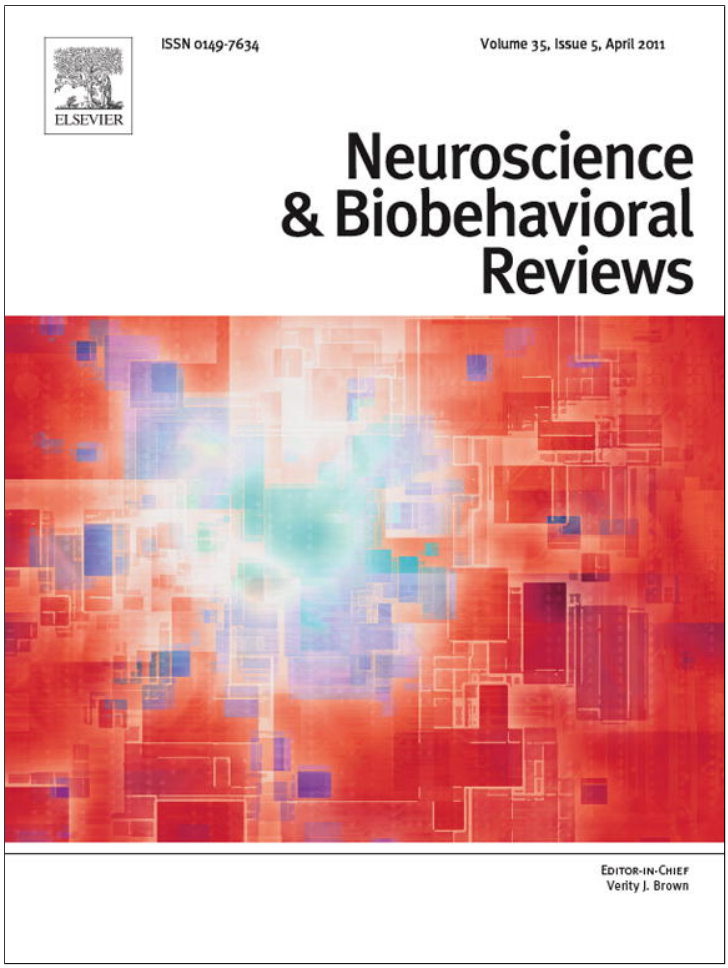

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Review

The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation

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ABSTRACT

Until recently, the electrophysiological mechanisms involved in strengthening new memories into a more permanent form during sleep have been largely unknown. The sleep spindle is an event in the electroencephalogram (EEG) characterizing Stage 2 sleep. Sleep spindles may reflect, at the electrophysiological level, an ideal mechanism for inducing long-term synaptic changes in the neocortex. Recent evidence suggests the spindle is highly correlated with tests of intellectual ability (e.g.; IQ tests) and may serve as a physiological index of intelligence. Further, spindles increase in number and duration in sleep following new learning and are correlated with performance improvements. Spindle density and sigma (14–16 Hz) spectral power have been found to be positively correlated with performance following a daytime nap, and animal studies suggest the spindle is involved in a hippocampal–neocortical dialogue necessary for memory consolidation. The findings reviewed here collectively provide a compelling body of evidence that the function of the sleep spindle is related to intellectual ability and memory consolidation.

Contents

1. Introduction

What mechanisms are involved in the process of consolidating newly learned information into a more stable form of long-term memory? Sleep has been identified as one of the biological states necessary for efficient memory consolidation; the process of transforming a newly acquired, labile memory into an endur-

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ing long-term memory. A compelling body of research exists from both human (Smith, 1985, 1995; Stickgold and Walker, 2007) and animal studies (Hennevin et al., 1995; Smith, 2003) establishing a link between rapid eye movement (REM) sleep and memory. Despite this, an ongoing (and sometimes heated) debate continues about the many functions of sleep (Brawn et al., 2010; Maquet, 2001; Rickard et al., 2008; Siegel, 2001; Stickgold and Walker, 2005; Vertes and Siegel, 2005).

More recently, non-REM sleep has been implicated in the consolidation of new learning as well (Buzsáki, 1984, 1989; Gais and Born, 2004; Nader and Smith, 2003; Smith and MacNeill, 1994). Here we summarize recent evidence which suggests that the sleep spindle – an electroencephalographic (EEG) event that characterizes and predominates non-REM sleep – reflects, at the electrophysiological level, a mechanism involved in the consolidation of memory during sleep. Moreover, it appears that native sleep spindles reflect intellectual ability as measured by aptitude batteries including intelligence quotient (IQ) tests, and may serve as a physiological index of intelligence. We propose that baseline inter-individual differences in sleep spindles are correlated with learning potential. On the other hand, we suggest that learning-related increases in sleep spindles reflect processes specific to memory consolidation and may involve different neural substrates. Furthermore, we suggest that important dissociations between sleep states and memory systems have been identified in humans (Fogel et al., 2007b; Plihal and Born, 1997). For example, REM sleep appears to be involved in procedural learning that is cognitively complex and involves the acquisition of new rules (Fogel et al., 2007b; Plihal and Born, 1997; Smith et al., 2004b), whereas Stage 2 sleep is involved in procedural learning that involves the refinement of existing skills (Fogel et al., 2007b). Recent findings in animals suggest learning-related increases in sleep spindles may indicate one step in a series of sequential steps of sleep-dependent memory consolidation processes during non-REM sleep that follow previously identified learning-related changes in REM sleep (originally suggested by Buzsáki, 1984, 1989; for review see Smith, 1985; and for more recent findings Fogel et al., 2009). Before describing evidence implicating sleep spindles in memory consolidation and their relation to IQ, it is necessary to describe the memory systems and memory processes involved (Section 2), followed by a brief overview of sleep–wake states (Section 3) and factors related to sleep spindles (Section 4). This is not intended to be a comprehensive review of memory systems, nor sleep–wake states, but should provide adequate background for the reader to understand the role of the sleep spindle in intellectual ability (Section 5) and memory consolidation (Sections 6–9). Finally, we provide important future directions (Section 10) which we hope will lead us to a better understanding of the processes involved in sleep-related synaptic plasticity and memory consolidation.

2. Memory systems and memory consolidation processes

2.1. Declarative memory

Human long-term memory is not dependent on a unitary system of brain structures and mechanisms and can be subdivided into a number of subtypes. Declarative memory has traditionally been subdivided into episodic and semantic memory. The paired associates task is one task commonly used to study declarative learning that is explicitly learned. In this task, pairs of words (or pictures) are visually presented, where the goal is to explicitly memorize the word pairs by either rehearsal, or some other mnemonic strategy. This type of learning involves the hippocampus, and is impaired in patients with medial temporal lobe damage (Scoville and Milner, 1957; Warrington, 1996). Declarative memory is generally considered memory for learning and knowing "*what*" as opposed to "*how*".

