------|-----------------------|--------------|----------------------------|-----|-------------------------|
| PHASE A <sup>(1)</sup>       |       |                       | ≥ 3 – 7 days | PHASE B <sup>(1)</sup>     |     |                         |
| Evening Acquisition (16-18h) | NIGHT | Morning Recall (7-9h) |              | Morning Acquisition (7-9h) | DAY | Evening Recall (16-18h) |

(1) Phase A<sup>(1)</sup> and B<sup>(1)</sup> to be counterbalanced across participants

### b) Protocol for TSD Experiment 3.

|                              |       |                       |               |                              |     |                       |
|------------------------------|-------|-----------------------|---------------|------------------------------|-----|-----------------------|
| PHASE A <sup>(2)</sup>       |       |                       | ≥ 3 – 14 days | PHASE B <sup>(1)</sup>       |     |                       |
| Evening Acquisition (16-18h) | NIGHT | Morning Recall (7-9h) |               | Evening Acquisition (16-18h) | TSD | Morning Recall (7-9h) |

(1) Phase, B<sup>(1)</sup> total sleep deprivation (TSD)

(2) A<sup>(2)</sup> and B<sup>(1)</sup> to be counterbalanced across participants

Table 4: Protocol for Experiments 1 & 2, Normal Sleep/Daytime Wake (see top, Table a). Protocol for Experiment 3, Nocturnal Sleep/TSD (see bottom, Table b).

### 7.3 Questionnaires

All subjects filled out a sleep agenda (see Appendix 3) reporting subjective estimates in the number of hours of sleep three days prior to testing and throughout their participation in the experiment, which included nights (sleep or TSD) in the laboratory. The mean numbers of hours of sleep during the night in the laboratory were analyzed with two-tailed paired t-tests to see if there were any statistically related differences. A paired-sample t-test for repeated measures was used to analyze the number of nocturnal awakenings and sleep onset (minutes) in the laboratory on the morning questionnaire (Appendix 4) compared to that of a normal night of sleep in the home.

Information regarding the quality of the night of sleep in the laboratory was obtained in the morning on a Evening Questionnaire (Appendix 4). To ensure that sleep was equal in both sessions, participants were asked to fill out questionnaires about sleep habits, sleep quality at home and in the laboratory and the Stanford Sleepiness Scale (see Appendix 4). For the daytime condition (Experiments 1 & 2), the subjects were able to carry on their routine daily activities and then return to the laboratory for the recognition phase. Upon return to the laboratory, a daytime questionnaire was filled out reporting their activities and vigilance levels immediately prior to testing (Appendix, 4). For the sleep deprivation condition (Experiment 3), the subjects were allowed to play video games, go for supervised walks, watch videos, read or do school work. During the deprivation procedure, a vigilance scale (visual analog scale, VAS) was filled out every half hour (Appendix 4). At the end of the

deprivation procedure all subjects reported their activities on a questionnaire prior to the testing.

#### 7.4. Recordings and Signal Extraction

The electrophysiological signals were recorded by means of an amplifier (S.A. Instrument Inc, San Diego, Calif). The EEG was recorded from 27 scalp electrodes placed according to the extended 10-20 International System montage (Fp1, Fp2, Fpz, F3, F4, F7, F8, Fz, FC3, FC4, FT7, FT8, Cz, CP3, CP4, P3, P4, Pz, T3, T4, T5, T6 TP7, TP8, O1, O2, Oz) (American EEG Society, 1994) (Figure 9).

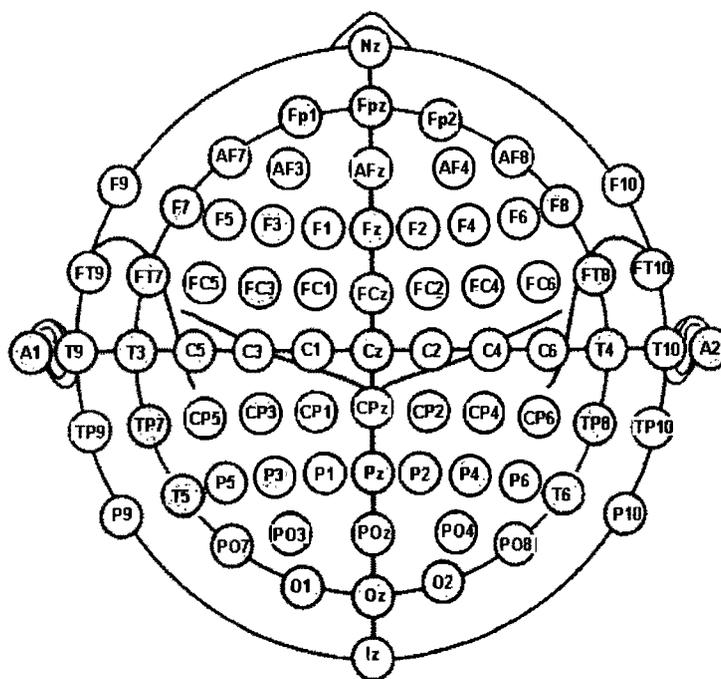


Figure 9: The extended 10-20 International System for electrode placement (grey = electrode sites used in analysis). Abbreviations: FP=fronto-polar; AF=anterio-frontal; F=frontal; FC=fronto-central; C=central; CP=centro-parietal; P=parietal; PO=parieto-occipital; O=occipital; TP=temporo-parietal; T=temporal; A=oreille; I=inion; N=nasion; z=midline.

All channels were referenced to the linked earlobes. Vertical and horizontal eye movements were monitored via electrodes respectively placed below and on the outer canthus of the left and right eyes. During the recording, the impedance of all electrodes was maintained below 5 K $\Omega$ . The EEG was recorded continuously with a bandpass of 0.01-30 Hz, digitized on-line at a rate of 250 Hz and stored along with the codes identifying the experimental condition, the stimulus onset and the subject's response for subsequent off-line averaging. Off-line averaging was performed after EOG correction using statistical software algorithms (InStep software Montreal, Canada) and after rejection for epoch with amplifier blocking. ERPs for correctly identified new items and correctly identified old items were then computed separately from 0- to 1000-millisecond post-stimulus onset with a 200-millisecond pre-stimulus baseline.

#### 7.5. Stimulus & Procedure

Stimuli consisted of color photographs representing persons' faces unknown to the subjects. These stimuli were taken from the Face MED bank that are composed of front view faces taken in the same conditions (background and light). Each face in this bank has been scored as neutral, friendly, or unfriendly by a large group of persons in a prior study (Debrulle et al., 1997). Thus, to minimize the possible confounding effects of emotional expression, the 160 faces chosen as stimuli for this experiment were those with the higher neutral scores. The whole set was divided into two sub-sets of 80 faces counterbalanced for gender. Each of these sets served to construct a study series of 40 stimuli and a test series of 80 stimuli in which the 40

previously presented were intermixed with an additional 40 ‘new’ stimuli. There were two different study-test series so that the presented items were different during each session (Sleep/Wake or Sleep/TSD).

Subjects sat in a comfortable chair in a sound-attenuated room. Stimuli were presented on a gray background at the center of this screen 56 cm away from the subjects sustaining a visual angle of 5° and with an inter-interval stimulus of 4.5s. Each stimulus remained for 1000 ms and was replaced by a mask with the word ‘blink’ for 600ms (Figure 13). During the study (learning) phase, the subjects were told to memorize each stimulus for a subsequent recognition test. Following a night’s sleep (Experiments 1 & 2) or a night of sleep deprivation (Experiment 3), the subjects were tested. During the test session, the subjects were asked to indicate for each stimulus, as accurately and quickly as possible whether it has been previously presented (‘old’) or not (‘new’) by pressing the arrow keys on the computer keyboard.

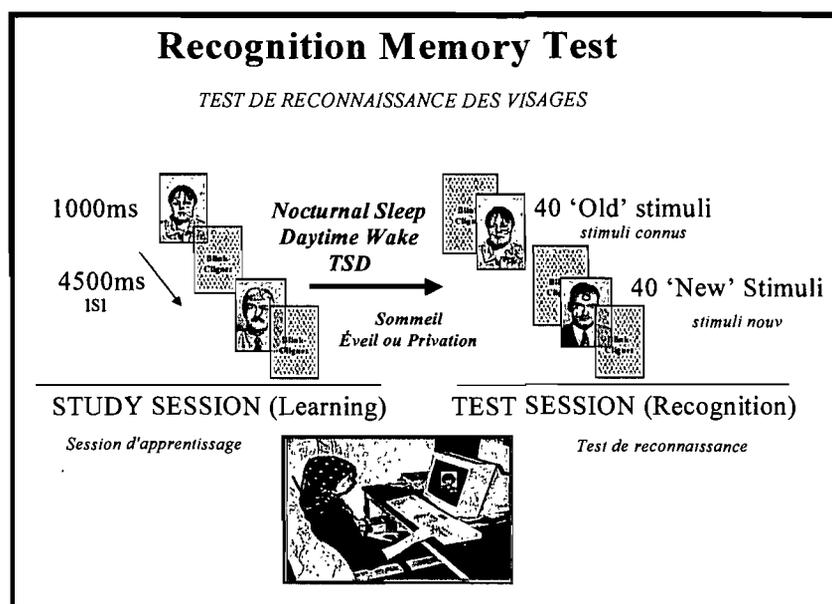


Figure 10: Schematic representation of the stimulus protocol.

## 7.6. Data Analysis

The analysis of the ERPs began with a visual inspection of each participant's waveforms recorded at Cz within stimulus onset to 1000 milliseconds. The amplitudes were then measured in every electrode from the baseline (200ms pre-stimulus) in successive windows of latency corresponding to every peak (Guillem et al., 2001). The data was subsequently reduced to 6 regions of interest (6 regions/hemisphere) see section below, ERP at Recognition (Figure 11).

*Behavioral performance* data were obtained simultaneously with EEG data. Behavioral performance assessed on the *reaction times* (RTs) and *scores* (% correct and % miss). *Response times* (RT) obtained for former stimuli and new were compared by means of a factorial design 2 session (Experiment 1 & 2: Sleep, Wake; Experiment 3: Sleep/TSD) x 2 condition (Old, New) ANOVA in repeated measures (subjects). The RTs were collected for correct trials only. This analysis allowed to verify the existence of the Old / New behavioral effect (cf. above.) and to determine if it is influenced by the sleep. *Scores* of both sessions (Sleep, Wake or Sleep, TSD) were compared by means of a Repeated Measures ANOVA. This analysis allowed us to determine if the sleep influences the memorization of items.

### 7.6.1 The ERP at Study (Difference in Memory (DM) Effect

The ERP difference for recognition (hits) vs. unrecognized (miss) at test is referred to as the difference in memory, DM effect (Paller, Kutas, & Mayes, 1987f). This analysis was used to assess potential difference in the encoding quality on

subsequent recognized item. It was used as a control for possible confounding effect of time of day during the morning and evening study sessions (Experiment 2 & 3).

#### 7.6.2 ERP Measure of Vigilance (N100/P200 Components)

Two early ERP peaks N100 & P200 were analyzed to statistically control potential confounding effects of arousal/vigilance differences between test sessions. The N100 and P200 components were quantified within 61 – 146 ms and 141 – 214ms time window, respectively, at midline sites (Fz, Cz, Pz) for correct recognition (hit) and correct rejection. The analysis consisted of a 2 ‘session’ (Sleep, TSD) or (Sleep, Wake) x 2 ‘condition’ (Old, New) x 3 ‘site’ (Fz, Cz, Pz) repeated measure ANOVA. For significance involving session x site on the N100 or P200 amplitude, follow-up post-hoc analysis were employed to determine the specific site.

If preliminary analysis showed significant effects and interactions involving the session factor observed on N100 or P200, the ERP data were subsequently re-analyzed using the same factorial design in an (N100 or P200 amplitude) ANCOVA model.

#### 7.6.3. The ERP at Recognition

Memory ERPs quantified for correctly recognized old and correctly rejected new stimuli on the whole coverage within 200 – 800ms post-onset. This time window was typical for previous studies of the ERP ‘Old/New’ effect (Guillem et al., 2003) and in our pilot study (Mograss, Guillem & Godbout, 2003). ERP data were analyzed

separately for midline and lateral sites using repeated measures ANOVAs. For the midline sites, the model included the 2 'session' (SLP, TSD or Wake), the 2 'condition' (Old, New) and 3 'site' (Fz, Cz, Pz) as within-subject variables. For the lateral sites, the model included the 2 'session' (SLP, TSD or Wake), the 2 'condition' (Old, New), the 6 'region' inferior frontal (Fp1-2, F7-8), superior frontal (F3-4, FC3-4), parietal (CP3-4, P3-4), anterior temporal (FT7-8, T3-4), posterior temporal (TP7-8, T5-6) and occipital (O1-2) and 2 'laterality' (left, right) as within-subject variables. Figure 14, below, shows the data obtained from the 27 electrodes were regrouped into 12 regions of interest, 6 for the left hemisphere and 6 for the right hemisphere. Of note, is that the 5 midline electrodes are not shown in this figure.

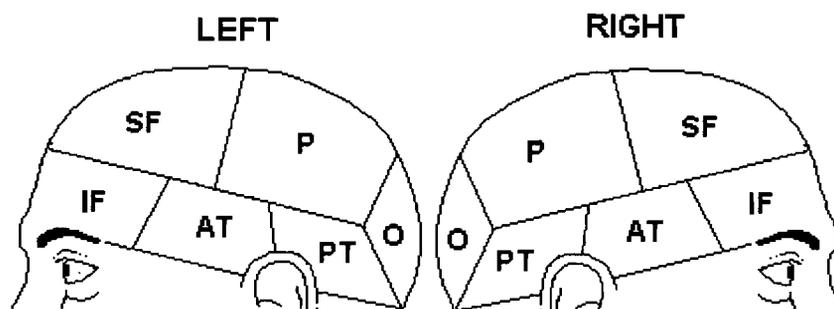


Figure 11. The topographic regions (6 per hemisphere): SF: superior frontal, IF: inferior frontal, P: parietal, AT: anterior temporal, PT: posterior temporal, O: occipital.

In all analyses, degrees of freedom were adjusted using the Geisser-Greenhouse procedure where appropriate (uncorrected  $df$  are reported with the  $\epsilon$  values and corrected  $p$  values). For the topographic analysis, raw data were, afterward, normalized compared to the maximal distance from amplitude, with the

following equation, see below (McCarthy & Wood, 1985). This procedure allows one to account for the possibility that a given scalp distribution effect can be due to multiplicative differences in distinct neural source strength.

$$NC = (Co - Cm) / (CM - Cm) \text{ where,}$$

NC = Normalized Component  
Co = Originally measured component (Raw data)  
Cm = Minimal topographic component for the 27 sites  
CM = Maximal topographic component for the 27 sites

Normalization allows one to decrease within and between subjects because the transformed value (NC) varies between 0 and 1. It is used to confirm observed effects in raw data in all the interactions involving sites. Interactions involving the factor of site were reported if significant in the normalized data set (Swick & Knight, 1997). In the case of significant interactions, the highest order interaction is reported.

## VALIDATION OF A PROTOCOL & EXPERIMENT 1: The Old/New Effect

The goal of the pilot study was to verify that the classic "Old/New" ERP memory effect can be detected after a long delay. The use of such a protocol allowed us to study the differential influence of declarative (episodic and semantic) subsystems, with a delay when it is filled with wakefulness or sleep, in subsequent experiments.

The pilot study was originally given as an oral presentation and published as a short paper in 2003: Mograss MA, Guillem F, Godbout R. (2003) (see Appendix 6), *The Influence of Sleep on Memory: An Event-Related Potential Study. Sleep; 26; Vol 26* and subsequently as a full paper: *The ERP Old/New effect: a useful indicator in studying the effects of sleep on memory retrieval processes. Sleep 2006; 29(11) 1401-1500*. Since then, others have used longer delays (half hour, hour, day & week) (Joyce & Kutas, 2005) and (hours, days) (Curran & Friedman, 2004) but have not systematically investigated the same delay of nocturnal sleep vs. daytime wakefulness.

The Classic Old/New effect:  
A useful indicator in studying the effects of Sleep on  
Declarative Memory Processes.

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Running head: Sleep and ERP Memory Effect

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## Abstract

**Study Objectives:** To verify that the classic "Old/New" memory effect can be detected after a long delay, and to investigate the differential influence of declarative memory processes after normal sleep and daytime wake.

**Design:** The protocol is a variation of a more traditional study-recognition test used in event-related potential (ERP) studies in which sleep or wake is inserted between the learning and recognition session in order to verify the existence of the Old/New effect (ie, positive shift that occurs when stimuli are repeated). ERPs were recorded during the recognition-test session. The protocol was based on early work that compared the effect of sleep on memory without recording sleep.

**Setting:** Data collection occurred in the outpatient sleep laboratory.

**Patients or Participants:** Results from 13 subjects (6 men) aged between 21 and 39 years.

**Measurements and Results:** The subjects performed the recognition memory test after sleep and daytime wake periods. More-accurate performance for the old (studied) stimuli occurred after the sleep session. Analysis of variance on correctly answered reaction times revealed a significant effect of condition (old/new) with no difference across session. A repeated-measure analysis revealed differences in "Old/New" effect, whereby the amplitude difference between the old and new items was larger after sleep than after wake.

**Conclusions:** This effect of sleep was found in early frontal and later posterior ERP components, processes that represent strategic or contextual processing and facilitation of episodic memory, respectively. Memory representation was not different across sessions. These findings suggest that sleep and wake facilitate 2 components of memory unequally, ie, episodic recognition and memory representation functioning.

**Key Words:** Declarative, episodic, memory ERP, sleep, memory processes

## INTRODUCTION

The position that sleep may play a role in the process of memory formation dates back to the report of Jenkins and Dallenbach in 1924, claiming that recall performance improves following an intervening period of sleep.<sup>1</sup> Early studies showed that sleep can have an important role in memory retrieval.<sup>2-4</sup> However, research has resulted in mixed and contradictory conclusions.<sup>5,6</sup> This lack of agreement between studies may be a consequence of the differences in task characteristics<sup>7,8</sup> or the type of stimuli used,<sup>6</sup> likely addressing different subtypes of memory.

Initially, memory was thought to be unitary, until the idea of multiple memory system arose. Many different multimemory models have been proposed and supported. One makes the distinction between a declarative system, responsible for learning facts and events, and a nondeclarative system, which is referred to as procedural memory and is responsible for motor skills and procedures.<sup>9</sup> A complimentary memory model proposes that declarative memory (episodic, semantic) is further separated into 2 different interacting systems: a semantic memory system, encompassing recall of concepts and general knowledge not associated with contextual information, and an episodic memory system, linked with recall of specific events encoded in relationship to their temporal-spatial context.<sup>10</sup>

A review by Smith<sup>6</sup> found little evidence for the role of sleep in the enhancement of declarative memory performance. It appears that the function of sleep deprivation would vary with different types of memory. There is evidence that declarative memory subtypes may be differentially affected by the lack of sleep<sup>11</sup> or

by awakenings from specific sleep stages.<sup>12</sup> The type and complexity of the task and the influence of sleep stages with different parts of the nighttime sleep cycle have been shown to be critical.<sup>6</sup> In addition to changes in the sleep stages, sleep parameters (eg, the number of rapid eye movement episodes and spindles) have been shown to be important in intensive learning situations.<sup>13-15</sup> For example, researchers report increases in spindle density following learning in a variety of tasks.<sup>15</sup>

Event-related potentials (ERPs) provide a good tool to investigate the underlying neural mechanisms of cognitive processes. Past studies have suggested that the earlier ERP components within a latency of 80 to 200 milliseconds (eg, N1-P2 complex) are linked with states such as fatigue, arousal, and vigilance.<sup>16</sup> In support of these findings, more recently it has been shown that the influence of sleepiness generally results in lower amplitudes and/or longer latencies in these early components.<sup>17</sup> Only a few ERP studies during sleep have involved complex tasks, and those studies report evidence of information processing during sleep relating to memory and semantic processing.<sup>18,19</sup> It has been well established that, during wakefulness, the N400 component is enhanced in response to word pairs or words in sentences that are semantically anomalous relative to a given context, the amplitude of this effect relating to the degree of effort required to integrate a word in its semantic context.<sup>20-22</sup> ERPs have been recorded during various sorts of declarative memory tasks during wake, and results have consistently shown that differential ERP responses to old (studied) and new items may be useful for studying memory and retrieval processes.<sup>23</sup> The most reliable ERP index identified in memory has been referred to as the Old/New effect. It corresponds to the facts that the ERPs elicited by

the first presentation of a new item are more negative than those elicited by the second repeated presentation of the same item (old item).<sup>24</sup> This modulation is typically observed whether the items to be recognized are pictures, faces, or verbal material.<sup>25,26</sup> This effect appears to have a specific role in memory, since it is not observed for incorrect judgments, ie, misses and false alarms.<sup>27</sup> The ERP Old/New effect develops approximately 250 milliseconds after a stimulus and lasts for a duration of 800 milliseconds. It is composed of a series of components or effects distinct by their timing, scalp topography task correlates, and instructions.<sup>24,28-30</sup> Each of these effects reflects the contribution of a particular cognitive process to recognition. The main contribution to the classic ERP Old/New effect is provided by the modulation of 2 posterior components. The first is a parietal distributed negative wave (N400) that has been attributed to integration of the stimulus with the already-present information in memory (semantic knowledge). A reduction in its amplitude for repeated (old) items is interpreted as easier access to the trace.<sup>31,32</sup> The second component involves a late positive component, also termed *P600*.<sup>33</sup> The P600 has been attributed to elaboration or mnemonic binding that leads to formation or retrieval of an episodic trace consisting of the item and its context. The modulation of this component is thought to reflect the reactivation of memory representation and to constitute the substrate of episodic information retrieval.<sup>34</sup> As characterized previously, the P600 modulation is larger for old stimuli<sup>23,35</sup> than for new stimuli.

The recent development of topographic ERP studies has made it possible to dissociate a number of frontal components of the classic Old/New effect.<sup>28,36</sup> The frontal Old/New effect begins approximately at 250 to 350 milliseconds after the

stimulus. One interpretation is that it reflects strategic control and contextual integration of the stimulus.<sup>37</sup> These effects are manifested by a decrease in the amplitude of the frontal component on old faces, as compared with new ones. It has been suggested that this anterior effect reflects the contribution of the prefrontal cortex to episodic memory. Thus, by utilizing "Old/New" effect protocol, indexes related to both semantic and episodic processes could be used to investigate the contributions of sleep on the different subtypes of declarative memory.

The goals of the present study were 2-fold. First, this study will verify that the classic Old/New effect can be detected after a long delay. Second, the use of such a protocol will allow us to study the differential influence of declarative (episodic and semantic) subsystems, with a delay when it is filled with wakefulness or sleep. To our knowledge, no study to date has used a protocol in which ERPs are recorded before and after such an extended delay to characterize declarative memory processes.

## **Methods**

### **Participants**

Participants were paid volunteers, recruited by personal contact or by public announcement. Medical history, sociodemographic information, and inclusion and exclusion criteria were collected for each subject. Exclusion criteria were a past or current history of psychiatric, neurologic, or other medical condition. Subjects were also excluded if any of their first-degree relatives had a history of primary sleep disorder or major psychiatric illness. Any subjects with uncorrected visual problems were excluded. None were using medications with a known effect on the central

nervous system or sleep. The final group of participants consisted of 13 right-handed adults (7 women, 6 men) aged from 21 to 39 years with an education level of  $18.3 \pm 3.9$  years.

### Procedure

To study the effects on memory, we adopted an experimental protocol similar to that of Jenkins and Dallenbach<sup>1</sup> that compared the effects of a night's sleep and a daytime wake period on recognition memory. Although the amount of specific sleep stages and sleep variables are unavailable, our primary purpose was to evaluate the ERP protocol. In addition, this study design attempts to minimize the potential negative effects of the sleep-recording apparatus on the quality of the subject's sleep.

The ERP protocol is a variation of the classic study test used in ERP memory studies but into which a night of sleep or an equivalent period of daytime wake was inserted between the learning and recognition test (Figure 1).

#### a) Protocol for Experiment

|                              |       |                       |            |                            |     |                         |
|------------------------------|-------|-----------------------|------------|----------------------------|-----|-------------------------|
| PHASE A <sup>(1)</sup>       |       |                       | ≥ 3-7 days | PHASE B <sup>(1)</sup>     |     |                         |
| Evening Acquisition (16-18h) | NIGHT | Morning Recall (7-9h) |            | Morning Acquisition (7-9h) | DAY | Evening Recall (16-18h) |

(1) Phase A<sup>(1)</sup> and B<sup>(1)</sup> to be counterbalanced across participants

Subjects came twice to the laboratory, once for the study (learning) phase and the other for the test (recognition) phase, during which ERPs were recorded. ERPs were recorded during the recognition phase only. All conditions were counterbalanced to control the effects of practice, and participants were randomly assigned to either condition. To limit the possible confounding effects of cognitive variations throughout the day, time of testing was kept constant (Figure 1).

The night of sleep was spent in the sleep laboratory. Information regarding the quality of the night of sleep in the laboratory was obtained in the morning on a questionnaire (see Appendix 4, Table 1 & 2). For the daytime condition, the subjects were able to carry on their routine daily activities and then return to the laboratory for the recognition phase. Upon return to the laboratory, subjects filled out a daytime questionnaire (Appendix 4) reporting their activities and vigilance levels immediately prior to testing (Table 3). To ensure that sleep was equal in both sessions, participants were asked to fill out questionnaires (Appendix 4) about sleep habits, sleep quality at home (sleep agenda) and in the laboratory (morning questionnaire and the Stanford Sleepiness Scale (SSS) (see Table 3).

### **Sleep Agenda**

This measure allowed participants to self-report their sleep experience on a daily basis throughout the experimental procedure. The scale was used as a control to verify that the quality of sleep was no different than that of a typical night's sleep in the home. For a 3-day period before all ERP recordings and throughout participation in the experiment, the number of hours per night of sleep was reported on the sleep agenda and then calculated for each subject. Space was provided for comments such as the quality of sleep, alcohol consumed, medications taken, or physical complaints for each day.

### **Morning Questionnaire**

This measurement asks participants to self-define as having problems sleeping in the laboratory. It estimates (in minutes) the amount of time it takes to fall asleep (sleep onset) or return to sleep after nocturnal awakenings and the number of hours of

sleep 3 days prior to ERP testing. The information provided allowed us to determine the amount of sleep prior to testing, along with the presence of difficulty initiating and the absence of maintaining sleep in the laboratory (Table 1 and 2).

### **Stanford Sleepiness Scale**

The SSS<sup>38</sup> is a frequently used measure of daytime sleepiness that provides a measure of affective evaluation. This scale was included on the Daytime Questionnaire and consists of 7-point scaled items ranging from 1 (feeling active and vital; alert; wide awake) to 7 (lost struggle to remain awake); a higher number indicates increased sleepiness (ie, lower levels of arousal) (see bottom Table 3). The participants select 1 option that best described how sleepy they felt prior to testing. It was administered just before the daytime ERP test recording. For analysis, the scale was collapsed to 1 to 4 points, in which a higher number indicated increased sleepiness (ie, lower levels of arousal) (see bottom Table 3).

### **Memory Task: Study-Recognition Test**

Subjects sat in a comfortable chair in a sound-attenuated room. Stimuli were presented on a gray background at the center of a screen 56 cm away from the subjects, subtending a visual angle of 5° with an interstimulus interval of 4 to 5 seconds. Each stimulus remained on the screen for 1000 milliseconds and was replaced by a mask with the word *blink* for 600 milliseconds. During the study (learning) phase, the subjects were asked to memorize each stimulus. During the recognition phase, participants were required to indicate for each stimulus as

accurately and quickly as possible whether it has been previously presented ('old') or not ('new') by pressing arrow keys on the computer keyboard using the dominant hand.

### **Stimuli**

The learning of unfamiliar faces was used because face processing makes use of semantic information (age, sex, expression, or resemblance with known persons)<sup>39</sup> whereas their unfamiliarity necessitates the formation of a new trace that fosters episodic processes.<sup>40</sup> These stimuli coincided with those used in other papers<sup>41,42</sup> that comprised front-view color photographs of persons' faces. Each face has been quoted as neutral, friendly, or unfriendly by a large group of persons in a prior study.<sup>43</sup> The 160 faces chosen as stimuli for this experiment were those with the higher neutral scores. Eighty of these 160 faces were used for the day test; the other 80 were used for the sleep test. Of each 80-face series, 40 were used for the learning phase and also corresponded to the 40 "old" (during the recognition phase). The other 40 faces served as the "new" stimuli during the recognition phase.

### **Recordings and Signal Extraction**

The electrophysiologic signals were recorded by means of an amplifier (S.A. Instrument Inc, San Diego, Calif). The electroencephalogram was recorded from midline scalp electrodes (Fz, Cz, Pz) placed according to the 10-20 International System.<sup>44</sup> All channels were referenced to linked earlobes. Vertical and horizontal eye movements were monitored via electrodes respectively placed below and on the outer canthus of the left and right eyes. During the recording, the impedance of all electrodes was maintained below 5 K $\Omega$ . The electroencephalogram was recorded

continuously with a bandpass of 0.01 to 30 Hz, digitized on-line at a rate of 250 Hz and stored along with the codes identifying the experimental condition, the stimulus onset, and the subject's response for subsequent off-line averaging. Off-line averaging was performed (InStep software Montreal, Canada) after electrooculogram correction using statistical software algorithms<sup>45</sup> and after rejection for epochs with amplifier blocking exceeding 100 milliseconds. ERPs for correctly identified new items and correctly identified old items were then computed separately from 0- to 1000-millisecond poststimulus onset with a 200-millisecond prestimulus baseline. The ERPs were baseline corrected with respect to a 200-millisecond prestimulus recording interval for all sites, during both sessions.

ERP positive (P) and negative (N) peaks were identified by visual inspection of each participant's waveforms recorded at Cz within stimulus onset to 800 milliseconds. This epoch was selected as typical for previous studies of ERP Old/New effects. Peak amplitudes were quantified with respect to the baseline within time windows (see below) centered on the peak. As in our previous studies, the first component was a negative peak at 258 milliseconds after the stimulus. The N250 was analyzed in a 205- to 311-millisecond time window. The other components were a P350, (312-416 ms), a N400 (417-558 ms), and a P600 (559-753 ms). This procedure resulted in nonoverlapping time window of varying duration that allowed us to capture amplitude effects separately for each component.<sup>46</sup> Behavioral performance was obtained simultaneously with electroencephalographic data. Behavioral performance assessed on the scores (percentage correct and percentage missed) and reaction times (RTs). RTs were collected only for correct trials.

## **Statistical Analysis**

Home and laboratory sleep data were compared with 2-tailed paired t-test. The effect of sleep and wake on cognition scores (percentage correct) was tested with a repeated-measure analysis of variance (ANOVA). RTs obtained were compared by means 2-session (sleep/wake)  $\times$  2-condition (old/new) ANOVA with repeated measures on subjects.

