excitability (or self-excitation) during extended periods of waking, there does not appear to be a mechanism for distinguishing between correct and incorrect choices – that is, sequences of movements (and associated neural circuitry) responsible for correct or incorrect choices. It would seem that activity would be as "heightened" in waking (and carrying to sleep) with incorrect as with correct movements, and if so, the net effect of their co-strengthening would be an equivalent potentiation in sleep. Accordingly, based on Walker's scheme, it would be difficult to account for the reduction in errors (i.e., correct choices) during sleep as shown for the finger-tapping task in Figure 3 (B and D) of the target article.

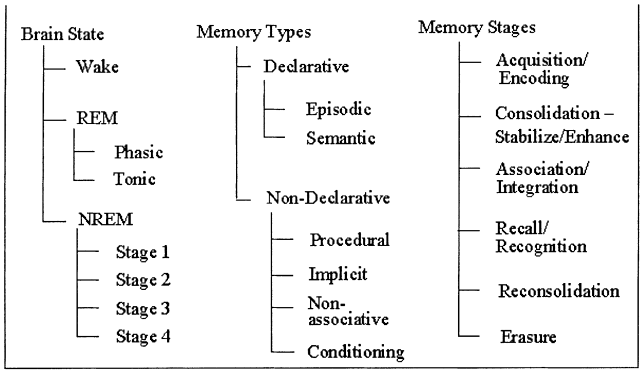



Figure R1. Brain states, memory types, memory stages.

# Author's Response

## Past, present, and the future: Discussions surrounding a new model of sleep-dependent learning and memory processing

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**Abstract:** Following on from the target article, which presented a new model of procedural skill memory development, in this response I will reflect on issues raised by invited commentators and further expound attributes of the model. Discussion will focus on: evidence against sleep-dependent memory processing, definitions of memory stages and memory systems, and relationships between memory enhancement, sleep-stages, dreaming, circadian time, and sleep-disorders.

I will start by saying how delighted I am that such a diverse body of commentators took the time to contribute to the discussion of the target article by way of their valuable commentaries in this publication. From reading the commentaries several issues are clear. First, we have yet to arrive at a consensus on what we think *memory consolidation* means – evidently it means different things to different people – as well as how many subcategories there may be. Second, it is striking that some commentators describe definitions of *consolidation* classically in terms of behavioral outcomes, as the target article does, others conceive of consolidation as defined by forms of plasticity; and still others define it in pure physiological measures. On the one hand this indicates the rich diversity of research focusing on memory consolidation, while on the other, it demonstrates the variability with which we conceptualize the term and thus the difficulties in interpretation we may face.

To that end, in writing the original target article I had several goals in mind. Perhaps most grand was an attempt to bring a degree of consensus to the field in terms of brain-state dependent memory stages, specifically the varied forms of memory consolidation that are becoming apparent. My approach was to introduce the concept of consolidation as two forms, either stabilization or enhancement, and describe their relationship to time, wake, sleep, and the physiological characteristics of sleep. Based on the even *more* varied potential forms of consolidation noted by a host of commentators here, I accept that in this endeavor, greater refinement is required. Indeed, the target article may not have gone far enough in its dissection of the term and the necessary role sleep plays. Furthermore, while the current memory-stage model appears to fit a large proportion of the literature, several findings (either noted by commentators or raised by myself in this response) appear not to fit comfortably into the model, indicating areas of future modification.

My second, perhaps more realistic goal, was to trigger a dialogue between researchers in the field of sleep and memory. We need to recognize that the blanket term "consolidation" is not only too broad in our own conceptions, having multiple meanings, but also that this generality results in a confusion of how and when we consider factors such as wake and sleep causal to memory processing. In this respect, I feel the target article has made progress. There seems to be little resistance to the concept of consolidation developing in a variety of ways across a variety of forms of learning during either wake or sleep.

By way of these discussions, I feel we are moving closer to understanding how stabilization, enhancement, and the additional steps of memory, either between or beyond, relate to brain states. It is no longer acceptable to simple state that "sleep" is involved in "memory," or that "REM sleep" is not involved in "consolidation." We must be more specific. To all but a few commentators, this now seems obvious and is embraced. I emphatically state that we do not yet have a complete understanding of how brain states, memory categories, and memory stages are related. But before this statement is used obstinately as a quotation to support a lack of evidence for the role of sleep in memory stage processing, let me explain. To demonstrate the complexity that we face, consider Figure R1. Here we can appreciate, even with the admittedly gross simplification of subcategories, the scope of questions we must ask, and the directions of causality we must test. The model embodied within my current target article represents just one component of this larger framework, as noted in the article's conclusions. Looking beyond the target article and the associated commentaries, it is this level of complexity, and the specificity of terminology, I hope we can keep in mind as we continue exploring memory processing.

From reading the commentaries, several common themes appear, which I will use as a structure to reply to the pertinent aspects of each. These topics are: (1) evidence that sleep does not play a role in memory processing; (2) different systems of memory and different forms of learning; (3) the multiple stages of memory that may or may not exist; (4) definitions surrounding plasticity and sleep characteristics; (5) potential mechanisms of sleep-dependent memory plastic-



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Table R1. *Cross-reference guide to commentary responses*

| Author / Theme | Is there evidence against sleep-dependent memory processing? | Memory systems and forms of learning | Memory stages | Definitions | Sleep consolidation mechanisms | Memory and dreaming | Circadian time, attention and sleep deprivation | Sleep abnormalities and memory |
|---|---|---|---|---|---|---|---|---|
| Atienza & Cantero | | | X | | X | | | |
| Bramham | | | | | X | | | |
| Clarke | | X | | | | | | |
| Coenen | | | X | | X | | | |
| Doyon et al. | | X | X | | | | | |
| Dumay & Gaskell | | X | X | | | | | |
| Finelli & Sejnowski | | | | | X | | | |
| Foster & Wilson | | X | | X | | | | X |
| Greenberg | | | | | | X | | |
| Groeger & Dijk | | X | | | | | X | |
| Korman et al. | | | | | X | | | |
| Pagel | | | | | | X | | |
| Payne et al. | | | | X | X | | | |
| Peigneux et al. | | | X | | | | | |
| Piggott & Perry | | | | | | | | X |
| Porte | | | | | X | | | |
| Schredl | | X | | | | | | X |
| Sheth | | | | | X | | | |
| Siegel | X | | | X | | | | |
| Smith | | X | | | | | | |
| Szymusiak | | | | | X | | | |
| Tononi & Cirrelli | | | | | X | | | |
| Vertes | X | X | X | | | | | |

ity; (6) the relationship between dreaming and memory processing; (7) the influence of circadian test time, attention, and sleep deprivation on memory processing; and (8) sleep abnormalities and alterations of sleep-dependent learning. A cross-reference guide for these topics and their relationship to specific commentaries can be found in Table R1.