The taxonomy of memory has been extensively researched at both the cognitive and behavioral level and many of the associated brain structures have been localized by means of imaging techniques (Doyon et al., 2003; Schacter, 1997). Newly learned memory traces are initially in a labile form, and the process of forming a stable and lasting memory requires long periods of post acquisition time ranging from hours to years (Haist et al., 2001; Kim and Fanselow, 1992; Korman et al., 2007; Mednick et al., 2003; Scoville and Milner, 1957; Zola-Morgan et al., 1992). Generally defined, memory consolidation is the process by which newly acquired, labile memories are transformed into more stable, permanent long-term memories. This process is thought to primarily involve brain structures such as the hippocampus and the thalamus. Over the course of declarative memory consolidation, the influence of the hippocampus and/or the thalamus diminishes until the memory is permanently stored in the neocortex (Dudai and Eisenberg, 2004; Frankland et al., 2004). It is not yet entirely clear which physiological mechanisms are involved in declarative memory consolidation, especially with regards to memory processes exclusive to sleep. However, recent evidence suggests that certain features of sleep appear to be linked to memory consolidation processes such as slow wave activity (Mölle et al., 2002), hippocampal sharp waves (Buzsáki, 1984), ripples (Mölle et al., 2009) theta activity (Fogel et al., 2007b), rapid eye movements during REM sleep (De Koninck et al., 1989; Fogel et al., 2007b; Smith and Lapp, 1991), sleep spindles in humans (e.g., Fogel and Smith, 2006; Gais et al., 2002; Schabus et al., 2004; Clemens et al., 2005) and for spatial memory and avoidance learning in animals (Fogel et al., 2009; Mölle et al., 2009; Schiffelholz and Aldenhoff, 2002). For a recent review see Diekelmann and Born (2010).

2.2. Procedural memory

Procedural memory is generally considered memory for learning and knowing "*how*" as opposed to "*what*". Non-declarative memory can be subdivided into procedural (skills and habits), classical conditioning, priming and non-associative learning (Gabrieli, 1998; Milner et al., 1998; Squire and Zola, 1998). Procedural memory can be further subdivided depending on the cognitive complexity, or novelty of the task. For example, procedural memory is usually further subdivided (and especially so in the sleep and memory literature) into motor (or simple) procedural memory, and cognitive (or complex) procedural memory. For example, the pursuit rotor (Grafton et al., 1992) and the finger tapping task (Ungerleider et al., 2002) have been classified as a simple motor procedural memory task that involve the refinement of skills and habits (usually motor skills) for which there is an already pre-existing set of skills to learn the task. On the other hand, the artificial grammar task (Cleeremans and McClelland, 1991; Fischer et al., 2006), Tower of Hanoi and the mirror tracing task have been classified as complex cognitive procedural memory tasks (Fogel et al., 2007b; Smith, 1995, 2001), however, other terminology is commonly used to describe the same types of tasks (Gabrieli, 1998). Complex cognitive procedural learning involves the understanding of new rules or the acquisition of entirely new skills in order to improve performance (for review see Smith, 1995, 2001; and Smith et al., 2004a for a more recent formulation of these ideas).

Interestingly, procedural memory is largely spared in amnesia resulting from damage to the medial temporal lobe. Procedural memory is dependent on a variety of structures such as the striatum, cerebellum, pons, globus pallidus and cortical regions that are independent of the hippocampus (Doyon et al., 2003; Schacter, 1997). The compartmentalization of the types of procedural memory to different brain structures suggests that there may be separate mechanisms for consolidating various subtypes of memory. Proce-

dural memory involves learned motor procedures, skills or habits, that are usually independent of conscious retrieval.

Memory for procedural skills and habits has been found to be associated with the striatum; priming and perceptual learning are dependent on the neocortex; simple classical conditioning involves the cerebellum; and non-associative learning is dependent on reflex pathways (Squire and Zola, 1998). The thalamus has been suggested as one possible structure that may be an analog to the hippocampus, playing a role in earlier stages of declarative memory consolidation (Winocur, 1985) and may be of importance for procedural learning (Asanuma and Pavlides, 1997). It is known that the long-term storage of procedural memory requires repeated trials or practiced learning which occurs primarily in the neocortex. This type of memory encoding requires spaced and repeated stimulation for long-term potentiation (LTP) to occur (Chapman et al., 1998; Trepel and Racine, 1998). Projections from the thalamus to the neocortex and back to the thalamus form thalamocortical loops that fire in an oscillatory pattern. The oscillatory activation of these circuits has been implicated as one of the mechanisms for LTP. Steriade (1999) has shown that the reactivation of thalamocortical circuits are particularly synchronized during sleep, and are thought to be one of the mechanisms that induce long-term potentiation in the brain (Destexhe and Sejnowski, 2001).

3. Sleep–wake states

Over the course of a night, sleep varies in terms of brain activity and behavior in a regular cyclic pattern (Carskadon and Dement, 2000). In young adults, the first half of the night is composed of primarily non-REM sleep including Stage 2, Stages 3 and 4 (comprising slow wave sleep; SWS), but little REM sleep. The last half of the night is composed almost entirely of Stage 2 and REM sleep whereby the periods of REM sleep lengthen as the night progresses, while SWS is either minimal or absent. Over the course of a night, there are four to five non-REM–REM cycles. About 50–60% of a night's sleep is made up of Stage 2 sleep, and only about 20–25% is REM sleep (Carskadon and Dement, 2000).

Tonic and phasic EEG and overt behavior systematically vary over the course of the night (Rechtschaffen and Kales, 1968). While resting with eyes closed but still awake, the EEG becomes more rhythmic, slower and synchronized compared to alert waking. Relaxed waking EEG is characterized by alpha frequency (8–12 Hz) activity. A number of physiological and behavioral indices systematically change with sleep onset (Ogilvie, 2001; Ogilvie et al., 1991). For example, decreases in alpha, the appearance of vertex sharp waves, and reduced allocation of attentional resources accompany reduced responsiveness to external stimuli (Cote et al., 2002).

Stage 2 sleep is characterized by the occurrence of sleep spindles and K-complexes. K-complexes have a well-defined negative sharp wave followed by a high amplitude positive component (Colrain, 2005). K-complexes occur spontaneously, but can also be evoked with auditory stimuli (Davis et al., 1937; Roth et al., 1956) and are thought to reflect information processing during sleep. Another defining event of Stage 2 sleep is the sleep spindle (for review, see De Gennaro and Ferrara, 2003). The sleep spindle is a waxing and waning oscillation in the EEG of non-REM sleep which typically falls within the range of 12–16 Hz (Iber, 2007). They occur predominantly in Stage 2 sleep, although sleep spindles persist throughout SWS, and by definition do not occur during wakefulness or REM sleep (Rechtschaffen and Kales, 1968). The electrophysiological characteristics of the sleep spindle are well understood (Davis et al., 1937; De Gennaro and Ferrara, 2003; Destexhe and Sejnowski, 2001; Steriade, 1999; Steriade and Amzica, 1998a). Sleep spindles originate from the oscillatory firing of thalamo-cortical neuronal loops. When this activity is synchronized, sleep spindles are visually apparent in the ongoing scalp-recorded EEG. For an extensive recent review of the characteristics and distribution of the sleep spindle see De Gennaro and Ferrara (2003), but also the following Section 4.

Stage 3 sleep is defined by 20–50% of the epoch containing waves < 2 Hz (Rechtschaffen and Kales, 1968). Autonomic activity such as heart rate and breathing begins to slow and becomes more regular. Stage 4 sleep has more than 50% delta activity. Sleep spindles continue to occur during SWS, however, dominant delta frequencies usually mask their appearance. The American Academy of Sleep Medicine (AASM) guidelines no longer distinguish between Stages 3 and 4 (Iber, 2007). Together, Stages 3 and 4 are commonly referred to as SWS. SWS is the deepest stage of sleep where arousal thresholds are higher than Stages 1 and 2 (but not REM) (Rechtschaffen et al., 1966), and the brain's response to external stimuli is reduced relative to Stage 2 and REM sleep (Campbell et al., 1992; Tyson et al., 1984).