The ERPs were analyzed by a 2-session (sleep/wake)  $\times$  2-condition (Old/New)  $\times$  3-site (Fz, Cz, Pz) ANOVA with repeated measures. The Greenhouse-Geisser<sup>47</sup> nonsphericity correction was employed in repeated measures ANOVA when appropriate. Following convention, unadjusted degrees of freedom are reported along with the Greenhouse-Geisser adjusted p value. Main effects are reported first but described only if they did not interact with other variables. Statistical significance is assumed at  $\alpha$  .05 level.

## **RESULTS**

### **Experimental Measures**

#### Morning Questionnaire

Table 1, shows the results of a paired t test between the laboratory and home sleep. It was concluded that there was no significant difference between the mean number of hours in the morning after sleeping in the laboratory versus those reported at home on the sleep agenda 3 days prior,  $t_{12} = -1.7$ ,  $p = .10$ , NS or with those reported daily on the sleep agenda (weekdays),  $t_{12} = -.79$ ,  $p = .44$ , NS ) Furthermore, there were

no significant changes in the time it took to fall asleep or mean number of nocturnal awakenings between the 2 scores (lab vs. home) (see Table 1).

**Table 1: Laboratory Sleep vs. Home Sleep Information (N=13)**

|   | Home      | Lab       | t (12)            |
|---|-----------|-----------|-------------------|
| <u>Sleep Onset Latency (min)</u>        |           |           | 1.78 <sup>a</sup> |
| 1-10                                    | 6         | 3         |                   |
| 10-30                                   | 4         | 5         |                   |
| 30-45                                   | 3         | 4         |                   |
| > 45                                    | 0         | 1         |                   |
| <u>Sleep Duration (hrs)<sup>b</sup></u> |           |           |                   |
| Morning Questionnaire                   |           | 7.0 ± 1.2 |                   |
| Sleep Agenda (weekdays)                 | 7.2 ± .82 |           | -.79 <sup>a</sup> |
| Sleep Agenda (3 days prior to testing)  | 7.7 ± 1.2 |           | -1.7 <sup>a</sup> |
| <u>Number of Awakenings</u>             |           |           | -.60 <sup>a</sup> |
| 0                                       | 4         | 2         |                   |
| 1-2                                     | 7         | 8         |                   |
| 3-4                                     | 1         | 3         |                   |
| 5                                       | 1         | 0         |                   |

<sup>a</sup>p > .10, NS pairwise t test between sleep at home vs. in the laboratory.

<sup>b</sup>Data are presented as mean ± SD.

Seventy-six percent of the subjects reported a similar to better quality of sleep in the laboratory, as compared with at home. In addition, the depth of sleep in the laboratory in 11 out of 13 (85%) of the subjects was reported as deep (see Table 2).

**Table 2.** Nighttime Laboratory Sleep Information (N=13)

|   | Number (%) |
|---|------------|
| <u>Nighttime Sleep Quality</u> , as compared with usual |            |
| Less  | 3 (23)     |
| Similar   | 8 (61)     |
| Better  | 2 (15)     |
| <u>Dreamt</u>   | 7 (54)     |
| <u>Sleep Depth</u>                                      |            |
| Light   | 1 (8)      |
| Moderate  | 1 (8)      |
| Deep  | 11 (85)    |

#### Daytime Questionnaire

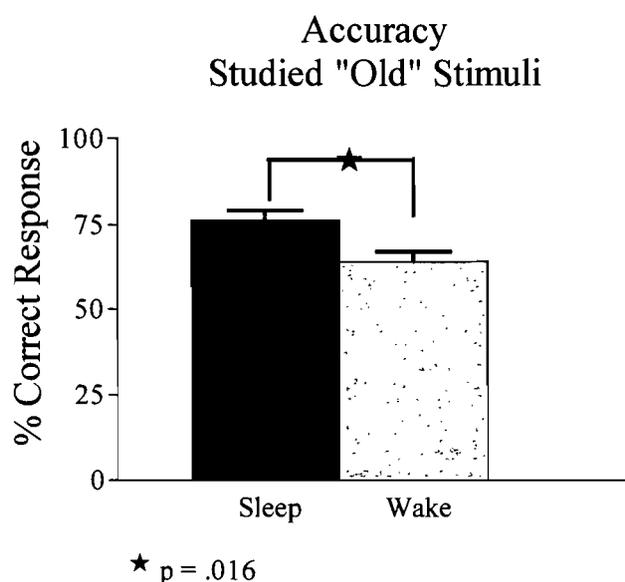
Participants were asked to record the total sleep time at home 3 days prior to the daytime session test, and a paired-sample t-test was used to evaluate the data. The results showed no significant difference between the hours of sleep prior to daytime ERP testing and that in home ( $t_{12} = 43$ ,  $p = .670$ , NS) (Table 3).

**Table 3.** Daytime Session Information (N=13)

|  | Results   | p Value <sup>a</sup> |
|--|-----------|----------------------|
| <u>Amount of sleep (hrs)<sup>a</sup></u>     |           |                      |
| Sleep Session                                | 7.8 ± 1.1 | .670                 |
| Daytime Wake Session                         | 7.7 ± 1.0 |                      |
| <u>Stanford Sleepiness Scale<sup>b</sup></u> |           |                      |
| Very Alert                                   | 4         |                      |
| Alert  | 6         |                      |
| Foggy  | 1         |                      |
| Very Sleepy                                  | 2         |                      |

<sup>a</sup>Paired t-test comparing amount of sleep, in hours, in the 3 days before sleep or wake session. Data are presented as mean ± SD.

<sup>b</sup>Data are presented as number of subjects in the category and are collapsed from 1-4.



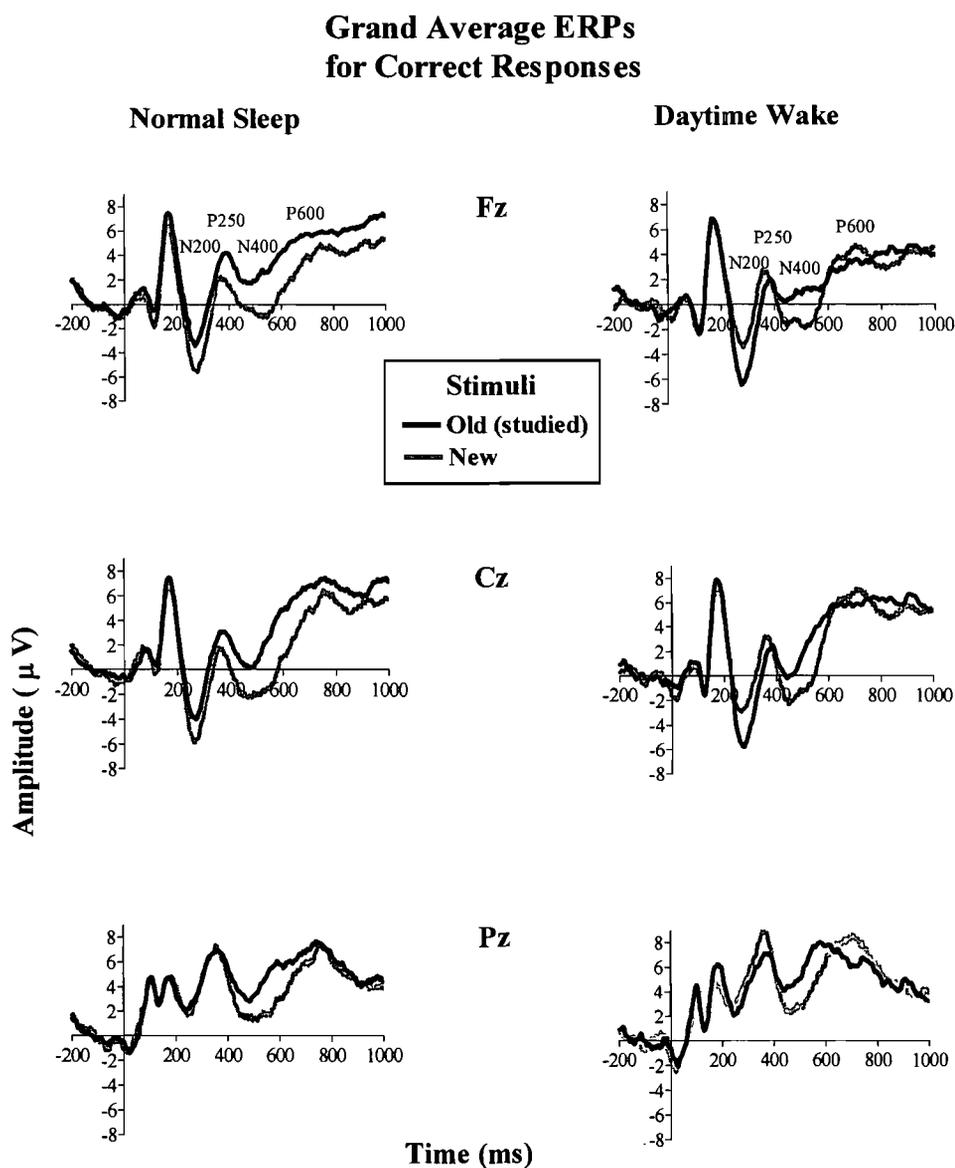
**Figure 2.** Behavioral performance (mean % and SEM) results showing that less correct responses for the old or previously studied stimuli were produced following a period of daytime wake vs. nighttime sleep.

The ANOVAs on correct-answer RT data showed a significant effect of condition (Old/New) ( $F_{1,12} = 10.65$ ;  $p = 0.007$ ). There was no significant effect of Session or interaction between the 2 factors, indicating that the subjects' Old/New effect on RTs was equally present both after the night or day session. The Old versus New items, however, were recognized faster both after sleeping (mean  $\pm$  SD) ( $1121.0 \pm 296.1$  ms vs.  $1183.9 \pm 335.5$  ms) and after a period of daytime wakefulness ( $1103.0 \pm 404.2$  ms vs.  $1144.9 \pm 425.7$  ms).

### ERP Data

The grand average waveforms presented in Figure 3 shows 4 main peaks associated with the Old/New effect, similar to those previously reported and for those

reported in a similar design after the normal sleep and daytime wake conditions. In both sessions, similar components were identified with slightly different window latencies.



**Figure 3.** Grand average event-related potentials (ERPs) elicited by correctly recognized *old* or studied stimuli (black line) and *new* (grey line) at the midline (Fz Cz, Pz) sites. Left: Normal sleep session; Right: Daytime wake session. Four peaks appear at within 250 to 800 ms after the stimulus.

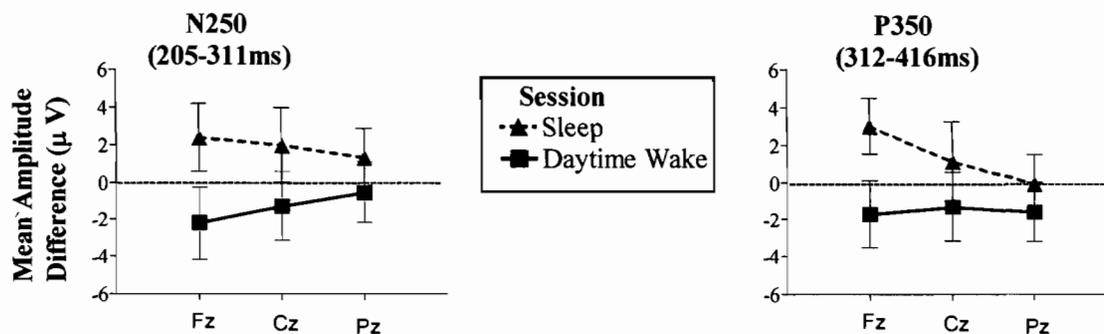
## Memory ERP Components

### N200-P350 Time Window

The ANOVA for the N200 time window resulted in a significant main effect of Site ( $F_{2,24} = 22.21$ ;  $p < .001$ ). There were also significant interactions between Session and Condition (Old/New) ( $F_{1,12} = 14.66$ ;  $p = .002$ ) and a significant Site by Condition by Session 3-way interaction ( $F_{1,12} = 4.28$ ;  $p = 0.04$ ). Further analysis on the N200 component showed that the Old/New effect was significant after the nighttime sleep session ( $F_{1,12} = 11.86$ ;  $p = .005$ ) but not after the daytime wake session ( $F_{1,2} = 4.00$ ;  $p < 0.07$ ).

Similarly, ANOVA on the P350 time window resulted in significant effect of Site ( $F_{2,24} = 26.06$ ;  $p < .001$ ) and a significant interaction between Session and Condition ( $F_{1,12} = 7.58$ ;  $p < 0.02$ ) but no other interactions. The P350 component showed a trend in the Old/New effect after both the sleep ( $v = 4.32$ ;  $p = .06$ ) and the daytime ( $F_{1,12} = 3.44$ ;  $p < .09$ ) sessions. Figure 4 shows the generally larger effect after sleep at the frontal site and an interaction involving the daytime wake session.

These results indicate that ERPs within the N200 and P350 time window are differentially modulated by the Old/New effect in night and daytime wake sessions, and this effect is significant for the N200 ( $F_{1,12} = 4.28$ ;  $p = .04$ ) and P350 ( $F_{1,12} = 7.58$ ;  $p < .02$ ) complex at the frontal site after the sleep session (Figure 4).



**Figure 4.** Mean amplitude difference (old minus new) for the N200 (left) and P350 (right) from midline (Fz, Cz, and Pz) electrodes corresponding to the early “Old” or “New” effect in the Sleep (dotted line) and Daytime Wake (solid line) sessions. Error bars represent the SEM of the old-new difference.

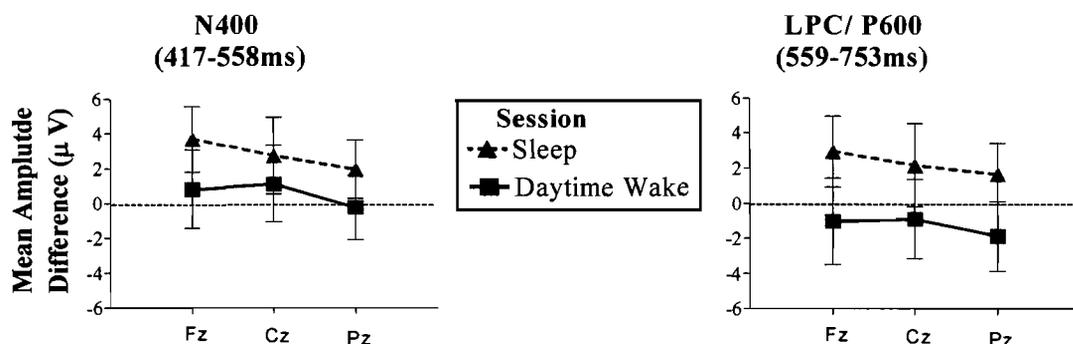
#### N400 Time Window

The ANOVA on the data obtained in the N400 time window showed significant effects of Site ( $F_{2,24} = 4.11$ ;  $p = 0.04$ ) and Condition (Old/New) ( $F_{1,12} = 6.28$ ;  $p < 0.03$ ). There were no interactions involving the other factors, indicating that the classic Old/New effect was present following a long period of either daytime wakefulness or after a night of sleep. Figure 5 (left) shows that the N400 Old/New effect was larger over the more fronto-central sites (Fz-Cz). These results indicate a shift in topography of the Old/New effect for the N400 component.

#### LPC/P600 Time Window

The ANOVA on data obtained in the LPC/P600 time window showed no main effects of any of the 3 factors. There was, however, a significant interaction between

Session and Condition, i.e., Old-New, ( $F_{1,12} = 6.24$ ;  $p < .03$ ). Post-hoc comparisons performed separately showed that the Old/New effect occurred following only the sleep session ( $F_{1,12} = 13.73$ ;  $p = .003$ ). Figure 5 (right) shows that the LPC/P600 Old/New effect is generally larger after the subjects slept.



**Figure 5.** Mean amplitude difference (old minus new) for the N400 (left) and LPC/P600 (right) from Fz, Cz, and Pz electrodes corresponding to the late “Old” or “New” effect in the Sleep (dotted line) vs. Daytime Wake (solid line) session. Error bars represent the SEM of the old-new difference.

The grand average (Figure 3) suggests a latency shift for the Old versus New stimuli following the daytime session. To test for this effect, an additional analysis was carried out on the LPC/P600 peak latency, defined as the maximum amplitude at Pz within 558 to 753 milliseconds. The analysis consisted of a 2 (Session)  $\times$  2 (Condition) design that showed no significant effect or interaction.

## **DISCUSSION**

The first goal of the study was to examine whether sleep affects behavioral performance (e.g., RTs, percentage correct) and the ERP Old/New effect differently than that seen after a period of wakefulness. The second aim was to establish if the ERP Old/New effect typically described after short time periods was also present after a long delay of a night of sleep or an equivalent period of daytime wakefulness.

### **Sleep Assessment**

The results show that sleep prior to the ERP testing was no different than usual. Falling asleep and the number of nocturnal awakenings were also not different than that at home. Despite the fact that the night in the laboratory resulted in slightly less sleep than on the sleep agenda 3 days prior (39.6 minutes), the majority of the subjects reported sleeping deeply and having a moderate to high quality of sleep (Table 1).

### **Behavioral Data**

As expected according to the literature,<sup>24</sup> participants' responded faster for the old studied stimuli compared to the new stimuli. However, there was no evidence for a beneficial effect of sleep on RTs. This indicates that the motor component of the Old/New effect does occur after a long delay, whether it is filled with sleep or wake. On the other hand, participants made more accurate responses (percentage hits) after a night of sleep compared with after an equivalent period of daytime wakefulness. This enhanced performance could well reflect the role of sleep in memory

consolidation. The idea is supported by the fact that the participants committed fewer miss responses (ie, information actually forgotten) after sleep, which is consistent with the role of sleep in memory consolidation. Our results are in concordance with other behavioral sleep studies demonstrating a facilitatory effect on performance after sleep, compared with wake, on declarative memory tasks.<sup>1,49,50</sup>

Alternatively, the effect of sleep on memory processing may reflect circadian influences on the time of testing. Past research in this area has shown increases in performance in college-aged participants if tested at their “optimal time of day,” ie, in the afternoon, but not if tested at their “worst time of day,” ie, in the morning.<sup>52,53</sup> The pattern of our data, however, showed an opposite effect during the recognition test: after a night of sleep, there was more-accurate performance in the morning recognition test than after a period of daytime wakefulness. We also found no difference in RT measures for the recognition test at the evening and morning times, which would argue against circadian influences. It is possible that the impairments in accuracy performance during the wake session may be attributable to poor encoding of material that would lead to an increase in false alarms (ie, an inability to discriminate new from old items) on the recognition test.<sup>54</sup> However, we did not find this to be the case, since our data revealed an increase in the number of miss responses (forgotten items) and very few false alarms.

## **ERP Data**

### **Effects of Arousal/Vigilance (N1-P2)**

As mentioned previously, the earlier ERP components identified in this study (ie, N1-P2) have been linked to arousal<sup>55</sup> fatigue and vigilance<sup>16</sup> and have been reported to be diminished with drowsiness and in sleep. Therefore, the lack of a difference between sessions on N100 and P200 amplitudes indicates that any differences found on the later ERP components cannot be explained by differences in levels of arousal, fatigue, or vigilance across sessions.

### **Memory ERP Effects**

In general, the results from the later components showed that the ERP to old stimuli differs from the ERP to new stimuli. That is, an Old/New effect is elicited after a long delay in the same way that numerous other researchers have shown this effect using shorter delays.<sup>23-25,56-58</sup> This finding further validates our protocol from an ERP perspective. Additionally, our results show differences in the Old/New effect across sessions. The magnitude of the effect is generally larger after sleeping, as compared with after a period of wakefulness, which is in agreement with a role of sleep in declarative memory consolidation. Moreover, it shows that sleep does not affect the later ERP component homogeneously. To the extent that the various components contributing to the Old/New effect are associated with distinct aspects of declarative memory (ie, semantic and episodic processing) or with the activity of the frontal coordinating systems (see introduction), this observation indicates that sleep influences these processes in a differential manner.

Within the N250 to P350 time window, the results showed an early Old/New effect that is frontally distributed and is larger after sleep than after wakefulness. Recently, there have been a growing number of studies showing modulation of these components by contextual processing.<sup>36,59,60</sup> Similarly, our results indicated that sleep influences context processing differently than does wakefulness. In the same vein, there have been studies supporting the role of sleep in context processing. For instance, Harrison and Horne have shown that individuals deprived of sleep can correctly recognize previously presented stimuli (eg, faces) but have difficulty in remembering in which set of stimuli the faces had appeared (ie, the source of information).<sup>11</sup> This difficulty in context processing has been further associated with the sensitivity of the frontal-cortex function to sleep loss,<sup>61</sup> which is consistent with the scalp topography reported here.

Our scalp-recorded ERP data were limited for further localizing this frontal effect. Expanding the ERP topography would allow further dissociation between 2 recently described frontal effects—a bilateral fronto-polar effect<sup>28,41</sup> and a fronto-central effect<sup>37</sup> that overlap with the N400 and P600 components—but differs in the functional meaning.<sup>64</sup>

The results from the subsequent time window showed an Old/New effect involving the posterior N400 component, similar to the effect classically observed after short delays. The consensual view is that the amplitude of this negative component is inversely proportional to the ease with which the information supplied by the stimulus can be integrated with the already-present information in semantic memory.<sup>64-66</sup> Accordingly, the decreased or more-positive amplitude to previously

presented information (ie, old stimuli) corresponds with the fact that it is more easily integrated than are the new stimuli. It could be argued that the facilitatory effect of sleep on memory found in the present study does not reflect differences in memory per se but, rather, may be due to interference from subsequent information in the daytime. As previously mentioned, we found a significant difference in the N400 in the old (studied), compared with the new, stimuli, but there was no difference on the N400 component across session (Sleep/Wake). If one accepts that the N400 reflects the access to the memory trace, then the absence of a sleep-wake difference across sessions and no interactions involving the Session factor clearly indicate that the trace has not been erased by daytime interference.

The N400 is typically followed by a late positive component or P600 that exemplify the Old/New modulation generally observed in memory studies.<sup>66,70,71</sup> However, our data show that the P600 Old/New effect occurred only after sleep. Characteristically, the functional interpretation of the P600 is that the amplitude of the P600 is proportional to the elaboration of the information retrieved from episodic memory.<sup>18,72</sup> By this account, the larger amplitude to old stimuli, as compared with the amplitude to new stimuli, simply reflects that previously memorized information accesses more-elaborated information than the new ones. Hence, our results indicate that information retrieved after sleep is more elaborated than after wakefulness, which is consistent with the enhancement phase of the 2-stage model of consolidation proposed by Walker et al. As for the N400, other ERP studies showing that a P600-like component can be elicited *during* sleep<sup>73,74</sup> may well reflect that the processes underlying elaboration contribute to the sleep stage of consolidation.

An additional point concerning the P600 results in our study requires further comment, despite the fact that it was not found to be significant. After wake, there was a tendency of the P600 latency to old stimuli to occur earlier than for new stimuli, and it was also seen for the old stimuli after sleep (Figure 4). A longer latency of the late positive component has been related to increased task complexity<sup>75,76</sup> and higher workload. In the context of the present memory task, this can be best understood as the difficulty in making the recognition decision. By this account, the latency difference observed here in our study after wake would indicate that this decision is easier for old than for new stimuli, which is consistent with the stabilization stage of consolidation.

### **Conclusions**

This study demonstrates that ERP (Old/New) effect on the declarative memory process is enhanced by sleep both in terms of behavioral performance and electrophysiologic measures. Furthermore, it appears that the various components and the changes in their parameters (ie, increase vs decrease in amplitude and latency) permit inferences upon the influence of the different stages of consolidation (ie, stabilization vs enhancement) on specific episodic, semantic, or coordination processes involved in recognition. Although some of the observations remain to be confirmed, the protocol presented here could thus provide a useful basis to investigate further how sleep, wake, or sleep loss, affects declarative memory processes.

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## **EXPERIMENT 2: EFFECT OF SLEEP ON RECOGNITION MEMORY PROCESSES.**

In Experiment 2, my objective was to replicate our previous findings of an Old/New difference from 250 to 800 ms that was larger after nocturnal sleep vs. daytime wake, suggesting a role for sleep in memory consolidations (Moggras, Godbout, & Guillem, 2006). By employing an extended montage I expected to better characterize the frontal effects associated with recognition memory processing by sleep. More specifically, the additional EEG sites allowed dissociating the early frontal (N200) and later frontal (LFC) effects reported in the literature. As for the later posterior Old/New effects (i.e., N400 LPC/P600), I hypothesized that the N400 will be unaffected by session and that the LPC/P600 will be larger in the sleep vs. wake session (Moggras, Godbout, & Guillem, 2006). Lastly, to ensure adequate statistical power for the analysis of the study (learning) session data, I expanded the subject population of our first experiment (N=13) to include five additional subjects (N=18) in this experiment.

As in the previous experiment, the possible differences in level of vigilance between the sleep and wake test sessions were controlled for by analysis of the N100 and P200 amplitudes (Moggras, Godbout, & Guillem, 2006). In addition, we controlled for the possible confounding effects of time of learning (study) that may have influence the subsequent test session.

Running head: EFFECTS OF SLEEP ON RECOGNITION MEMORY PROCESSES

Event-Related Potentials Differentiates the Processes Involved in the  
Effects of Sleep on Recognition Memory

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### Abstract

This study examined the role of sleep on event related potential (ERPs) indicators of memory following sleep and wake. We expected a larger ERP effect due to a facilitory effect of sleep on memory. During the study session, subjects memorized a series of stimuli (faces). At test, after a retention interval characterized by either sleep or by normal waking activities, subjects were asked to recognize old items intermixed with new. Results revealed differences in the Old/New effect whereby the amplitude between old/new items was larger after sleep vs. wake, suggesting a role of sleep in consolidation. Retention over sleep vs. wake was associated with modified early and late frontal and posterior components possibly manifesting reduced interference inhibition, increased contextual processing and facilitation of episodic memory. These findings suggest that ERP indices are differentially affected by sleep, reflecting differences in memory processing.

**Descriptors:** Sleep, Event-related potentials, ERP Old/New effect, Early frontal component, Late frontal component, N400, Late positive component (LPC), Recognition Memory.

## Event-Related Potentials Differentiates the Processes Involved in the Effects of Sleep on Recognition Memory

Research has provided evidence that sleep is critically involved in the consolidation of memories (Fischer, Hallschmid, Elsner, & Born, 2002; Gais, Plihal, Wagner, & Born, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Support for sleep-dependent memory consolidation has come from a range of studies reporting improvements in behavioural performance linked with changes in sleep stages (Horne & Walmsley, 1976; Smith, 1995; Plihal & Born, 1999) neuronal activity (Wilson & McNaughton, 1994) and regional blood flow (Peigneux et al., 2003) that occur during sleep. As to why some researchers report no evidence for a role of sleep in the consolidation of memory (Smith, 2001) while others suggest that sleep can enhance recognition memory (Nesca & Koulack, 1994; Plihal et al., 1999) is a matter of debate. It has been hypothesized that this lack of agreement between studies may be a consequence of the different task characteristics (Empson & Clarke, 1970; Tilley & Empson, 1978), specific sleep states (Plihal et al., 1999) or the type of stimuli (Smith, 2001; Stickgold, 2004) that can influence the degree of sleep dependency. For instance, experiments by Plihal and Born demonstrated that the beneficial effects of sleep on memory are influenced by the early or late sleep periods depending on the kind of memory task employed, e.g. word paired association vs. mirror tracing skills (Plihal et al., 1999; Plihal & Born, 1997). Recent studies using related word pairs as stimuli show sleep-dependent improvements (Gais & Born, 2004; Gais, Molle, Helms, & Born, 2002), whereas those that use unrelated word

pairs do not (Stickgold, 2004). This indicates that sleep and sleep stages may have a differential effect on the multiple memory systems and processes.

Functional neuroimaging studies have reported changes during sleep in many of the brain regions involved in memory (Braun et al., 1997; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997; Nofzinger et al., 2002; Nofzinger et al., 2000) suggesting that sleep is somehow involved in memory. Compared to wake, dreaming or rapid eye movement (REM) sleep imaging studies indicate activation of the limbic and paralimbic regions (Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997; Maquet et al., 2000; Maquet, 1997; Maquet et al., 2004) with simultaneous deactivation of the dorsolateral prefrontal cortex, PFC (Braun et al., 1997; Maquet, 1997). During REM compared to NonREM sleep, Braun *et al.* (1997) noted relative activation in the limbic, medial prefrontal and inferior temporal cortices along with decreases in parietal association cortices. Regional deactivation during NonREM sleep is also seen in the orbitofrontal cortex and medial temporal lobe (Braun et al., 1997; Maquet et al., 1997). Taken from above, diverse changes in functional neuroanatomy are connected with NonREM and REM sleep states, making it distinct from the waking brain. Thus, sleep similar to memory cannot be treated as a homogeneous state.

A neuroimaging study, using a spatial memory task, revealed that hippocampal areas activated during route learning were reactivated during subsequent NonREM sleep (Peigneux et al., 2004). In addition, the hippocampal re-activation was positively correlated with improved retrieval performance the following day. In the same vein, a recent imaging study investigated how consolidation affects the

neural correlates of memory retrieval over short and long retention periods (Takashima et al., 2006). Their results indicated that the pattern of brain activation was dramatically different at the different retention intervals. For example, the confident recognition of previously studied items was associated with hippocampal activation at 1-2 day intervals; whereas, longer retention delays were associated with activation of medial PFC. The data show that the neural circuits supporting recognition memories undergo synaptic re-organization over time. Furthermore, the duration of NonREM sleep one day after learning positively correlated with recognition memory performance on subsequent testing, indicating that sleep-dependent processes may play a role in memory. However, in contrast to these positive findings, earlier work investigating sleep and recognition memory offered contradictory conclusions (Smith, 1995; 2001). A review by Smith (2001) suggested that the inconsistencies in the literature on the effects of sleep on memory may be attributed to the overuse of verbal stimuli, that is, paired associate word lists (Smith, 2001). To overcome this problem, we used unfamiliar faces. These stimuli permit extraction of semantic information; such as, age, gender, expression or resemblance to known persons (Bruce & Young, 1986) while at the same time their unfamiliarity necessitates the formation of a new trace that fosters episodic processes. Accordingly, such stimuli are bound to generate information related to episodic and semantic memory processing and/or their interaction.

Over the past years, this picture has become more complex, indicating that simple procedural skills tasks require light, NonREM sleep (Smith & MacNeill, 1994), whereas other types of procedural tasks involving visual discrimination

depend on REM and deeper NonREM sleep (Gais, Plihal, Wagner, & Born, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Event related potentials (ERPs) allow a promising avenue for addressing several of these discrepancies by allowing for dissociating the different cognitive and memory processes.