## R1. Is there evidence against sleep-dependent memory processing?

The commentaries by **Siegel** and **Vertes** both argue against the empirical evidence for sleep-dependent memory processing; I would like to rebut.

Both these authors describe studies of patients treated with monoamine oxidase inhibitors (MAOIs), which alter sleep structure and interfere with REM sleep. They claim that these patients show no signs of impaired memory, even after receiving such medication for years, and believe this is strong evidence against the role of sleep in memory consolidation. First, although MAOIs appear to reduce REM sleep to varying degrees early in medication (Landolt et al. 2001; Monti et al. 1990), REM sleep re-emerges later in course of medication (Landolt & de Boer 2001; Mendelson et al. 1982; Minot et al. 1993), suggesting a strong REM compensatory mechanism. Furthermore, there is a potent REM rebound during the frequent periods when medication is paused (Minot et al. 1993; Steiger et al. 1987; 1994). As such, the claim that patients live for years with no REM sleep is unfounded.

Second, using just a simple one-off test of memory tells us nothing about intact or impaired sleep-dependent learning, or consolidation of any sort, the perils of which are evident in the misgivings of **Vertes** and **Siegel** surrounding MAOIs. For example, Vertes and Eastman (2000) cite 29 articles to argue that such REM suppressants had no deleterious effects on memory. Of these, 19 were available in the Harvard Medical School's electronic and print libraries. An analysis of these (see Table R2) shows that of the 16 primary source articles, 5 reported no memory tests at all. Of the remaining 11, 7 retested memory within minutes of training, and only one had a retest interval of greater than 30 minutes. Most strikingly, none involved retesting following sleep, none tested tasks that have been reported


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Table R2. *Analysis of reports studying effects of REM suppressant drugs on memory*

| **Studies of REM suppressants and memory** | | | | |
|---|---|---|---|---|
| Reports | 19 | | | |
| Reviews | 3 | | | |
| Primary sources | | 16 | | |
| No memory tests | | 5 | | |
| Tested memory | | | 11 | |
| Immediate retest (< 10 min) | | | 7 | |
| Retest at 10–30 min | | | 3 | |
| Retest at 30 min–5 hr | | | 1 | |
| Sleep-dependent tasks | | | | *0* |
| Retest following sleep | | | | *0* |
| Sleep recorded | | | | *0* |

Of 19 studies, cited as evidence that REM-suppressing antidepressants show normal learning despite REM suppression, none investigated sleep-dependent tasks, none tested memory after a post-training night of sleep, and none confirmed the degree of REM suppression.

to undergo sleep-dependent consolidation, and none recorded subjects' sleep to determine the extent of REM suppression. It therefore seems clear that such studies provide no useful information regarding the role of REM sleep in memory consolidation, let alone the role of sleep in general.

In his commentary, **Siegel** does not appear to consider all the evidence for my thesis. For instance, Siegel raises an issue about fatigue during performance/practice preventing the expression of possible waking consolidation. He states

> [I]t also needs to be shown that recovery from the performance decrements during learning that are known to be caused by intense practice were not creating an illusion of consolidation or "enhancement" when retesting after a recovery period. These sorts of controls have not been thoroughly and systematically done in studies claiming a role of sleep in memory consolidation (Siegel 2001; Vertes & Eastman 2000).

However, such studies *have* been systematically and thoroughly carried out to control for this specific objection. For example, my colleagues and I have shown that following extended practice, neither a 10-minute rest period, a 4-hour rest period, an 8–12-hour rest period, nor even a 12-hour period with total hand rest, can trigger significant improvement across waking intervals (Walker et al. 2002). Only during time periods containing sleep does such enhancement occur (Walker et al. 2002). This negates the argument that practice-induced fatigue without enough recovery time falsely inflates, or triggers an illusion of, sleep-dependent memory enhancement.

Then, **Siegel** claims (albeit using a newspaper citation) that researcher Carlyle Smith has previously concluded that sleep has no role in the consolidation of declarative memory. Similarly, **Vertes** attempts to suggest that the target article declares no role for sleep in declarative learning. Both these points are incorrect, as is the assertion that I, too, believe sleep plays no role in declarative memory. On the contrary, I believe sleep does contribute significantly to declarative memory processing (see sect. R2). Smith does not in fact conclude that sleep plays no role in declarative learning in his article, but rather that the evidence for a link between *REM* sleep and consolidation of declarative memory has not been consistently found, while there was evidence for such a link between declarative memory and other sleep stages.

Finally, **Siegel** argues my claims are excessively ad hoc, for example, that only Stage 2 non-REM (NREM) sleep in the last quarter of the night is important. In that report (Walker et al. 2002), all appropriate statistical tests, together with correction for multiple statistical comparisons, highlighted Stage 2 NREM sleep as important in the described overnight improvement (therefore not an "ad hoc" claim). Indeed, the sleep-dependent nature of this motor task has since been replicated by two independent groups (Fischer et al. 2002; Korman et al. 2003).

**Vertes** raises the issue that practice-dependent learning during the short retest session after sleep (2–3 trials, a total of just 60–90 seconds) may be the true cause of what we claim to be delayed sleep-dependent improvement. However, our experiments have explicitly addressed this issue. First, in our past studies (Walker et al. 2002; 2003b), we have demonstrated that the amount of improvement expressed after sleep (but not wake) is far beyond that which can be predicted based on practice-dependent learning rates alone, modeled specifically on each subject's own practice-dependent learning curve during training. Second, an even more compelling reason to reject Vertes's hypothesis is that the number of retest trials that subjects perform after either wake or sleep are identical, and therefore, subjects have just as many trials to demonstrate improvement at retest following wake or sleep. However, there is a very clear difference between retest performance after wake or sleep, with improvement developing only after sleep and not wake, despite subjects gaining just as much practice (and opportunity to improve) at each time point (Walker et al. 2002; 2003a; 2003b). As such, a practice-dependent explanation for improvement after sleep but not wake is implausible.