After about 60–90 min following sleep onset, the characteristics of sleep change markedly with the onset of REM sleep. Tonic EEG appears much more desynchronized – similar to waking EEG – with the exception that there is usually little to no alpha activity (Rechtschaffen and Kales, 1968). The most marked feature of REM sleep is the appearance of phasic events termed rapid eye movements. During REM sleep, the brainstem produces muscle atonia in the major muscle groups to prevent movement with only a few exceptions including the saccadic muscles of the eye.

4. Factors related to sleep spindles

A number of factors relate to the temporal and spatial variability in spindles including: scalp location (Jobert et al., 1992; Werth et al., 1997a,b; Zeitlhofer et al., 1997), endogenous generators (Anderer et al., 2001; Merica, 2000), menstrual cycle (Driver, 1996; Driver et al., 1996; Huupponen et al., 2002; Ishizuka et al., 1994), age (Huupponen et al., 2002; Landolt and Borbély, 2001; Landolt et al., 1996; Nicolas et al., 2001) and sleep cycle (De Gennaro et al., 2005; Himanen et al., 2002).

The topographical distribution of spindles in adults is maximal over centro-parietal midline derivations (Cz and Pz) compared to Fz and Oz in both Stage 2 sleep and SWS (De Gennaro and Ferrara, 2003). In addition, the intra-cycle variation in spindles during Stage 2 sleep change across sleep cycles, but generally spindle density increases over the course of the night, primarily due to increased spindles at centro-parietal midline derivations.

There is evidence to suggest there are two distinct types of sleep spindles, depending on their frequency characteristics and topographic scalp distribution. Slow spindles (~12–14 Hz) have an anterior distribution while fast spindles (~14–16 Hz) have a posterior distribution (Jobert et al., 1992; Werth et al., 1997a,b; Zeitlhofer et al., 1997). The topographic distribution of slow and fast spindles differs over the time course of each individual spindle event (Doran, 2003). Slow spindles are distributed over areas that are more widespread and frontal than fast spindles, whereas fast spindles can be localized centro-parietally and are more focal. In summary, these studies suggest that there are two types of spindles, which originate from separate generators (Merica, 2000).

Spindles vary across the menstrual cycle (Ishizuka et al., 1994) as indicated by power in the 14.25–15.0 Hz band maximal at the mid luteal phase (Driver et al., 1996). Other covariates such as hormonal influences, or body temperature may also be involved in these cyclic variations in spindle activity (Driver et al., 1996).

Sleep quantity and quality change over the lifespan. For example, increased awakenings, lower sleep efficiency, reduced SWS, increased Stage 1 (for review see Bliwise, 2000), are observed with age in addition to age-related changes in sleep spindles (Guazzelli et al., 1986; Nicolas et al., 2001; Wei et al., 1999). The power in

the lower-sigma band (12.25–14.00 Hz) is reduced in middle-age (40–60 years) compared to younger subjects (20–39 years) in the latter part of the night (Carrier et al., 2001) in groups with equivalent amounts of Stage 2 sleep (Landolt et al., 1996). Nicolas et al. (2001) divided participants into 6 age groups spanning 10 years each from ages 10–69. They found that the amount of Stage 2 sleep, the number, density (number/minute) and duration of sleep spindles decreased gradually with age. In addition, peak sleep spindle frequency and inter-spindle interval were found to increase with age.

Silverstein and Levy (1976) conducted one of the first studies to investigate intra-individual variations in sleep spindles. The number of Stage 2 sleep spindles was found to have a curvilinear distribution across the night: starting low at the beginning of the night, peaking in the middle of the night, and dropping off at the end of the night. De Gennaro et al. (2005) found that spindle density (number/minute) during non-REM sleep increased over the course of the night and had a centro-parietal distribution. In addition, the frequency of sleep spindles has been found to vary across sleep cycles (Himanen et al., 2002). Himanen et al. (2002) found that within each of the first four sleep cycles spindle frequency followed a curvilinear U-shaped pattern. The frequency of sleep spindles started off ~13–14 Hz at the beginning of each cycle and by the middle of the cycle spindle frequency reached a minimum of 12–13 Hz. By the end of the cycle, spindle frequency returned to 13–14 Hz. Thus, higher frequency spindles appeared to be associated with stage transitions. In the fifth sleep cycle, spindle frequencies were more stable across the cycle that ranged on average within 13–14 Hz. This may be related to reduced sleep pressure at the end of the night, or greater homeostatic pressure for REM sleep at that time of night.

One of the possible reasons for the variation in sleep spindles within and across non-REM cycles is the inverse relationship between sleep spindles and slow wave (i.e., delta) activity (Aeschbach and Borbély, 1993; Dijk et al., 1993; Uchida et al., 1991, 1994). Slow wave activity is highest in early sleep when sleep pressure is high, and this activity decreases as sleep progresses and sleep pressure is reduced (Aeschbach et al., 1996). Slow wave activity is considered a marker of non-REM sleep intensity, and thought to reflect sleep homeostatic processes (Borbely, 1982). Spindle activity (power density 13–15 Hz) increases with sleep duration across non-REM periods (Aeschbach and Borbély, 1993). It has been suggested that slow wave activity and sleep spindles are generated by a common thalamocortical system (Steriade and Amzica, 1998a,b; Steriade et al., 1993) and that these two types of activity cannot co-occur. Using power spectral analyses Ueda et al. (2001) found that delta activity gradually decreased in the 7.5 s prior to spindle onset, and increased gradually in the 10 s following spindle occurrence. Interestingly, these changes were localized; increased delta occurred at frontal sites following slow (12 Hz) spindles and contro-parietally for fast (14 Hz) spindles. The depolarization of thalamocortical neurons is involved in the generation of both sleep spindles and slow oscillations (Contreras et al., 1996). The thalamic reticular nucleus is thought to be the pacemaker for sleep spindles (Bal et al., 1995a,b; Bazhenov et al., 1999, 2000; Destexhe et al., 1994; Steriade et al., 1985; Steriade et al., 1987, 1993; vonKrosigk et al., 1993; Wang and Rinzel, 1993). Periods of hyperpolarization in reticular neurons precede sleep spindles (Fuentealba et al., 2004) along with the depolarization of cortical neurons (surface positive, depth negative) during slow oscillations. This triggers the onset of the sleep spindle, which is then decreased during the hyperpolarizing (surface negative, depth positive) phase of the slow oscillation (Steriade and Timofeev, 2003). Thus, there is a complex interplay between reticular, cortical and thalamocortical neurons, grouped by slow wave activity. This inter-relationship is observed on a larger scale as slow activity varies over the course of a night's sleep as homeostatic pressure is reduced, and less slow wave activity occurs.