The most reliable ERP index identified in complex memory tasks has been referred to as the "Old/New" effect (Allan, Wilding, & Rugg, 1998; Rugg & Doyle, 1994; Friedman & Johnson, Jr., 2000). It is typically observed whether the items to be recognized are pictures, faces or verbal material (Allan, Wilding, & Rugg, 1998; Jemel, George, Chaby, Fiori, & Renault, 1999). During recognition, old items as compared to new ones are associated with a positive shift at the posterior sites (Wilding, Doyle, & Rugg, 1995; Wilding & Rugg, 1996; Wilding & Rugg, 1996; Smith & Halgren, 1987; Barrett & Rugg, 1989). This effect appears to have a specific role in memory, since it is not observed for incorrect judgments, i.e., misses and false alarms (Wilding, 1999). It is composed of a series of components or effects distinct by their timing, scalp topography and task correlates (Friedman et al., 2000). The main contribution to the ERP Old/New effect is provided by the modulation of two posteriorly distributed components. The first is a negative component elicited within 300-500ms, termed N400 seen in both direct and indirect tests. The N400 effect is not elicited by meaningless items, such as, distorted pictures, impossible objects or illegal non-words (Rugg et al., 1994), which cannot access preexisting information. When using facial stimuli ERP studies of Old/New effect show findings similar to that of verbal stimuli, i.e. the old or studied items elicit an amplitude that is more positive. The effect is larger for familiar faces vs. unfamiliar

faces (Schweinberger, Klos, & Sommer, 1995). Studies using intracranial (Allison, Puce, Spencer, & McCarthy, 1999) and extracranial (Bentin, Deouell, & Soroker, 1999) ERPs reveal a posterior negativity at approximately 200ms post-stimulus to faces. The latencies to nonverbal, face stimuli are earlier than that found in words (Nelson, Thomas, deHaan, & Wewerka, 1998), and often has a right-sided predominance, which is consistent with previous imagery studies (Puce, Allison, Gore, & McCarthy, 1995).

One interpretation is that the N400 reflects the integration of the information provided by the stimulus with personal knowledge (Rugg et al., 1994; Holcomb, 1993). The N400 possesses a centro-parietal distribution, suggesting a contribution of the posterior associative regions (Guillem, Bicu, & Debrulle, 2001). Intracranial studies of event-related potentials also confirms that the N400 is generated at the level of the posterior parietal and temporal cerebral cortex (Guillem, Rougier, & Claverie, 1999). The second contribution to the Old/New Effect is a posterior positivity elicited within 400-800ms termed late positive component, LPC (or P600). The LPC it is thought to represent the mnemonic binding processes that links the different aspects of information to form a coherent representation of the event (Guillem, Bicu, & Debrulle, 2001; Rugg, Doyle, & Holdstock, 1994; VanPetten, Kutas, Kluender, Mitchiner, & McIsaac, 1991). The functional interpretation is in concordance with the previously mentioned imagery studies involved in episodic memory. Furthermore, intracranial ERPs (Halgren, 1990) has shown that the neural generator of the LPC involves, at least partly, the medial temporal cortex (Squire, 1992; Bunsey & Eichenbaum, 1995; Squire, 1992).

Recently, anteriorly distributed Old/New effects overlapping the N400-P600 latency range have been reported (Friedman & Johnson, Jr., 2000). An early, bilateral

inferior frontal negativity is elicited between 250 and 350 ms (Barrett et al., 1989) particularly in tasks involving inhibition of interfering stimuli during retrieval (Tendolkar & Rugg, 1998; Guillem, Bicu, & Debruille, 2001). Later frontal effects elicited between 300-500 ms or longer have been related to strategic monitoring processes (Wilding & Rugg, 1997; Wilding & Rugg, 1997; Wilding, 1999) or more specifically to integration of context, e.g. source (Guillem, Bicu, & Debruille, 2001). These interpretations receive support from imagery studies showing right frontal activity related to recollection and strategic processes (Henson, Rugg, Shallice, Josephs, & Dolan, 1999) that pertain to information retrieved from episodic memory (Nolde, Johnson, & D'Esposito, 1998). This is in concordance with other imagery studies showing that frontal regions are particularly important for successful episodic retrieval (Ranganath & Paller, 1999; Ranganath & Paller, 2000). Alternatively, frontal effects may also reflect the degree of retrieval effort (Schacter, Savage, Alpert, Rauch, & Albert, 1996). For instance, when retrieval is complex and difficult there is a bilateral or left lateralized frontal contribution (Johnson, Raye, Mitchell, Greene, & Anderson, 2003) that has been interpreted as reflecting retrieval of semantic information.

A recent study by us addresses the question of the effects of sleep on next day performance and cognitive processes with the use of a classical memory task in a study-test design (Mogras, Godbout, & Guillem, 2003). In that study, ERPs were utilized in a recognition task of unfamiliar faces with learning prior to and testing after nocturnal sleep or following an equivalent period of daytime wake. It was established that the classic "Old/New" memory effect (i.e. positive shift from 250 to

800 msec) was elicited after a long delay in the same way numerous other researchers have shown this effect with shorter delays (Friedman & Johnson, Jr., 2000). More importantly, results revealed differences in "Old/New" effect on the LPC whereby the magnitude was larger after sleeping compared to wake, suggesting a role for sleep in memory consolidation. The earlier components identified within the 60-200ms time window (i.e. N1-P2) were not affected, indicating that any differences found on the later memory components cannot be explained by differences in vigilance across session. Furthermore, it was shown that sleep does not affect the ERP components homogeneously. In that study, we reported an increase in episodic retrieval on the LPC (elaboration/episodic memory) that was greater following sleep vs. wake but no difference in amplitude across session on the posterior N400 (trace/semantic access). Unfortunately, the midline scalp-recorded ERP data prevent precise identification of the frontal processes (e.g., interference and/or contextual processing) involved.

The present study was aimed to replicate our previous findings of an Old/New difference from 250 to 800 msec that was larger after nocturnal sleep vs. daytime wake, suggesting a role for sleep in memory consolidations (Mogras, Godbout, & Guillem, 2003; 2006). As for the later posterior Old/New effects (i.e., N400 LPC/P600), we hypothesize that the N400 will be unaffected by session and that the LPC will be larger in the sleep vs. wake session (Mogras, Godbout, & Guillem, 2006). By employing an extended montage we expect to better characterize the frontal effects associated with recognition memory processing by sleep. More specifically, the additional EEG sites will allow dissociating the early frontal (N200)

and later frontal (LFC) effects reported in the literature. Lastly, to ensure adequate statistical power, we expanded the subject population of our preliminary study.

As in the previous study, the possible differences in level of vigilance between the sleep and wake test sessions were controlled for by analysis of the N100 and P200 amplitudes (Mograss, Godbout, & Guillem, 2006). The earlier ERP components within a latency of 60 to 200ms (e.g. N1-P2 complex) have been previously linked to changes in vigilance (Haider, Spong, & Lindsley, 1964). Although these earlier components do not address memory, they can be used to control for unwanted effects of differences in vigilance across different times of testing.

In addition, and contrary to other studies including ours (Mograss, Guillem, & Godbout, 2003) we controlled for the possible confounding effects of time of learning (study) that may influence the subsequent test recognition sessions. ERP enable one to sort the study (learning) phase trials into subsequently recognized versus subsequently unrecognized. The corresponding ERP difference for recognized (hits) vs. unrecognized (miss) items at test is referred to as the difference in memory (DM) effect (Paller, Kutas, & Mayes, 1987) that can be used to assess encoding quality. This difference, DM effect, has been observed in numerous studies using recognition memory tests (Fabiani, Karis, & Donchin, 1986; Paller, McCarthy, & Wood, 1988; Karis, Druckman, Lissak, & Donchin, 1984; Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980). It consists of a larger posterior LPC for successfully recognized items (Hit responses) than for those that were not (Miss responses) (Paller, Kutas, & McIsaac, 1998; Wilding & Rugg, 1996) approximately 300 msec post-stimulus (Sanquist et al., 1980). In view of this, we computed the ERP difference at study on

the posterior sites (Cz, Pz) from 300 – 800 msec post-stimulus, where this effect is known to be prominent.

## **Methods**

### Participants

Eighteen healthy individuals (9 males and 9 females) aged between 18 and 39 years old (mean age 29) were tested twice, with a period of 4 to 7 days between experimental sessions. All of the participants had completed some years of university education (mean education level: 18.3 +/- 3.9 years). Standard questionnaires were used to collect the socio-demographic characteristics, sleep and medical history of each subject prior to the experiment (see Appendix 4). Eligible participants underwent an interview and questionnaire session in the laboratory, approximately ½ hour in duration. Exclusion criteria were a past or current history of psychiatric, neurological, sleep disorder or other medical condition. Participants were also excluded if any of their first-degree relatives had a history of primary sleep disorder or major psychiatric illness. All had normal or corrected to normal vision. Participants were asked to keep regular sleep-wake schedules for at least a three-day period before coming to the laboratory. They were also required to fill out a sleep agenda during the course of the experiment and, refrain from taking naps during the day of the testing. The local Ethics Committee approved the protocol where the study was conducted. All participants were fully informed of the recording methods and signed a consent form before participating in this experiment. Participants were financially compensated.

### Procedure

Participants were tested twice in a counterbalanced fashion to control the effects of practice (see General Methods, Table 4, p 83). To limit the potential confounding effects of circadian factors across the two test sessions, recordings with similar delay periods were made during the same time window (8:00 a.m. +/- 1 hr and 6:00 p.m. +/- 1 hr) in the morning following follow sleep or in the evening preceding wake. During the wake session, participants were presented with the task for learning between 7 – 9h and tested between 16-18h. During the sleep session, learning was between 16-18h and the test session was between 7 – 9h. The general protocol was built as a classical study-test design. The study (learning) phase and the test (recognition) phase, each lasting about 15 minutes, were separated either by a night of sleep (sleep session) or an equivalent period of daytime wakefulness (wake session) (see General Methods, Figure 13). The night of sleep was spent in the sleep laboratory. Information regarding the quality of sleep in the laboratory was obtained in the morning on a questionnaire (Appendix 4). For the daytime wake condition, subjects were able to carry on their routine daily activities and then return to the laboratory for the recognition test session. Upon return, a daytime questionnaire was filled out reporting their activities and rating their level of daytime sleepiness on the Stanford Sleepiness Scale (SSS) prior to the testing (Appendix 4). Included in the daytime questionnaire was the SSS, a frequently used measure of daytime sleepiness that provides a measure of affective evaluation (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973). This scale consisted of 7-point scaled items ranging from 1 (feeling active & vital; alert; wide-awake) to 7 (lost struggle to remain awake) a

higher number indicates increased sleepiness (i.e. lower levels of arousal). The participants select one option that best describes how sleepy they felt prior to testing. It was administered just before the daytime ERP test recording. For analysis, the scale was collapsed to 1 – 4 points, where a higher number indicates increased sleepiness (i.e. lower levels of arousal).

### Stimuli

Stimuli consisted of color photographs representing persons' faces unknown to the subjects. These stimuli were taken from the MED bank of faces (Debrulle, Pelchat, Dubuc, & Brodeur, 1997) that is composed of front view color photographs of faces taken in the same conditions (background and light). Each face of this bank has been rated as neutral, friendly or unfriendly by a large group of persons in a prior study (Debrulle et al., 1997). Thus, to minimize the possible confounding effects of emotional expression, the 160 faces chosen as stimuli for this experiment were those with the higher neutral scores. The whole set was divided into two sub-sets of 80 faces balanced for gender. Each of these sets served to construct a study series of 40 stimuli and a test series of 80 stimuli in which the 40 previously presented were intermixed with an additional 40 'new' stimuli. There were two different study-test series so that the presented items were different during both sessions (sleep/wake). Subjects sat in a comfortable chair in a sound-attenuated room. Stimuli were presented on a gray background at the center of this screen 56 cm away from the subjects yielding a visual angle of 5° and with an interval inter-stimulus of 4.5 s. Each stimulus remained for 1000 ms and was replaced by a mask with the word 'blink' for 600ms. During the study (learning) phase, the subjects were told to memorize each

stimulus for a subsequent recognition test. Following a night's sleep or daytime wake period, the subjects were tested in recognition test phase. During this phase, they were required to indicate for each stimulus, as accurately and quickly as possible whether it has been previously presented ('old') or not ('new') by pressing the arrow keys on the computer keyboard.

#### Recordings and signal extraction

The EEG was recorded from 27 tin scalp electrodes in a commercially available cap (Electrocap International) placed according to the extended 10-20 International System montage (Fp1, Fp2, Fpz, F3, F4, F7, F8, Fz, FC3, FC4, FT7, FT8, Cz, CP3, CP4, P3, P4, Pz, T3, T4, T5, T6 TP7, TP8, O1, O2, Oz) (American EEG Society, 1994). All channels were referenced to the linked earlobes. For horizontal EOG, electrodes were placed at the outer canthus of each eye, and for the vertical EOG infra- and supra-orbital to the left eye in line with the pupil when looking straight ahead. During the recording, impedance of all electrodes was maintained below 5 K $\Omega$ . The EEG and EOG were amplified through a bio-electrode amplifier (SA Instrumentation, San Diego) with respective gain of 20, 000 and 10, 000. The EEG was recorded continuously with a bandpass of 0.01 to 30 Hz, digitized on-line at a rate of 250 Hz and stored along with the codes identifying the experimental condition, the stimulus onset and the subject's response for subsequent off-line treatment. Off-line EEG averaging (InStep, Canada) was performed after EOG correction using statistical software algorithms by Woestenburg method (Woestenburg, Verbaten, & Slangen, 1983) and after rejection for epoch with

amplifier blocking exceeding 100ms. ERPs were then computed separately from 0 to 800 ms post-onset with a 200 ms pre-stimulus baseline.

### Questionnaires

All subjects filled out a sleep diary reporting subjective estimates in the number of hours of sleep three days prior to testing and throughout their participation in the experiment, which included one night of sleep in the laboratory. The mean numbers of hours of sleep were analyzed with two-tailed paired t-tests to see if there were any statistically related differences. Pair wise sample t-tests for dependent measures was used to analyze the number of nocturnal awakenings and sleep onset (minutes) in the laboratory compared to that of a normal night of sleep in the home.

### **Behavioral Performance**

The behavioral performance data were obtained simultaneously with EEG data.

Accuracy: The % Hits (i.e. correctly recognized old items) and % Miss (i.e. not recognized response to old items) of both sessions (sleep/wake) were compared by measures of a Repeated Measures ANOVA. This enabled us to determine if sleep influences the memorization of items.

Reaction Times Reaction time (RTs) means were obtained in both sessions for old (studied) and new stimuli were compared by method of a factorial design with 2 'condition' (Old, New) and 2 'session' (sleep, wake) ANOVA in repeated measures (subjects). The RTs were collected for correct trials only.

**ERP data**

ERP peaks were identified by visual inspection of the individual traces recorded at Cz within stimulus onset to 800 ms. This epoch was selected as typical for previous studies of ERP Old/New effects. Peak amplitudes were quantified with respect to the baseline within four time-windows (see: Memory ERPs at Test section). For each peak, the time window was defined as the half distance (median latency) between the current and following peak. This procedure results in non-overlapping, consecutive time windows that captures each ERP peak separately (Guillem, Bicu, & Debrulle, 2001; Guillem & Mograss, 2005; Mograss et al., 2003). While the ERPs were being quantified, we recorded the latency time windows for each subject and calculated the mean time windows for the group.

ERPs at Study (Dm Effect)

The ERP difference for recognition (hits) vs. unrecognized (miss) at test was analyzed to assess potential differences in encoding quality across session. Thus, the DM effect (Paller, Kutas, & Mayes, 1987) was used as a control for possible confounding effect time of day differences during the morning and evening study sessions. ERPs were averaged as a function of performance on subsequent recognition test using midline sites within 300 to 800 ms time window where the DM is prominent and affect the LPC (Sanquist et al., 1980). The responses (hits, miss) were teased out from the later Recognition Test for each subject. The ERP DM effect was analyzed during the Study Session. The analysis consisted of a 2

‘session’ (morning, evening) x 2 ‘condition’ (hit, miss) x 2 ‘site’ (Cz, Pz) repeated measure ANOVA.

#### N1-P2 Complex at Test (Vigilance)

Two ERP peaks within the 50-200 ms (N1 & P2) time window were analyzed. As previously mentioned in the introduction, early ERP studies have linked changes in N1-P2 complex with vigilance (Haider et al., 1964). They have been analyzed to assess potential confounding effects of vigilance differences between the morning and the evening test recognition session. N1-P2 complex was quantified within 67 – 145 ms and 145 – 210 ms time window, respectively, at midline sites for correct recognition (hit) and correct rejection. The analysis consisted of a 2 ‘session’ (wake, sleep) x 2 ‘condition’ (Old, New) x 3 ‘site’ (Fz, Cz, Pz) repeated measure ANOVA.

#### Memory ERPs at Test

Memory ERPs amplitudes and latencies were analyzed for correctly recognized old and correctly rejected new stimuli on the whole coverage from 0 to 800 ms with a -200 ms pre-stimulus baseline. We have used this time window previously in our laboratory (Mograss et al., 2003; Guillem & Mograss, 2005). ERP data were analyzed separately for midline and lateral sites using repeated measures ANOVAs. For the midline sites, the ANOVA included the 2 ‘session’ (wake, sleep), the 2 ‘condition’ (old, new) and 3 electrode ‘site’ (Fz, Cz, Pz) factors as within-subject variables. For the lateral sites, the model included the 2 ‘session’ (sleep, wake), the 2 ‘condition’ (Old, New), the 6 ‘region’ (Inferior Frontal (Fp1-2, F7-8), Superior Frontal (F3-4, FC3-4), Parietal (CP3-4, P3-4), Anterior Temporal (FT7-8,

T3-4), Posterior Temporal (TP7-8, T5-6) and Occipital (O1-2) and 2 'laterality' (left, right) factors as within-subject variables.

In all analyses, degrees of freedom were adjusted using the Geisser-Greenhouse procedure where appropriate (uncorrected  $df$  are reported with the epsilon,  $\epsilon$  values and corrected  $p$  values). Differences in scalp distribution across conditions were also analyzed after normalization of the data (McCarthy & Wood, 1985). This procedure allows one to account for the possibility that a given scalp distribution effect can be due to multiplicative differences in distinct neural source strength. In the case of significant interactions, post-hoc analysis was conducted where appropriate. All main effects and interactions were reported on the raw data. Interactions involving the 'site' factor were reported if significant in the normalized data set (Swick & Knight, 1997).

Due to the large number of analysis in our study, it was necessary to lower the alpha level required by significance in order to control for Type I error and increase the confidence that findings identified as significant would be reliable. A highly conservative approach (i.e. Bonferroni) would result in a p-value so low that it substantially increases the risk of Type II errors. Thus, we elected to compromise between these two risks and choose a p-value of .005 that must be reached in order for a particular finding to be deemed statically significant.

## Results

### Morning Sleep Questionnaire

Results of a dependent t-test concluded showed that there was no significant difference between the mean number of hours reported on the weekday sleep agenda ( $M = 7.5$ ,  $SE = .22$ ) and those reported in the morning after sleeping in the laboratory ( $M = 7.0$ ;  $SE = .26$ ),  $t(17) = -1.75$ ,  $p = .09$ , ns). In spite of the fact that the participants' slept less (30 min) in the laboratory, 78% reported a similar to better quality of sleep in the laboratory compared to home. In addition, the depth of sleep in the laboratory in 16 out of 18 (89%) of the subjects was reported as deep (see Table 1b).

Table 1

Participants Sleep History Data (means & SEM in parentheses) N=18

|   | Home          | Lab           | p value* |
|---|---------------|---------------|----------|
| <u>(a) HOURS OF SLEEP (Means +/-SEM)</u>    |               |               |          |
| Sleep Diary                                 | 7.5(+/- .22)  |               |          |
| Day Study                                   | 7.8 (+/- .23) |               | ns       |
| Laboratory Study                            |               | 7.0 (+/- .26) | ns       |
| <u>(b) MORNING SLEEP QUESTIONNAIRE</u>      |               |               |          |
| Nocturnal Awakenings (number of Ss)         |               |               | ns       |
| None  | 7             | 2             |          |
| 1 – 3 times                                 | 14            | 10            |          |
| 5 times                                     | 1             | 1             |          |
| Sleep Onset (number of Ss)                  |               |               | ns       |
| 1-10 minutes                                | 8             | 5             |          |
| 10-30 minutes                               | 6             | 10            |          |
| 30-45 minutes                               | 4             | 2             |          |
| Greater than 45                             | 0             | 1             |          |
| Sleep Quality Home vs. Lab                  |               |               |          |
| Lesser Quality                              |               | 4             |          |
| Similar in Quality                          |               | 12            |          |
| Better than usual                           |               | 2             |          |
| Sleep Depth Home vs. Lab                    |               |               |          |
| Light                                       |               | 1             |          |
| Moderate                                    |               | 1             |          |
| Deep  |               | 16            |          |
| <u>(c) DAYTIME QUESTIONNAIRE</u>            |               |               |          |
| Stanford Sleepiness Scale (collapsed) 1 – 4 |               |               |          |
| Very Alert                                  |               | 5             |          |
| Alert                                       |               | 10            |          |
| Foggy                                       |               | 1             |          |
| Very Sleepy                                 |               | 2             |          |

\*Dependent t-test between sleep information in the home and laboratory environment from the Sleep Diary and sleep questionnaires.

The dependent t-test conducted to evaluate the possible change in the subjects' estimate of awakenings (number of times) during sleep in the laboratory (see Table 1b) showed that there was no significant difference from sleep in the home ( $M = 1.11$ ,  $SE = 1.32$ ) to that of sleeping in the laboratory ( $M = 1.83$ ,  $SE = 1.29$ ),  $t(17) = -1.58$ ,  $p = .13$ , ns). In addition, the dependent t-test conducted to evaluate any change in the subjective estimate of time it takes to fall asleep (sleep onset) showed no significant difference in sleep onset (minutes) between home ( $M = 24.96$ ,  $SE = 27.1$ ) and laboratory ( $M = 21.72$ ,  $SD = 21.1$ ),  $t(17) = .99$ ,  $p = .33$ , ns (see Table 1b).

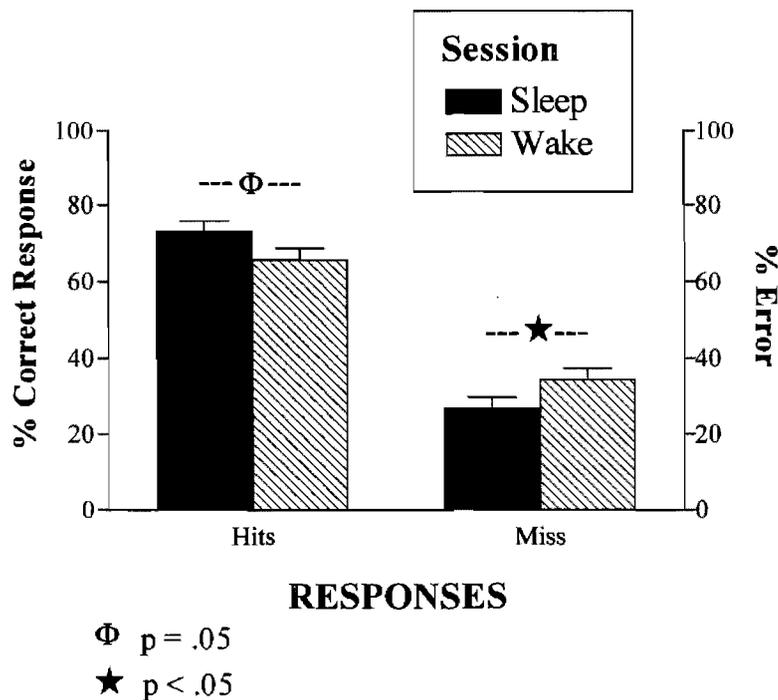
#### Daytime Session Questionnaire

Results of a dependent t-test concluded that there was no significant difference between the number of hours of sleep at home 3 days prior to the daytime recognition test and those reported on the sleep agenda;  $t(17) p = .91$ , ns, (Table 1a). On the daytime questionnaire (see Table 1c), only 3 out of 15 participants reported lower levels of arousal, while 83% (15 out of 18) participants reported being alert to very alert on the Stanford Sleepiness Scale prior to daytime ERP testing.

#### Behavioral Performance Data

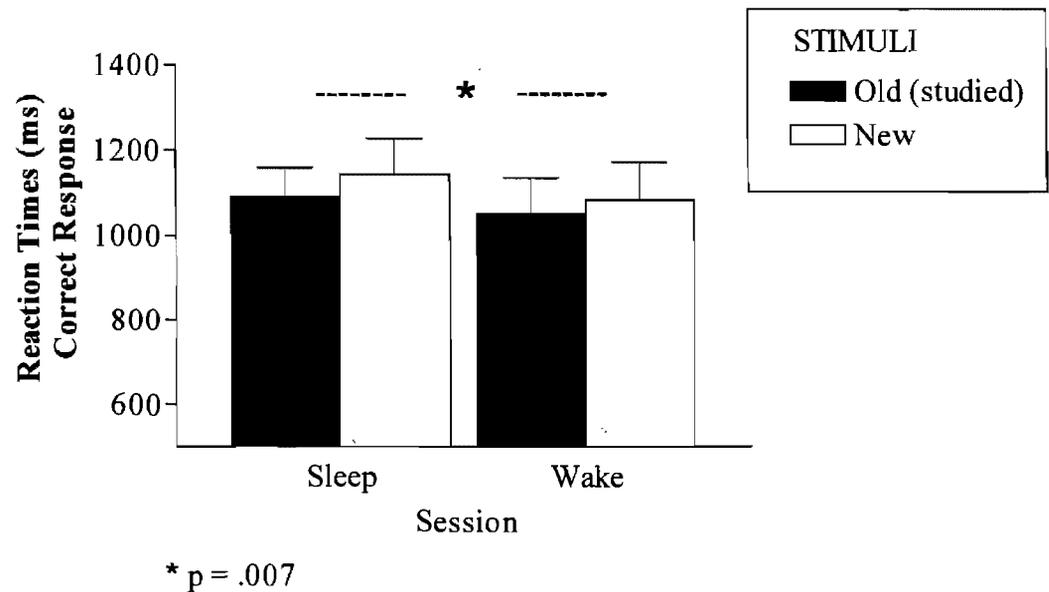
ANOVA on the scores for the previously studied stimuli (old) revealed that there was a significant difference between nighttime sleep ( $M = 73.2$ ,  $SE = 2.8\%$ ) and daytime wake ( $M = 65.8$ ,  $SE = 3.0\%$ ) on accuracy performance. As illustrated in Figure 1, there were significantly more correct responses ( $F(1,17) = 4.45$ ;  $p = .05$ )

and less missed response ( $F(1,17) = 4.8$ ;  $p < .05$ ) on the old stimuli after a night of sleep.



**Figure 1.** Behavioral performance (mean % and standard error) results showing that (left) fewer correct responses (Hits) and (right) more missed response for the old or previously studied stimuli were produced following a period of daytime wake vs. nocturnal sleep.

ANOVAs on correct answer RT data (see Figure 2) showed a significant effect of condition (Old/New) ( $F(1,17) = 9.56$ ;  $p = .007$ ). There was no significant effect of session or interaction between the two factors, indicating that the subjects Old/New effect was present both after the sleep and wake session.



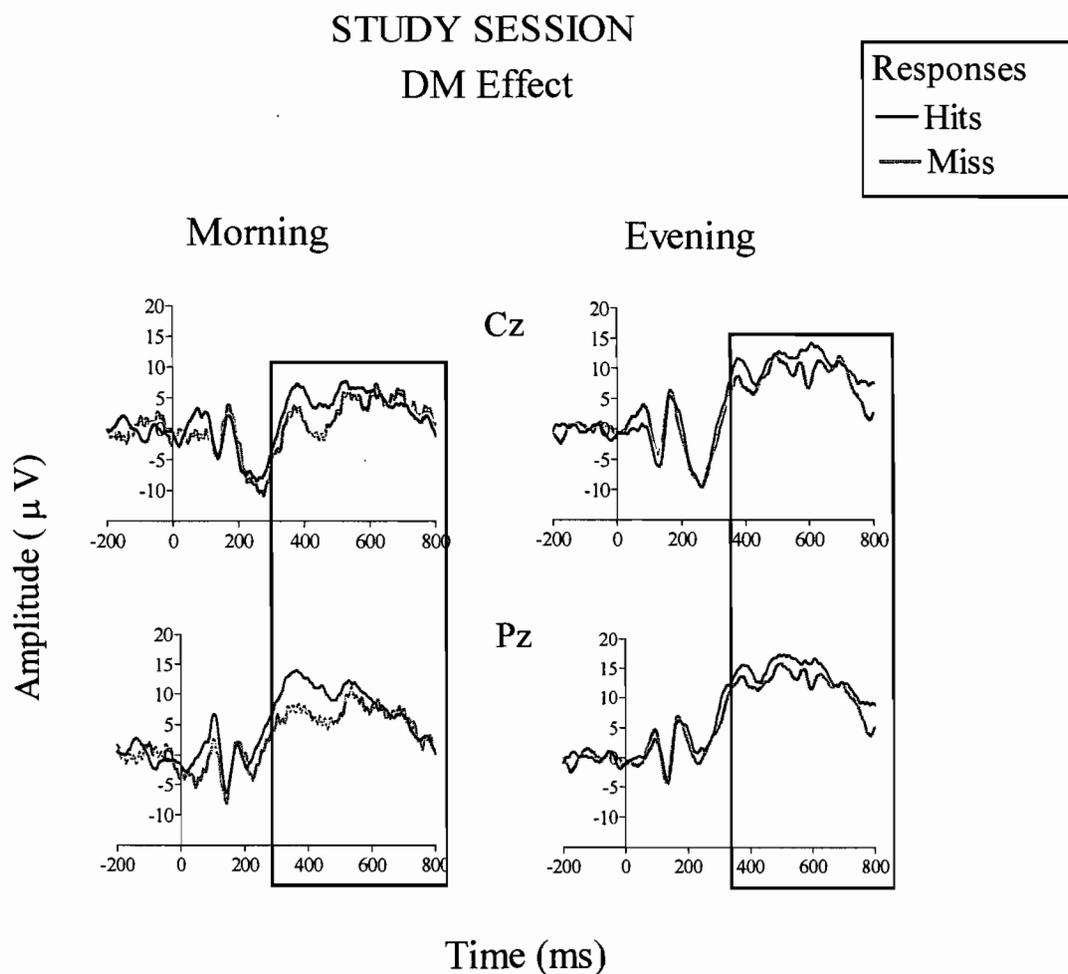
**Figure 2.** This figure shows the behavioral response (mean RTs) for the studied stimuli compare to the new stimuli after nocturnal sleep and a period of daytime wake. Error bars represent the standard error of the mean.

## ERPs

### Study Session

ERPs elicited from the midline site during the study session from 0 to 800ms time window for the evening and morning study sessions are shown in Figure 3. Only 10 out of the 18 subjects had more than 10 miss responses and therefore were included in the study session grand average. The ANOVA on the midline (Cz, Pz) data for the 300-800ms time window, where this effect is known to be prominent, resulted in a significant main effects site ( $F(1,9) = 22.08$ ;  $p < .01$ ) and Condition (hits, miss) ( $F(1,9) = 7.15$ ;  $p < .03$ ). Figure 3 shows that the later recognized (hits) elicited a larger posterior positivity compared to the miss stimuli beginning at approximately 300ms during both the evening and morning study sessions. There were no main effects of session ( $F(1,9) = 3.77$ ;  $p = .08$ , n.s.) or interactions involving site x

Condition (hit,miss) ( $F(1,9) = 2.85$ ;  $p = .12$ , n.s.) or session x Condition (hit, miss) x Site ( $F(1,9) = 3.37$ ;  $p = .10$ , n.s.), indicating that the DM was present and similar across sessions.