**Vertes** also suggests that I have stated sleep-dependent learning is modest or even small compared to practice-dependent learning during training, stating that "it is important to note, as pointed out by Walker et al. (2003b), that the gains in performance with the mere passage of time (in waking or sleep) are very small compared to improvements with repeated practice on motor tasks." I have never made this claim. To be clear – and to correct this statement: One session of practice on this motor task produces, on average, a 55% improvement in performance speed and approximately a 45% improvement in accuracy (Walker et al. 2002; 2003a; 2003b). Yet, just one night of sleep triggers an average 20% additional improvement in speed and approximately an extra 35% improvement in accuracy (Walker et al. 2002; 2003a; 2003b), which is not "very small" in comparison to training. Furthermore, three nights of sleep, without further training, trigger speed improvements of nearly 30% and accuracy improvements of 50%, almost equivalent to training (Walker et al. 2003b). In addition, if practice- versus sleep-dependent improvement is being compared, it is also pertinent to note that a second training session before sleep offers only a 9% additional improvement in speed and no significant further improvement in accuracy, while the subsequent night of sleep triggers



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improvements in both speed and accuracy far in excess of these additional practice-dependent improvements (Walker et al. 2003b). Thus, sleep-dependent learning appears to provide a very large and highly significant amount of the improvement one can develop on this task.

Ultimately, the expanding database of sleep-dependent studies exploring the links between sleep, learning, and plasticity, will resolve these objections even more clearly.

## R2. Memory systems and forms of learning

Regarding memory and anatomy, it is tempting to assign an exclusive, one-to-one isomorphic exemplar of a particular memory type (such as declarative memory) with an anatomical structure (such as the hippocampus), as some commentators attempt; but this would be a mistake. It is correct to note that declarative memory has consistently been associated with the medial temporal lobe, particularly the hippocampus. Yet, this does not mean that the medial temporal lobe is only concerned with declarative memory. In fact, semantic memory (another form of declarative memory) is largely considered to be independent of the hippocampus. In contrast, models of associative and also sequential skill learning do implicate involvement of the hippocampus (Poldrack & Packard 2003; Poldrack & Rodriguez 2003). Thus, the question raised by **Foster & Wilson**, about sleep-dependent hippocampal replay in animals (learning spatial navigation tasks and associative learning paradigms) being seemingly at odds with the inconclusive findings of REM sleep-dependent declarative memory formation, is moot (also see commentaries by **Groeger & Dijk**, and **Dumay & Gaskell**). The important issue here is the need to resist trying to fit the properties of a procedural memory model onto declarative memory (and vice versa), and instead accept that complex systems, the brain being the quintessential example, are highly unlikely to be explained by generalized rules. This was part of the target article's direction – to specifically focus on one form of memory and explain the patterns of memory-stage development apparent within that framework, rather than suggest it was a "one model fits all memory domains" theory.

As noted in the target article, the effects of sleep on declarative memory may be very different. **Foster & Wilson** misquote the target article as suggesting that "sleep may be less important in declarative memory than in procedural memory." In fact, **Vertes** misreads (or misinterprets) this point completely, as have other non-memory researchers (**Seigel**), suggesting that the target article concludes sleep plays no role in declarative learning. The target article does nothing of the sort. Instead, the target article simply states that the evidence is currently less resolved than in the procedural domain. It does not mean sleep plays no role in declarative memory. Sleep may very well have important effects on declarative memory processing. First, sleep may prevent the gradual decay of declarative memory over time. Second, sleep may be essential in terms of declarative memory transfer between storage sites (translocation), a theory already put forward by Buzsaki (1998) and Hasselmo (1999). Third, sleep may also be important for improving associative connections between newly learned information and previously retained information, a point discussed further in the commentary and discussion of **Dumay & Gaskell**.

Following on an issue raised by **Groeger & Dijk**, **Smith**, and **Dumay & Gaskell**, I would also note that categorical separations of memory, such as declarative and non-declarative, while useful in their simplicity, may preclude subtle nuances in understanding. I would be more than happy if future models attempted to move away from these theoretical memory categories and their generalized assignment to anatomical structures, and instead, be guided more by specific task characteristics and their relationship to sleep: For example, investigating the question "is there a relationship between NREM sleep and tasks that require sequential ordering" – be it the ordered recall of a specific word list (a "declarative episodic task"), or the ordered retrieval of a specific series of finger movements (a "non-declarative procedural task"). This orthogonal approach to understanding the relationship between sleep and learning may well be a useful exercise as discussed below. Alternative methods of investigating these novel predictions may also be useful, such as modeling the influence of sleep or wake in neural networks (**Clarke**), and artificially testing hypotheses across a variety of altered conditions (Hinton et al. 1995).

Commentaries by **Schredl**, **Smith**, and **Doyon, Carrier**, **Simard**, **Tahar**, **Morin**, **Benali**, **& Ungerleider** (**Doyon et al**.) all address a point of importance often overlooked by those who deny the role of sleep in memory processing. Although delayed overnight improvement appears to occur robustly and consistently across a wide variety of procedural tasks in the motor (Fischer et al. 2002; Maquet et al. 2003; Robertson et al. 2004; Smith & MacNeill 1994; Walker et al. 2002; 2003a; 2003b), visual (Gais et al. 2000; Karni et al. 1994; Mednick et al. 2002; 2003; Stickgold et al. 2000a; 2000b), and auditory (Gaab et al. 2004) domains, they do not all show a relationship with the same stage of sleep. For the naysayer, this has been taken as evidence against the role of sleep in memory processing stages. Why? As the above commentators and the target article note, these tasks, despite being grouped under the rubric of "procedural skill learning," undoubtedly rely on vastly different neural systems. Moreover, the functional changes occurring within these networks to produce behavioral improvement are also likely to be equally diverse.

The fact that, for example, a motor skill task shows a different sleep-stage correlation to a visual discrimination task surely does not represent inconsistency within a theory. Such a claim would be an oversight of brain mechanistic complexity. Even within the seemingly uniform domain of "motor skill learning," all things are not equal. Take for example the task of learning to use a computer mouse, and compare that to learning of a piano scale. Both are motor skill tasks, but while the effector limb may be the same, this is where many similarities end. Mouse skills require adaptation to environmental forces (e.g., the mouse mat texture), the software settings (e.g., fast or slow acceleration), and the quality of on-line feedback one receives (e.g., can you see the mouse arrow on the screen and use it as visual feedback to correct erroroneous movements?). In contrast, learning a piano scale requires the formation of a different and very specific program of motor sequence units (e.g., a series of unique finger flexions and extensions), the execution of which must be timed in a temporally specific manner (not depressing the third piano key position before the second), and a tactile or even auditory (rather than visual) feedback system for error monitoring.