5. Sleep spindles and intellectual ability

The density of sleep spindles is very consistent for any individual from night-to-night (De Gennaro et al., 2005; Gaillard and Blois, 1981; Silverstein and Levy, 1976). It has been remarked that inter-individual characteristics in sleep spindles are reliable enough to serve as an "electrophysiological fingerprint" (De Gennaro et al., 2005). However, the functional significance of this 'fingerprint' has historically not been well understood. A number of studies reviewed here have shown that the inter-individual differences in sleep spindles may be a physiological marker for intellectual ability. Gibbs and Gibbs (1962) observed that children with mental disability had abnormal spindles that were high in amplitude and longer than normal in duration which they termed "extreme spindles". Bixler and Rhodes (1968) commented that the abnormally large spindles of these children may reflect deficient gating mechanisms of the thalamo-cortical system. Shibagaki and Kiyono (1983) found that children with below normal IQ scores had abnormal spindles characterized by epileptiform activity. It is tempting to speculate based on these studies that the normal and efficient generation of sleep spindles is necessary for normal intellectual abilities to develop – and recent evidence provides additional support for this suggestion. Nader and Smith (2001, 2003) discovered that the number of sleep spindles and sigma power (12–14 Hz) were correlated with general intellectual abilities as measured by IQ (using the Multidimensional Aptitude Battery – II; MAB-II). In other words, individuals with a higher number of sleep spindles and more sigma power had higher IQ scores. More specifically, Nader and Smith (2001, 2003) reported that the number of sleep spindles positively and highly correlated with general intellectual abilities including Full-scale IQ, and Performance IQ, but not Verbal IQ. They concluded that sleep spindles in general appear to be specifically related to abilities that involve the use of procedural knowledge and skills. One of the caveats was that Verbal and Performance IQ are highly inter-correlated. A subsequent study (Fogel et al., 2007a) found that when individual differences in Verbal IQ are controlled for, only Performance IQ relates to the number of sleep spindles and that this relationship is strongest in the last third of the night (Fig. 1A). Performance IQ is made up of a number of subscales. Both the Spatial and Picture Completion Performance IQ subscales were found to be correlated with the number of sleep spindles. When only the unique predictors (semi-partial correlations) were considered, only the Picture Completion subscale related to the number of sleep spindles over and above the other subscales (Fig. 1B). A positive correlation between right frontal spindle density and the Raven Progressive Matrices Test (Bódizs et al., 2005), a measure of fluid intelligence has also been identified. In addition, a second study found that individuals with high scores on the Wechsler Memory Scale and the Raven Progressive Matrices Test had more native spindle activity (amplitude × duration in 11–16 Hz spindles) than poor performers (Schabus et al., 2006). Taken together, these studies provide compelling evidence to suggest that sleep spindles in general may be a physiological index of intellectual ability.

In a recent study, the relationship between baseline sleep spindles and the ability to learn a difficult avoidance task (2-way shuttle active avoidance) was investigated in rats. While learning proceeds quickly in 1-way active avoidance training for all animals, not all rats are capable of learning to make avoidance responses in the 2-way shuttle avoidance task. Fogel et al. (2010) investigated whether baseline sleep spindle density would predict whether rats could learn to make avoidance responses or not. Surprisingly, there was a negative correlation between the baseline spindle density (num-

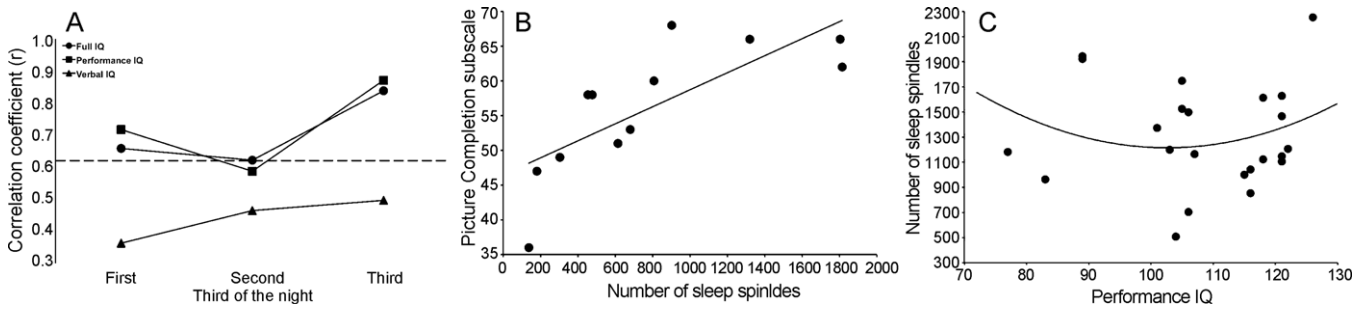

Fig. 1. (A) Correlation coefficients between intelligence quotient (IQ) scales and Stage 2 sleep mean sigma power (12–14 Hz; C3 and C4) in the 1st third, 2nd third, and 3rd third of the night. Statistical significance is indicated at $p < 0.05$ by the dashed horizontal axis. (B) Scatter plot of Picture Completion subscale scores and Stage 2 sleep spindles (12–16 Hz; C3 and C4), $r(10) = 0.75$, $p < 0.002$. (C) Scatter plot of Performance IQ scores and Stage 2 sleep spindles (12–16 Hz; Cz) in the high-IQ ($r(9) = 0.75$, $p = 0.008$) and low-IQ ($r(10) = -0.17$, $p = 0.61$) groups. Trendline is a second order polynomial best-fit.

ber per minute in SWS) and the number of correct avoidances. While the opposite pattern (i.e., a positive correlation) is generally observed in humans (see above, this section), most studies include individuals who fall within the normal (or above normal) range of IQ scores. When a larger sample with a wider range of IQ scores is used (Fogel et al., 2007a), the relationship between spindles and IQ appears to be U-shaped (Fig. 1C): positive for high IQ, unrelated in normal range (data not shown), and negative for low IQ. An earlier study by Gibbs and Gibbs (1962) suggest that increased spindle activity is observed in individuals with below normal IQ scores. Thus, taken together, these results suggest that the relationship between baseline sleep spindles and learning potential may be curvilinear when a wider range of IQ scores are considered. Thus, individuals with a high number of spindles can have either a high IQ or a low IQ, perhaps for different reasons with the former representing an efficient and active thalamocortical system, the latter representing possible neurological pathology (Bixler and Rhodes, 1968; Gibbs and Gibbs, 1962; Shibagaki and Kiyono, 1983).