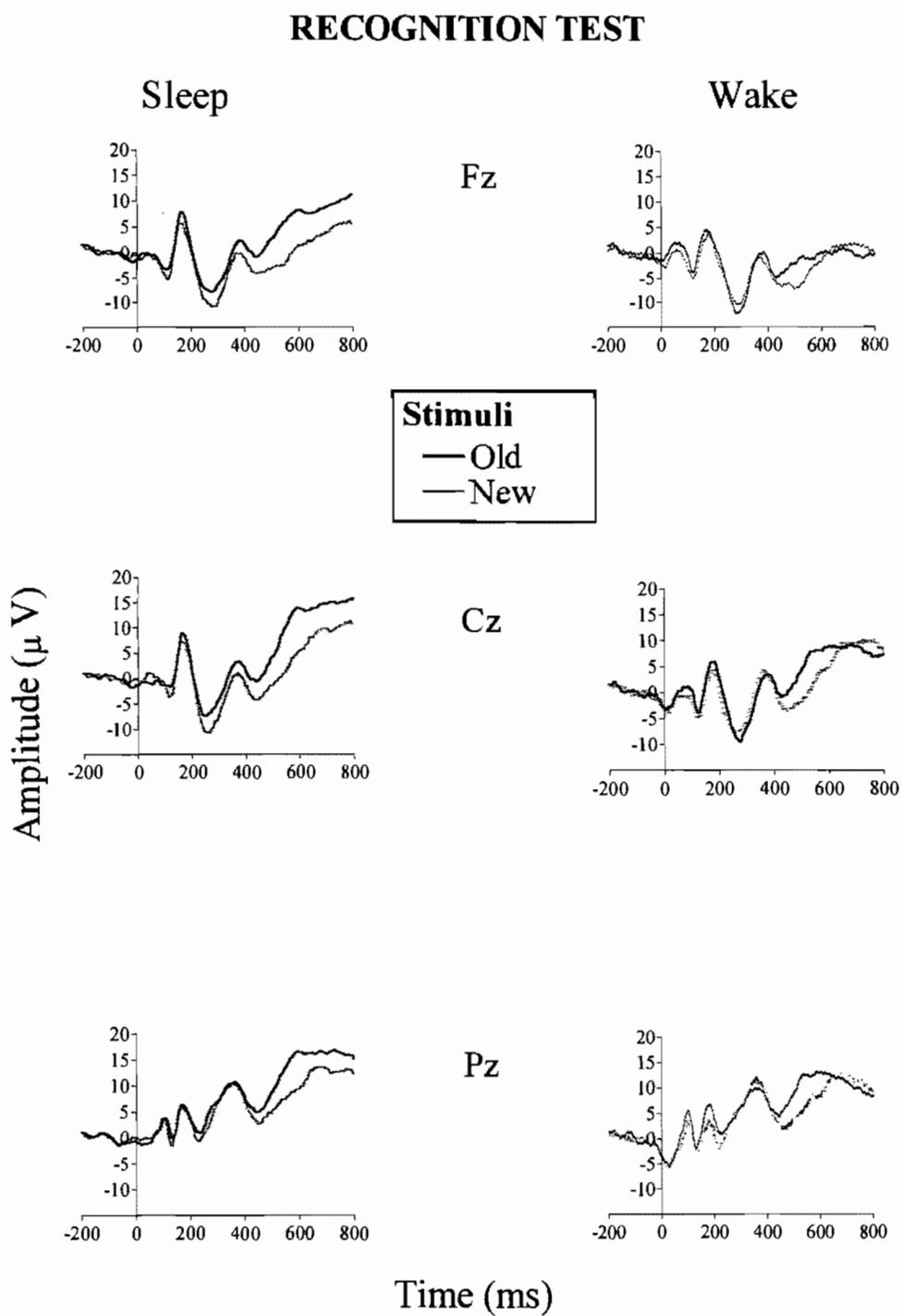
**Figure 3.** Grand Average ERPs for the difference in memory (DM) effect from the midline sites (Cz, Pz) during the Study Session by the stimuli that were (Hits) or were not (Miss) subsequently recognized.  $N=10$

### N1-P2 at Test

The ANOVA on the N1 midline data showed a significant main effects of site ( $F(2, 34) = 16.41$ ;  $p < .001$ ;  $\epsilon = .768$ ) but no main effects or interactions involving the other two factors. For the P2 midline data there were no main effects or interactions involving any of the three factors. Thus, on these components within the 50 to 200 ms time window, there were no effects involving session and no significant interactions involving the session factor.

### Memory ERPs at Test

The grand average ERP waveforms elicited during the test Recognition Test session by the correctly identified stimuli is presented in Figure 4 for the Wake session and Sleep sessions. For both sessions, components were identified with slightly different window latencies. ERPs were analyzed in non-overlapping, consecutive time windows based on the group means of the time window latencies: 205-311ms (including a negative peak), 312-415 ms (including a mid-latency positive peak), 415-553ms (including late negativities, i.e. N400) and 553-755ms (including late positive components).



**Figure 4.** Grand-average ERPs from midline sites (Fz, Cz, Pz) in all of the subjects (N=18) during the recognition test session by correctly recognized 'old' stimuli (black line) & 'new' stimuli (gray line).

Time Window: 205-311ms

The ANOVA on the midline data for the 205 – 311ms time window resulted in a significant effect of site ( $F(2,34) = 4.49$ ;  $p < .01$ ;  $\epsilon = .684$ ) and a significant interaction between session x condition (Old, New) ( $F(1,17) = 7.36$ ;  $p = .02$ ). Post-hoc analysis showed that the Old/New effect was significantly more positive after the nighttime sleep session ( $F(1,17) = 18.18$ ;  $p = .001$ ) compared to the daytime wake session ( $F(1,17) = 0.35$ ;  $p = .56$  ns).

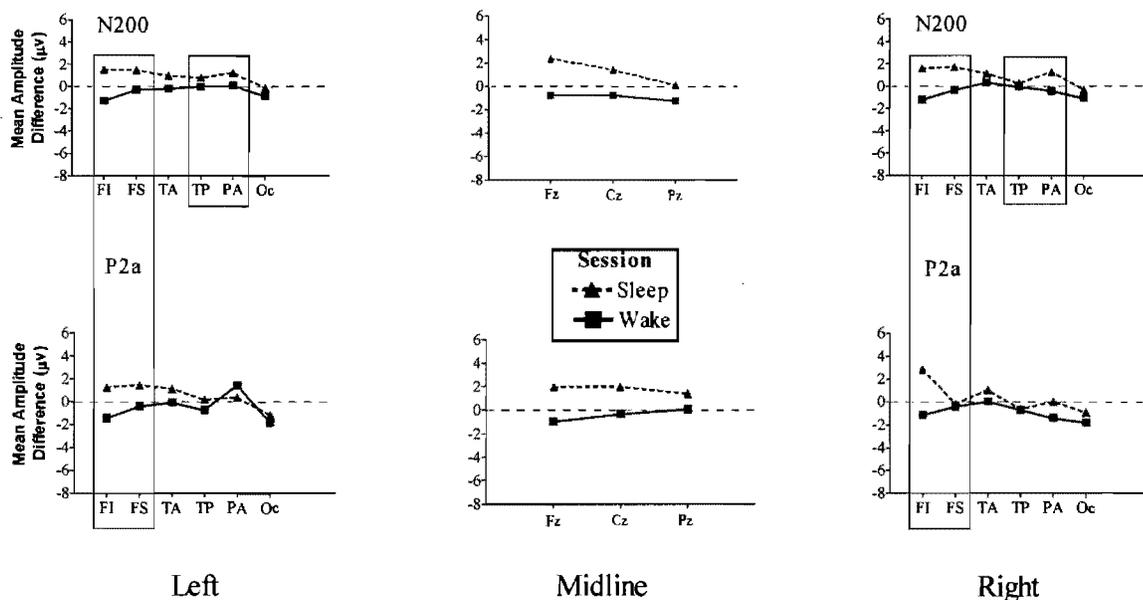
The analysis on lateral regions revealed significant effect of site ( $F(5,85) = 10.94$ ;  $p < .001$ ;  $\epsilon = .294$ ) and laterality (left, right) ( $F(5,85) = 5.81$ ;  $p = .03$ ) with a significant two-way laterality x site interaction ( $F(5,85) = 12.07$ ;  $p < .001$ ;  $\epsilon = .608$ ). As was the case with the midline data, the lateral data shows also a significant interaction between session x condition (Old, New) ( $F(1,17) = 4.76$ ;  $p = .04$ ). Further analysis revealed a main effect of Old/New that was significantly more positive after the sleep session ( $F(1,17) = 7.90$ ;  $p = .01$ ) compared to wake ( $F(1,17) = .61$ ;  $p = .44$ , ns). In addition, Figure 5 shows a posterior component, in which post-hoc analysis on the posterior sites revealed significant effect of laterality ( $F(1,17) = 1.03$ ;  $p = .001$ ). Visual inspection of the mean amplitudes (not shown) revealed that the Old/New effect was slightly larger over the right posterior site after sleep.

Time Window: 312-415ms

Similarly, ANOVA in the 312-415-time window on the analysis of midline data resulted in significant effects of site ( $F(2, 34) = 32.90$ ;  $p < .001$ ;  $\epsilon = .987$ ). There was also a significant interaction between session x condition (Old,New) ( $F(1,17) =$

6.06;  $p = .02$ ) that was significant after sleep ( $F(1,17) = 9.08$ ;  $p = .008$ ) but not after wake ( $F(1,7) = 1.61$ ;  $p = .22$ , ns).

The lateral regions reveal main effects of site ( $F(5,85) = 4.18$ ;  $p = .001$ ;  $\epsilon = .335$ ) and laterality (left, right) ( $F(1,17) = 7.08$ ;  $p = .001$ ) and a laterality x site ( $F(5,85) = 5.68$ ;  $p < .001$ ;  $\epsilon = .837$ ) interaction. There were no effects of condition (Old,New) and session or interactions involving these two factors. Figure 5 (midline, Fz) suggests that this effect appears as a continuation of the effect seen in the previous time window at the frontal sites.

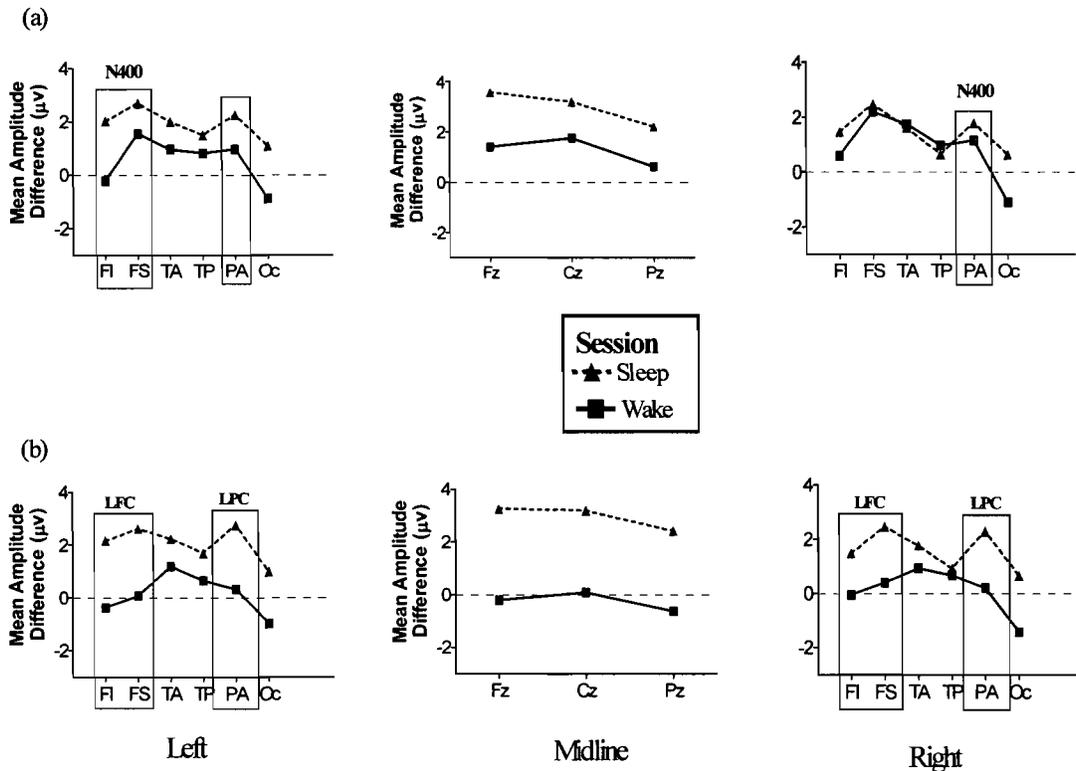


**Figure 5.** Mean amplitude ( $\mu\text{V}$ ) difference (old minus new) corresponding to the early effects (frontal N2-P2a and posterior N2b). Mean amplitude difference across the midline (Fz, Cz, Pz) and lateral (left/right) head regions from 205 to 415 ms. Rectangles indicate the various components involved in the Old/New effect. Interior frontal, IF; superior frontal, FS; anterior temporal, TA; posterior temporal, TP; parietal, PA; occipital, Oc.  $\blacktriangle$  = sleep;  $\blacksquare$  = wake

Time Window: 416-553 ms

ANOVA on the midline data obtained in this time window showed a significant effect of site ( $F(2, 34) = 6.60$ ;  $p < .01$ ;  $\epsilon = .877$ ) and condition (Old,New) ( $F(1,17) = 12.15$ ;  $p < .01$ ) with no effect or interaction involving the factor of session, e.g. session x condition (Old, New),  $F(1,17) = 3.89$ ;  $p = .07$ , n.s.; session x condition (Old,New) x site,  $F(2,34) = .79$ , n.s.; session x site,  $F(2,34) = .35$ ;  $p = .64$ , n.s.)

The ANOVA on the lateral regions revealed significant effects of laterality ( $F(1,17) = 8.27$ ;  $p = .01$ ). There was also a significant main effect of condition (Old,New) ( $F(1,17) = 7.78$ ;  $p < .02$ ) and significant interactions involving condition (Old, New) x site ( $F(5,85) = 3.72$ ;  $p < .03$ ;  $\epsilon = .474$ ) and laterality (left, right) x site ( $F(5,85) = 3.95$ ;  $p < .01$ ;  $\epsilon = .699$ ), but no interaction involving the factor of session. Figure 6(a) show that the condition (Old, New) and condition (Old, New) x site interaction reflect two components within this time window. The first is a frontal effect likely corresponding to F-N400 effect described elsewhere (Curran, 1999g). The second is a bilateral, parietal (PA) effect likely involving the classic N400 component of the Old/New effect. Further inspection of the effect involving the laterality factor revealed that the mean amplitude (not shown) of the parietal N400 is smaller over the left hemisphere (mean amplitude  $4.95 \mu\text{V}$ ) versus right hemisphere (mean amplitude  $1.79 \mu\text{V}$ ), which is the usual distribution for the N400 when using nonverbal (face) stimuli vs. words



**Figure 6.** ERP mean amplitude difference (old minus new) for the late (a) 415 to 554 ms and (b) 553-755 ms time windows from the lateral (left/right) and midline (Fz, Cz, Pz) regions. Rectangles indicate the various components involved in the Old/New effect: anterior and posterior N400, late frontal (LFC) and late positive component (LPC/P600). Interior frontal, IF; superior frontal, FS; anterior temporal, TA; posterior temporal, TP; parietal, PA; occipital, Oc. ▲ = sleep; ■ = wake

#### Time Window: 553-755 ms

ANOVA on data obtained in this midline time window showed main effects of site ( $F(2,34) = 3.78$ ;  $p < .03$ ;  $\epsilon = .807$ ). There was an interaction involving session x condition (Old, New) ( $F(1,17) = 8.38$ ;  $p = .01$ ). In addition, the normalized data revealed a condition (Old, New) x site interaction ( $F(2,34) = 4.77$ ;  $p = .03$ ;  $\epsilon = .699$ ).

The ANOVA on lateral regions revealed significant effects of site ( $F(5,85) = 4.63$ ;  $p = .03$ ;  $\epsilon = .784$ ). There were significant interactions involving laterality x site interaction ( $F(5,85) = 5.89$ ;  $p = .01$ ;  $\epsilon = .632$ ) and session x condition (Old, New) ( $F(1,17) = 3.89$ ;  $p = .05$ ). These results indicate differences in the topographical distribution of the Old/New effect across session. Figure 6(b) shows that the Old/New effect involves the modulation of two topographically distinct components. The first effect is at the posterior site corresponding to the classic LPC/P600 component. The second effect is a right-lateralized, late frontal effect. Post-hoc analysis indicates that the posterior Old/New effect (LPC/P600) was larger after sleep ( $F(1,17) = 14.19$ ;  $p = .002$ ) vs. wake ( $F(1,17) = 7.88$ ;  $p = .61$ , n.s.).

## **Discussion**

The present study investigates the effects of nocturnal sleep on indicators of recognition memory with the aid of ERPs in a recognition memory task of unfamiliar faces. The experiment reported here extends findings from a previous study (Mograss, Godbout, & Guillem, 2006), and helps characterize how sleep affects the various cognitive processes involved in memory.

### Sleep Assessment

The result shows that participants' sleep in the laboratory or when tested prior to the daytime test was not different than usual. Falling asleep and the number of nocturnal awakenings were also not different than that at home. Despite the fact that

the night in the laboratory resulted in slightly less sleep on the sleep diary (30 minutes), the majority of the subjects reported sleeping deeply and having a moderate to high quality of sleep (Table 1b).

#### Behavioral Performance Data

As expected according to the literature (Friedman & Johnson, Jr., 2000; Johnson, Jr., Pfefferbaum, & Kopell, 1985) accuracy and response latency (RT) differed significantly between old and new faces. The difference seen in accuracy performance indicates an enhancement in performance after sleep compared to an equivalent period of daytime wake. This enhanced performance could well reflect the role of sleep in memory consolidation. The idea is further supported by the observation that the participants also committed fewer misses, i.e. less information is actually forgotten after sleep. Our results are in concordance with behavioral sleep studies demonstrating a facilitory effect on memory performance following sleep compared to wake (Gais, Molle, Helms, & Born, 2002; Gais & Born, 2004; Nescá & Koulack, 1994; Plihal & Born, 1999). Although in our study there was a significant effect of accuracy (% hits), there was no significant difference on responding (RTs) across the sleep and wake sessions i.e., participants showed the usual faster response to the studied (old) stimuli compared to the new stimuli on both sessions.

## **ERP Data**

### Study Session (DM) Effect

The analysis of the study session allowed us to obtain ERPs at learning corresponding to items that were subsequently correctly recognized (at test) and those not recognized (Paller, Kutas, & Mayes, 1987). As shown in Figure 3, differential responses for recognized (Hits) versus forgotten (Miss) faces took the form of an enhanced late positive component (LPC/P600) elicited within 300 – 800 ms. This latency and topography are typical for the DM effect shown in other studies (Paller, 1990). The effect (DM) is usually taken as an indication of the quality of the encoding, and was used as a control for the time of learning effect on recognition. Analysis of our data showed that this effect does not differ as a function of the time of encoding (morning vs. evening). This suggests that any effect on the later ERP components after wake or sleep cannot be attributed to cyclic variations at time of encoding.

### N1-P2 Complex at Test:

As mentioned in the introduction, the earlier ERP components identified in this study (i.e. N1-P2) have been linked to vigilance (Nordby, Hugdahl, Stickgold, Bronnick, & Hobson, 1996; Haider et al., 1964). Our data shows no difference between the sleep and wake sessions on the N1 and P2 amplitudes. This indicates that any differences found on the later memory ERP components cannot be explained by differences in levels of vigilance across session. It is also in agreement with our

behavioral results showing the lack of effect on the RTs performance across the sleep and daytime wake recognition test sessions.

### Memory ERPs at Test

In general, the results from the later components showed that the ERP to old stimuli differs from the ERP to new in the same way numerous other researchers have shown this effect with similar (Mograss, Guillem, & Godbout, 2003; Mograss, Godbout, & Guillem, 2006), longer (Curran & Friedman, 2004) and the usual shorter retention intervals (Johnson, Jr., 1995; Noldy et al., 1996; Rugg et al., 2000; Smith & Halgren, 1987; Friedman & Sutton, 1987; Nordby, Hugdahl, Stickgold, Bronnick, & Hobson, 1996; Rugg, 1995; Barrett et al., 1988; Friedman & Johnson, Jr., 2000). Given the type of stimuli used in our study, the latencies are in agreement with the differences seen in the Old/New effect across nonverbal stimuli, such as pictures (Friedman, Sutton, Putnam, Brown, Jr., & Erlenmeyer-Kimling, 1988) and faces (Guillem, Bicu, & Debrulle, 2001; Nelson, Thomas, deHaan, & Wewerka, 1998). In general, these data show differences in the Old/New effect across session; whereby, the magnitude of the effect is larger after sleep compared to wake. This is in agreement for a role of sleep in memory consolidation. Still, the fact that the various ERP components are differentially affected, indicates that sleep influences the processes involved in the ERP Old/New effect in a differential manner.

### Early Effects (205-416 ms)

Within the early time windows, the results showed a bilateral, frontal Old/New effect that is larger after sleep compared to wake. Recently, ERP studies

have described an early fronto-polar effect elicited by pseudo-words (Curran, 1999) and unfamiliar faces (Guillem, Bicu, & Debruille, 2000; Guillem, Bicu, & Debruille, 2001). Some researchers have suggested, when using a memory protocol similar to ours, that this early effect over the frontal lobe is associated with inhibition of interference (Guillem, Bicu, & Debruille, 2001; Guillem, Bicu, & Debruille, 2000; Goldstein, Spencer, & Donchin, 2002), whereby more positive amplitude to old items means that these stimuli entailed *less* interference inhibition than the new items. Along the same line, other researchers have found frontal components (frontal N2 and P2a) within the same latency modulated by stimulus salience (Breton, Ritter, Simson, & Vaughan, Jr., 1988; Potts et al., 1996). In support of the above studies, intracranial ERPs studies suggest that the neural generator of this inferior frontal component is at the level of the orbito-frontal cortex (Guillem, Rougier, & Claverie, 1999; Halgren, Marinkovic, & Chauvel, 1998). This region of the PFC is known to play a role in maintaining information in the face of interference (D'Esposito, Postle, Jonides, & Smith, 1999; Fuster, 1980). Figure 5 shows more positive amplitude for the old compared to the new stimuli after sleep. If we agree with the above interpretation, then the larger effect after sleep indicates that old items are more salient and/or require less interference inhibition to be retrieved than after a period of wake. This is consistent with both memorization and memory consolidation of the (old) stimuli.

Within the same latency window there was a significant difference observed across session over the posterior sites that was increased after sleep and slightly larger over the right hemisphere. This effect likely involves the classical N2b that is associated with discrimination or the automatic categorization of the stimulus

(Breton, Ritter, Simson, & Vaughan, Jr., 1988; Ritter, Simson, Vaughan, Jr., & Friedman, 1979; Novak, Ritter, Vaughan, Jr., & Wiznitzer, 1990). This early posterior negativity within the 200 ms time window has been related to detection and the final stages of structural encoding during face processing (Bruce & Young, 1986) when the representation is generated for use (Eimer, 1998; Eimer, 2000). It is acknowledged as an indicator of face specific categorization processes (George, Evans, Fiori, Davidoff, & Renault, 1996). In the present study, increased N200 amplitude could represent that less structural processing is required following sleep compared to wake also consistent with the idea of consolidation.

#### Frontal (F-N400) & Posterior (N400) Effects

It has been demonstrated that the posterior and the frontal Old/New effects are functionally dissociable (Allan, Wilding, & Rugg, 1998). Our data reveals a left-sided, frontal effect beginning at 400 ms (Figure 6a) that did not differ across session. During wake, studies have described a similar Old/New effect elicited within 400 – 700 ms termed the F-N400, which has been related to familiarity assessment (Curran, 1999; Smith, 1993). Recent evidence has supported that the F-N400 Old/New effect is maintained across one-day retention interval, indicating that familiarity processes last and contribute to LTM (Curran & Friedman, 2004). The fact that there was no difference in the F-N400 across session would also indicate that sleep does not affect familiarity processing. In concordance with our results, several other studies report that familiarity is not enhanced by sleep (Rauchs, Desgranges, Foret, & Eustache, 2005). More recently, other researchers (Drosopoulos, Wagner, & Born, 2005)

compared the effects of sleep in a word recognition task using a process-dissociation procedure (Jacoby, 1999). Their results showed that while NonREM sleep enhanced recollection, familiarity-based memory did not benefit from sleep.

As typically reported in ERP studies using a comparable protocol (Friedman & Johnson, Jr., 2000), our results also show a reduction (or more positive amplitude) in the posterior N400 for the old (studied) stimuli. The consensus is now that the posterior N400 reflects the ease or difficulty of integrating the stimulus bound information with semantic knowledge (Holcomb, 1993; Rugg et al., 1994); whereby, a more positive amplitude to the old items is thought to indicate increased ease of semantic integration as a result of pre-exposure to the stimulus. In support of this idea are brain-imaging studies that report activation of the posterior, parietal region in studies of semantic memory (Petrides, 1989; Schacter et al., 1999). As mentioned in the introduction, the relationship between sleep and semantic processing has been investigated using ERPs. Brualla, *et al.* (1998), reported a negative component peaking at 430 ms after stimulus onset (N400) to semantically unrelated words during wake that persists during light sleep and REM sleep (Brualla, Romero, Serrano, & Valdizan, 1998). Taken together with our data, this implies that the integration process on the posterior N400 Old/New effect was similar across sleep and wake and is not affected by nocturnal sleep.

#### Late Frontal & Late Positive Component (LPC/P600)

The scalp topography of the late frontal effect is shown to differ across the retrieval sessions. After sleep, there was a larger modulation seen bilateral over the frontal regions (Figure 6b) not seen during wake. Wilding & Rugg (1996) were the

first to identify a late frontal component of the Old/New effect in tasks requiring the retrieval of contextual information (Wilding & Rugg, 1996). Similarly, ERP Old/New effects in tasks employing source judgments have exhibited a late frontal component (Johnson, Jr., Kreiter, Russo, & Zhu, 1998; Senkfor & Van, 1998; Johnson, Jr., Kreiter, Russo, & Zhu, 1998). Functional neuroimaging studies of human memory have shown frontal/PFC activation during episodic memory retrieval (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998; Rugg et al., 1998). More specifically, imagery studies report a right frontal effect associated with contextual retrieval about a prior episode (Nolde, Johnson, & D'Esposito, 1998). Consistent with this known role of the frontal region during episodic retrieval, the late frontal component has been attributed strategic or contextual processing effort necessary for conscious retrieval (Wilding & Rugg, 1997; Allan, Dolan, Fletcher, & Rugg, 2000) and to a post-retrieval process (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Allan, Dolan, Fletcher, & Rugg, 2000). Our data shows an enhanced late frontal effect after sleep, indicating more contextual processing effort after sleep. If one accepts that consolidation entails abstraction of information in memory and greater "re-contextualization" effort required at retrieval, then our results are consistent with the role of sleep in consolidation.

Our results also showed the Old/New modulation involving a late positive component (LPC/P600). This posterior LPC/P600 Old/New effect is thought to reflect binding of information (e.g. context, semantic) into a coherent representation that is necessary to permit accurate recognition judgments (Rugg, 1995; Allan,

Wilding, & Rugg, 1998). The LPC/P600 is partly generated in the MTL lobe and adjacent cortices (Zola-Morgan, Squire, & Amaral, 1986) known to be crucial for LTM. Characteristically, the functional interpretation of the LPC/P600 effect is that its amplitude is proportional to the elaboration of the information retrieved from episodic memory (Rugg et al., 1994). By this account, the larger amplitude to old stimuli compared to new stimuli simply reflects that previously memorized information accesses more elaborated information than the new ones. Our results further show that the Old/New effect on LPC/P600 is larger after sleep than after wake (Figure 6b). This would indicate that the information retrieved after the sleep session is more elaborated, which is consistent with the idea of memory consolidation. This also concurs with the above behavioural data (i.e. accuracy) that sleep affects the qualitative aspects of the trace.

### **Conclusion**

This study replicates and extends the results of previous work (Mogras, Godbout, & Guillem, 2006) demonstrating that the Old/New effect occurred after a long delay. The current study indicates a similar effect on retrieval and dissociates the different subcomponents of the effect allowing assessing the actual contributions of sleep on memory consolidation. In general the behavioral results show that sleep favors or acts more on accuracy vs. RTs, which is consistent with that the idea that consolidation consists in restructuring or re-organizing weak associations in order to strengthen associative links. Moreover, our experiment shows that sleep influences two frontal processes: early interference inhibition and later contextual integration

effort. Recently researchers have proposed that consolidation is a two-stage process (Walker, Brakefield, Hobson, & Stickgold, 2003) stabilization process occurring only during wake, making the trace more resistant to interference, followed by an enhancement process after sleep. While our results are in agreement with the two-stage model, stabilization may not occur only after wake as proposed by this model. Further research is necessary to clarify this issue.

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### **EXPERIMENT 3: EFFECTS OF TSD ON RECOGNITION MEMORY**

In Experiment 3, we asked the question: *How does sleep deprivation influence memory processing and related brain function?* We examined the effects of sleep deprivation on ERPs by comparing a night of sleep and TSD in a study-test task. As in our previous experiments, the possible difference in level of vigilance between the two sessions were controlled for by preliminary analysis of the N100 and P200 amplitudes (Mograss, Guillem, & Godbout, 2003; Mograss, Godbout, & Guillem, 2006). We expected an Old/New difference from 200 to 800 ms, larger after sleep compared to a night of sleep loss, suggesting a role for sleep in memory consolidations (Mograss, Godbout, & Guillem, 2006). Furthermore, we predicted that retention over TSD vs. sleep condition will be associated with modified early and later posterior components (N200, LPC/P600) manifesting a reduction in stimulus categorization and less elaboration, respectively. Lastly, we hypothesized that a reduction in the frontal effects (LFC) reflecting less contextual processing would occur following TSD.

The Effects of Total Sleep Deprivation on  
Recognition Memory Processes: An Event-Related Potential Study.