Without laboring the point, this example illustrates how


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vastly different two apparently similar "procedural motor skill memory tasks" can be, and presumably how different the governing mechanisms of learning may be; something Doyon and colleagues have recently discussed (Doyon et al. 2003). In this respect, it seems very unsurprising that different neural processes relating to different tasks would be dependent on different brain states (sleep stages in this case). The distinction of different forms of learning may already be helpful in explaining differences in sleep-stage dependence. **Smith** notes that while many sequential motor skill tasks appear to correlate with Stage 2 NREM sleep, a mirror tracing task, a form of visuo-motor adaptation, has been associated with REM sleep. Appreciation of such subtle but important differences in task characteristics within the same memory category (procedural motor skill learning) thus offers more refined interpretations of the above correlations, rather than reflecting inconsistency. It also supports the sentiments of Smith in his commentary that a "'motor' versus 'cognitive'" learning taxonomy is overly simplistic.

**Smith** also remarks that sleep-stage correlation diversity may arise for other possible reasons across a range of experimental axes – for example, task complexity (simple or easy), sensory or motor characteristics, novelty or familiarity, and degree of training duration, to name but a few. Though it may be easy to trivialize these factors as the cause of differences in sleep-stage correlation, this would be unwise. However, we, the memory researchers, could aid our own cause in this respect. Even when using the same task in independent studies, we sometimes use slightly modified task versions, together with different testing regimens, be it the number of training trials during acquisition, the number of retest trials before or after sleep, or the number of those respective trials at training and at retest that we compare. Based on the variability this may cause, I would urge those in the field to communicate more readily and find ways in which we can standardize our methods, an act I'm sure will only produce even greater degrees of successful replication than those we have already achieved.

So, before we simply dismiss findings that different sleep-stages correlate with different memory tasks, effectively throwing the baby out with the bath water, it maybe a wiser tactic to look a little deeper into the task characteristics and ask what differences and similarities can help explain these varied correlations.

## R3. Memory stages

**Atienza & Cantero** and **Peigneux**, **Destrebecqz**, **Hotermans**, **& Cleeremans** (**Peigneux et al.**) correctly point out that it remains unknown whether consolidation-based stabilization (CBS) occurs for procedural sensory memory representations, as it does for certain motor memories. They discuss the results of Mednick et al. (2002; 2003), which demonstrate that repeated practice on a visual skill task causes deterioration in performance through the course of the day, but that short episodes of sleep enhance learning – either to initial baseline levels following a 60-minute sleep epoch, or beyond these baseline levels after a 90-minute sleep period. However, such a result can be interpreted in at least two possible ways. First is that the return of performance to baseline levels following a 60-minute sleep period constitutes a process of stabilization, relieving the deficit induced by training, while any additional learning beyond this point reflects a different mechanistic process of enhancement. However, a second alternative interpretation – not noted – is that the improved performance following any period of sleep, be it returning performance levels to baseline following practice-induced impairment or enhancing it beyond baseline levels, simply reflects the same process at work, that of consolidation-based enhancement (CBE) all along. That is to say, sleep episodes always trigger a process of enhanced learning from whichever end point has been achieved following practice, whether it is one of a deficit following prolonged or repeated practice, or an initial baseline following just one training session. Unfortunately, the claim that two discrete processes exist can only be defined using an interference paradigm, which has yet to be carried out using such sensory tasks. Without such an experimental challenge, we are not able to differentiate between these alternative interpretations, rendering modification of the current model premature.

**Atienza & Cantero** also point out that on an auditory discrimination task, some aspects of behavior do not show the expected deficits in learning following sleep deprivation, deficits that have been seen using visual and motor skill tasks (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). This echoes the commentaries by **Smith** and **Korman**, **Flash**, **& Karni** (**Korman et al.**), as well as the point at the beginning of this response, that even sensory and motor categories of procedural memory may be too broad. Instead, more subtle classifications could increase our understanding regarding different behavioral outcomes following sleep and wake. Interesting, the studies of Atienza and colleagues did demonstrate that although certain behavioral measures on this task showed no change with sleep deprivation, neurophysiological measures of automaticity (a specific waveform peak in the event-related brain potential) demonstrated severe impairments following sleep deprivation. It would therefore be interesting to find a behavioral measure of automaticity to complement these electophysiological measures of sleep-dependent consolidation. For example, if a secondary concurrent task were introduced, presumably the automaticity that developed on the first task following sleep would effectively prevent a large proportion of impairment by the second concurrent task. Yet, subjects who had not slept and not gained the benefit of automaticity would presumably show profoundly impaired performance in the presence of a concurrent interfering task. By investigating alternate behavioral measures of consolidation, the distinction of sleep-dependent enhancement may still exist in this case.

On a related issue, **Vertes** describes work by Donchin et al. (2002) using a motor skill adaptation task. This is the same task that has previously shown evidence of both consolidation-based stabilization across wake, and subsequent delayed consolidation-based enhancement across 24 hours following a night of sleep (Brashers-Krug et al. 1996). But, Donchin and colleagues reported no change in performance at a later 24-hour retest, either with or without sleep. However, a closer examination of these reports reveals that different performance variables are reported as the measure of learning – a correlation coefficient in the earlier study Brashers-Krug et al. describing both CBS and CBE, and a "learning index" in the report by Donchin et al. showing no delayed performance changes. Which of these mea-



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sures represents consolidation is unresolved, and the utility of this description by Vertes is uncertain.

**Dumay & Gaskell** offer important suggestions regarding the potential role of sleep beyond stages of memory consolidation and propose that sleep may facilitate a process of integration, in addition to the enhancement of newly formed memory representations. They build on this interesting idea using data from a lexicalization task, describing a delayed learning effect over 24 hours, following a night of sleep, which persists for at least one week. A related study by Fenn et al. (2003) adds to these ideas and may expound on the time course of the effects in even more detail. Using a naturalistic spoken-language task (learning synthetic speech), Fenn and colleagues investigated the generalization of phonological categories across different acoustic patterns, and observed how this learning changed over practice and time. The task required forming new mappings from complex acoustical patterns to pre-existing linguistic categories, which then generalized to new stimuli. As such, it involved both a declarative process of forming specific memories associated with the learned words, together with a procedural component involving mapping across the set of learned words that supports generalization to novel stimuli. During the initial training session there was a significant improvement in recognition performance on the task. However, when retested after a 12-hour waking interval, performance decreased – either due to waking interference (although see discussion on **Coenen**, below) or a process of memory decay. Yet, if subjects were retested following a night of sleep, the recognition performance was completely restored. Furthermore, this effect was present irrespective of whether the post-sleep retest occurred in the morning or later in the evening, illustrating that these performance changes could not be explained by different circadian test times.