6. Sleep spindles and procedural memory

The most compelling evidence for the role of sleep spindles in memory consolidation comes from studies using procedural memory tasks. In one of the first studies investigating the link between Stage 2 sleep and procedural memory in humans, memory for the Pursuit Rotor task was found to be impaired following selective Stage 2 sleep deprivation (Smith and MacNeill, 1994). Studies from our group (Fogel and Smith, 2006; Nader and Smith, 2003) have shown that an intense period of procedural learning alters subsequent sleep architecture by increasing the amount of Stage 2 sleep. Further, the density of sleep spindles (spindles/minute) increased in participants that learned the task compared to their own preceding baseline night where no learning task was given, and compared to a non-learning control (Fig. 2A). In this "no learning" condition, participants spent an equivalent amount of time reading and filling out forms, using both pen-and-paper and using a computer mouse for an equivalent duration to control for general visuo-motor activity. In addition, the increase in visually identified sleep spindles (~12–16 Hz) was found to be correlated with the magnitude of learning (Fig. 2B). A multiple regression revealed that overall, the four motor procedural tasks (the Pursuit Rotor, Simple (i.e., Direct) Tracing task, Ball-and-Cup task, and Operation™) accounted for 98% of the variability in spindle density. In a subsequent study (Fogel et al., 2007b), these findings were replicated, where in addition to the increase in the number of visually identified spindles (~12–16 Hz) in Stage 2 sleep (Fig. 3A), it was found that the average duration of the visually identified sleep spindles increased following learning (Fig. 3B), and the change in spindles persisted into SWS (Fig. 3C). The frequency and topographic characteristics of the learning-dependent changes in sleep were also investigated. An increase in EEG power density in the slow spindle frequency range (sigma power from 12 to 14 Hz) was observed during Stage 2 sleep (Fig. 4A) and SWS (Fig. 4B) in frontal and occipital regions (n.b. it is possible that increased 12–14 Hz power density at occipital sites could reflect increased fast occipital alpha) following simple procedural learning, whereas high frequency sigma (14–16 Hz) did not change significantly for this same task. There was no increase in Stage 2 sigma power in a non-learning control group, or in a group that performed a complex cognitive motor procedural task. These studies (Fogel and Smith, 2006; Fogel et al., 2007b) measured post-sleep memory performance one week later, thus, the immediate gain observed following one night of sleep could not be determined. A subsequent study (Morin et al., 2008) investigated the effect of motor sequence learning (MSL) on one night of sleep, and in performance gains following sleep versus a motor activity control group. Overnight gains in MSL performance and on the control task were observed, however, sleep had a significantly larger effect on MSL performance. Both the number, duration and density of visually identified sleep spindles (12–16 Hz) were increased following MSL learning compared to following the control task across the entire night, but increased number and duration of spindles was maximal in the second third of the night. Increased spectral power (mean of all midline derivations) of the MSL versus control night at 13 Hz corroborated these results. These results suggest that slow-frequency spindles may be involved in memory consolidation, whereas fast-frequency spindles may support some other function. Interestingly, using a different procedural task, a modified version of the mirror tracing task (Tamaki et al., 2008, 2009) training-dependent changes in fast spindles were observed, but not slow spindles. Similarly, a recent study (Barakat et al., 2011) found that fast spindles density (number/minute) at right centro-parietal (C4, P4) and left fronto-central (F3, C3) derivations increased, but not slow spindle density following learning on a motor sequence task but not following performance of a motor activity control task. Furthermore, they found that the overnight gain in performance was positively correlated with the change in fast spindle density at these sites from the control to training night. Together, these studies have demonstrated that sleep spindle activity increases in a number of ways following procedural learning including the number, density (number/minute), average duration, and intensity (power density) from the slow frequency (12–14 Hz) generator for rotary pursuit learning and the fast frequency (13–15 Hz) generator for sequence learning in underlying cortical regions that are known to be involved in this type of learning. Further study of spindle characteristics may help to functionally dissociate between these two generators. These studies indicate that not only is Stage 2 sleep of particular importance to procedural memory consolidation, but the sleep spindle may reflect a mechanism for the consolidation of

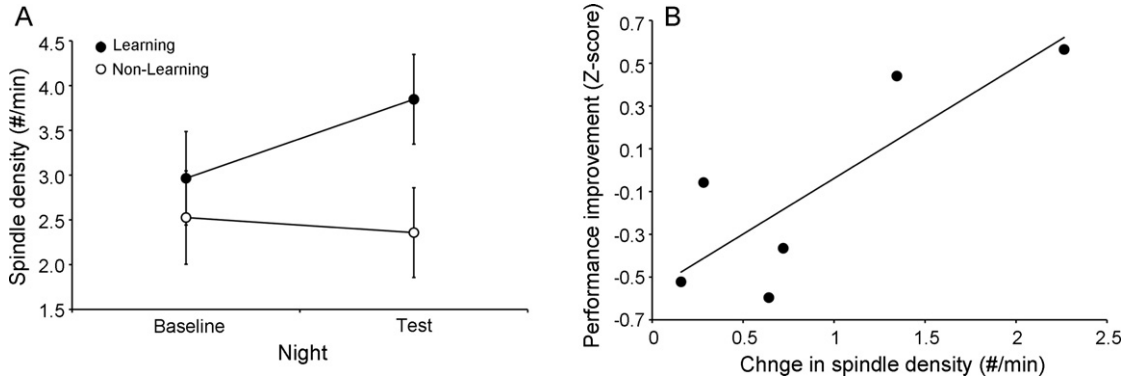

Fig. 2. (A) Increase in spindle density (number/minute, 12–16 Hz; C3 and C4) from baseline to test night ($t(9) = 3.63$, $p < 0.01$) following new simple procedural motor learning. Comparison between the learning and control group on test night ($t(10) = 2.28$, $p < 0.05$). The groups did not differ significantly on the baseline night, and there was no change in spindle density from baseline to test night in the control group. Vertical bars indicate standard error of the mean. Adjusted means controlling for inter-individual differences in sleep spindles using Performance IQ as a covariate. (B) Learning on the motor tasks was significantly correlated ($r(5) = 0.83$, $p = 0.04$) with the increase in sleep spindle density (number/minute, 12–16 Hz; C3 and C4). Individuals with a higher spindle density had the largest performance improvement, whereas those with the smallest change in sleep spindles had little (or decreased) change in performance. The learning scores were standardized into a composite score (z-scores) reflecting the total improvement across four simple motor procedural tasks.

learning. Interestingly, Rasch et al. (2009a) reported improved performance on the MSL task following administration of serotonergic and norepinephrnergic reuptake inhibitors commonly used to treat depression, also known to suppress REM sleep. The administration of these compounds significantly reduced REM sleep as compared to placebo, and paradoxically, the change in the number of sleep spindles was positively correlated with MSL performance improvement. This study indicates that spindles are related to procedural memory performance improvements in the face of reduced REM sleep. However, when cholinergic tone is reduced during REM sleep (Rasch et al., 2009b), motor skills performance but not declarative memory was impaired.

One important unresolved issue in the sleep and memory literature is whether the dissociation between sleep stage and type of learning (e.g., Stage 2 sleep and simple procedural learning vs. REM sleep and complex cognitive procedural learning) is dependent on the type of learning or the difficulty of the task demands (see Fogel et al., 2007b; and Smith, 2001 for an earlier formulation of these ideas). Another group has demonstrated that overnight retention of a verbal memory task correlates with the number of sleep spindles over left fronto-central areas (Clemens et al., 2005), whereas visuospatial memory retention correlates with the number of sleep spindles over parietal regions (Clemens et al., 2006) suggesting that the number of sleep spindles over different brain regions is task dependent. The level of expertise with a given task seems to be an important factor for learning-dependent changes in sleep, as well. Smith et al. (2004a) proposed that complex tasks require REM sleep whereas the refinement of simple, and already learned or existing skills would require Stage 2 sleep. It was hypothesized that the initial skill level of the individual would determine what stage of sleep would be necessary to consolidate new learning. Thus according to their hypothesis, for example, low skill individuals would *learn new skills*, thus post-learning changes in REM sleep would be hypothesized. On the other hand, high skill individuals would *refine existing skills*, thus post-learning changes in Stage 2 sleep would be expected. Peters et al. (2007) designed an experiment to test this hypothesis, and found that the increase in REM density from a baseline night to a post-training test night and the improvement in Pursuit Rotor performance was positively correlated in a low skill group, but not in a high skill group. Conversely, the increase in sleep spindle density and Pursuit Rotor performance improvement was positively correlated in the high skill group, but not in the low skill group. These results suggested that an individual's initial skill level is an important factor to consider when investigating post-learning changes in sleep. Thus, the sleep spindle appears to be involved in the consolidation of the *refinement* of existing motor skills, but not necessarily with the consolidation of the *initial acquisition* of completely novel and newly learned skills.