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Running head: TSD & Memory Retrieval

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### Abstract

This study examined the influence of sleep in memorization of information after a delay of one night of total sleep deprivation (TSD) and a night of sleep by means of event-related potentials (ERPs). We expected a larger ERP memory effect due to a facilitory effect of sleep on memory consolidation. Eighteen subjects aged between 18 and 29 years old were tested twice in a counterbalanced fashion to control the effects of practice. During the study session, subjects were presented with a series of stimuli (unfamiliar faces) and asked to memorize them for a subsequent recognition memory test. At the test session, the subjects were presented with the previously learned "old" items intermixed with "new" and asked to indicate as quickly and accurately as possible the previously presented items while ERPs were recorded. The early N100 amplitude was used as a covariate to control for the differences in level of vigilance across the session. Behaviorally, TSD compared to sleep results in less accurate performance of the new items, indicating an inability to discriminate what is and is not in memory. A significant effect was found in the RTs to the studied vs. new items, however, there was no difference in responses across sessions, indicating that the subjects were responding the same. Electrophysiological data revealed differences related to the existence of the "Old/New" ERP memory effect (i.e. the positive shift that occurs when stimuli are repeated). The effects of TSD were reflected in an impaired early posterior process of stimulus classification and a later frontal process representing contextual processing, both dependent on vigilance. There was a significant difference in the N400 Old/New effect between the old and new, however, the semantic integration process was found to be similar across session. Finally, a late posterior component (LPC/P600) reflecting explicit recollection and elaboration was reduced following deprivation, independent of lower vigilance.

### The Effects of Sleep Deprivation on Memory Retrieval Processes.

There is a significant amount of evidence from studies in the literature indicating that cognitive performance is adversely affected under conditions of sleep deprivation (McCarthy & Waters, 1997; Dinges et al., 1992; Killgore, Balkin, & Wesensten, 2006; Horne, 1985; Durmer & Dinges, 2005). Consistently, sleep deprivation produces a variety of impairments in higher order cognitive processes; such as, inhibition (Harrison & Horne, 1998), decision making, temporal memory (Harrison & Horne, 1999), divergent thinking, problem solving (Horne, 1988; Wimmer, Hoffmann, Bonato, & Moffitt, 1992), and error detection (Tsai, Young, Hsieh, & Lee, 2005; Nilsson et al., 2005; Tsai et al., 2005). These complex cognitive processes often referred to as 'executive functions' largely rely on the prefrontal cortex. Functional neuroimaging studies have shown decreased (Drummond et al., 1999; Thomas, Rosen, Stern, Weiss, & Kwong, 2005) and increased prefrontal and parietal regions (Drummond et al., 2000; Drummond & Brown, 2001; Drummond, Brown, Salamat, & Gillin, 2004) as a function of total sleep deprivation together with changes in performance.

Sleep deprivation studies have also shown deficits in declarative memory tasks. After a night without sleep, memory impairments in recognition tests of nonsense syllables, pairs of letters or digits (Polzella, 1975; Idzikowski, 1984), recall memory for stories, (Blagrove, Cole-Mogran, & Lambe, 1994) route learning (Ferrara et al., 2006) and retention of emotional texts (Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005). Recently, Harrison & Horne (2000) have shown subjects

deprived of sleep remembered that the (face) stimuli were previously presented, but they had difficulty remembering in which of two sets of photographs the faces had appeared (i.e. context or source information). This indicates that sleep deprivation affects more the contextual organization of information in memory than the trace or representation.

However, the effects of sleep deprivation on memory have been shown to depend on the specific task and/or testing procedures utilized. Simple and arousing tasks are relatively unaffected by total sleep deprivation (Dinges & Kribbs, 1991), whereas, more complex tasks are more vulnerable and require shorter periods of sleep loss to show performance decrements (Angus, Heslegrave, & Myles, 1985; Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Williams, Gieseeking, & Lubin, 1966). This project attempts to explain some of the inconsistencies in the sleep deprivation literature by using a brief, complex memory task of unfamiliar faces. A review by Smith (2001) outlines the inconsistencies in the research on the effects of sleep on declarative memory may be attributed to the overuse of verbal stimuli along with the lack of complexity of the stimuli used (Smith, 2001). To overcome this problem, we used nonverbal stimuli of unfamiliar faces. These stimuli permit extraction of semantic information; such as, age, gender, expression, or resemblance to known persons (Bruce & Young, 1986) while at the same time their unfamiliarity necessitates the formation of a new trace representation that fosters episodic processes. Thus, this type of stimuli provide information related to the two aspects of declarative memory (episodic, semantic) processing and/or their interaction (Guillem, Bicu, & Debruille, 2001). In addition, we expect that such stimuli, due to

their greater complexity, will show greater sensitivity and involvement of the frontal lobes.

Event related potentials (ERPs) allow a promising avenue for addressing inconsistencies in the literature on the effects of sleep on declarative memory. ERPs provide indices of the different stages of information processing from perception, attention to integration and retrieval, and allowing dissociate the respective contribution of each. The latency and amplitude of the ERPs components and the scalp topography is used to make inferences about the time-course of processing in the brain. For example, an early negative deflection (N100), peaking at approximately 80 – 100 (Naatanen & Picton, 1987) followed by a positive peak (P200) at approximately 175-200 ms have been linked with states such as fatigue, arousal and vigilance (Haider, Spong, & Lindsley, 1964). The latency of the N100 (Gauthier & Gottesmann, 1983) and P200 (Peeke, Callaway, Jones, Stone, & Doyle, 1980) has been reported to increase during sleep deprivation. The prolonged latency is in accordance with early researchers reporting findings of a reduction N100-P200 amplitude with decreasing vigilance before sleep onset (Weitzman & Kremenn, 1965), during sleep-wake transitions (Ferrara et al., 2001) and after taking sedatives, e.g. Benzodiazepines (Noldy, Neiman, el-Nesr, & Carlen, 1990).

Similarly, sleepiness and sleep deprivation has been shown to change the amplitude and the latency on the later ERP components. For example, the N200-P300 complex is delayed during sleepiness (Colrain, DiParsia, & Gora, 2000; Gora, Colrain, & Trinder, 2001; Harsh, Voss, Hull, Schrepfer, & Badia, 1994; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Salisbury, Squires, Ibel, & Maloney, 1992). The

posterior N200 (or N2b) is thought to reflect the earlier stages of recognition such as stimulus categorization (Naatanen & Picton, 1986; Ritter, Simson, Vaughan, Jr., & Friedman, 1979) and discrimination (Renault, Ragot, Lesevre, & Remond, 1982). Corsi-Cabrera and *colleagues* evaluated subjects' reaction times & EEG in a visual discrimination task of procedural memory, during 40 hours of TSD (Corsi-Cabrera, Arce, Del Rio-Portilla, Perez-Garci, & Guevara, 1999) and reported that TSD resulted in a progressive amplitude reduction and a longer latency in the sleep "N2s". However, the stronger effect was for the negativity within the 300-400 msec time-window with its amplitude reaching only 40% of the original amplitude with TSD. This indicates that stimulus discriminating becomes impaired and requires a longer time during deprivation. Others have reported a reduced amplitude in a positive wave extending from 400 to 800 ms with TSD (Corsi-Cabrera et al., 1999). After one night of recovery sleep, all of the earlier components recovered their initial amplitudes and latencies, except for this late positivity. This suggests that one night of recovery sleep was not enough to restore this late positive component to baseline after sleep deprivation. In general, the functional significance of this late positivity is thought to reflect the final evaluation of information processing, a process associated with frontal lobe function (Corsi-Cabrera et al., 1999). These authors suggested that its reduction in TSD might reflect deterioration at this processing stage (Corsi-Cabrera et al., 1999). Except for a few studies, much of the ERP literature involved in the effects of sleep on information processing utilizes simple tasks and stimuli. Although useful to investigate how arousal and sleep affect perception, attention and classification processes, these tasks do not directly address memory.

In a series of studies in our laboratory, we addressed the question of the effects of sleep on next day performance and memory processes with the use of a recognition task in a study-test paradigm (Moggras, Godbout, & Guillem, 2006; Moggras, Guillem, & Godbout, 2007). The most reliable ERP index identified in this type of memory task has been referred to as the "Old/New" ERP memory effect (Allan, Wilding, & Rugg, 1998) and corresponds to the fact that event-related potentials are more positive for previously studied items than for new ones (Halgren, 1990; Rugg & Doyle, 1994) from approximately 250 to 800 msec post-stimulus. It is typically observed whether the items to be recognized are pictures, faces or verbal material (Allan, Wilding, & Rugg, 1998; Jemel, George, Chaby, Fiori, & Renault, 1999). Using this type of task with a long delay of sleep or wakefulness between study and test, we previously reported an "Old/New" ERP memory effect, whereby the amplitude difference on the studied vs. new items on some of the components were larger after sleep (Moggras, Guillem, & Godbout, 2003; Moggras, Godbout, & Guillem, 2006), suggesting a role for sleep in memory consolidation. We reported, for example, a posterior N400 Old/New effect elicited within 300-500msec that was significantly reduced to previously presented information (i.e., old stimuli). We interpreted this as suggesting that the old stimuli were more easily integrated into semantic memory than the new stimuli (Donaldson & Rugg, 1999; Curran, 1999; Rugg & Doyle, 1994), however, there was no effect of session (Moggras et al., 2007). Furthermore in that study we reported a late posterior positivity elicited within 400-800msec termed late positive component (LPC or P600) that was found to be significantly larger following sleep and nonsignificant after wake. We interpreted this

as indicating that the information retrieved after sleep was more elaborated, representing sleep-dependent facilitation in episodic memory processing (Moggras et al., 2007). There were additional contributions of frontal effects overlapping the N400 and LPC time window. Among them, there was a larger early frontal negativity (N200) and an enhanced late frontal component, (LFC) effect, reflecting greater interference inhibition following wake and increased contextual processing following sleep, respectively.

In the current experiment we asked the question: *How does sleep deprivation influence memory processing and related brain function?* We examined the effects of sleep deprivation on ERPs by comparing results following a night of normal sleep and a night of TSD in a study task. The possible differences in level of vigilance across the two sessions were controlled for by preliminary analysis of the N100 and P200 amplitudes (Moggras, Godbout, & Guillem, 2006). We hypothesized an Old/New difference from 250 to 800 msec would be larger after sleep compared to a night of TSD. It was also expected that retention over TSD vs. sleep condition would be associated with modified posterior LPC manifesting a reduction in the process of elaboration and that frontal effects (N200, LFC) reflecting inhibition and contextual processing would be reduced following TSD.

## **Methods**

### Participants

Eighteen healthy individuals (9 males and 9 females) aged between 18 and 29 years (mean =  $21.9 \pm 2.8$  SD) were tested twice with a period of 3 to 7 days between the experimental sessions. Participants were undergraduate university students (mean education level:  $15.9 \pm 1.4$  years). Exclusion criteria were a past or current history of psychiatric, neurological, sleep disorder or other medical condition. Participants were also excluded if any of their first-degree relatives had a history of primary sleep disorder or major psychiatric illness. All had normal or corrected to normal vision. Participants were asked to keep regular sleep-wake schedules for at least a three-day before coming to the laboratory. They were also required to fill out a sleep diary during the course of the experiment and, refrain from taking naps during the day of the testing. Standard questionnaires were used to collect the socio-demographic characteristics, sleep and medical history of each subject prior to the experiment. Eligible participants underwent an interview and questionnaire session in the laboratory, approximately 30 min. in duration. The local Ethics Committee approved the protocol where the study was conducted. All participants were fully informed of the recording methods and signed a consent form before participating in this experiment.

### Procedure

Participants were tested twice in a counter balanced fashion to control the effects of practice (see General Methods, Table 4). The general protocol was built as a classical study-test design. The study (learning) phase and the test (recognition)

phase, each lasting about 15 minutes, were separated either by a delay of a night's sleep (SLEEP session) or a period of total sleep deprivation (TSD session) (see General Methods, Figure 13). The ERPs were recorded during the test phase only. Both nights were spent in the sleep laboratory under the supervision of at least two other staff members. Information regarding the quality of the night of sleep in the laboratory was obtained in the morning on a questionnaire (Table 1). For the sleep deprivation condition, the subjects were allowed to play video games, go for supervised walks, watch videos, read or do school work. During the deprivation procedure, a vigilance scale (vigilance analog scale, VAS) was filled out every hour (see Appendix 4). At the end of the deprivation procedure all subjects reported their activities on a questionnaire prior to the testing (Table 1).

### Stimuli

Stimuli consisted of color photographs representing persons' faces unknown to the subjects. These stimuli were taken from the MED bank of face that is composed of front view color photographs of faces taken in the same conditions (background and light). Each face of this bank has been quoted as neutral, friendly, or unfriendly by a large group of persons in a prior study (Debrulle, Pelchat, Dubuc, & Brodeur, 1997). Thus, to minimize the possible confounding effects of emotional expression, the 160 faces chosen as stimuli for this experiment were those with the higher neutral scores. The whole set was divided into two sub-sets of 80 faces balanced for gender. Each of these sets served to construct a study series of 40 stimuli and a test series of 80 stimuli in which the 40 previously presented were intermixed

with an additional 40 'new' stimuli. There were two different study-test series so that the presented items were different during both sessions (SLEEP, TSD).

Subjects sat in a comfortable chair in a sound-attenuated room. Stimuli were presented on a gray background at the center of this screen 56 cm away from the subjects sustaining a visual angle of 5° and with an inter-stimulus interval of 4.5sec. Each stimulus remained for 1000 msec and was replaced by a mask with the word 'blink' for 600msec. During the study (learning) phase, the subjects were told to memorize each stimulus for a subsequent recognition test. Following a night's sleep or a night of sleep deprivation, the subjects were tested. During the test session, the subjects were asked to indicate for each stimulus, as accurately and quickly as possible whether it has been previously presented ('old') or not ('new') by pressing the arrow keys on the computer keyboard.

#### Recordings and signal extraction

The electrophysiological signals were recorded by means of an amplifier (S.A. Instrument Inc, San Diego, CA). The EEG was recorded from 27 scalp electrodes placed according to the extended 10-20 International System montage (Fp1, FP2, Fpz, F3, F4, F7, F8, Fz, FC3, FC4, FT7, FT8, Cz, CP3, CP4, P3, P4, Pz, T3, T4, T5, T6 TP7, TP8, O1, O2, Oz) (American EEG Society, 1994). All channels were referenced to the linked earlobes. Vertical and horizontal eye movements were monitored via electrodes respectively placed below and on the outer cantus of the left and right eyes. During the recording, the impedance of all electrodes was maintained below 5 K $\Omega$ . The EEG was recorded continuously with a band-pass filter of 0.01-30 Hz, digitized on-line at a rate of 250 Hz and stored along with the codes identifying the

experimental condition, the stimulus onset and the subject's response for subsequent off-line averaging. Off-line averaging was performed after EOG correction using statistical software algorithms (InStep software Montreal, Canada) and after rejection for epoch with amplifier blocking exceeding 100 msec. ERPs for correctly identified new items and correctly identified old items was then computed separately from 0- to 1000-msec post-stimulus onset with a 200 msec pre-stimulus baseline.

## **Data analysis**

### Questionnaires and Vigilance Ratings

All subjects filled out a sleep diary reporting subjective estimates in the number of hours of sleep three days prior to testing and throughout their participation in the experiment, which included both nights (sleep or TSD) in the laboratory. The mean numbers of hours of sleep during the night in the laboratory were analyzed with two-tailed paired t-tests to see if there were any statistically related differences. A paired-sample t-tests for repeated measures was used to analyze the number of nocturnal awakenings and sleep onset (minutes) in the laboratory compared to that of a normal night of sleep in the home.

The Visual Analog Scale (VAS) was obtained to measure level of vigilance throughout the sleep deprivation procedure every half hour. This instrument is one of the most widely used subjective measures of alertness (Johnson, 1992) It consists of a 10 cm line, with the inscription "Very sleep" at the left end and "Very alert" at the right end. Participants are asked to draw a line at the point corresponding to their subjective alertness level at the time. This measure was expressed in distance (in cm)

between left end of the scale and the bar drawn by the participants. Results are computed as “low arousal” (0 to 3 cm), “normal arousal” (3 – 7 cm), and “high arousal” (7 to 10 cm). A bivariate correlation analyses using Pearson’s coefficient were conducted between VAS data and N100 ERP component, and the VAS and reaction times, as a confirmation of the quality of the covariate.

### **Behavioral Performance**

Reaction Times. RTs Behavioral performance data were obtained simultaneously with EEG data. RT on responses was obtained in both sessions for old (studied) and new stimuli were compared by means of a factorial design with 2 ‘condition’ (Old, New) and 2 ‘session’ (Sleep, TSD) with repeated measures. RTs were collected separately for correct trials and error trials.

Accuracy Scores The accuracy scores (% correct and % miss) of both sessions (Sleep, TSD) were compared by measures of a Repeated Measures ANOVA, enabling us to determine if a night of sleep compared to TSD influences the memorization of items.

### **ERP data**

ERP positive (P) and negative (N) peaks were identified by visual inspection of each participant’s waveforms recorded at Cz within stimulus onset to 1000 milliseconds. Peak amplitudes were quantified with respect to the baseline within several time-windows (see below) centered on the specific ERP component. For each peak, the time window was defined as the half distance (median latency) between the current and following peak. This procedure resulted in non-overlapping

time window that allow to capture amplitude effects separately for each peak (Guillem et al., 2001). While the ERPs were being quantified, we recorded the latency time windows for each subject and calculated the mean time windows for the group.

#### N100/P200 Components (Vigilance)

Similar to our previous studies, the N100 and P200 components were analyzed to statistically control potential confounding effects of vigilance differences between the Sleep and the TSD test sessions (Mograss et al., 2006; Mograss et al., 2007). Two ERP peaks within the 61-214 msec (N100 & P200) time window were analyzed. The N100 and P200 components were quantified within 61 – 146 msec and 141 – 214msec time window, respectively, at midline sites (Fz, Cz, Pz) for correct recognition (hit) and correct rejection. The analysis consisted of a 2 ‘session’ (Sleep, TSD) x 2 ‘condition’ (Old, New) x 3 ‘site’ (Fz, Cz, Pz) repeated measure ANOVA.

Preliminary analysis showed significant effects and interactions involving the session factor observed on N100, indicating an effect of lower level of vigilance. When there was an interaction involving the session factor, the later memory ERP data were re-analyzed using the same factorial design in a covariate (N100 amplitude) ANCOVA model.

#### **Memory ERPs**

Memory ERPs quantified for correctly recognized old and correctly rejected new stimuli on the whole coverage within 200 – 800msec post-onset. This time

window was typical for previous studies of the ERP 'Old/New' effect (Guillem & Mograss, 2005; Friedman & Johnson, Jr., 2000) and studies using a similar delay (Mograss et al., 2003; Mograss et al., 2006). ERP data were analyzed separately for midline and lateral sites using repeated measures ANOVAs. For the midline sites, the model included the 2 'session' (Sleep, TSD), the 2 'condition' (Old, New) and 3 'site' (Fz, Cz, Pz) as within-subject variables. For the lateral sites, the model included the 2 'session' (Sleep, TSD), the 2 'condition' (Old, New), the 2 'laterality' (left, right) and the 6 'region' inferior frontal (Fp1-2, F7-8), superior frontal (F3-4, FC3-4), parietal (CP3-4, P3-4), anterior temporal (FT7-8, T3-4), posterior temporal (TP7-8, T5-6) and occipital (O1-O2) as within-subject variables.

In all analyses, degrees of freedom were adjusted using the Geisser-Greenhouse procedure where appropriate (uncorrected  $df$  are reported with the  $\epsilon$  values and corrected  $p$  values). Differences in scalp distribution across conditions were also analyzed after normalization of the data (McCarthy & Wood, 1985). This procedure allows one to account for the possibility that a given scalp distribution effect can be due to multiplicative differences in distinct neural source strength. In the case of significant interactions, the highest order interaction is reported and follow-up post-hoc tests were conducted where appropriate. Interactions involving the factor of site were reported on the raw data if significant in the normalized data set (Swick & Knight, 1997).

## Results

### ERP data: N100/P200 Components (Vigilance)

The N100 and P200 components were quantified within 61 – 146 ms and 141 – 214ms time window, respectively, at midline sites (Fz, Cz, Pz) for correct recognition (hits) and correct rejection. The analysis consisted of a 2 ‘session’ (SLP, TSD) x 2 ‘condition’ (Old, New) x 3 ‘site’ (Fz, Cz, Pz) repeated measure ANOVA.

Preliminary analysis showed significant effects and interactions involving the session factor observed on N100, indicating an effect of lower level of vigilance. When there was an interaction involving the session factor, the later memory ERP data were re-analyzed using the same factorial design in a covariate (N100 amplitude) ANCOVA model.

### Morning Sleep Questionnaire

Results of a dependent t-test concluded that there was no significant difference between the mean number of hours reported on the sleep agenda and those reported prior to TSD session, see Table 1 ( $\underline{M} = 8.2$ ,  $SE = .21$ ,  $\underline{M} = 8.1$ ,  $SE = .27$ ;  $t(17) = .23$ ,  $p = .81$ , n.s., respectively). Furthermore, Table 1 shows no difference between the mean number of hours of sleep in the home sleep agenda and those reported in the morning after sleeping in the laboratory ( $\underline{M} = 7.6$ ;  $SE = .32$ );  $t(17) = 1.87$ ,  $p = .08$ , n.s.).

**TABLE 1.**  
Participants Sleep Agenda Information (number of hrs of sleep) N=18

|                            | Mean<br>+/-SD | p value* |
|----------------------------|---------------|----------|
| <u>HOURS OF SLEEP</u>      |               | *n.s.    |
| Sleep Agenda               | 8.2 (+/- .21) |          |
| Laboratory Sleep Session   | 7.6 (+/- .32) |          |
| TSD Session (3 days prior) | 8.1 (+/- .27) |          |

\*p >.05, n.s. Dependent t-test comparing hrs of sleep on Sleep Agenda vs. Laboratory Sleep session. Sleep Agenda vs. 3 day before the night of sleep deprivation (TSD).

In addition, 77% reported a similar quality of sleep in the laboratory compared to home (Table 2). As well, the depth of sleep in the laboratory in 16 out of 18 (89%) of the subjects was reported as deep (see Table 2).

The dependent t-test conducted to evaluate the possible change in the subjects' estimate of awakenings (number of times) during sleep in the laboratory (see Table 2) showed no significant difference from sleep in the home ( $M = 2.0$ ,  $SE = .20$ ) to that of sleeping in the laboratory ( $M = 1.94$ ,  $SE = .33$ ),  $t(17) = .14$ ,  $p = .84$ , n.s.) The dependent t-test conducted to evaluate any change in the subjective estimate of time it takes to fall asleep (sleep onset) showed no significant difference in sleep onset (minutes) between home ( $M = 21.5$ ,  $SE = 2.89$ ) and laboratory ( $M = 23.9$ ,  $SD = 3.77$ ),  $t(17) = -.54$ ,  $p = .59$ , n.s. (see Table 2).

**TABLE 2.**  
 Nighttime Laboratory Sleep & Home Sleep History Information N=18

|                                      | Home | Lab | p value* |
|--------------------------------------|------|-----|----------|
| a) Nocturnal Awakenings (# of times) |      |     | n.s.     |
| None                                 | 0    | 2   |          |
| 1 – 3 times                          | 17   | 12  |          |
| 5 times                              | 1    | 4   |          |
| b) Sleep Onset (# of Ss)             |      |     | n.s.     |
| 1-15 minutes                         | 8    | 8   |          |
| 16-30 minutes                        | 8    | 6   |          |
| 31-45 minutes                        | 2    | 3   |          |
| Greater than 45                      | 0    | 1   |          |
| c) Sleep Quality (compared to home)  |      |     |          |
| Lesser Quality                       |      | 4   |          |
| Similar in Quality                   |      | 14  |          |
| Better than usual                    |      | 0   |          |
| d) Sleep Depth (lab vs. home)        |      |     |          |
| Light                                | 1    | 2   |          |
| Moderate                             | 3    | 0   |          |
| Deep                                 | 14   | 16  |          |

*Paired Sample t-test between information obtained on Morning Sleep Questionnaire & Sleep History Questionnaire; \*p > .05, n.s*

#### Behavior Performance Data

Table 3, top shows a significant difference in accuracy performance (%correct) for the old stimuli compared to the new stimuli ( $F(1, 16) = 13.05; p < .01$ ) without an effect of session ( $F(1,16) = 3.40; n.s.$ ) that survived the ANCOVA analysis. In addition, there was a trend towards a difference on the correct rejection

of the new stimuli following sleep compared to TSD ( $M=81.9\%$ SD 9.4,  $M=75.9\%$ SD 14.8, respectively;  $F(1, 16) = 3.59$ ;  $p = .07$ ).

Although the Old items were recognized faster after the sleep session (see Table 3, bottom), there was no significant difference in the effect of condition (Old/New) on RT data for the correct responses. However, when removing three participants ( $N=15$ ) whose accuracy was less than 50%, a significant effect of condition (Old/New) was found ( $F(1, 14) = 7.26$ ;  $p < .02$ ). Furthermore, the overall means on the error RTs revealed significantly slower responses on the false alarms after TSD compared to a night of sleep ( $1106.99\text{ms} \pm \text{SD}298.9$  vs.  $1023\text{ms} \pm \text{SD}256.6$ , respectively) ( $F(1, 17) = 5.87$ ;  $p < .03$ ).

**TABLE 3.**

Behavioral Results from the Recognition Memory Task (Mean  $\pm$ SD) N-18

|                                    | SLEEP          | TSD             |
|------------------------------------|----------------|-----------------|
| <b>ACCURACY SCORES (% correct)</b> |                |                 |
| <u>Correct Response</u>            |                |                 |
| New                                | 81.9 (9.4)     | 75.9 (14.8)     |
| Old (studied)                      | 66.9 (12.3)    | 64.9 (10.0) **  |
|                                    |                |                 |
| <b>REACTION TIME (ms)</b>          |                |                 |
| <u>Errors Response</u>             |                |                 |
| False Alarms                       | 1023.2 (256.6) | 1106.9 (298.0)  |
| Miss                               | 1048.8 (289.3) | 1136.9 (355.7)  |
|                                    |                |                 |
| <u>Correct Response *</u>          |                |                 |
| New                                | 1025.6 (270.4) | 1009.8 (249.6)  |
| Old                                | 981.4 (198.0)  | 976/3 (250.2) + |

\*RTs for Correct Responses in subjects with  $>50\%$  accuracy.  $N=15$ .

+  $p < .03$ ; \*\* $p < .01$ ; §  $p = .07$

### N100/P200: Effects on Vigilance

Table 4 shows a significant negative correlation was found between difference in the mean amplitude of the N100 component (Fz site) and the Visual Analog Scale (VAS) rating of vigilance data 1-hour prior ( $r = -0.46$ ,  $p = .03$ ), but not VAS data ½ hr prior to testing. A positive correlation ( $r = 0.40$ ,  $p = .055$ ) was found in the TSD condition between RTs (Old stimuli) and the VAS data ½ hr prior to ERP testing.

**TABLE 4.**  
Pearson Correlations between Visual Analog Scale Scores (30, 60- & 120min values) & Other Vigilance Measures (ERPs, RTs)

|                           | VAS<br>1/2hr | VAS<br>1hr | VAS<br>2hr |
|---------------------------|--------------|------------|------------|
| <b>VIGILANCE MEASURES</b> |              |            |            |
| N100 Amplitude            | -0.37*       | -0.46***   | -0.38*     |
| Reaction Times            |              |            |            |
| Old (repeated)            | -0.40**      | 0.06       | -0.04      |
| New                       | 0.28         | 0.09       | 0.03       |

Vigilance Analog Scale (VAS) = fatigue in TSD session.

N100 Amplitude ( $\mu\text{V}$ ) = Difference (TSD<sup>old+new/2</sup> – Sleep<sup>old+new/2</sup>) at the Fz site.

Reaction Times = TSD session RTs (ms) for correct responses.

\*\*\*  $p = .03$ ; \*\*  $p = .05$ ; \*  $p = .07$ , *n.s.*

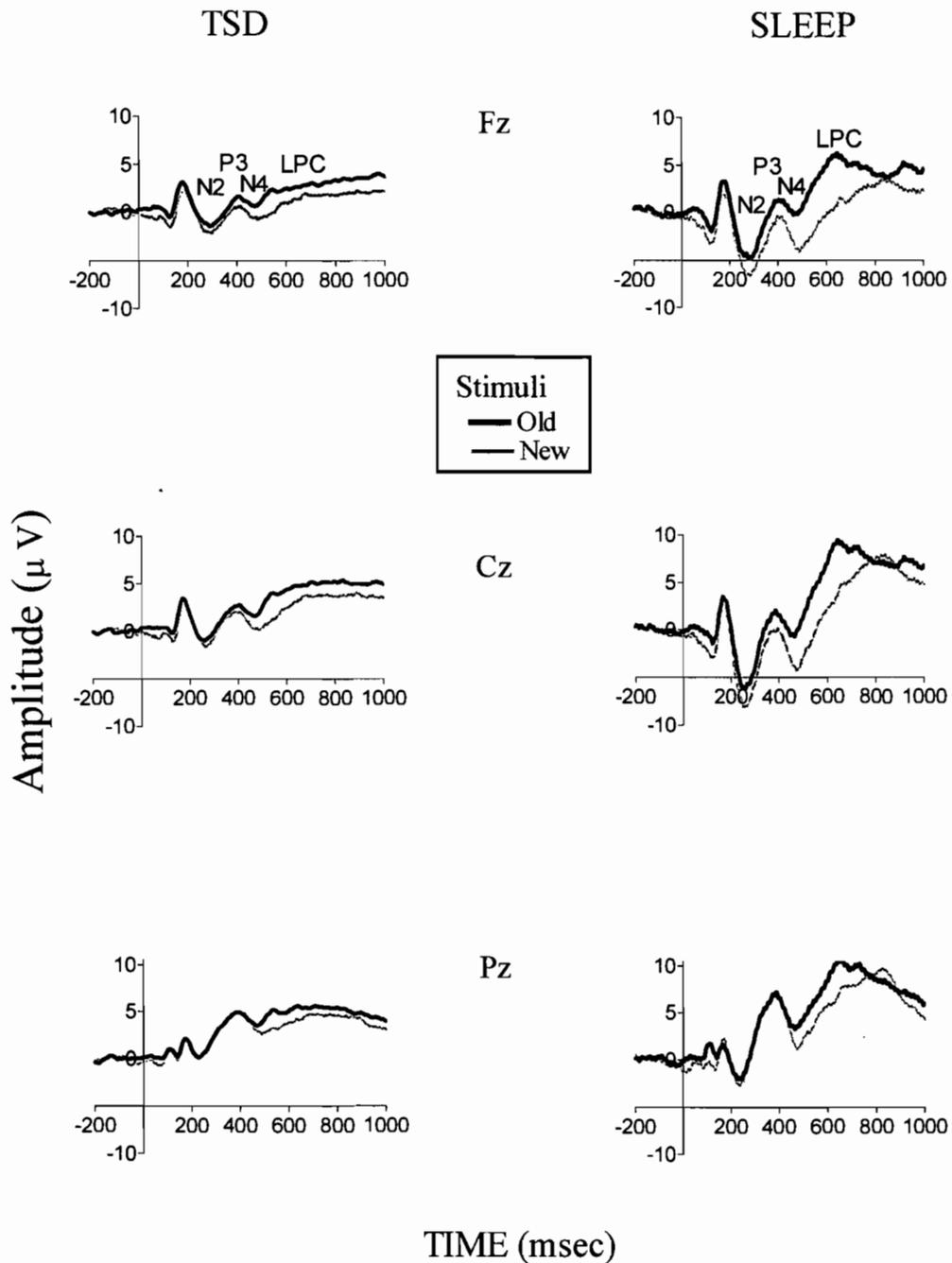
The ANOVA on the N100 midline data showed a significant main effect of session ( $F(1, 17) = 5.31$ ;  $p = .03$ ), site ( $F(2, 34) = 9.58$ ;  $p < .01$ ;  $\epsilon = .605$ ), and condition (Old/New) ( $F(1, 17) = 8.43$ ;  $p < .001$ ) with a session x site interaction ( $F(2,34) = 3.96$ ;  $p = .05$ ;  $\epsilon = .299$ ) due to the differences in vigilance/arousal across the two sessions. Post-hoc analysis revealed that this effect was at the Fz frontal ( $F(1,17) = 6.98$ ;  $p = .02$ ) site. Thus, the difference in the N100 component at the frontal site (Fz) for each subject was used as the covariate in the ANCOVAs model to

control for the effects of variation in vigilance across session. For the P200 midline data there were no main effects or interactions involving any of the three factors.