These data would indeed fit with the notion that sleep can enhance performance, effectively recovering representations and mappings associated with generalization of previously learned phonological memories. Moreover, such findings suggest a sleep-dependent effect beyond enhancement, potentially offering a generalization of learning to other newly encountered stimuli. However, this sleep-facilitated generalization may not be evident in all tasks, since sleep-dependent learning of certain visual and motor skills is specific to the characteristics of the original task stimuli (i.e., retinotopic visual stimulus location, or the specific motor sequence), and does not transfer to similar stimuli in different configurations (i.e., switched retinotopic location or a new motor sequence pattern).

**Coenen** raises the issue of consolidation-based enhancement and its dependence on sleep. Coenen questions whether sleep itself plays a proactive role in memory consolidation, or whether the behavioral state of sleep (lacking external sensory perception and outward motor action) simply offers a permissive time for memory consolidation. In this sense, there is nothing unique to the biology of the sleeping brain that triggers memory consolidation. Instead, it is simply an offshoot of the sleeping state itself (devoid of interaction with the external world, preventing sensory and motor activity), which allows the brain to consolidate memories; something the brain may not be able to do during wake.

First, the notion of the sleep brain as simply quiescent (thus passively offering "downtime" for consolidation) is somewhat outmoded. While clearly the visual external environment is not perceived during sleep, nor is there considerable motor output, this by no means suggests that visual and motor regions of the brain are not highly active. In fact, animal and more recent human neuroimaging studies demonstrate that sensory and motor regions are particularly active during sleep, especially REM sleep (for reviews see Hobson et al. 2000). Therefore, if the presence of sensory and motor activity during time awake is the argument to explain a lack of consolidation, this reasoning must also be applied to the sleeping brain as well, since here too we find prolific sensory and motor activation, equally capable of blocking consolidation. However, the fact that delayed performance enhancements only occur during sleep and not wake, even though sensory and motor activity prevails during both states, makes a classical interference explanation untenable.

Second, the possibility that waking activity prevents consolidation has been specifically tested in several sleep-dependent visual and motor learning studies, the results of which are difficult to reconcile with the reasoning put forth by **Coenen**. These reports have used control experiments to demonstrate that periods of quiet rest without motor or visual activity during the day (mimicking the behavioral features during sleep) are still not able to produce consolidation-based enhancements during these waking intervals. For example, after having learnt a finger-tapping motor skill task in the morning, subjects in one such study had enforced total hand rest for an 11-hour waking interval – far in excess of the average 8-hour sleeping period (Walker et al. 2002). Nevertheless, subjects still expressed no behavioral improvement across the waking interval with total hand rest, yet they went on to demonstrate improvement after a night of sleep. In a similar experiment, following training on a visual skill task, a control group of subjects were required to lie supine, in a dark quiet room, without any visual stimulation, and were blindfolded for a 90-minute period (although they remained awake, as verified by full polysomnography recordings), while an experimental group of subjects were allowed to sleep during the 90-minute period (Mednick et al. 2002). When retested, only the group that had slept showed consolidation-based enhancements in performance, whereas subjects who spent this time awake, but without visual stimulation or interference, showed no improvement. Such studies therefore do not support a classical theory of simple passive rest (either during sleep or during wake), promoting consolidation. Instead, the only viable explanation given these data is that sleep itself, and not the lack of interference during this state, is responsible for the consolidation-based enhancement triggered by sleep.

Some tasks have been reported to show delayed improvement across time intervals without the need for sleep, and would therefore not fit easily into the sleep-dependent, consolidation-based enhancement framework of the target article – findings that can help refine the current model.

The first result, reported in the commentary of **Doyon et al.**, describes evidence that learning of a motor adaptation task shows improved performance as a function of time and not necessarily sleep. Several observations may be of interest. One is that the data comparison involved the last 32 trials at testing relative to the first 32 trials of retesting, within which there may be significant practice-dependent learning, perhaps making it more difficult to conclude


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whether these differences reported between each time point are truly time-dependent rather than practice-dependent. For example, our previous motor studies investigating delayed learning used just the last 2–3 trials on day 1, relative to the first 2–3 trials on day 2 (only 60–90 seconds of performance measure at each retest), removing a practice-dependent learning contribution to the comparison (**Vertes**). It would therefore be interesting to change the former comparison from Doyon et al. to, say, the last 2–5 trials at testing relative to the first 2–5 trials at retesting, effectively removing a practice-dependent influence. If the performance differences remained across the 8-hour period, it would indeed indicate that this form of delayed enhancement was sleep-independent.

Also, the 5-hour and 8-hour delay periods without intervening sleep (groups 1 and 2) appear to show quite similar amounts of percentage improvement (about 9% and 10%, respectively, calculated from the figure provided), while the 24-hour delay period (group 3), containing a night of intervening sleep, express greater improvement (about 14%), although this difference is noted as not significant. It is interesting to speculate that this variation may also be related to intervening sleep. Regardless, **Doyon et al**. make an important separation between forms of motor skill learning, and highlight the possibility that these forms of learning may follow different courses of delayed learning over time and brain state, notions that hold important implications for refining the CBS-CBE model.

The second report is an ingenious study by Robertson et al. (2004), which demonstrates that explicit procedural learning of a motor sequence, but *not* an implicitly learned version of the task, requires sleep for delayed consolidation-based enhancement. Performance on the implicit version of the task demonstrated delayed learning across 12 hours irrespective of whether it contained sleep or not. This also raises two interesting possibilities. One is that the comparable behavioral improvement in delayed implicit procedural learning occurs by way of a similar process of CBE to that observed with explicit skill learning (such as a systems level plastic change; **Korman et al**.), but without the need for intervening sleep. An alternative possibility is that while behavioral improvement on both forms of the task appear similar (albeit developing across different brain states), the underlying mechanisms of this improvement are different. In either case, it would seem that the current model put forth in the target article can be modified. The former possibility suggests an exception to the exclusivity of CBE to sleep, occurring when awareness of learning is absent. The latter suggests a fundamentally different mechanistic form of CBE may exist which does not rely on the physiological specificities of the sleeping brain. With continued research on delayed learning in explicit and implicit task paradigms, these issues will become clearer.

## R4. Definitions

Several issues were raised in the commentaries regarding definitions concerning memory stages, systems, and sleep stages.