Recent studies using neuroimaging techniques have identified the neural correlates of sleep spindle activity including activation of the thalamus, anterior cingulate, midbrain, insular and frontal cortex (Schabus et al., 2007). Slow spindle activity is related to the common pattern of activity of both slow and fast spindles, however, fast spindles have a unique activation of structures including the hippocampus, mesial prefrontal cortex, precentral gyrus, and postcentral gyrus. Given the role of these structures for memory function, these results suggest that during spindle activity, networks of structures important for memory are activated.

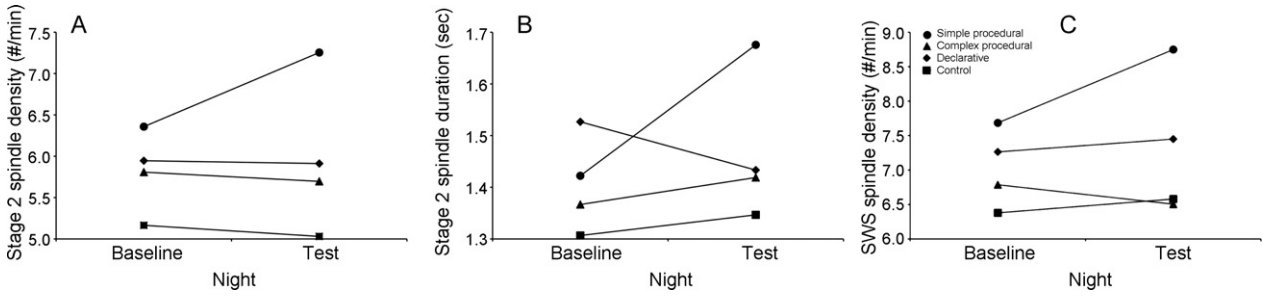

Fig. 3. Changes in sleep spindles during Stage 2 and SWS following Pursuit Rotor learning (simple procedural). (A) Sleep spindles density (number/minute, 12–16 Hz, Cz) in Stage 2 sleep from baseline to test night, $p < 0.05$. (B) The average duration of the sleep spindle (12–16 Hz; Cz) in Stage 2 sleep from baseline to test night, $p < 0.01$. (C) The number of sleep spindles per minute (12–16 Hz; Cz) in SWS from baseline to test night, $p < 0.05$. There was no change in sleep spindles following learning on the Mirror Tracing task (complex procedural), Paired associates learning (declarative), or in a non-learning control condition (control).

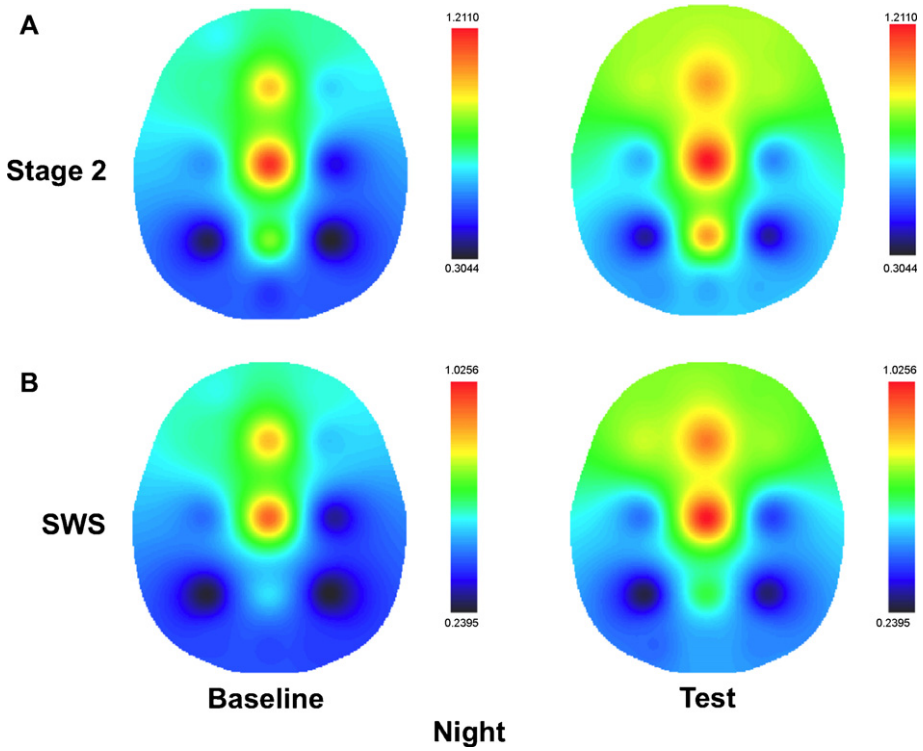

Fig. 4. Learning-dependent changes from baseline (left maps) to test night (right maps) in sleep EEG power density (μV^2). (A) Increase in low frequency sigma (12–14 Hz) power during late Stage 2 sleep (top maps) in the 2nd half of the night following Pursuit Rotor learning as indicated by an increase in warmer colors at frontal regions. Sigma power was maximal at the vertex, however, the largest increase (from baseline to test night) was maximal over right frontal regions. (B) Increase in low frequency sigma (12–14 Hz) power during SWS (bottom maps) following Pursuit Rotor learning as indicated by an increase in warm colors widely distributed across frontal, central, parietal and occipital regions. Sigma power was maximal at the vertex, however, the largest increase was maximal at central and occipital regions. There was no change in Stage 2 sleep or SWS sigma power in a non-learning control group (maps not shown).

Neuroimaging studies have revealed that in comparison to wake, increased activity from test to retest in the striatum are observed following motor sequence learning (Debas et al., 2010). Increased activity in the cerebellum was also observed following a motor adaptation task irrespective of whether sleep or wake occurred during the retention interval. Using both EEG and functional neuroimaging, Doyon et al. (in press) found that during an intervening period of sleep between motor sequence training and retest, the amplitude of slow sleep spindles (defined as ~11–13 Hz) in frontal derivations and of fast sleep spindles (defined as ~13–15 Hz) at the central midline derivation were positively correlated with activation in the putamen and with gains in performance.