### Memory ERPs

The grand average ERP waveforms elicited during the test recognition session by the correctly identified stimuli is presented in Figure 1 shows four main peaks, N200 (N2), P250 (P3), N400 (N4), LPC (late positive component, or P600), similar to those previously reported (Guillem, Bicu, & Debrulle, 2001) and for those reported in a similar design (Mogross, Guillem & Godbout, 2003; 2006). In both sessions, similar components were identified with slightly different window latencies. As in our previous studies, the first peak was a negativity elicited within a 214-311ms time window, thereafter referred to as N200 (N2). The other peaks were a P250 (P3), 312-429ms, a N400 (N4) 430-574ms and a LPC ( or P600) 575-760ms.

## TEST SESSION Grand Average ERPs



**Figure 1.** Grand average ERPs elicited by correctly recognized 'old' or studied stimuli (black line) & 'new' (gray line) at the Fz Cz & Pz sites. Right: Nighttime Sleep Session; Left: Total Sleep Deprivation (TSD) Session. ERP components: N200(N2); P250 (P3); N400 (N4); LPC (late positive component or P600).

Time Window: 214-429 ms:

The ANOVA on the midline data for the N200 resulted in significant main effects of site ( $F(2,32) = 8.07$ ;  $p < .01$ ;  $\epsilon = .424$ ), session ( $F(1,16) = 8.08$ ;  $p = .01$ ) and a trend for a main effect of condition (Old/New) ( $F(1,16) = 3.72$ ;  $p = .07$ ). There was a significant interaction between session x site ( $F(2,32) = 4.24$ ;  $p < .04$ ;  $\epsilon = .668$ ) and a session x condition (Old/New) x site three-way interaction ( $F(2,34) = 3.86$ ;  $p < .05$ ;  $\epsilon = .752$ ). Figure 2 (midline) shows a posterior (Cz-Pz) N200 Old/New effect that was larger following sleep, however, this effect did not survive in ANCOVA controlling for N100.

The N200 lateral data revealed main effects of site ( $F(1,17) = 4.49$ ;  $p < .001$ ;  $\epsilon = .353$ ), laterality ( $F(1,17) = 4.28$ ;  $p = .05$ ), condition (Old/New) ( $F(1,17) = 7.30$ ;  $p < .02$ ) and session ( $F(1,17) = 4.49$ ;  $p < .05$ ). The lateral data also revealed significant interactions between session x site ( $F(5,80) = 5.05$ ;  $p < .02$ ;  $\epsilon = .013$ ), another between laterality x site ( $F(5,80) = 2.51$ ;  $p = .03$ ;  $\epsilon = .573$ ), and a 3-way session x laterality x site interaction ( $F(5,85) = 5.67$ ;  $p < .01$ ;  $\epsilon = .469$ ). Figure 2 shows a more negative Old/New difference following TSD at the posterior sites bilaterally, however, this effect did not survive when controlling for N100. In addition, visual inspection and analysis of the N200 mean amplitude (not shown) revealed a more positive (reduced) modulation over the left vs. right posterior site following TSD, and this effect was independent of vigilance.

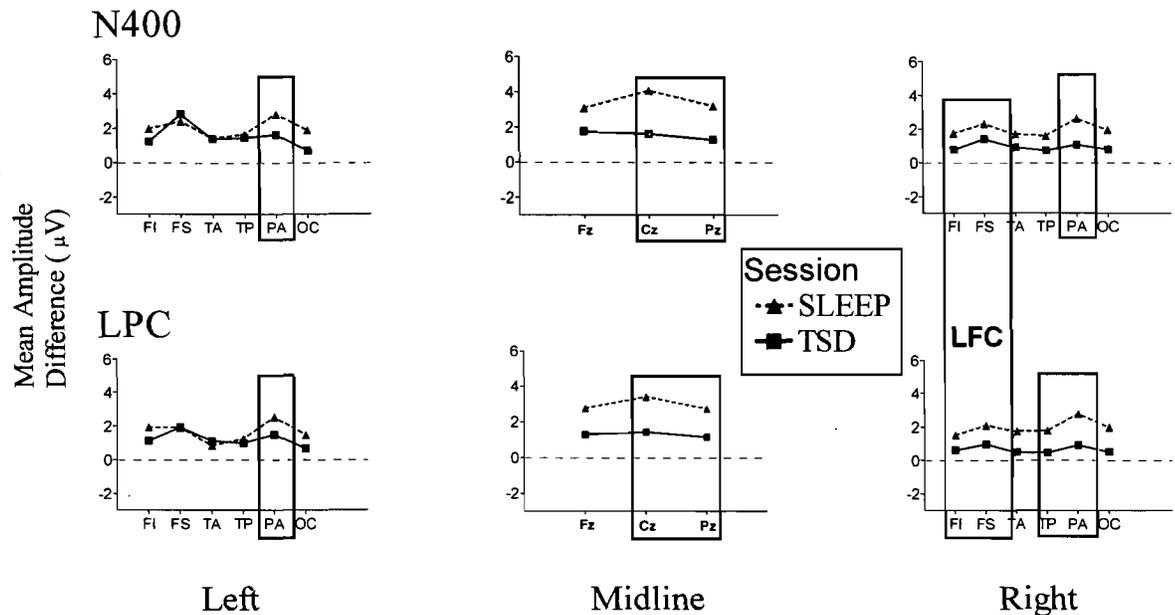


Time Window: 430-574 ms

The ANOVA on the N400 midline data obtained in this time window showed a significant effect of site ( $F(2,34) = 15.78$ ;  $p < .001$ ;  $\epsilon = .646$ ) and condition (Old/New) ( $F(1,17) = 37.84$ ;  $p < .001$ ). Further, there was a significant interaction involving session x condition (Old/New) ( $F(1,17) = 5.30$ ;  $p < .04$ ). Figure 3, top shows a larger Old/New effect after sleep compared to TSD, however, this effect did not survive when controlling for N100 and thus is dependent on vigilance ( $F(1,16) = .67$ ;  $p = .42$ , n.s.).

The ANOVA on the lateral N400 data revealed significant effects of condition (Old/New) ( $F(1,17) = 25.82$ ;  $p < .001$ ), laterality ( $F(1,17) = 8.00$ ;  $p = .01$ ) and site ( $F(5,85) = 3.61$ ;  $p < .03$ ;  $\epsilon = .505$ ). ANCOVA analysis revealed a vigilance masking effect whereby two interactions involving condition (Old/New) appeared following the application of the N100. One involved a condition (Old/New) x site interaction ( $F(5,80) = 24.32$ ;  $p < .04$ ) and the other involved a condition (Old/New) x laterality ( $F(1,16) = 2.47$ ;  $p < .04$ ). Figure 3, top shows that the N400 Old/New effect involves two distinct components. The first is a parietal (PA) effect seen bilaterally likely involving the classic, posterior N400 Old/New effect. There were no effects of session on the posterior N400 component, indicating that this posterior Old/New effect was similar across sleep and TSD sessions. The second effect is a late, anterior (FI, SF) effect, more negative after TSD, that continues into the following time window (LFC) at the right frontal site (see below for explanation).

## Late ERP Components



**Figure 3** (Top) ERP Mean Amplitude Difference (old minus new) for the late N400 memory component from midline and lateral head regions. (Bottom) Figure shows the difference in mean amplitude for the LPC time windows for the midline and lateral (left/right) sites. Rectangles indicate the various components involved in the Old/New effect: N400, late frontal (LFC) and late position component (LPC). Inferior frontal, FI; superior frontal, FS; anterior temporal, TA; posterior temporal, TP; parietal, PA; occipital, Oc. ▲ = Sleep; ■ = Total Sleep Deprivation, TSD

### Time Window: 575-760 msec

The ANOVA data obtained in the 575-760 midline time window on the LPC showed main effects of site ( $F(2,32) = 3.78$ ;  $p < .001$ ;  $\epsilon = .828$ ), condition (Old/New) effect ( $F(1,16) = 19.59$ ;  $p < .001$ ) and session ( $F(1,17) = 8.56$ ;  $p < .01$ ). There were interactions between session x site ( $F(2,34) = 6.05$ ;  $p = .01$ ;  $\epsilon = .770$ ) and another involving a trend towards a significant session x condition (Old/New) interaction ( $F(1,17) = 3.62$ ;  $p = .07$ ), dependent on vigilance since both interactions were lost when controlling for the N100. Figure 3 (midline, bottom) shows a reduced LPC after

TSD compared to the sleep session most likely involving the classic, posterior LPC/P600 Old/New effect.

The ANOVA on lateral data within this time window revealed significant main effects of site ( $F(5,80) = 6.46$ ;  $p = .003$ ;  $\epsilon = .443$ ), condition (Old/New) ( $F(1,16) = 16.06$ ;  $p = .001$ ), session ( $F(1,16) = 5.91$ ;  $p < .03$ ) and laterality ( $F(1,16) = 5.12$ ;  $p < .04$ ). There was a significant 2-way interaction involving laterality x site ( $F(5,80) = 3.64$ ;  $p = .02$ ;  $\epsilon = .567$ ) unaffected by vigilance. There were interactions involving a session x condition (Old/New) x laterality ( $F(1,16) = 5.56$ ;  $p = .05$ ), and another that involved a trend towards a session x laterality x site interaction ( $F(5,85) = 2.61$ ;  $p = .05$ ;  $\epsilon = .645$ ) in the normalized data.

Figure 3 shows a right, lateralized LFC modulation was reduced over the frontal sites (FI, FS) following TSD, through lower vigilance. In addition, Figure 3 shows a posterior effect with a slightly right-sided predominance at the temporo-parietal sites corresponding to the classical LPC/P600. Post-hoc analysis on the posterior sites (TP, PA) revealed a significant effect of laterality ( $F(1,16) = 7.10$ ;  $p < .02$ ), which was unaffected by vigilance.

## **Discussion**

The present study explores the effect of a night of sleep and sleep deprivation on indicators of declarative memory assessed by ERPs in a recognition memory task. The experiment described here extends the findings from previous research (Mogras, Godbout, & Guillem, 2006) where a night of sleep was compared to an equivalent

period of daytime wake, and help characterize the processes involved in recognition memory after one night of sleep deprivation.

#### Sleep Assessment

The results show that the participants' number of hours of sleep in the laboratory was not different from that in the home environment or before the sleep deprivation procedure (Table 1). The subjective number of nocturnal awakenings, time it takes to fall asleep (i.e. sleep onset) and depth of sleep in the laboratory were not different from usual (Table 2). In fact, the majority of the subjects reported having a quality of sleep similar to that in the home when sleeping in the laboratory environment (Table 2).

#### Behavioral Performance Data

Although there was no evidence for a beneficial effect of sleep on RTs to the studied (old) items across session, there were significantly faster RTs to false alarms (i.e. an inability to discriminate new from old items) after a night of sleep compared to sleep deprivation (Table 3, top). In the same vein, recent studies in the literature indicate that sleep deprivation produces impairments in higher order cognitive processing (Nilsson et al., 2005) such as deficient error detection (Tsai, Young, Hsieh, & Lee, 2005). This is in agreement with our previous study looking at the effects of a night of sleep compared to daytime wake and reported sleep-dependent "consolidation" changes in the electrophysiological (ERPs) data that were not reflected in RT performance gains (Mograss, Godbout, & Guillem, 2006). In addition, several electrophysiological studies utilizing sleep deprivation techniques report no change in behavioral performance but changes in ERPs suggesting that

ERPs may be more sensitive than behavioral measures (Szelenberger, Piotrowski, & Dabrowska, 2005; Morris, So, Lee, Lash, & Becker, 1992).

In general, there was a significant difference in % correct responses of the old compared to the new items across both sessions (Table 3). Furthermore, the data revealed a trend in the accuracy of correct rejection of the new items across sessions; that is, less accurate performance after TSD compared to sleep (75+/-14.8 vs. 81.9+/-9.4%), indicating that a night of sleep loss results in difficulty discriminating new stimuli from old. This is also consistent with the significantly slower RTs found for the false alarms after TSD (see above).

## **ERP Data**

### N100-P200 Complex (Vigilance)

As mentioned in the introduction, the earlier ERP components identified in this study have been linked to fatigue, arousal and vigilance (Nordby et al., 1996; Haider et al., 1964). As expected, our data shows a significant difference between the sleep compared to the TSD session on the N100 component amplitude. This is also in agreement with our behavioral data showing a significant correlation between vigilance on the Visual Analog Scale (VAS) and the amplitude of the N100 component 1-hr prior to testing (see Table 4). To control for the confounding differences in the levels of vigilance across the sleep and sleep deprivation sessions and on the later ERP components, the difference in the N100 amplitude was used as a covariate variable.

In general, most of the effects over the midline regions throughout the 200 to 800 time windows, i.e. N200 to LPC, did not survive the ANCOVA model. One interpretation is that following sleep deprivation, there was a general effect on cortical excitation, likely of sub-cortical origin. An effect that was not homogeneous for the lateral brain regions. This highlights the importance of using expanded sites during a protocol that employs sleep deprivation.

### **Memory ERPs**

#### Early Effect (215-416 ms)

Within the 215-416ms time window there was a more negative N200 amplitude at the posterior (Cz-Pz) sites after TSD than when the subjects' slept (Figure 2, midline). Similarly, a bilateral, posterior N200 Old/New effect was more negative in the TSD compared to the Sleep condition (Figure 2, right, left). This effect likely involves the N2b that is associated with the processes of stimulus discrimination or the automatic categorization of the stimulus (Simson, Vaughan, & Ritter, 1976; Novak, Ritter, Vaughan, Jr., & Wiznitzer, 1990; Ritter, Simson, Vaughan, Jr., & Friedman, 1979). In the present study, a significantly more positive posterior N200 Old/New effect after sleep may represent facilitation by sleep on the early processes of categorization and stimulus discrimination, an effect that was abolished after TSD.

As mentioned previously, visual inspection and analysis of the N200 mean amplitude showed reduced left-sided, posterior modulation following TSD. This hemispheric asymmetry is consistent with previous ERP studies (Heinze & Munte,

in a posterior negativity peaking at 250 ms (i.e. N200). More recently, Yamaguchi *et al.* reported differences in neural activities in the N200 amplitude that was greater in the left hemisphere for local targets and in the right hemisphere for global targets (Yamaguchi, Yamagata, & Kobayashi, 2000). Consistent with this idea is neuropsychological evidence demonstrating that lesions in the left hemisphere result in selective difficulty in identifying component parts (local level); whereas, damage to the right posterior temporal gyrus results in selective difficulty in identifying features at the global level (Robertson, Lamb, & Knight, 1988; Lamb, Robertson, & Knight, 1989). In our study, the data indicates that across sessions, there was no disruption of global processing, however, following TSD there may have been less local processing in identifying component parts. Taken together, this would suggest that sleep loss affects discrimination of the old vs. new stimuli perhaps due to less attentional processes allocated at the local level or to details. The idea is further supported by the fact that the participants committed more false alarms after TSD compared to sleep (24. +/-14.8 vs. 17.9+/-9.6%, respectively).

#### Posterior N400 Effect

The reduction of the posterior N400 for the studied (old) stimuli replicates the finding typically reported in ERP studies using the same protocol (Friedman et al., 2000). The consensus is that the amplitude of the posterior N400 is inversely proportional to the ease with which a stimulus is integrated with semantic knowledge (Rugg et al., 1994; Holcomb et al., 1990). The reduced (or more positive amplitude) to the old items is thought to indicate increased ease of integration. In support of this

to the old items is thought to indicate increased ease of integration. In support of this idea, neuroimaging studies report activation of the posterior and parietal regions in studies of semantic memory (Petrides, 1989; Schacter et al., 1999). Our analysis revealed that this difference in N400 Old/New amplitude across session relates to the general effect of vigilance (see result section), suggesting that the N400 Old/New effect is not affected by sleep deprivation. Taken together this implies that TSD does not affect semantic processing and that the integration process is similar after nocturnal sleep and following sleep loss.

#### Late Frontal Component (LFC)

The scalp topography of the late frontal effect is shown to differ across the sessions. After TSD compared to the sleep session, there was a significant reduction in the mean amplitude seen bilaterally over the frontal sites (Figure 3, bottom insert) and a slightly smaller modulation seen unilateral over the right frontal region (Figure 3, bottom right). Only the former effect of a smaller LFC was found affected by TSD, independent of lower vigilance (N100).

Several electrophysiological studies involving event-related potentials have shown modulation of this component by strategic or contextual processing (Allan, Wilding, & Rugg, 1998; Ranganath & Paller, 2000; Wilding & Rugg, 1996). Our data shows an increase in LFC amplitude seen bilaterally that suggests more processing resources available after sleep.

### Late Positive Component (LPC)

Our results also showed the Old/New modulation involving a late positive component, LPC. This posterior LPC Old/New effect is thought to reflect binding of information (e.g. context, semantic) into a coherent representation that is necessary to permit accurate recognition judgments (Allan, Wilding, & Rugg, 1998). Characteristically, the functional interpretation of the LPC effect is that its amplitude is proportional to the elaboration of the information retrieved from episodic memory (Rugg et al., 1994). By this account, the larger amplitude to old stimuli compared to new stimuli simply reflects that previously memorized information accesses more elaborated information than the new ones. Our results further show that the Old/New effect on LPC is dramatically lower after TSD than after sleep (Figure 3, bottom). This would indicate that the information retrieved after the sleep session is more elaborated which is consistent with the role of sleep in memory consolidation. More importantly, TSD prevented elaboration (i.e. consolidation), which further supported the role of sleep in memory consolidation.

## **Conclusion**

Behaviorally, sleep deprivation results in the inability to discriminate what is and is not in memory. Similarly, the electrophysiological data shows an early posterior effect representing the processes of stimulus classification and discrimination that was affected by TSD through lower vigilance. An unexpected finding was the reduced anterior N200 mean amplitude following the TSD condition implying less inhibition on the studied and new items that may represent less structural processing. On the other hand, the semantic integration process, was unaffected by sleep loss. Thus, it would appear that sleep deprivation does not affect the retrieval of the trace per se, but discrimination between what is and what is not memory. Information retrieved after TSD was less elaborated, consistent with the idea of impairment in higher order cognitive processing following sleep loss. Finally, explicit recollection was affected by TSD, as it can be expected for the outcome of previous stages. These data suggest that the effects of sleep on memory consolidation are complex and affect the various stages of memory processing during retrieval in a differential manner.

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## 8. GENERAL DISCUSSION

For the first step of the thesis it was necessary to develop, to set up, and to verify the aptness of a general protocol in a pilot study. The pilot study protocol was used as a basis for more extensive investigations (see Appendix 6).

The objectives of the 1<sup>st</sup> Experiment was to verify, using only the midline EEG sites, that the Classic Old/New ERP memory effect was elicited after a long delay. The major findings were as follows: 1) Semantic integration process (N400) was not affected by sleep. 2) More importantly, the Old/New memory effect and behavioral performance to the studied stimuli was larger after nocturnal sleep vs. daytime wake, suggesting a role for sleep in memory consolidation.

For the 2<sup>nd</sup> Experiment, an expanded EEG montage was employed, and the ERPs were recorded during both during the study session (as a control) and during the test recognition session. The objective of this experiment was to better characterize the frontal effects seen in the first experiment. The major findings of the second experiment were as follows: 1) A larger late frontal effect occurred after sleep that was not seen following wakefulness and this may have resulted in a more elaborated episodic trace, 2) There was increased interference inhibition in the daytime wake condition, not seen following sleep, and 3) The affects found on the later ERP components during the recognition session were probably not due to differences in time of encoding across session.

Lastly, the 3<sup>rd</sup> Experiment was aimed to compare the effects of one night of sleep and sleep deprivation on neural activity (Old/New effect) and behavioral performance, while at the same time attempting to control for differences in

arousal/vigilance (N1-P2) across session. The data showed that TSD affected the ERPs measures of recognition when there was a prolonged delay but not in a homogeneous way. The major findings of Experiment 3 were: 1) The semantic integration process (N400) was not affected by sleep deprivation, and 2). A more elaborated LPC effect occurred after sleep representing sleep dependent facilitation of episodic memory processing, an effect that was abolished following TSD.

### 8.1 Limitations: Potential Effects of Circadian Rhythms

Circadian rhythms can influence cognitive and memory functioning (Folkard & Monk, 1988). In our experiments, the effect of sleep on memory processing may reflect circadian influences on the time of testing. We kept, however, time of testing constant, which has been shown to be an important control for circadian factors (Plihal & Born, 1997). Nevertheless, it has been shown that circadian patterns in memory functions are substantially moderated by individual- and age-related differences in vigilance levels in the day (morning types) versus later in the day (evening types) (Petros, Beckwith, & Anderson, 1990; May, Hasher, & Foong, 2005; Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1999). Research in this area has shown increases in performance in college-aged participants if tested at their “optimal time of day,” i.e., in the afternoon, but not if tested at their “worse time of day,” i.e., in the morning (Petros et al., 1990; May, Hasher, & Stoltzfus, 1993). The pattern of our data, however, showed an opposite effect during the recognition test, i.e. there was more-accurate performance in the morning after sleep than in the early evening. We also found no difference in RT measures for the recognition test at the

evening and morning times, which would argue against circadian influences. Thus, it is unlikely that our results are due to circadian factors.

On the other hand, early work by Folkard & Monk (1988) report that while the time of day does not significantly affect your ability to remember (e.g. retrieve) information, it may affect your ability to encode, i.e. learn (Folkard & Monk, 1988). We addressed this issue of the possible confounding influence of time of learning (encoding) on subsequent recognition, in the second experiment by assessing the DM Effect. Our data showed that this effect does not differ as a function of the time of encoding (morning vs. evening). However, our lack of a difference between the two sessions may be due to Type II error since we had a small number of subjects ( $N = 10$ ) for the analysis of the DM effect. In order to determine if more subjects would have resulted in differences in the DM across session, we analyzed in a repeated measure ANOVA on the original 10 subjects and added 5 subjects from the original group (total  $N=15$ ). Once again, we found no difference in the DM effect between evening and morning, indicating that our results cannot be explained by difference in the time of the prior learning episode.

## 8.2 Stabilization (N400) vs. Enhancement: (LPC/P600)

As mentioned in the introduction, the two major ERP components representing the classic Old/New ERP memory effect that have been consistently reported in the literature are the posterior N400 and the LPC/P600 components (Friedman et al., 2000). Our data showed that the amplitude of the N400 component was decreased or more positive to previously presented information (i.e., old stimuli)

corresponds to the fact that the studied items were more easily integrated with semantic knowledge than the new stimuli. Nevertheless, there was no significant difference between the daytime and night sessions on the N400 Old/New effect. This would suggest that there is no facilitation by sleep on the semantic integration process, which is *a priori* inconsistent with the consolidation hypothesis.

One explanation that may account for these results can be seen in the procedural memory literature (Walker & Stickgold, 2006; Walker, 2005). A study by Walker *et al.* using procedural skills task demonstrated that consolidation is a two-stage process (Walker, Brakefield, Hobson, & Stickgold, 2003). He proposes that the first stage occurs within approximately six hours after learning, is a stabilization period by which the trace becomes more resistant to interference. This initial stage of consolidation has been shown to occur after learning during wake. Given the data from our experiments it may explain the fact that there was no difference in the N400 following wakefulness because at some point the trace (N400) became stabilized in the same manner both during wake and during wakefulness imposed by the deprivation procedure. We put forward the idea that the stabilization phase occurs not only during wake as proposed by the 2-stage model but in some memory tasks also during sleep reflected in the posterior N400 component. The N400-like component recorded by Brualla and *colleagues* (1998) that persisted *during* wakefulness into light sleep, i.e. Stage-II, and REM but not deeper SWS (Brualla, Romero, Serrano, & Valdizan, 1998) may potentially reflect the first stage of consolidation. This idea is further supported by the fact that the stabilization stage is accompanied by changes in the activity of the parietal and premotor cortices (Shadmehr & Holcomb, 1997;

Shadmehr & Brashers-Krug, 1997) consistent with the topography and neural generators of the N400 (Guillem, Bicu, & Debruille, 2000; Guillem, Rougier, & Claverie, 1999).

The 'enhancement' phase is the second phase in the model that is thought to occur only during sleep and facilitates next-day performance. The higher scores (% accuracy) obtained in our experiments after sleep compared to wake or TSD is consistent with this view. Furthermore, the final stage of information processing, i.e. memory synthesis and facilitation of episodic memory reflected in the LPC/P600 was significantly different across session. Its functional interpretation is that its amplitude is proportional to the elaboration of the information retrieved from episodic memory (Rugg et al., 1994). By this account, the larger LPC Old/New amplitude indicates that information retrieved after sleep is more elaborated than after wake or following TSD, consistent with the role of sleep in memory consolidation. This is also consistent with the enhancement phase of the 2-stage model of consolidation (Walker, Brakefield, Hobson, & Stickgold, 2003). As mentioned in the introduction, Perrin *et al.* report that a P600-like component can be elicited *during* sleep (Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999; Pratt, Berlad, & Lavie, 1999). This ERP component may reflect the processes underlying elaboration contribution to consolidation of episodic memory.

### 8.3 Interference Processing (N200) & Stabilization

Several researches have reported deficits in tests of executive functioning, after one night of TSD (Harrison & Horne, 2000). Early work by Horne (1988)

utilizing neuropsychological tests showed that sleep deprivation impairs performance on divergent thinking abilities, e.g. the number of ideas produced, the ability to change strategies, and the generation of ideas (Horne, 1988). As mentioned in the Introduction, the capacity to inhibit an inappropriate response, divergent and strategic thinking is a mechanism regulated by executive functions (Lezak, 1995), and has been shown to be sensitive to sleep disturbances (Horne & Walmsley, 1976; Horne, 1993). Our data on accuracy performance following TSD in Experiment 3 showed a larger number of discrimination errors (i.e. false alarms). One possible explanation is that there was an inability to inhibit an inappropriate response following loss of sleep.

Likewise, we reported a more negative early frontal effect (N200) for the old stimuli after wake compared to sleep that could represent *increased* interference inhibition following wakefulness to retrieve studied (old) items. A reversed effect was observed on the early frontal component after sleep. In this case, there was a reduced (more positive) ERP amplitude (N200) following sleep compared to wake. This suggests that the studied stimuli entailed less interference inhibition than the new items after sleep than after wake, consistent with the idea of consolidation. In concordance with our data, Ellenbogen *et al.* have recently reported the protective effect of sleep on declarative memory from interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). Furthermore, it has been shown that stabilization is reached following learning after 4 to 6 hours in procedural skills tasks; however, further enhancements are seen following sleep (Walker, Brakefield, Hobson, & Stickgold, 2003). If one assumes that stabilization reaches the same level after a number of hours of sleep, wake or TSD (see N400), then our data may be

viewed as a consequence of sleep protecting memories by preventing interfering events occurring over the course of the day. One possible mechanism responsible for the beneficial effects of sleep may be hippocampal replay of newly formed memories resulting in a strengthening of the trace (Buzsaki, 1998) with or without interference (for review see Norman, 2006). More work, however, is needed to determine the actual mechanism(s) responsible for this beneficial effect of sleep on memory.

#### 8.4 Contextual Process (LFC) & Enhancement

Our results indicated that sleep influences context processing but differently than that seen in the wake or TSD condition. As previously mentioned in the Introduction, these frontal components reflect context processing. The data showed a reduced effect after TSD compared to sleep, indicating that TSD affects the processing of contextual information, which is consistent with a number of other researchers (for review Harrison & Horne, 2000).

There have been studies utilizing sleep deprivation protocols that supported the role of sleep in context processing. For instance, Harrison and Horne (2000) have shown that individuals deprived of sleep can recognize correctly previously presented stimuli (e.g. faces) but have difficulty at remembering in which set of stimuli it had appeared, i.e., the source of information (Harrison & Horne, 2000). This difficulty in context processing has been further associated with the sensitivity of the frontal cortex function to sleep loss (Harrison & Horne, 2000) which is consistent with the topography reported here. This is consistent with an imaging study by Drummond (1999). Drummond *et al.*, (1999) showed that sleep deprivation resulted in *decreased*

activation that was more severe at the level of the prefrontal cortex compared to parietal and motor cortices during an arithmetic task (Drummond et al., 1999; Drummond & Brown, 2001). This is also in agreement with the hypothesis of prefrontal cortex vulnerability to sleep deprivation (Horne, 1988; Harrison & Horne, 2000). However, it is inconsistent with other studies by the same authors showing that when using a task of verbal learning (Ayalon, Ancoli-Israel, Klemfuss, Shalauta, & Drummond, 2006; Drummond et al., 2000) and a task of divided attention (Drummond, Gillin, & Brown, 2001; Drummond, Paulus, & Tapert, 2006), an *increased* signal from the prefrontal cortex was observed following TSD. This pattern of change could be dependent on the level of difficulty or type of task involved.

Our data shows larger mean amplitude difference on the frontal component for the old stimuli that was significant after sleep but not after wake, indicating greater effort is required to re-integrate the contextual details with the information already in memory. This is *a priori* inconsistent with memory consolidation. *So how could this assumption be consistent with the observed difficulties in context retrieval after sleep deprivation and with the consolidation hypothesis?* Consolidation is a mechanism by which the trace in memory becomes 'stronger' or re-structured and subsequently integrated into memory. Integration means that the new information and the (contextual) attributes with which it has been encoded are merged with previous semantic knowledge into a more abstract and distributed representation. Therefore, to be accurately retrieved on a subsequent presentation, a consolidated trace would have to be "re-contextualized". This may explain why in our experiments greater

contextual processing effort is elicited after sleep. Consequently, after a period of wakefulness or TSD, the information and its contextual attributes are likely to remain associated into an episodic representation, hence requiring less processing effort. Exactly how recently acquired knowledge comes to be processed during sleep is unclear. Cipolli *et al.* has shown evidence that one way sleep positively influences memory is through the repeated processing during REM for consolidation of items of declarative knowledge (Cipolli, Fagioli, Mazzette & Tuozi, 2005, 2006). The repeated incorporation of presleep stimuli into dreams occurs in such a way that only parts of the stimuli are accessed and elaborated on in subsequent dream recall across the night, demonstrating an iterative process (Cipolli, Fagioli, Mazzette & Tuozi, 1983). In such a case, one would expect increased processing and would argue in favor of our data showing a more elaborated trace and increased processing effort following sleep.