With respect to defining the sleep characteristics we choose to correlate with learning, I too sympathize with **Payne**, **Britton**, **Bootzin**, **& Nadel** (**Payne et al**.) in the hope of supplementing classical Rechtschaffen and Kales sleep scoring with more independent physiological variables in attempting to understand the basis of sleep-dependent memory processing. For example, rather than correlating word-pair retention or visual skill improvement with slow wave sleep (SWS), we should instead investigate relationships between these learning measures and EEG delta power (Huber at al. 2004), or investigate overnight enhancement of motor skill learning with sleep spindles (number, frequency, or amplitude), rather than just Stage 2 NREM sleep. While it would be unwise to abandon the classical Rechtschaffen & Kales scoring method completely, it is surely as dangerous not to co-investigate these alternative sleep characteristics as explanatory variables.

**Foster & Wilson** question the use of the term *consolidation* across memory categories. I agree with Foster & Wilson that declarative memory has received greater research attention, and thus the term consolidation is similarly more strongly associated with this form of memory. However, it has never prohibited the association of procedural memory with the term consolidation, and nor should it. Consolidation refers to a process, and does not belong to one memory category. But such a debate of semantic origin serves little benefit for the current framework, other than perhaps a historical reference. It has not precluded the utility of the term throughout the neuroscience community, applied across most all memory domains (see McGaugh 2000). If we are to continue using the term *consolidation* in a meaningful way, which I think we still can, we must accept that it requires subdivisions, each of which may be applied and modified to different memory systems (a point discussed further below).

As an aside, in perhaps a misreading, **Foster & Wilson** suggests that the word "passive" was used in the target article to define procedural learning. However, *passive* was used in reference to implicit learning, not procedural learning. To clarify, I specifically cast procedural learning in proactive terms, noting that it often requires subjects to undergo a "training interval involving repeated engagement with the procedure being learned."

Finally, I feel that the subdivisions of consolidation are clearly described using operational definitions (**Siegel**, **Coenen**). Indeed, rather than accepting this more refined level of definition of different stages of memory development, **Siegel** propounds a less differentiated framework that does not appear to fit a vast majority of the empirical data. My position, however, remains that the careful separation of different consolidation forms will help resolve areas of perceived conflict in the sleep and memory field.

## R5. Sleep consolidation mechanisms

A host of commentaries offer important mechanistic information corresponding to unique stages of consolidation and how sleep may be important. In addition, **Szymusiak** notably provides a careful consideration of issues surrounding sleep-dependent plasticity, and how to test these ideas empirically.

In his commentary, **Bramham** focuses on brain-derived nerve growth factor (BDNF), which may participate in the regulation of the sleep-wake cycle, and is also reported to trigger protein synthesis essential to plasticity. It is possible that increased release of BDNF during synchronous activity in NREM sleep may play a role in sleep-dependent con-



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solidation. Here too, terminology becomes different, with the contribution of protein synthesis to plasticity discussed as *stabilizing* synapses that have undergone learning-dependent changes, which is different compared with the *stabilization* of behavioral performance suggested to occur with wake, as put forth in the target article. This aside, Bramham builds a very attractive model, recognizing that the combined processes of synaptic potentiation and depotentiation together may lead to the behavioral effect of improved task performance after sleep. To interpret this theory in terms of the current framework, it may be that without synaptic stabilization during wake (occurring via early neural changes [(Lamprecht & LeDoux 2004)], or following a first wave of protein synthesis which protects newly formed synaptic connections), subsequent overnight enhancement may not occur, and instead may actually lead to weakened synaptic strength.

**Tononi & Cirelli** add a valuable contribution in proposing possible molecular mechanisms of CBE during sleep. Their commentary is a tour de force indicating why we can no longer consider neural activity in wake and sleep as active or restful respectively. Indeed, as they point out, absolute levels of cerebral metabolism are in fact *higher* after having been awake than after a night of sleep (Braun et al. 1997), a finding which would work against a theory of neural fatigue progressing across waking hours, preventing expression of consolidation that may have occurred. In light of such evidence, theories that suggest a passive repletion process occurring during sleep, whereby neural function is restored and masquerades as overnight improvement, become harder to accept. **Tononi & Cirelli**'s sophisticated level of description goes far beyond the sleep-associated neuronal rest theory for memory networks, and describes a more complex series of *active* events which could trigger true post-sleep memory enhancements, evidence that is also difficult to reconcile with more restitutive theories that have been proposed (see **Sheth** and **Coenen**). Indeed, several factors run counter to the argument that simple rest triggers learning rather than sleep itself, or that fatigue impairs expression of learning during wake (**Siegel**). First, human studies of sleep-dependent learning have provided several control conditions that mimic the behavioral rest characteristics of sleep, but during periods of wake, and still result in no significant evidence of consolidation-based enhancement (see detailed response to Siegel and Coenen above). Additional evidence has been offered by Frank et al. (2001), who have described cellular level sleep-dependent plasticity using a monocular deprivation paradigm. They reported a considerable enhancement of synaptic plasticity following 6 hours of sleep, while an equivalent period of wake caused a *reduction* in the size of this plasticity measure. Most telling, however, Frank et al. note that these effects were not just an offshoot of a non-waking brain (i.e., a time during which transmitter concentrations could be restored, or a time without external competing sensory stimuli, which normally block consolidation), since the state of anesthesia actually impairs this form of ocular column plasticity, rather than enhancing it, as sleep does. Again, this appears to contradict the predictions of a restitutive model.

Supporting the active, sleep-dependent model of memory processing, and slightly different to the mechanism proposed by **Bramham**, **Tononi & Cirelli** suggest that SWS dynamically promotes the depression of synaptic strengths, effectively reducing synaptic connections, improving efficiency. These claims are supported by empirical data suggesting that molecules associated with synaptic depression are indeed up-regulated in a sleep-dependent manner. Given these findings, they propose a SWS model whereby an active process of balancing synaptic efficiency, in the endeavor to create a refined memory representation, takes place during sleep. As a consequence, neuronal networks benefit from improved signal-to-noise ratio within the system, a process that may not be possible during the time of initial memory acquisition or across waking hours which confer stabilization.