7. Learning-dependent changes in sleep spindles in the rat

Steriade and colleagues have played an important role in characterizing the physiological characteristics and generating mechanisms of the sleep spindle, and have speculated that sleep spindles are involved in memory consolidation. Destexhe and Sejnowski (2001) have provided a detailed theoretical and computational background for the long-term synaptic changes sleep spindles may produce necessary for memory consolidation. Several recent studies in rats provide physiological evidence to support the idea that sleep spindles are involved in LTP necessary for memory consolidation. Pairs of hippocampal cells that are coactive during wake have been shown to be reactivated during subsequent sleep (Pavlides and Winson, 1989; Wilson and McNaughton, 1994). During SWS, bursts of high frequency activity originating from CA1 pyramidal cell activity in the hippocampus provide ideal conditions for long-term synaptic plasticity to occur (Bliss and Collingridge, 1993; Buzsáki, 1989). Siapas and Wilson (1998) demonstrated that hippocampal ripples are temporally synchronized with sleep spindle activity recorded from the medial prefrontal cortex. Hippocampal ripples precede cortical spindles by less than 1 s, whereby spindle and ripple onset times are highly correlated with one another. New learning in an odor-reward conditioning task increased slow oscillation activity amplitude, spindle and ripple activity (Mölle et al., 2009). These results suggest that sleep spindles may be involved in hippocampal–neocortical dialogue taking place during SWS (Buzsáki, 1989), and may be an important mechanism or identifiable feature in the EEG related to sleep-dependent memory consolidation. More recently, they have shown that cells in the prefrontal cortex fire within 100 ms of hippocampal cells during non-REM sleep, but not during REM sleep (Wierzynski et al., 2009) and that following hippocampal bursts of activity, spindle activity is increased. Furthermore, it has been demonstrated that induction of long-term potentiation results in increased reliability of evoked sleep spindles (Werk et al., 2005) and conversely, that sleep spindle-like activity can produce LTP in preparations of rat somatosensory cortex *in vitro* (Rosanova and Ulrich, 2005). The transition from non-REM sleep to REM sleep (pre-REM sleep) in rats is particularly rich in sleep spindle activity, and it has been demonstrated that following novel object presentation, increases in pre-REM sleep were observed (Schiffelholz and Aldenhoff, 2002). More recently, it has been shown that sleep spindle density increased for 60 min following reward learning in rats (Eschenko et al., 2006). When the reward was available at random, there was no subsequent change in sleep spindles. A similar increase in sleep spindles was observed following retrieval of remote memories. Thus, learning-dependent changes in sleep spindles appear to be similar in rats as compared to humans. Learning-dependent changes in sleep spindles in the rat may provide a useful model for investigating the source of spindle generation, and the effect of sleep spindles on synaptic plasticity.

A recent study (Fogel et al., 2009) investigated the EEG changes observed following 2-way active avoidance training, and similar to earlier studies (for review see Smith, 1985), a learning-dependent increase in REM sleep was observed in the latter part of the first training day (17–20 h post-training) accompanied by increased theta power. In the following 4-h period (21–24 h post-training) an increase in sleep spindles was observed compared to non-learning rats. The results of this study indicate that increased sleep spindles may represent one step in a series of steps involved in sleep-dependent memory consolidation. First, REM sleep increases occur which may represent hippocampal activation (as indicated by increased theta activity) of the newly formed memory trace in order to facilitate hippocampal–neocortical dialogue. Second, increased sleep spindles may serve to further strengthen the neocortical trace, resulting in a memory that is more independent of the hippocampus, and thus less susceptible to interference.

8. Sleep spindles and declarative memory

Sleep spindles have also been implicated in the consolidation of declarative memory. The same pattern of hippocampal activation observed during wakefulness is reactivated during non-REM sleep in rats (Lee and Wilson, 2002; Wilson and McNaughton, 1994) and REM sleep (Kudrimoti et al., 1999; Nadasdy et al., 1999). Lee and Wilson (2002) recorded the activity of spatially receptive hippocampal place cells while running rats through a simple maze and found the same pattern repeated over consecutive runs. This pattern was repeated during SWS, albeit on a compressed time scale, but was not found in the sleep prior to maze exposure. Using a similar technique, Ji and Wilson (2007) found that electrophysiological patterns during maze running were replayed during SWS in both the hippocampus and neocortex, and this activity was temporally coordinated. These results suggest that during sleep, episodic information is replayed, via hippocampal–neocortical dialogue that may reflect memory consolidation processes. Neocortical-hippocampal communication is necessary for the consolidation of declarative learning, and sleep is considered to be an important time for this process to occur (Smith, 1995). Sharp-wave ripple activity in the hippocampus is a mechanism for neocortical–hippocampal dialogue during sleep (Mölle et al., 2006; Sirota and Buzsáki, 2005). Siapas and Wilson (1998) found that hippocampal ripples were correlated with spindle activity. Thus, sleep spindles may be involved in hippocampal–neocortical dialogue during sleep. Following declarative learning Gais et al. (2002) found that compared to a non-learning condition there was an increase in spindle density during Stage 2 sleep which was largest in the first 90 min of sleep, and diminished over the course of the night. Sleep spindles were maximal at central regions and the largest learning-related difference in spindle density was at frontal sites. The increase in spindle density was positively correlated with recall performance before and after sleep. Schabus et al. (2004) investigated changes in performance in individuals who had increased spindle activity (a composite measure of spindle amplitude and duration) following declarative learning, compared to those who did not. Individuals with increased spindle activity during Stage 2 sleep had increased recall from pre-sleep to post-sleep testing, whereas those who did not have increased spindle activity did not improve on the task. Individuals with increased spindle activity also had higher spindle activity prior to learning than those who did not have a change in spindle activity. The change in spindle activity was found to be correlated with the change in memory performance which was even stronger when the duration of Stage 2 sleep was statistically controlled. These studies indicate that sleep spindles may also be involved in the consolidation of declarative memory, and may be involved in the neocortical–hippocampal dialogue necessary for the long-term storage of newly learned declarative material.

Sleep spindles are temporally related to the slow oscillation (Steriade and Timofeev, 2003). A study by Marshall et al. (2006) found that declarative memory recall improved following the induction of slow oscillatory activity during slow wave sleep using transcranial magnetic stimulation (TMS). They also reported that slow 'sigma' power (8–12 Hz) and the number of sleep spindles were increased, however, given that the frequency band is more commonly defined as alpha activity, this increase likely represents increased sleep disruption (i.e., cortical arousal) due to the experimental manipulation rather than increased spindle activity. Further study using TMS is required to ascertain the effects of TMS on sleep spindles and memory consolidation.

9. Learning-dependent changes in sleep spindles during a daytime nap

The benefits of a daytime nap on performance have been well documented (Broughton and Dinges, 1989) however, it is not clear what processes are involved in producing these benefits. The role of the sleep spindle in simple motor procedural memory performance improvement was investigated following a short daytime nap (Milner et al., 2006). Four groups were used to assess pre–post-nap changes in performance including habitual nappers and habitual non-nappers who both slept during a 20-min nap opportunity containing Stage 1 and Stage 2 sleep, or who stayed awake for 20 min between motor performance testing sessions. Following the nap, the non-habitual nappers performance worsened over the course of the trials. Both nappers who slept or stayed awake improved at the same rate as the non-habitual nappers who stayed awake. For the habitual nappers only, spindle density, sigma power (12–14 Hz) at frontal sites and sigma power (14–16 Hz) at central and parietal sites during Stage 2 sleep positively correlated with post-nap performance. These results indicate that habitual nappers tend to have naps with EEG that is characteristic of lighter sleep (higher alpha power), but also higher in sigma activity. Habitual nappers improved compared to non-habitual nappers, which indicates a differential benefit to napping. A similar more recent study also investigated the role of the sleep spindle in motor learning performance in a longer daytime nap containing all sleep stages (Nishida and Walker, 2007). The MSL task was administered before and after a 60–90 min daytime nap. Following the nap, there was a highly significant gain in motor performance, whereas those in the wake condition did not improve over the same period of time indicating that the nap enhanced performance. Subjects with the longest duration of Stage 2 sleep during the nap had the largest improvements in performance, whereas there was no correlation between the amount of SWS or REM sleep and performance improvements. The difference in spindle density and in sigma power density (12–16 Hz) between the learning and non-trained hemisphere (the right hemisphere, contralateral to task performed using left hand) positively correlated with motor skill improvement from pre- to post-nap testing.