### 8.5 Summary

In summary, the three experiments demonstrated that influence of sleep on memory results in at least four distinct ERP Old/New memory effect. Figure 12 (below) represents a synthesis of the relationships associated with the role of sleep on the memory processes involved in the Old/New effect, and incorporates the 2-stage model along with the earlier model of Jenkins & Dallenbach (1924). We can say the following:

1. \*The posterior N400 is associated with the *Stabilization* phase of the 2-stage model. Based on our N400 data and behavioral RTs it occurs following wake, TSD and sleep.
    - a. \*The anterior N200 effects are connected to the fronto-tempo-parietal circuit responsible for the early processes of inhibition interference that is seen following wakefulness.
    - b. The posterior N200 is also connected to the fronto-tempo-parietal circuit and is responsible for discrimination and categorization of the stimuli. This early process is more positive following sleep vs. wake and after TSD. It may well be related to the “sleep” N2s.
  2. The Posterior LPC/P600 component of the temporo-parietal cortex is associated with the *Enhancement* phase of the 2-stage model. It is significantly larger following sleep but reduced after wake and after TSD, independent of vigilance.
    - a. \*The later frontal effect (LFC) of the superior frontal cortex reflecting contextual processing is increased during retrieval in the sleep condition. It is reduced, however, following sleep loss or wakefulness, and implicates the fronto-temporal cortex.
- \*The ERP processes associated with vigilance (N100) following TSD.

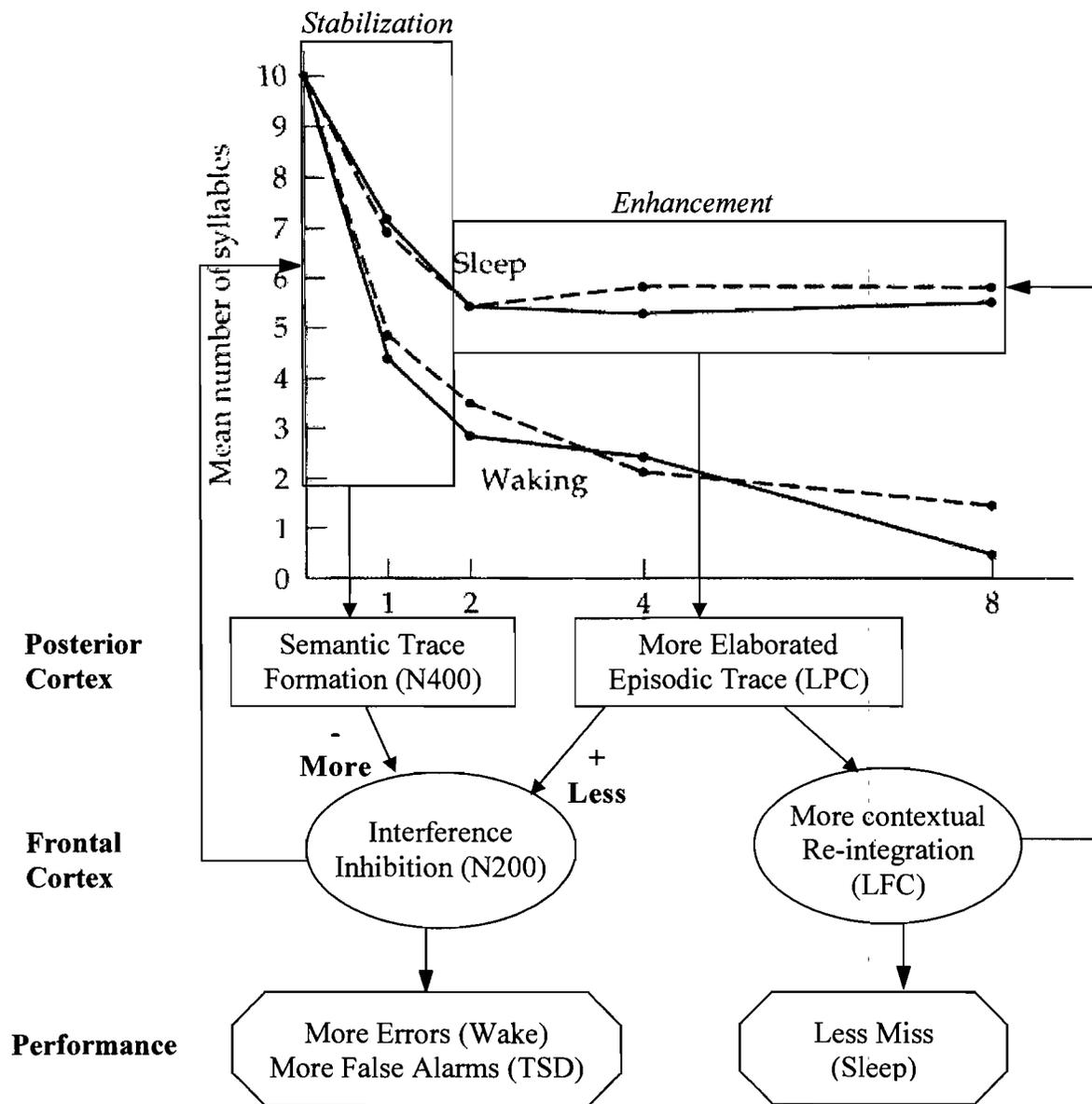


Figure 12. Synthesis of the Relationships: Sleep/Wake, ERP Memory Effect and the 2-Stage Model.

Despite the many inconsistencies in the sleep literature, results from our experiments support the idea that sleep has restorative function for some memory processes (interference, N2a; context, LFC; elaboration/episodic binding, LPC) and no effect on others (semantic integration, N400). These effects can be dissociated

into episodic processes based on their respective involvement in a direct test of recognition memory. ERP measures showed differences that were not at first glance obvious, for instance, the difficulties in contextual processing seen as increased processing effort were later easily explained by the facilitation of episodic memory resulting in a more elaborated trace. Strategic processing *is* likely to constitute another critical variable, particularly in distinguishing between the two frontal effects in terms of interference inhibition and contextual processing. Results of our data shed some new light on the memory processes by which sleep influences episodic and semantic memory. These findings make an addition to an accumulation of literature on the role of sleep in declarative memory.

## 9. FUTURE DIRECTIONS & CONCLUSION

One last point that should be mentioned is that this first series of experiments were designed to assess whether it is possible to investigate how sleep influence memory from an ERP perspective. Focusing on that, we did not record sleep EEGs in an attempt to minimize the potential negative effects of the sleep recording apparatus on the quality of the subject's sleep. The experimental protocol was based on early work that compared the effects of sleep and wake on memory retrieval. However, in the Introduction we emphasized the importance of specific sleep stages and sleep variables (e.g., the number of REMs, slow waves, and spindles, etc.) that have been shown to be essential in learning and memory processing (Fogel & Smith, 2006; Gais, Molle, Helms, & Born, 2002; Smith & Lapp, 1991). One of the follow-up studies should analyze the data looking at the effects of specific sleep stages and sleep parameters on the various memory processes while controlling for circadian influences. As highlighted in the Introduction, NonREM SWS has been reported to exert a beneficial influence on tasks typical for declarative memory, e.g. recognition and recall, and REM sleep appears to be more supportive in tasks representing procedural motor skill (Smith, 2001). In order to test for the effects of NonREM and REM sleep stages on memory, one could adopt an experimental protocol similar to Ekstrand and *colleagues* and more recently several others (Plihal & Born, 1997) that compared the effects of early and late nocturnal sleep on declarative memory (Barrett & Ekstrand, 1972; Ekstrand, 1967; Fowler, Sullivan, & Ekstrand, 1973; Yaroush, Sullivan, & Ekstrand, 1971; Gais, Plihal, Wagner, & Born, 2000; Plihal, Weaver, Molle, Fehm, & Born, 1996; Plihal et al., 1997; Plihal & Born, 1999). In such an

experiment, the subjects would be allowed to sleep for three hours between the encoding and retrieval sessions. There would be two experimental groups; one group would be allowed to sleep early in the night including mostly NonREM or SWS, and the other experimental group, would be allowed to sleep later in the night, which would include mostly REM. As a control, some participants would stay awake between learning and test to assess the general sleep effects and as an estimate of circadian influences. In addition, this design minimizes the negative effects of stress on sleep deprivation, and by using this procedure one can assess more precisely which ERP components are affected by different sleep stages and sleep parameters.

It should be mentioned that there are limitations in this design. One is that while a specific sleep stage is obtained, and the NonREM-REM sleep cycling is disturbed. Over the past years, the role of specific sleep stages in memory has become more complex. Stickgold and *colleagues* report improvements on a procedural visual task correlated with deep NonREM sleep (SWS) from the first quarter of the night and REM sleep from the last quarter of the night, suggesting a two-step or sequential process (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Along the same lines, Ficca *et al* have shown reduced performance on morning recall in young adults when a night of disturbed or fragmented sleep cycles occurred but not if the sleep-cycle organization remained preserved (Ficca, Lombardo, Rossi, & Salzarulo, 2000). This indicates the importance of both sleep stages and/or the NonREM-REM cycle organization in some types of memory tasks. In fact, many others have proposed a sequential model for memory processing during sleep in which optimal learning first requires the memory trace to be processed in

NonREM sleep, and then REM sleep (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Gais, Plihal, Wagner, & Born, 2000; Ambrosini, Mariucci, Bruscelli, Colarieti, & Giuditta, 1995; Giuditta et al., 1995). Implicated in this model is that specific stages of sleep are needed for the regeneration of neurons within the cerebral cortex while other stages of sleep may be used for forming new memories and generating new synaptic connections.

In our Experiments 1 and 2, the subjective number of nocturnal awakenings during sleep in the laboratory, which has been shown to be reliable, was reported to be similar to that in the home. This would indicate that the sleep-cycle organization was preserved across the night in our experiments and may have contributed to the improvements in recognition performance. Our data does not disprove the dual hypothesis i.e. NonREM sleep alone may have contributed to the improved performance on our declarative memory task, since sleep stages were not addressed in our experiments. However, based on our subjective reports of arousals following sleep in the laboratory, it would argue more in favor for sequential processing, i.e. that both sleep stages are required to be fully effective in our recognition task. In this perspective, the combination of both sleep stages could be more important than an individual sleep stage. The two models (i.e. dual hypothesis, sequential hypothesis) are not necessarily mutually exclusive and may be employed as needed to perform the task at hand (Peigneux, Laureys, Delbeuck, & Maquet, 2001; Peigneux et al., 2004; Ficca, Lombardo, Rossi, & Salzarulo, 2000; Ficca & Salzarulo, 2004). Event related potentials (ERPs) allow a promising avenue for addressing several of these issues by allowing for dissociating the different cognitive and memory processes.

Nor does the dual hypothesis or sequential hypothesis contradict Walker's 2-stage model of consolidation. The 2-stage model simply adds the differential effects of the wakefulness in producing consolidation. Wakefulness, NonREM and/or REM sleep stages could play a role, with a different impact according to the different cognitive demands and the various memory processes imposed by the task.

We have suggested an association between ERPs on a task of declarative memory and Walker's 2-stage model of consolidation originally developed in the context of skill learning. The present study opens a new window of investigation on the two-stages of consolidation on declarative memory.

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*Appendix 1*

## Screening Questionnaires

- a. Sociodemographic & Medical History
- b. Sleep (Habits) Questionnaire
- c. Inclusion/Exclusion Criteria

*Appendix 2*

## Informed Consent

*Appendix 3**Sleep Agenda**Appendix 4**Description & Examples of the Questionnaires*

- a. *Evening Questionnaire*
- b. *Morning Questionnaire*
- c. *Daytime Questionnaire*  
*includes Stanford Sleepiness Scale*
- d. *Visual Analog Scale (VAS)*

*Appendix 5**Subject's Task Instructions**Appendix 6*

Demande d'autorisation de rédiger un mémoire ou une thèse  
par article

Accord des co-auteurs et permission de l'éditeur

Article: The Influence of Sleep on Memory: An evoke-related  
potential study.

Appendix 1  
Screening Questionnaires

## Appendix 1

### Screening Questionnaires

Following screening and prior to beginning the experiment, participants were required to complete questionnaires intended to collect the general socio-demographic information (SES Questionnaire; Medical Questionnaire); sleep habits and/or on possible problems of sleep (Sleep Habits Questionnaire).

#### *Socio-Demographic Measures*

Socioeconomic Status (SES) Questionnaire: This questionnaire was used to collect the descriptive and socio-demographic characteristics of the participants. It includes a number of socio-demographic variables.

#### *Instruments used in the Inclusion/Exclusion Criteria:*

Medical Questionnaire: This instrument concerns the medical history of the participants. It gives the information on the general mental and physical health of the subject. For the mental health, the participants who have been or had first-degree relatives treated for psychiatric problems are excluded from the study. For the physical health, all of the persons who suffer from problems of epilepsy, loss of consciousness and other head-related traumas were excluded. This questionnaire was filled out prior to participating in the experiments and was used as a screening device.

#### *Measures of Daytime Sleepiness*

Sleep Habits Questionnaire: This frequently used measurement asks participants to self-define as having problems sleeping and inquires about both affective and behavioral aspects of typical sleep experiences, including time spent in bed, bedtime and arising times during a typical week and frequency (0-7 days/week) of difficulty falling asleep or getting back to sleep after nocturnal awakenings. The information provided allowed us to (1) determine the presence or absence of difficulty initiating or maintaining sleep (DIMS) and (2) obtain ratings of respondent's subjective perceptions of frequency of sleep problems (0-7 days/week).

### Medical History Questionnaire

This questionnaire is used to gather information pertaining to your present situation and past history, as well as certain aspects of your family history. This information will assist us in understanding the results of your participation by placing it in the context of your background.

Your answers will be held in strict confidence by the study team and will not be revealed to anyone without your written consent.

**Please write all your answers clearly and in block letters**

Date: \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Family Name: \_\_\_\_\_ First Name: \_\_\_\_\_

Age: \_\_\_\_\_ yrs. Gender (check one): Male  Female

Home address: \_\_\_\_\_

Phone Number: Work (\_\_\_\_\_) Home(\_\_\_\_\_) \_\_\_\_\_

Current or most recent (if unemployed) occupation (please describe as clearly as possible):

Current marital status (check one):

Married  Single  Divorced  Cohabiting

If you are a student and/or rely primarily on another person(s) source of income (e.g. parents),

Please indicate the source \_\_\_\_\_

And their approximate average annual income (check one):

\$ 0-10,000  \$ 10,000-15,000  \$15,000-20,000   
 \$ 20,000-25,000  \$25,000-30,000  \$ 30,000+

Race (check one): Caucasian (white)  African-American (black)   
 Asian  Latin-American (Hispanic)

Other (please specify): \_\_\_\_\_

In what religion were you raised (check one):

Catholic  Protestant  Hindu   
 Jewish  Moslem

Other (please specify): \_\_\_\_\_

Rate the strength of your religious belief (check one):

0  1  2  3  4  5   
 None Very strong

## SUBJECT INFORMATION QUESTIONNAIRE (continued)

How did you come to participate in the present study (check one):

- Referred   
 (By whom? \_\_\_\_\_)  
 Newspaper announcement   
 Heard about the study from friends or relative

**EDUCATION**

How many years of education have you completed (include kindergarten)? \_\_\_\_\_ yrs.

What is the highest level of education you attained (check one)?

- Grade School  High School  CEGEP  Bachelor   
 Master  Ph.D.  M.D.  other: \_\_\_\_\_

How were your grades during the highest level you completed (check one)?

- Mostly A  A and B's  Mostly B  B and C   
 Mostly C  C and D  Mostly D  below D

Did you get into fights at school? Yes  No

If yes, in what academic period was this most common (check one)?

- Grade School  High School  CEGEP  University

Were you ever suspended from school because of fighting? Yes  No

**DEVELOPMENTAL HISTORY**

Were there any problems with your own birth? Yes  No

If yes, describe: \_\_\_\_\_

As far as you know, did you talk and walk at about the same age as other children?

Yes  No

If we would like to contact someone in order to obtain more information with regards to your birth and development, what is the name and location of the hospital in which you were born?

**PRESENT MEDICAL HISTORY (only within the past one year)**

Do you currently have any medical illness? Yes  No

If yes, describe: \_\_\_\_\_

Do you currently have allergies to any medication? Yes  No

If yes, what medication: \_\_\_\_\_

Do you have any other allergies? Yes  No

If yes, describe: \_\_\_\_\_

**PAST MEDICAL HISTORY (only before the past one year)**

Have you ever had an injury to your head? Yes  No

If yes, indicate your age at the time of head injury and whether and for how long you lost consciousness. \_\_\_\_\_

Have you had any medical illness? Yes  No

**SUBJECT INFORMATION QUESTIONNAIRE (continued)**

If yes, describe: \_\_\_\_\_

Did you have any allergies? Yes  No

If yes, describe: \_\_\_\_\_

Have you ever had surgery? Yes  No

If yes, indicate your age at the time of surgery, and the type of surgery.

\_\_\_\_\_

**PRESENT PSYCHIATRIC HISTORY (only within the past one year)**

Were you hospitalized for a psychiatric illness in the past year? Yes  No

If yes, please specify: what is your diagnosis: \_\_\_\_\_

where were you hospitalized : \_\_\_\_\_

Have you received treatment for a psychiatric illness without being hospitalized in the past year? Yes  No

If yes, please specify: what is your diagnosis: \_\_\_\_\_

what type of treatment: \_\_\_\_\_

Did you intentionally stop your treatment? Yes  No

If yes, explain why: \_\_\_\_\_

**PAST PSYCHIATRIC HISTORY (only before the past one year)**

Have you been hospitalized for a psychiatric illness? Yes  No

If yes, please specify: what is your diagnosis: \_\_\_\_\_

where were you hospitalized : \_\_\_\_\_

Have you received treatment for a psychiatric illness? Yes  No

If yes, please specify: what is your diagnosis: \_\_\_\_\_

what type of treatment : \_\_\_\_\_

Did you intentionally stop your treatment? Yes  No

If yes, explain why: \_\_\_\_\_

\_\_\_\_\_

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**SUBJECT INFORMATION QUESTIONNAIRE (continued)**
**MEDICATION AND SUBSTANCE USE**

Have you use any medication(s) (other than medical treatment and psychotropic)?

Yes

No

If yes, please specify: what medication: \_\_\_\_\_

For what purpose: \_\_\_\_\_

Do you drink alcohol? Yes

No

If yes, please specify: how many glasses, on average,  
per day? \_\_\_\_\_ per week? \_\_\_\_\_ per occasion of drinking? \_\_\_\_\_

How often do you get drunk per week? \_\_\_\_\_ per month? \_\_\_\_\_

Have you ever been to a hospital because of drinking? Yes  No

Have you ever received treatment because of drinking? Yes  No

Do you smoke tobacco? Yes

No

If yes, how many cigarettes, on average, per day? \_\_\_\_\_

Have you ever used illegal drugs (e.g. cocaine, marijuana)? Yes  No

If yes, what drug(s) and how often? \_\_\_\_\_

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**FAMILY HISTORY**

Mother: Age \_\_\_\_\_ Occupation (before retirement): \_\_\_\_\_

Highest level of education: \_\_\_\_\_

Handedness (check one) left  right  mixed

If deceased, please indicate cause of death: \_\_\_\_\_

Father: Age \_\_\_\_\_ Occupation (before retirement): \_\_\_\_\_

Highest level of education: \_\_\_\_\_

Handedness (check one) left  right  mixed

If deceased, please indicate cause of death: \_\_\_\_\_

Current status (check one):

Married  Divorced  Cohabiting

Have you brother(s) and/or sister(s)? Yes  No

If yes, indicate how many brothers: \_\_\_\_\_ sister(s): \_\_\_\_\_ and your rank: \_\_\_\_\_

Are you adopted? Yes  No

If yes, do you know your biological parents? Yes  No

## SUBJECT INFORMATION QUESTIONNAIRE (continued)

Who raised you for the majority of time during your childhood (check one)?

Mother and father       Mother only       Father only   
 Grandparents       Uncle and /or Aunt       Other (specify): \_\_\_\_\_

Were or is someone of your family hospitalized for psychiatric illness?

Yes       No

If yes, please specify:      which member : \_\_\_\_\_

what illness : \_\_\_\_\_

where were or is he/she hospitalized : \_\_\_\_\_

Were or is someone of your family receiving treatment for psychiatric illness without being hospitalized? Yes       No

If yes, please specify:      which member: \_\_\_\_\_

what illness : \_\_\_\_\_

Were or is someone of your family hospitalized or receiving treatment for any other medical illness? Yes       No

If yes, please specify:      which member : \_\_\_\_\_

what illness : \_\_\_\_\_

where were or is he/she hospitalized : \_\_\_\_\_

## QUESTIONNAIRE D'INFORMATION

Ce questionnaire est destiné à recueillir des informations concernant votre situation présente et passée, ainsi que sur certains aspects de votre histoire familiale. Ces informations nous aideront à comprendre les résultats de votre participation en les replaçant dans le contexte de votre situation individuelle. Vos réponses seront gardées de façon strictement confidentielle par l'équipe de recherche et ne seront transmises qu'avec votre autorisation écrite.

**Écrivez toutes vos réponses en lettre d'imprimerie**

Date : \_\_\_\_\_ / \_\_\_\_\_ / \_\_\_\_\_

Nom de famille : \_\_\_\_\_ Prénom : \_\_\_\_\_

Âge : \_\_\_\_\_ ans Genre (cochez): Homme  Femme

Adresse pers. : \_\_\_\_\_

Téléphone : Travail (\_\_\_\_\_) Pers. (\_\_\_\_\_) \_\_\_\_\_

Profession ou plus récent emploi (si au chômage) (décrivez aussi clairement que possible) :

Situation maritale actuelle (cochez) :

Marié  Célibataire

Divorcé  Concubin

Race (cochez) : Caucasiens (blanc)  Africain-Américain (noir)   
Asiatique  Latino-Américain (hispanique)

Autre (spécifiez) : \_\_\_\_\_

Dans quelle religion avez vous été élevé (cochez) :

Catholique  Protestante  Hindoue

Juive  Musulmane

Autre (spécifiez) : \_\_\_\_\_

Évaluez la force de votre croyance religieuse (cochez) :

0  1  2  3  4  5   
Inexistante Très forte

## QUESTIONNAIRE D'INFORMATION

### EDUCATION

Combien d'années d'éducation avez vous effectuée (maternelle incluse) ? \_\_\_ ans

Quel est le niveau le plus élevé que vous ayez atteint (cocher) ?

Primaire     Secondaire     CEGEP     Bac   
 M.p.s.     Ph.D.     M.D.     Autre : \_\_\_\_\_

Quelles étaient vos notes au dernier niveau que vous avez atteint (cochez) ?

Souvent A     A et B     Souvent B     B et C   
 Souvent C     C et D     Souvent D     DessousD

### DEVELOPPMENT

Y a t-il eu de complications à votre naissance ?      Oui     Non

Si oui, décrivez : \_\_\_\_\_

Autant que vous vous souvenez, avez parlé et marché au même âge que les autres enfants ?

Oui       Non

### HISTOIRE MEDICALE ACTUELLE (seulement au cours de l'année écoulée)

Êtes vous actuellement malade ? Oui     Non

Si oui, décrivez : \_\_\_\_\_

Êtes vous allergique à des médicaments ? Oui     Non

Si oui lesquels : \_\_\_\_\_

Avez vous d'autres allergies ? Oui     Non

Si oui lesquelles : \_\_\_\_\_

## QUESTIONNAIRE D'INFORMATION

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### HISTOIRE MEDICALE PASSEE (seulement avant l'année écoulée)

Avez vous déjà eu un traumatisme à la tête ? Oui  Non

Si oui, indiquez votre âge quand c'est arrivé et combien de temps êtes vous resté inconscient.

\_\_\_\_\_

Avez vous été malade ? Oui  Non

Si oui décrivez : \_\_\_\_\_

Avez vous eu des allergies? Oui  Non

Si oui décrivez : \_\_\_\_\_

Avez vous subi une chirurgie ? Oui  Non

Si oui, indiquez à quel âge et le type de chirurgie.

\_\_\_\_\_

\_\_\_\_\_

### HISTOIRE PSYCHIATRIQUE ACTUELLE (seulement au cours de l'année écoulée)

Avez vous été hospitalisé pour une maladie mentale durant l'année passée ?

Oui  Non

Si oui, précisez : quel diagnostic : \_\_\_\_\_

quel hôpital : \_\_\_\_\_

Avez vous eu un traitement pour un trouble mental sans être hospitalisé durant l'année passée? Oui  Non

Si oui, précisez: quel diagnostic: \_\_\_\_\_

quel traitement : \_\_\_\_\_

Avez vous arrêté intentionnellement votre traitement ? Oui  Non

Si oui, pourquoi : \_\_\_\_\_

### HISTOIRE PSYCHIATRIQUE PASSEE (seulement avant l'année écoulée)

Avez vous été hospitalisé pour une maladie mentale? Oui  Non

Si oui, précisez : quel diagnostic: \_\_\_\_\_

quel hôpital : \_\_\_\_\_

Avez vous eu un traitement pour un trouble mental? Oui  Non

Si oui, précisez : quel diagnostic: \_\_\_\_\_

quel traitement: \_\_\_\_\_

Avez vous arrêté intentionnellement votre traitement? Oui  Non

Si oui, pourquoi : \_\_\_\_\_

## QUESTIONNAIRE D'INFORMATION

**UTILISATION DE MEDICAMENTS ET DE DROGUES**

Utilisez-vous des médicaments (autres que traitement médical et psychotropes) ?

Oui Non 

Si oui, précisez : quel médicament : \_\_\_\_\_

en quelle occasion : \_\_\_\_\_

Buvez-vous de l'alcool ? Oui  Non 

Si oui, précisez :

Combien de verres, en moyenne, par jour ?

par semaine? \_\_\_\_\_ par occasion de boire?\_\_

Combien de fois êtes vous ivres par semaine? \_\_\_\_\_ par mois? \_\_\_\_\_

Avez vous déjà été hospitalisé à cause de l'alcool ? Oui  Non Avez vous déjà reçu un traitement pour alcoolisme ? Oui  Non Fumez-vous du tabac ? Oui  Non 

Si oui, combien de cigarette par jour en moyenne ? \_\_\_\_\_

Prenez-vous des drogues illicites (cocaïne, marijuana)? Oui  Non 

Si oui, quelle(s) drogues et avec quelle fréquence ? \_\_\_\_\_

**HISTOIRE FAMILIALE**

Mère : Âge \_\_\_\_\_ Profession avant la retraite : \_\_\_\_\_

Niveau d'éducation : \_\_\_\_\_

Père : Âge \_\_\_\_\_ Profession avant la retraite : \_\_\_\_\_

Niveau d'éducation : \_\_\_\_\_

Statut marital (cochez) :

Mariés  Divorcés  Concubins Avez vous des frère(s) et sœur(s)? Oui  Non 

Si oui, combien de frère(s) : \_\_\_\_\_ de sœur(s) : \_\_\_\_\_ votre rang : \_\_\_\_\_

Avez vous été adopté ? Oui  Non

## QUESTIONNAIRE D'INFORMATION

Par qui avez vous été élevé la plupart du temps (cochez) ?

Mère et père  Mère seule  Père seul   
 Grand-parents  Oncle ou tante  Autre (specifiez) :

Un membre de votre famille a-t-il été ou est-il hospitalisé pour troubles psychiatriques ? Oui

Non

Si oui, précisez : quel membre : \_\_\_\_\_

quel trouble : \_\_\_\_\_

où était-il/elle hospitalisé : \_\_\_\_\_

Un membre de votre famille a-t-il reçu, ou reçoit-il, un traitement pour un trouble mental sans être hospitalisé ? Oui  Non

Si oui, précisez : quel membre : \_\_\_\_\_

quel trouble : \_\_\_\_\_

Un membre de votre famille a-t-il été hospitalisé ou a reçu un traitement pour d'autres maladies ? Oui  Non

Si oui, préciser : quel membre : \_\_\_\_\_

Quelle maladie : \_\_\_\_\_

où était-il/elle l hospitalisé : \_\_\_\_\_

## Appendix 1

LABORATOIRE DE RECHERCHE SUR LE SOMMEIL  
CENTRE DE RECHERCHE FERNAND-SEGUN

**Sleep (Habits) Questionnaire**

Name: \_\_\_\_\_ Date: \_\_\_\_\_ Project: \_\_\_\_\_

During the last month, what were your sleep habits:

1. Usual bedtime on week days: \_\_\_\_\_; during week-ends: \_\_\_\_\_
  
2. Usual morning wake-up time  
 on week days: \_\_\_\_\_ (with the help of an alarm clock? Yes \_\_\_ No \_\_\_)  
 on week-ends: \_\_\_\_\_ (with the help of an alarm clock? Yes \_\_\_ No \_\_\_)
  
3. On the average, how long does it take you to fall asleep, in minutes? \_\_\_\_\_ minutes.  
 How many times per week do you fall asleep within 5 minutes? \_\_\_\_\_  
 How many times per week does it take more than 30 minutes? \_\_\_\_\_
  
4. On the average how many times do you wake up during the night? \_\_\_\_\_  
 What is the average total duration of these awakenings? \_\_\_\_\_
  
5. Do you usually feel refreshed when you get up in the morning?  
 Very ( ) Moderately ( ) Somewhat ( ) Not at all ( )
  
6. Are you generally satisfied with your sleep? Yes \_\_\_ No \_\_\_
  
7. a) Do you take naps on week days? Yes \_\_\_ No \_\_\_  
 b) Do you take naps on week-ends? Yes \_\_\_ No \_\_\_
  
8. Have you taken medications during the last month? Yes \_\_\_ No \_\_\_  
 If so, please write down the name and the dose taken:

LABORATOIRE DE RECHERCHE SUR LE SOMMEIL  
CENTRE DE RECHERCHE FERNAND-SEGUIN

**Questionnaire sur les habitudes de sommeil**

Nom: \_\_\_\_\_ Date: \_\_\_\_\_ Projet: \_\_\_\_\_

Au cours du dernier mois, quelles ont été vos habitudes de sommeil:

1. Heure habituelle du coucher les jours de semaine: \_\_\_\_\_; les fins de semaine: \_\_\_\_\_
  
2. Heure habituelle du lever  
 les jours de semaine: \_\_\_\_\_; (à l'aide d'un réveil-matin ou autre? Oui\_\_\_ Non\_\_\_)  
 les fins de semaine: \_\_\_\_\_; (à l'aide d'un réveil-matin ou autre? Oui\_\_\_ Non\_\_\_)
  
3. En moyenne, combien de minutes cela vous prend-t-il pour vous endormir? \_\_\_\_\_  
 Combien de fois par semaine vous endormez-vous en moins de 5 minutes? \_\_\_\_\_  
 Combien de fois par semaine cela prend-il plus de 30 minutes? \_\_\_\_\_
  
4. En moyenne combien de fois vous réveillez-vous pendant la nuit? \_\_\_\_\_  
 Combien de temps au total durent ces réveils? \_\_\_\_\_
  
5. Vous sentez-vous habituellement reposé le matin en vous levant?  
 Très ( ) Modérément ( ) Peu ( ) Pas du tout ( )
  
6. Êtes-vous généralement satisfait de votre sommeil? Oui\_\_\_ Non\_\_\_
  
7. a) Faites-vous des siestes les jours de semaine? Oui\_\_\_ Non\_\_\_; durée: \_\_\_\_\_  
 b) Faites-vous des siestes les fins de semaine? Oui\_\_\_ Non\_\_\_; durée: \_\_\_\_\_
  
8. Avez-vous pris des médicaments au cours du dernier mois? Oui\_\_\_ Non\_\_\_  
 Si oui, s.v.p. en donner le nom et la dose ci-dessous:

## INCLUSION/EXCLUSION CRITERIA

### TITLE OF THE RESEARCH PROJECT

*Implementation of a protocol for evaluating the influence of the sleep on memory by means of cognitive evoked potentials. A Pilot Study*

|                             |                    |
|-----------------------------|--------------------|
| Principal Investigator:     | François Guillem   |
| Co-investigator:            | Roger Godbout      |
| Coordinator of the Project: | Melodee A. Mograss |

### QUESTIONS OF THE ETHICS COMMITTEE

1. **What are the characteristics of the subjects involved in your research, that is, the subjects having gone through the process of the criteria of exclusion?**

#### Criteria of Inclusion:

- [1] Males & females from 18 to 39 years old
- [2] Normal or corrected vision
- [3] Capable of understanding the purpose of the study
- [4] Agreeing to the signing of the evaluations and the tests and able to understand the instructions
- [5] Signing of the consent form

#### Criteria of exclusion:

- [1] Investigators and their immediate family (parents, children, grandparents).
- [2] Pregnant woman who are breast-feeding an infant.
- (2) Traumatic antecedents with neurological after-effects.
- [3] Identified neurological disorder or current degenerative processes.
- [4] Epilepsy or convulsive disorders with unknown etiologies.
- [5] Excitement or incompatible attentiveness with the tests.
- [6] Disorders of sleep (DSM IV: 307.4 Primary Insomnia and Primary Hypersomnia; 347 Narcolepsy; 780.59 Breathing related sleep disorder; 307.45 Circadian rhythm sleep disorder: specific type - typical Shift-work).
- [7] Others diagnosis psychiatric (DSM IV: Axis I or II and Axe III General Medical Disorder) current or past.
- [8] Familiar history of first-degree relatives with primary sleep disorder or major psychiatric illness.
- [9] Prescription or over-the-counter medication for sleep > 3/week &/or discontinued the drug < 2 months or excessive caffeine.