It may be that both processes – of synaptic potentiation and synaptic depression – occur during the different stages of sleep and both are essential requisites for memory enhancement, as the theories of **Porte** and **Finelli & Sejnowski** describe. They suggest that sleep spindles, another property of NREM sleep, may have a role to play in synaptic potentiation, leading to consolidation-based enhancement by cellular mechanisms discussed in the target article. Porte specifically notes the intriguing anatomical expression of sleep spindles in "(cortico)striatothalamocortical (CSTC) loops," a location that is likely to play a role in certain forms of procedural motor representations (see **Doyon et al**.). Moreover, it is just such procedural memory representations, among others, that have previously expressed CBE overnight, pertaining to NREM sleep (Robertson et al. 2004; Smith & MacNeill 1994; Walker et al. 2002; although see Fischer et al. 2002). If NREM sleep and particularly sleep spindles are crucial to certain types of sleep-dependent motor learning, we can invert this equation and ask the reverse question: Does increased daytime motor learning alter the physiological characteristics of NREM sleep or sleep spindles? One would predict that practice-dependent alterations of these circuits would, in turn, reciprocally modify the homeostatic expression of sleep spindles in the subsequent night(s). Interestingly, just such a modification has been reported by Fogel et al. (2001), who demonstrated that in humans, relative to a night of sleep without motor learning, intensive motor skill practice triggers a significant, 40% increase in the number of spindles during the post-training sleep night.

Taken together, the neurophysiological properties of NREM sleep could act in two different but mutually beneficial ways in terms of enhancing certain forms of memory. Slow wave oscillations may provide a form of synaptic downscaling of initially over-potentiated networks, which are formed (and stabilized) across waking episodes, while spindle events are able to selectively strengthen these refined representations by triggering intracellular cascade events important for synaptic potentiation. It is also intriguing to note the similar possibility that pontine-geniculate-occipital (PGO) burst activity may offer potentiation of synapses. This notion is supported by work from Datta and colleagues demonstrating enhanced avoidance learning which is dependent specifically on PGO activity in rats, and can even be dissociated from the process of REM sleep itself (Datta 2000; Datta et al. 2004).

**Payne et al**. make an important contribution by highlighting the potential influence of several neurochemicals known to fluctuate across brain states – chemicals that are intricately linked to mechanisms of learning and plasticity. Advancing the target article's statement describing the influence of molecules ranging from hormonal substances, to


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cytokines and even gaseous substances, Payne et al. focus on cortisol, noting the dramatic nocturnal concentration swings from early to late in the night. They build on seminal work by Born and colleagues, along with work outside the field of sleep, which demonstrates mediation of learning and plasticity by cortisol. In doing so, they convincingly remind us that a sole focus on classical neuromodulators may obscure other/complementary mechanisms at work during sleep; mechanisms that may also help in clarifying sleep-dependent findings in the field.

**Korman et al**. and **Atienza & Cantero** both discuss the possibility that plasticity can occur in a variety of alternate forms, across different brain states. Specifically, Korman et al. skillfully build on the concept of different forms of consolidation as determined by behavioral performance (similar to the stages of consolidation put forth in the target article), and introduce the concept that different types of plasticity may underlie these different forms of consolidation. They introduce the notion that plasticity can be extended beyond the local, Hebbian synaptic level of description, into what has been termed "systems level plasticity." While this concept may be operationally difficult to define (how "far" does the locus of a memory representation have to travel before it can be deemed different from the original memory representation and thus be termed a "systems level" plastic change?), it could hold utility in understanding the stages of learning and their brain-state dependency.

There is already evidence that sleep induces both local level plasticity as well as systems plasticity. For example, the monocular deprivation study by Frank et al., (2001) described in the target article, is indicative of a local synaptic plastic change. Yet, Ribeiro and colleagues have also described plasticity-related gene expression across large-scale anatomical areas during successive REM cycles (Ribeiro et al. 2002) consonant with the idea of systems-level plasticity. In addition, using the sleep-dependent visual and motor skill tasks separately, my colleagues and I have recently described fMRI data (Walker et al. 2005; in press) indicating that, following equivalent amounts of task training, a subsequent night of sleep produces a form of systems-level plasticity throughout several cortical and subcortical areas.

On a cautionary note, it must be considered that defining different forms of plasticity may be a derivative of experimental technique. For example, whole brain fMRI presumably offers the ability to investigate systems-level plasticity, while single-unit recordings in the CA3 region of the hippocampus, or even focused fMRI on one cortical region, precludes knowledge of systems-level plasticity. But neither technique tailored to investigate one form of plasticity should prevent consideration that the other is co-occurring, or that this unmeasured plasticity forms the basis of behavioral change. Contentions aside, the concept that different forms of plasticity may be related to different brain-state dependent stages of consolidation is both an appealing and insightful one, requiring further consideration.

## R6. Memory and dreaming

The eloquent and detailed psychophysiological discourse described in the commentaries of **Pagel** and **Greenberg**, as well as **Schredl**, are most encouraging. I too agree that we, as a field, are fast approaching a time when we have consistently and confidently explicated inimitable evidence of sleep-dependent learning and plasticity, and with this solid foundation in place, are ready to add new layers of experimental complexity which include a triangulation of behavior (performance), brain (sleep physiology and plasticity) and mind (dreaming). Early signs are already emerging (Cipolli et al. 2001; 2003). But we must proceed with rigor, and not fall into interpretive trappings. We must clearly demonstrate that any relationships between dreaming and memory development are functionally related and not simply epiphenomenal. For example, incorporation of newly learned words into sleep mentation does not alone indicate a functional role of dreaming in memory processing. Instead, demonstrating a link between the degree of next-day retention, improved memory recall, or even the degree of plasticity, and the frequency or intensity of prior nocturnal mentation is required to entertain a learning-related function of dreaming. As poignantly noted by Greenberg, triangulated research such as this offers a much richer appreciation of the entire process being studied, leading eventually to a complete understanding of all known sleep characteristics and how they contribute to different memory systems and stages.

## R7. Circadian time, attention, and sleep deprivation

When investigating potential sleep-dependent learning, several other factors, such as circadian test time (which may result in attentional differences) and testing in a sleep-deprived state, must also be excluded and controlled for. As described in the target article, while some earlier studies did not adequately control for this, many recent studies have effectively done so.

Several careful explications of the detrimental effects of total sleep deprivation have been carried out which circumvent the rote arguments around sleep deprivation. For example, several groups have investigated, in a thorough and systematic manner, how sleep deprivation interferes with memory consolidation (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). In these investigations, subjects first trained on the task (day 1), and across the following evening were deprived of sleep. However, rather than being retested the following morning in a sleep-deprived state (day 2), subjects were instead allowed either one or two subsequent nights of recovery sleep; thus being retested on day 3 or day 4 in a fully alert state. Results demonstrate that following first-night sleep deprivation, subjects still showed no significant improvement on the task at the later retest many days later, despite being evaluated in a fully recuperated state following ample recovery sleep (Fischer et al. 2002; Maquet et al. 2003; Stickgold et al. 2000a). It is not then possible to dismiss these results on the grounds of fatigue, deficits in basic attention, or stress. Instead, the conclusion that sleep, and specifically sleep in the first 24 hours after training, is crucial to the enhancement of procedural motor and visual skills becomes self-evident.