The role of sleep spindles for declarative memory improvements following a daytime nap has also been investigated. Schmidt et al. (2006) varied the difficulty of encoding by manipulating the concreteness of words using a paired associates task presented before and after a long 4-h daytime nap. Low frequency spindle activity (11.25–13.75 Hz) increased in the difficult encoding condition compared to the control condition. No change in spindles was observed in the easy encoding condition or for high frequency spindles (14–16 Hz) in either difficult or easy conditions. The increase in memory performance over the nap was correlated with the density of sleep spindles in the difficult encoding condition, but not for the

easy encoding condition. Thus sleep spindles also appear to play a role in the performance gains observed following a daytime nap for declarative memory, depending on the difficulty of the material to be learned.

10. Conclusions and future directions

The sleep spindle was one of the first electrophysiological features of sleep to be discovered (Loomis et al., 1935a,b), and is one of the identifying features of non-REM sleep (Rechtschaffen and Kales, 1968). Since that time and until recently, identifying the function of the sleep spindle has been elusive for neuroscientists. Many neurophysiological studies have suggested that the sleep spindle is ideal for memory consolidation (Destexhe and Sejnowski, 2001; Rosanova and Ulrich, 2005; Steriade, 1999; Steriade and Amzica, 1998a,b). Sleep spindles are highly correlated with intellectual abilities and may reflect a more efficient thalamocortical system. Individual differences in the innate number of sleep spindles are associated with learning ability as measured by IQ tests, and the learning-dependent changes in sleep spindles are related to of the amount of learning that has taken place. Thus, the studies reviewed here provide compelling evidence that sleep spindles may serve as a physiological index of the potential to learn and also as a marker of how well a task has been learned.

There are, however, a number of important unanswered questions that arise: (1) How does the sleep spindle and associated events such as ripples and the slow oscillation appear to be involved in the consolidation of such a wide variety of memory types including verbal and spatial declarative, simple motor procedural, and possibly others? (2) How can the sleep spindle be involved in both consolidation of new learning and predict the ability to learn; and are these processes interrelated? (3) What characteristics of the sleep spindle (i.e.; frequency, duration, amplitude, density) are specifically related to the consolidation process, and how do these characteristics affect cellular and molecular changes involved in synaptic plasticity? (4) How do the learning-dependent changes in sleep spindles change over the lifespan in children and in elderly populations? At present, studies investigating the role of the sleep spindle have been conducted mainly using young adults. Sleep architecture changes over the course of development and with aging (Bliwise, 2000), however, cognitive decline is not observed in all individuals (Rapp and Amaral, 1992). Are the changes in sleep related to the amount of learning taking place during development and the inter-individual differences in cognitive deficits observed with aging? The answer to these questions could provide insight into the involvement and importance of sleep for cognitive function across the lifespan. (5) Changes in sleep spindles have been documented in individuals with low IQ (Bixler and Rhodes, 1968; Gibbs and Gibbs, 1962; Shibagaki and Kiyono, 1983) and in developmental disorders such as Asperger's syndrome (Godbout et al., 2000). What can the differences in sleep spindles in individuals with disorders tell us about their cognitive impairments? (6) How accurately can we predict the ability to learn and identify specific aptitudes using sleep spindles; what characteristics of the sleep spindle most accurately predict performance?

One important and relatively unexplored question is whether there is an interaction between IQ and memory consolidation. It appears that when divided into subgroups, individuals that have improved declarative memory performance on the paired associates have increased spindle activity (using a composite measure of amplitude and duration) irrespective of whether they have high or moderate scores on aptitude tests such as the Raven's Progressive Matrices (Schabus et al., 2008). A similar approach could be used to investigate if memory improvements and increases in sleep spindles are observed in subgroups across a wider range of IQ scores (below average, average and above average) for procedural memory.

There are a number of issues that are generally overlooked when investigating the role of the sleep spindle. Spindle characteristics (amplitude, frequency) vary with age along with circadian rhythms and scalp location. Detection methods generally do not take these factors into account. A recent study from our group (Ray et al., 2010) has proposed a validation method that can be generalized to any detection method and across a variety of endogenous and exogenous factors. This method advocates the use of an individualized approach in spindle detection as spindle amplitude varies considerably from one individual to another. Another important factor to consider in an individualized approach is spindle frequency as the use of fixed frequency bands (e.g., 12–14 and 14–16 Hz) is a suboptimal approach. While there is evidence to support the notion that there are (at least) two types of spindles (slow and fast) that have different topographies and temporal characteristics, there is considerable overlap between slow and fast spindles, complicating detection techniques. To further complicate matters, there is little consensus in the literature on a definition for fixed frequency bins that range anywhere from 8 Hz (Marshall et al., 2006), generally considered alpha activity, up to 18 Hz (Nader et al., 2003), generally considered beta activity.

The physiological relationship between the sleep spindle and the slow oscillation (<1 Hz) is well understood. More specifically, in animals (Contreras and Steriade, 1995; Mölle et al., 2006) and humans (Clemens et al., 2007; Marshall et al., 2003; Mölle et al., 2002) sleep spindles are time-locked to the depolarizing phase (surface positive, up-states) of the slow oscillation. Recently, Mölle et al. (2009) investigated the learning-dependent changes in sleep spindles and the slow oscillation in both humans and rats. Increased amplitude of slow oscillation up-states at frontal regions and sleep spindle activity (increased number of spindle troughs and peaks) were observed following paired associates learning in humans. Similar, although less robust changes were observed in rats followed learning in an odor-reward association task. Several important questions remain unanswered: (1) are similar learning-related changes in sleep spindles and the slow oscillation observed following procedural learning, and (2) if both sleep spindles and the slow oscillation increase following learning and are temporally linked to one another, how can we determine if the sleep spindle alone, slow oscillation or both combined are involved in sleep-dependent memory consolidation? One limitation of investigating the slow oscillation from scalp-recorded EEG is the ability to dissociate the slow oscillation from other sources of slow activity such as k-complexes and delta waves, but also from artifactual sources such as eye movements and electrode movement due to respiration. Future studies are necessary to further disentangle these issues.

The role of sleep for memory consolidation has been studied for several decades, and until recently, the mechanisms involved in sleep-dependent memory consolidation have not been clearly identified. There are now a number of studies suggesting that an important function of the sleep spindle is the involvement in the consolidation of new learning. Furthermore, the substantial inter-individual differences in sleep spindles accounts for differences in learning potential as measured by IQ. Animal studies indicate that the sleep spindle reflects the cortical aspect of hippocampal–neocortical dialogue involved in the consolidation of new learning. Future studies of the sleep spindle could reveal the mechanisms for learning and memory consolidation during sleep. The sleep spindle is a possible physiological index of a variety of intellectual abilities and of the capacity for learning. Sleep recording may have a variety of applications for the assessment of intellec-

tual abilities for children, adults and elderly populations in a variety of settings including educational, industrial, business, clinical and mental health.

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