2. **To what operations and procedures will the subject be subjected?**

The protocol includes:

- 1- An interview and questionnaires intended to collect the demographic data (subject's characteristics)
- 2- Evoked Potential Recordings during a memory task.

The recordings will be made twice: once, with a night of sleep inserted between the learning task and the recognition phase. This night will be spent in the Sleep Laboratory of the F-Seguin Research Center.

The other test will have an identical delay period of awakening between both phases. During this period the subjects will go about their normal daily activities and will return to the center for recognition test.

### **3. How does the researcher intervene in these operations and procedures?**

The investigator will oversee each of the stages: the selection of the subjects, the invitation to participate in the experiment, answering all possible questions concerning the experiment and the informed consent.

### **4. In your opinion, what are the risks that the subject can incur?**

As for a standard EEG, there are no risks to the subjects.

The used elasticized cap can be uncomfortable for the subject.

### **6. What measures did you take to insure the confidentiality of the data?**

All subjects will be identified by a code protecting the patient's files - as specified in the informed consent, the data contained in the file will be accessible only to the persons involved in the project (investigators, evaluators or research assistants). Subject's information cannot be passed on to other persons without the written consent. - The name of the subjects will never appear in the publications.

### **7. What is, in your opinion, the value of the informed consent for which you ask the subjects to sign in this project?**

The consent will be obtained by taking into account recommendations of the Canadian Psychiatric Association concerning the capacity of the subjects to be granted (Grants in psychiatry. Internet site of the APC: <http://cpa.medical.org/cpa/public2/papers/position.papers/consent.html>).

These recommendations include in particular five of the following items:

- Does the subject possess competence & understand the meaning of this agreement?
- Does the consent form include the conditions of the study, which we propose to s(he)?
- Does the consent form include the nature and the purpose of the study?
- Does the consent form include the risks and benefits to the study?
- Does the subject include the risks and benefits *not* to participate in the study?

If a doubt persists as to the understanding of the subject, s(he) will not be included in the study.

### **8. Do the subjects receive personally certain advantages of this research?**

As specified in the consent form, no advantage or benefit is guaranteed to the subject. The subjects receive, for their participation, a compensation corresponding to the past protocol.

Scales and tests are used to establish a clinical and cognitive evaluation, which is not systematically made. The results of this evaluation can be passed on the subject on his(her) demand at the conclusion of the research.

**9. What is the financier for this research, which sum is attributed to this project and which is the mode of financing?**

There is no financier for this experimental study.

If the protocol turns out to be valid and relevant, a more complete study on a wider sample will be proposed in a body with peers' committee (CRSNG, FRSQ or ICRS)

**10. Are there supplementary costs for the hospital?**

Yes

No



If yes, then type and amount:

- Pharmacy \_\_\_\_\_
- Radiology \_\_\_\_\_
- EEG \_\_\_\_\_
- Others (specify) \_\_\_\_\_

Appendix 2  
Informed Consent

## APPENDIX 2



**HÔPITAL LOUIS-H. LAFONTAINE**  
**ÉTABLISSEMENT PSYCHIATRIQUE**  
**AFFILIÉ À L'UNIVERSITÉ DE MONTRÉAL**  
 7401, rue HOCHELAGA, MONTRÉAL (QUÉBEC) H1N 3M5  
 TÉL. : 251-4000

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**CONSENT FORM**
**Title of the Research Project**

A Protocol evaluating the influence of sleep on memory by means of cognitive evoke potentials: A Pilot Study.

F. Guillem (Ph.D.), Roger Godbout (PhD), M.A. Mograss (MA Psychology)

Centre de Recherche F-Seguin  
 7331 rue Hochelaga, Montréal, Qc H1N 3V2  
 Tel: (514) 251 4015  
 Fax: (514) 251 2617

Before agreeing to participate in this study, it is important to have read and understood the explanations of the protocol, which is proposed before you. This form describes the purpose of the test, the experiments, the benefits, these potential risks and discomfort, and any precautions that you should take. It also describes the options that you have and your rights to leave the study at any time. All your questions are welcome before deciding or not to participate in this study.

**Context & Objective of the Study**

The general theme of our project is the influence of sleep in memorization of information by means of recording evoked potentials. For this study, it will be first necessary to develop, to set up, and to verify the aptness of a general protocol that will be of use as a base for more extensive investigations. The protocol that we plan to use in this study is a variation of a classical protocol typically used in the studies on evoked potentials, but into which a night of sleep, that is 6 at 8 am, will be inserted between the learning and the recognition tasks. To our knowledge, no study has used such long delays. More often the distance separating both phases is 5 in 10 minutes in duration.

The first phase will consist of verifying that the indices of cognitive evoke potentials associated with memory present after a night and then after a similar period (6 to 8 hours) of awake during the day.

## **Your Participation in the Study.**

The Protocol includes:

- An interview and a questionnaire which will allow us to collect information about your age, profession, current and past medical history.
- Electroencephalographs (EEG) activity will be recorded during two different phases of a memory task. The study will take place in two phases (Learning Test phase, Recognition Test phase) separated by a delay of approximately 6 to 8 hours. You will be tested twice. For one test, an intervening night of sleep spent in the Sleep Laboratory at the Fernand-Seguin Research Center will occur between the two tests. In the other test session, the two tests will be separated by an equivalent wake period of approximately the same duration (e.g. 6 to 8 hours). During this delay period, you will be able to go about your normal daily activities, and then will return to the Fernand-Seguin Research Center for the Recognition Test. Prior to each recording, an elasticized cap equipped with electrodes will be placed over your head. Other electrodes will be placed on your ear lobes, below, and outside your eyes. A special electrode paste will secure the electrodes. After the installation of the electrodes, you will be tested in either learning or in recognizing faces presented to you on a computer screen.

### **Risk & Discomfort**

Your participation implies no risk for you.

During the test, you can ask to take as many breaks as necessary.

### **Potential Benefits**

No benefits of your participation in this study can be guaranteed you. However, the results of the tests and the exam, which you have made, can be communicated to you free of charge.

### **Voluntary Participation**

Your participation in this research study is voluntary.

You are free not to participate or to stop your participation when you want to, without justification.

The investigator can stop your participation in this study if you present incompatible effects with the study; for example allergic reaction to the electrode paste, napping during the awake phase, or an inability to sleep in the laboratory.

### **Compensation for Your Participation**

You will receive \$7.50 dollars per hour (approximately 70 dollars per test) at the end of the study as compensation for the cost of travel, discomfort from the test and for the time spent during the study.

If you decide to stop your participation before having completed the study, you will receive the amount corresponding to the amount of time spent in the study before you leave.

**Confidentiality**

The results obtained in this study will be kept strictly confidential. Your file will be identified by a code and not by your name. Only persons involved in the project (investigators) can have access to this file.

The information contained in your file can be passed onto no other person without your written permission. The results, which you will obtain in the different examinations and tests, can be presented at scientific meetings or publications. On no account will your identity be revealed.

**If you have, questions?**

At any time, if you have any questions concerning the study, do not hesitate to ask.

You can also contact:

**Dr. François Guillem, au (514) 251 4015 ext. 3511**

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**Informed Consent**

My signature below give evidence that I have read this consent form and that I had the opportunity to ask questions, helping me to understand what my participation implies.

I agree to participate in this study until I decide otherwise. I recognize to have received a copy of this consent form. I authorize the communication of the results in scientific meetings and publications.

**The Subject:**

Your Name: \_\_\_\_\_

Your signature: \_\_\_\_\_ X \_\_\_\_\_ Date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_

**The Investigator or Evaluator:**

Name : \_\_\_\_\_

Signature: \_\_\_\_\_ Date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_

Appendix 3  
Sleep Agenda

Nom/Name : \_\_\_\_\_

Subjet/Subject Code: \_\_\_\_\_

Test : \_\_\_\_\_

INSTRUCTIONS TO FILL OUT SLEEP LOG FORM

In order for us to assess your sleep habits, it is very important that you fill out the attached sleep log for the recommended period. Here is some advice:

- Fill in the date for each day.
- Blacken the spaces corresponding to your sleep periods.
- The spaces left blank represent you awake periods.

Example: You have slept from 10h00pm to 7h30 am, you will blacken the squares in the following manner:

| Day      | Date | MN | 1am | 2am | 3am | 4am | 5am | 6am | 7am | 8am | 9am | 10am | 11am | Noon | 1pm | 2pm | 3pm | 4pm | 5pm | 6pm | 7pm | 8pm | 9pm | 10pm | 11pm | Comments |
|----------|------|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|----------|
| Thursday | 1/3  |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
| Friday   | 1/4  |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |
|          |      |    |     |     |     |     |     |     |     |     |     |      |      |      |     |     |     |     |     |     |     |     |     |      |      |          |

-Write down all medication taken (with or without prescription), alcohol, drugs, as well as any change in your routine under the column "Comments".

The square "MN" corresponds to period MN to 01h00 (midnight to 01h00 am)..

Should you have any questions completing this information, do not hesitate to contact us at \_\_\_\_\_.

#### Appendix 4

#### Description & Examples of the Questionnaires

LABORATOIRE DE RECHERCHE SUR LE SOMMEIL  
CENTRE DE RECHERCHE FERNAND-SEGUIN

**Questionnaire du soir**

Nom: \_\_\_\_\_ Date: \_\_\_\_\_ Projet: \_\_\_\_\_

1. Combien de temps avez-vous dormi la nuit passée: \_\_\_\_ heures \_\_\_\_ minutes

2. À quelle heure vous êtes-vous couché hier soir? \_\_\_\_\_

3. Combien avez-vous mis de temps à vous endormir hier soir? \_\_\_\_ minutes

4. Vous sentiez-vous reposé au réveil ce matin? Oui \_\_\_\_ Non \_\_\_\_

5. Avez-vous fait une sieste aujourd'hui? Oui \_\_\_\_ Non \_\_\_\_

6. Avez-vous pris des médicaments ou de l'alcool aujourd'hui? Oui \_\_\_\_ Non \_\_\_\_  
Si oui: quoi, quand et combien?

LABORATOIRE DE RECHERCHE SUR LE SOMMEIL  
CENTRE DE RECHERCHE FERNAND-SEGUN

**Evening Questionnaire**

Name: \_\_\_\_\_ Date: \_\_\_\_\_ Project: \_\_\_\_\_

1. How long did you sleep last night: \_\_\_\_ hours \_\_\_\_ minutes
2. What time did you go to bed last night? \_\_\_\_\_
3. How long did you take to fall asleep last night: \_\_\_\_ minutes
4. Did you feel refreshed when you woke up this morning? Yes \_\_\_ No \_\_\_
5. Did you take a nap today? Yes \_\_\_ No \_\_\_
6. Did you take medications or alcohol today? Yes \_\_\_ No \_\_\_  
If yes: what, when, and how much?

## MORNING QUESTIONNAIRE

NAME : \_\_\_\_\_ DATE : \_\_\_\_\_

CODE : \_\_\_\_\_ HOUR : \_\_\_\_\_ PROTOCOL : \_\_\_\_\_

1. How long did it take you to fall asleep last night? \_\_\_\_\_

Was it more or less what you do at home? More ( ) Less ( ) Similar ( )

2. Once you fell asleep, how deep was your sleep? (Choose 1 to 10)

|            |   |   |   |           |
|------------|---|---|---|-----------|
| 1          | 3 | 5 | 7 | 10        |
| very light |   |   |   | very deep |

Was it more or less what you do at home? More ( ) Less ( ) Similar ( )

3. How many times do you remember waking up during the night? \_\_\_\_\_

For how long? \_\_\_\_\_

Why? \_\_\_\_\_

4. According to you, what was the duration of your sleep? \_\_\_\_\_

Was it more or less what you do at home? More ( ) Less ( ) Similar ( )

5. Are you well rested this morning? (Choose 1 to 10)

|            |   |   |   |             |
|------------|---|---|---|-------------|
| 1          | 3 | 5 | 7 | 10          |
| Not rested |   |   |   | Very Rested |

Was your sleep similar to what you do at home? More ( ) Less ( ) Similar ( )

6. Do you remember dreaming last night? Yes ( ) No ( )

*Comments*

## QUESTIONNAIRE DU MATIN

NOM : \_\_\_\_\_ DATE : \_\_\_\_\_

CODE : \_\_\_\_\_ HEURE : \_\_\_\_\_ PROTOCOLE : \_\_\_\_\_

1. Combien de temps avez-vous mis pour endormir hier soir? \_\_\_\_\_

Est-ce plus ou moins rapide qu'à la maison? Plus ( ) Moins ( ) Pareil ( )

2. Une fois endormi, quelle a été la profondeur de votre sommeil? (choisissez de 1 a 10)

|            |   |   |   |              |
|------------|---|---|---|--------------|
| 1          | 3 | 5 | 7 | 10           |
| très léger |   |   |   | très profond |

Est-ce plus ou moins rapide qu'à la maison? Plus ( ) Moins ( ) Pareil ( )

3. Combien de fois vous êtes-vous réveillé pendant la nuit? \_\_\_\_\_

Pour combien temps? \_\_\_\_\_

Et pour quelle raison? \_\_\_\_\_

4. Selon vous, quelle a été la durée de votre sommeil? \_\_\_\_\_

Est-ce plus ou moins rapide qu'à la maison? Plus ( ) Moins ( ) Pareil ( )

5. Êtes-vous repose ce matin? (choisissez de 1 a 10)

|                 |   |   |   |             |
|-----------------|---|---|---|-------------|
| 1               | 3 | 5 | 7 | 10          |
| très peu repose |   |   |   | très repose |

Est-ce plus ou moins récupérateur qu'à la maison? Plus ( ) Moins ( ) Pareil ( )

6. Vous souvenez-vous d'avoir rêvé cette nuit? Oui ( ) Non ( )

Commentaires

|  |
|--|
|  |
|--|

## Day Questionnaire

[1] What activities did you do today? Explain briefly

---

---

[2] Has today been an unusual day in any respect? No Yes If so, describe \_\_\_\_\_

---

---

[3] Do you have any physical complaints (pains, headaches, etc.)? No Yes  
If so, describe

---

[4] How did you feel immediately after awakening today? (check)

\_\_\_\_\_ Very alert, active  
\_\_\_\_\_ Alert, not up to peak  
\_\_\_\_\_ A little foggy  
\_\_\_\_\_ Very sleepy

[5] Did you take any medications or alcohol today? No Yes  
If so, list the type and amount.

---

VIGILANCE TEST  
Échelle Visuelle Analogue (EVA)

**Matériel**

Agrafer ensemble le nombre de feuillets nécessaires, y compris 3 feuillets de pratique.

Utiliser un crayon feutre (car sinon le sujet va voir sur chaque nouveau feuillet la trace laissée son évaluation précédente).

A chaque fois qu'un sujet complète un EVA s'assurer que l'heure est inscrite. Ne pas inscrire l'heure d'avance sur tous les feuillets; ne compléter cette partie qu'au fur et à mesure.

**Pratique**

Les sujets doivent être exposés à quelques reprises à l'échelle EVA afin de se familiariser avec elle.

Trois tests de pratique avant la nuit, à 20-30 minutes d'intervalle, par exemple:

-avant de se faire poser les électrodes (et au même moment, s'il y a lieu, à l'autre sujet qui attend);

-après s'être fait poser les électrodes (alors que le sujet qui attendait va se faire poser les électrodes);

-20-30 minutes plus tard (ou après que le 2<sup>e</sup> sujet se soit fait poser ses électrodes).

**Instructions aux sujets**

Expliquer au sujet en lui montrant l'échelle EVA qu'il doit considérer cette ligne de 10 cm comme représentant tout le spectre possible de sa vigilance: à gauche est le point le plus somnolent qu'il puisse s'imaginer pouvoir atteindre: à droite est le point le plus éveillé, vigilant qu'il puisse s'imaginer pouvoir atteindre.

Le sujet doit indiquer l'état dans lequel il se sent en traçant un seul trait perpendiculaire sur la ligne.

VIGILANCE TEST  
Échelle Visuelle Analogue (EVA)

Nom \_\_\_\_\_

Heure : \_\_\_\_\_ Date : (jour/mos/ans) \_\_\_\_\_

Très endormi Très éveillé

lé

.....

Nom:

Heure:

Date:

Très endormi Très éveillé

.....

Nom:

Heure-

Date:

Très endormi Très éveillé

.....

Nom-

Heure:

Date:

Très endormi Très éveillé

.....

Nom:

Heure-

Date:

Très endormi Très éveillé

.....

## Visual Analog Scale (VAS)

### Material

Staple together the number of pages that will be used, including 3 pages of practice.

Use a felt-tip pen (because otherwise the subject goes to see on every new page the left track its previous evaluation).

Every time a subject completes EVA make sure that the hour is registered. Do not register the hour beforehand on all the pages; complete this part which in the fur and has measure.

### Practice

The subjects have to be explain about started again has the scale EVA to get acquainted with her.

Three tests of practice before night, has 20-30 minutes of interval, for example:

- before being rested(posed) electrodes (and at the same moment, if necessary, has the other subject which waits);
  - better to have been rested(posed) electrodes (while the subject which waited is going be put electrodes);
- 20-30 minutes later (or bitter that the 2nd subject is put its electrodes).

### Instructions on the subjects

Explain to the subject by showing him(her) the scale(ladder) EVA that he has to consider this line of 10 cms as representing all the possible spectre of his attentiveness: has left-handler(left) is the sleepest point which he can imagine to be able to reach(affect): has right-hand side is the point most awaken, watchful that he can imagine to be able to reach(affect).

The subject has to indicate the state in which it feels by drawing a single perpendicular feature on the line

Visual Analog Scale (VAS)

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

Hour. \_\_\_\_\_ Date (day/month/yr) \_\_\_\_\_

Very sleepy Wide Awake

.....

Name: \_\_\_\_\_

## Appendix 5 Subject's Instructions

In the experiment you will be seated in front of a stimulus presentation monitor & presented with a series of male & female faces. Your memory for faces will be assessed in two phases: Study (Acquisition) Session & Test (Recognition) Session.

### ***STUDY (ACQUISITION) SESSION***

After the application of the electrode cap, you will be seated in front of a computer screen and exposed to 20 male & female face photographs, which will take approximately 5 minutes. The trial will begin with the presentation of a fixation stimulus (a word "Clignez – Blink") for about 1000 msec. Upon the disappearance of the fixation stimulus, a series of face stimuli will be briefly flashed.

Your tasks will be as follows:

Study the faces very carefully. You will be seeing them again during the Test (Recognition) Session.

Indicate whether the face is male or female.

If the face is **female**, press the **left arrow** key,

“ ← “, on the keyboard.

If the face is **male**, there is “**No Response**”.

A Practice Session will precede the Study (Acquisition) Session.

### ***TEST (RECOGNITION) SESSION***

The Test (Recognition) Session will follow the Study (Acquisition) Session, after a night of sleep or after 6 – 8 hours of wake.

During this test, you will see 40 face stimuli, 20 of which had been presented before during the Study (Acquisition) Session & 20 new faces, presented in a random order. The trial will begin with the presentation of a fixation stimulus (a word "Clignez – Blink"). It will take approximately 10 minutes.

The required response will be as follows:

Press the **left arrow** key, “ ← “, if the face has been **seen before**.

Press the **downward arrow** key, “ ↓ “, if the face is **new**.

A Practice Session will precede the Test (Recognition) Session, if you feel that it is necessary.

***FOR BOTH TASKS - Please make you responses as quickly and as accurately as possible. It is important to relax, remain as still as possible during the task and minimize eye movements and eye blinks with the exception of when the fixation stimulus, “Clignez-Blink”, is presented on the screen.***

### Instructions

Pour la présente expérience, vous serez assis devant un moniteur de présentation de stimuli et une série de visages d'hommes et de femmes vous sera présentée. Votre mémoire pour les visages sera évaluée en deux temps : session d'étude des stimuli (acquisition) et session d'évaluation (reconnaissance).

#### Session d'étude des stimuli (ACQUISITION)

Après l'application du chapeau d'électrode, vous serez assis face à un écran d'ordinateur et 40 photographies de visages d'hommes et de femmes vous seront présentées. Cette tâche durera approximativement 5-10 minutes. La session débutera par la présentation d'un stimulus de fixation (les mots "Blink-Clignez") pour une durée d'environ 600 ms. Après la disparition du stimulus de fixation, une série de stimuli représentant des visages sera brièvement projetée.

Votre tâche consiste à :

Étudier très attentivement les visages car vous les reverrez lors de la séance d'évaluation (reconnaissance).

Indiquer si le visage est celui d'un homme ou d'une femme.

Si le visage est celui d'un **homme**, pressez la touche munie d'une **flèche vers le bas** "↓".

Si le visage est celui d'une **femme**, pressez la touche munie d'une **flèche vers la gauche** "←".

Une session de pratique précédera la séance d'étude des stimuli (acquisition).

#### Session d'Évaluation (Reconnaissance)

La session d'évaluation (reconnaissance) suivra celle de l'étude des stimuli (acquisition), après une nuit de sommeil ou 6-8 heures d'éveil. Pendant cette séance, vous regarderez 80 stimuli représentant des visages. 40 ont été présentés précédemment durant la séance d'étude des stimuli (acquisition), tandis que 40 autres sont de nouveaux visages. La session débutera par la présentation d'un stimulus de fixation (les mots "Blink-Clignez"). La tâche durera environ 10 minutes.

Les réponses requises seront comme suit :

Si le visage a été vu **auparavant**, pressez la touche munie d'une **flèche vers la gauche** "←".

Si le visage est **nouveau**, pressez la touche munie d'une **flèche vers le bas** "↓".

Une session de pratique précédera la séance d'évaluation (reconnaissance) si vous estimez qu'elle est nécessaire.

**POUR LES DEUX TÂCHES** – S'il vous plaît, répondez aussi rapidement et aussi exactement que possible. Il est important de se détendre, de rester aussi immobile que possible pendant la tâche et de réduire au minimum les mouvements des yeux et les clignements des yeux à l'exception des moments durant lesquels le stimulus de fixation, "Blink-Clignez", est présenté sur l'écran.

## Appendix 6

Demande d'autorisation de rédiger un mémoire ou une thèse par article

Accord des co-auteurs et permission de l'éditeur

Article: The Influence of Sleep on Memory: An evoke-related potential study.

**DEMANDE D'AUTORISATION DE RÉDIGER  
UN MÉMOIRE OU UNE THÈSE PAR ARTICLE(S)**  
Éléments à préciser dans la demande écrite

L'étudiant doit noter qu'il devra obtenir, en temps opportun, l'accord de tous les coauteurs de chacun des articles pour qu'il puisse l'inclure dans son mémoire ou dans sa thèse. Il devra aussi respecter toutes les autres règles concernant la thèse ou le mémoire par article (*voir section D.1.2 du guide de présentation et d'évaluation des mémoires de maîtrise et des thèses de doctorat, mars 2001*).

**1- IDENTIFICATION DE L'ÉTUDIANT:**

Nom de l'étudiant : MOGRASS, Melodee

code permanent : MOGM12525502

**2- NOM DE L'UNITÉ ACADÉMIQUE :**

Département de psychologie, Faculté des arts et des sciences

**3- NOM DU PROGRAMME:**

Ph.D. en Psychologie -recherche  
l'option : Sciences Cognitive et  
Neuropsychologue

1. **LISTE DES ARTICLES PROPOSÉS :** Pour chaque article que l'étudiant veut inclure dans son mémoire ou dans sa thèse, il doit indiquer l'ordre des auteurs, le titre, la revue à laquelle l'article est normalement destiné et l'état actuel de l'article (publié, soumis pour publication ou en préparation).

Mini Article :

- A) Ordre des auteurs : \*Mogross MA, Guillem F, Godbout R
- B) Titre : The Influence of Sleep on Memory: An Event-Related Potential Study.
- C) Revue : Sleep; 26, Vol. 26.
- D) Etat actuel de l'article : *accepté*

Article 1 :

- a. Ordre des auteurs : \*Melodee Mogross, \*Roger Godbout & Francois Guillem
- b. Titre : The ERP Old/New effect : A useful indicator in studying the effects of sleep on memory retrieval processes.
- c. Revue : Journal Sleep
- d. Etat actuel de l'article : *accepté*

Article 2:

- A) Ordre des auteurs : \*Melodee Mogross, \*Francois Guillem & Godbout
- B) Titre : Event-Related Potentials Differentiates the Processes involved in the Effects of Sleep on Recognition Memory.
- C) Revue : Psychophysiology
- D) Etat actuel de l'article : *sous presse*

Article 3 :

- A) Ordre des auteurs : Melodee Mograss, Francois Guillem & Roger Godbout
- B) Titre : The Effects of Total Sleep Deprivation on Recognition Memory
- C) Revue : Learning & Memory
- D) Etat actuel de l'article : *Soumis*

2. **SIGNATURE ET DÉCLARATION DE L'ÉTUDIANT CONCERNANT LES ARTICLES:** Chacun des articles doit faire l'objet d'une déclaration de l'étudiant. Pour chaque article publié ou soumis pour publication, il doit indiquer brièvement la nature de sa participation aux travaux de recherche et, s'il y a lieu, l'importance de sa contribution à l'article par rapport à celle des coauteurs. Dans le cas d'un article en préparation, il indiquera sa contribution actuelle ou prévisible aux travaux de recherche et à l'article.

Mini Article : L'étudiante a effectuée tous les travaux de recherche et a écrit une première version de l'article *accepté*.

Article 1 : L'étudiante a effectuée tous les travaux de recherche et a écrit une première version de l'article *accepté*.

Article 2 : L'étudiante a effectuée tous les travaux de recherche et a écrit une première version de l'article *accepté*.

Article 3 : L'étudiante a effectuée tous les travaux de recherche et a écrit une première version de l'article *Soumis*

**Nom de l'étudiant :** MOGRASS, MELODEE

Signature : \_\_\_\_\_ date : \_\_\_\_\_

**6- AVIS ET SIGNATURE DU DIRECTEUR DE RECHERCHE:** Le directeur de recherche commentera de façon appropriée les informations présentées par l'étudiant dans sa demande et donnera son avis sur le projet de rédaction du mémoire ou de thèse par articles

Nom du directeur/co-directeur de recherche : Dr. F. Guillem ; Dr. R. Godbout

Signature : \_\_\_\_\_ date : \_\_\_\_\_

**7- DÉCISION OU RECOMMANDATION ET SIGNATURE DU DIRECTEUR DE PROGRAMME:**

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*17th Annual Meeting of the Association of Professional Sleep Societies, Chicago (IL),*

June, 2003. Submitted for publication in journal *Sleep*, 2003, Vol. 26.

### The Influence of Sleep on Memory: An Evoked Potential Study

**Introduction:** Behavioral and electrophysiological studies have shown that cognitive processes active in the wake state are also active during sleep, allowing memory consolidation during sleep and improved performance the following day. There is little information, however, on the nature of the mechanisms involved. The aim of the present study was to use cognitive evoked potentials (ERPs) in order to characterize some of the cognitive processes involved in the facilitation of recognition performance by sleep.

**Methods:** Ten healthy participants (5 females, 5 males) aged between 18 and 39 years were asked to keep regular sleep-wake schedules before coming to the laboratory, and filled an agenda during the course of the experiment. Each session comprised of two phases. During the acquisition phase, participants were presented on a computer screen with a series of stimuli (faces) and asked to memorize them. Either nocturnal sleep or an equivalent period of daytime awakening elapsed between the two sessions. At the recognition phase, participants were presented with the 40 previously learned "old" stimuli mixed with 40 "new" faces never learned and asked to recognize the learned faces while ERPs were recorded. All participants contributed to both conditions, in a counterbalanced fashion, with no more than one week between sessions. ERP data was analyzed using a 2 (night/day) x 2 (old/new) x 3 (Fz, Cz, Pz) ANOVA with repeated measures (subjects).

**Results:** Participants correctly recognized 74.4+/-9.9% the faces following nocturnal sleep versus 64+/-13.9% following daytime wake. Reaction times for correct responses were not different. Analysis of the N200 showed a main effect of recording site ( $p = .007$ ) and a significant session x repetition x site interaction ( $p = .04$ ). The ANOVA performed on the P300 data revealed a main effect of site ( $p = .03$ ) and a significant session x repetition x site interaction ( $p = .03$ ). N200 and P300 results reflected a larger day/night effect over Fz for the session following nocturnal sleep. The P600 results showed a session x site interaction ( $p = .03$ ), corresponding to a larger day/night effect over Pz for the session following nocturnal sleep.

**Conclusions:** The effect of sleep on recognition performance using ERP measures is made of early frontal and late parietal processes that could respectively represent facilitation of familiarity assessment and of trace access, following a night of sleep. These results are consistent with the role of sleep in memory consolidation.