**Groeger & Dijk** provide several important issues for consideration. First, they remind us about the concern regarding interactions between sleep-dependent learning and where across the day or night that sleep arrives in the



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circadian cycle. This is a relatively uninvestigated factor in studies of sleep-dependent memory process, and I agree that it should receive greater attention. Some data are relevant to this issue. For example, using a sleep-dependent motor skill task, Fischer et al. (2002) have demonstrated that nocturnal sleep triggers delayed improvements in task performance, as previously reported (Walker et al. 2002). In addition, they also reversed subjects' sleep phase, and had participants sleep during the day instead of at night. Despite sleeping at this reversed circadian phase, subjects expressed a near-identical amount of improvement across the sleep period during the day. Thus, improvement critically depended on sleep itself, rather than on where sleep occurred in the circadian cycle. Yet this is not a thorough examination of a completely desynchronized circadian phase, and it would be interesting to test the hypothesis that sleep at one particular time of the night (or day) is more efficacious for learning than another.

Further, **Groeger & Dijk** also note the possibility that simple sleep completion, rather than a specific sleep stage, may be a contributing factor to overnight learning. Interestingly, on a visual skill task that has been shown to correlate with the combined product of SWS early and REM sleep late (Stickgold et al. 2000b), the authors also reported evidence to suggest that subjects who slept less than 6 hours would potentially show no overnight improvement. This would lend support to the theory of Groeger & Dijk that sleep completion may not have been achieved at 6 hours, thus preventing the development of delayed learning. However, it has also been reported that short daytime sleep epochs of 90 minutes are sufficient to trigger delayed improvement on this task, a time period that would represent a curtailed sleep amount in the context of normal overnight durations, presumably being less supportive of a sleep completion theory. A recent study of avoidance learning in rats has also suggested that physiological sleep phenomena (in this case PGO waves), rather than sleep completion, or even the behavioral state of sleep itself, are the true causal trigger of this form of sleep-dependent learning (Datta et al. 2004). In summary, the idea of sleep completion is an interesting one but appears to require considerably more supportive evidence.

## R8. Sleep abnormalities and memory

**Foster & Wilson**, **Piggott & Perry**, and **Schredl** all raise the important issue of testing this model using clinical cohorts with sleep abnormalities, and also to evaluate the relationship between sleep and memory across the life span, since both these factors change as a consequence.

We have begun testing this memory model using a sleep-dependent motor skill task in schizophrenic patients (Stickgold et al. 2003), a disease with known sleep abnormalities expressing both insomnia and especially disrupted NREM sleep (Monti & Monti 2004). In a recent collaboration, Dara Manoach and colleagues trained schizophrenic patients and age match control subjects on a motor skill task and retested them following a night of sleep (Stickgold et al. 2003). As predicted by this model, across initial acquisition during training (claimed not to rely on sleep), schizophrenic subjects showed near-identical amounts of practice-dependent improvement on the task relative to age-matched controls. However, a clear dissociation became evident at retesting following a night of sleep. Control subjects showed normal overnight improvement on the task, yet schizophrenic subjects showed a complete absence of sleep-dependent learning. Indeed, even if schizophrenic subjects were allowed additional retest trials to display overnight learning, no such improvement could be expressed. Note that if the overnight retest session had not been conducted, one might be deceived into thinking that "procedural motor skill memory" is intact in schizophrenics. But clearly this is not the case, with an obvious impairment in delayed sleep-dependent learning. Therefore, similar encompassing studies testing both practice-dependent learning, and delayed overnight sleep-dependent learning must be carried out across the host of clinical disorders expressing sleep abnormalities, before any broad conclusions about sleep and memory processing are made.

An alternative way to test the model, albeit less directly, is to make predictions about sleep based on the intensity of prior learning. For example, if Stage 2 NREM, or specifically sleep spindles, are essential for sleep-dependent motor skill learning, then increased daytime motor learning should subsequently modify these sleep phenomena. Early evidence is also supportive of the model. As described above (see discussion of **Porte** and **Finelli & Sejnowski**), Fogel and colleagues (Fogel et al. 2001) have shown that intense motor skill learning in humans induces a significant increase in the number of sleep spindles across the proceeding night, relative to a night of sleep without prior motor skill learning.

Additional support for this argument comes from literature focusing on ontogenesis and development. Young human infants begin learning to coordinate their limbs and digits in skilled sequential programs around 12 months of age (Frankenburg & Dodds 1992). Therefore, if Stage 2 NREM sleep is important for consolidating these experiences, then Stage 2 NREM amounts should be correspondingly high at these times. Indeed, this is the case – while SWS and REM sleep show a continuing decrease across the first 2 years of life, Stage 2 NREM shows a very different profile. Instead, Stage 2 NREM increases and peaks at this 12-month mark (Louis et al. 1997), precisely at the time of intensive motor skill learning. These data are suggestive of a learning-related, homeostatic Stage 2 NREM sleep response to the ongoing intensity of motor skill learning.

Thus, with careful consideration and experimental design, together with instructive trends in the literature, support for sleep-dependent memory processing is evident in clinical and experimental data.

## R9. Conclusions

From both the target article and the associated commentaries, the question appears to be not *whether* sleep mediates specific forms of memory consolidation, but instead, *how* it does so. Our challenge will be, first, to uncover the mechanisms of brain plasticity that underlie both wake/time-dependent stabilization and sleep-dependent enhancement; and second, to expand our understanding of sleep's role in the constellation of different processing stages which are critical for efficient memory development. Work across the neurosciences will be necessary to answer these questions, but with the current rate of growth, the


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next decade should provide important advances in our understanding of this critical function of sleep.

Finally, with regard to memory processing and the terminology we choose, I would be happy to embrace a new vernacular for the ever-increasing dissociable stages of memory formation – be it an expansion of the terms put forward here, or even a reconstitution of the terms. Indeed, this paper was written, in part, to demonstrate the current restrictive nature of the term *consolidation*. Even the refined theory presented here is undoubtedly oversimplistic, and the true spectrum of different memory stages will, I'm sure, be amplified many times. I look forward to the community entering into continued and constructive discussion regarding the creation and use of new terms, defined by experimental data, with the hope of developing an expanded vocabulary for memory, agreed by consensus. This can only help further clarify, in more exacting terms, the factors that influence memory development, be they practice, time, wake, or sleep.

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**Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.**

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