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Article *in* AIMS Journal · September 2014

DOI: 10.3934/Neuroscience.2014.2.150

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Manuscript submitted to: Volume 1, Issue 2, 150-155.

AIMS Neuroscience DOI:10.3934/Neuroscience.2014.2.150

Received date 17 July 2014, Accepted date 8 August 2014, Published date 16 September 2014

Commentary

Neural Plasticity and Learning: The Consequences of Sleep

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1. Introduction

Originally likened to a wax tablet by Plato and Aristotle [1], memory has been the muse of philosophers and scientists alike. The discovery of the synapse separating individual neurons by early neuroscientists at the turn of the 20th century, and the subsequent proposal that increased activity at these synapses strengthens the connection between neurons [2] were pivotal ideas for expanding our understanding of memory beyond a philosophical concept or observed behavior to a complex process located in the brain. Today, we know that synaptic plasticity is important for memory formation, but there is still much to learn about how memory is formed at the neural level. As Cadonic and Albensi [3] point out, neural oscillations and receptors implicated in brain plasticity may hold the key to unlocking the mystery of how we form memories. Another essential player in this relationship, increasingly receiving support for its role in various memory processes, is sleep.

The ability to form new memories relies on synaptic plasticity, whereby high-frequency activation of a neural pathway increases the strength of later transmission across the affected synapses, a process termed long term potentiation (LTP) [4,5]. Amino-acid receptors have been implicated in the process of LTP, including the N-methyl-D-aspartate (NMDA) receptor and the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. During LTP, the NMDA receptor is first activated when both the Mg^{2+} blocking its channel is removed by depolarization, and co-agonists glutamate and glycine are bound to its receptors [5,6]. This allows Ca^{2+} to flow into the cell, which initiates a cascade of events, including the activation of synaptic proteins and the phosphorylation and transfer of AMPA receptors into the synapse, culminating in the strengthening of excitatory postsynaptic currents [7]. LTP consists of two phases: the initial phase may last for hours, while the longer maintenance phase lasts for weeks [8]. Many studies connect LTP to the formation of new memories. For instance, an increase in the phosphorylation and number of AMPA receptors at the synapse has been found for LTP established via high-frequency stimulation *in vitro,* as well as during inhibitory avoidance learning in rats [9]. Blocking LTP has also been

shown to block new learning [10].

Additionally, glutamatergic receptors like the NMDA receptor are important for the generation of neural oscillations, which have also been connected to memory formation. The rhythmic activity produced by the brain can be measured by electrophysiological measures such as the electroencephalogram (EEG), which has been used to delineate several frequency bands implicated in memory processes, including theta (4–7 Hz), alpha (7–14 Hz), beta (15–30 Hz), and gamma (30–100 Hz) frequencies [11,12]. Previous studies have found that NMDA antagonists block NMDA function and dramatically reduce electrically stimulated oscillations in the 4–9 Hz range [13]. Further, removal of the NMDA receptor in genetically altered mice decreases the power of theta and increases the power of gamma oscillations measured in the hippocampus compared to controls. This alteration negatively impacts spatial working-memory of these mice during a maze-learning task [14], which is in line with the proposal that such oscillations underlie varying types of memory formation and may represent transfer of information between brain regions [15]. In humans, changes in alpha, beta, gamma, and theta power are associated with memory for previously studied words [16], with encoding and retrieval strategies playing a role in the direction of such relationships [12].

While the review by Cadonic and Albensi [3] nicely outlines this relationship between glutamatergic receptors and oscillatory activity, pointing toward an important and fruitful area for future research on memory formation, further information may be provided by including sleep in this discussion, especially for the maintenance of already initiated LTP. Sleep is characterized by the alternation of dynamic stages, including non-rapid eye movement sleep (NREM), composed of stages 1, 2, and 3/4 or slow wave sleep (SWS), and rapid eye movement sleep (REM), each of which can be distinguished by unique physiological, chemical, and electrical properties [17,18]. Most important for the discussion here, NREM sleep, and particularly SWS, is characterized by slow oscillatory EEG patterns in the 0.5–4 Hz range, representing the alternation between up states (i.e., neural activity) and down states (i.e., neural silence), and punctuated by high-frequency bursts known as sleep spindles (12–15 Hz) in the cortex. These spindles are temporally correlated with sharp-wave ripples (150–250 Hz) in the hippocampus [19]. Conversely, REM sleep is characterized by theta EEG activity, which is synchronized with gamma oscillations in the hippocampus [18,20].

One of the most substantiated functions of sleep is its role in brain plasticity supporting both declarative and non-declarative memory processing [19]. The purported mechanism by which sleep has such a ubiquitous effect on memory is the reactivation and consolidation of recently potentiated synapses [21,22]. The Synaptic Re-entry Reinforcement hypothesis [21,22,23] proposes that the longevity of brain plasticity requires a reactivation of NMDA receptors following the initial learning event. Indeed, without proper synaptic stimulation and protein synthesis, LTP does not last beyond the several hours of its initial phase [24,25]. Thus, following the initiation of LTP during a learning event, potentiated synapses require reactivation to maintain synaptic plasticity. Sleep offers an optimum context for such reactivation to occur, given that activation of glutamate receptors and generation of neural oscillations are hallmarks of sleep processes [19].

Evidence for the reactivation of glutamatergic receptor mechanisms at potentiated synapses during sleep is abundant. Following monocular deprivation learning, whereby one eye is occluded to prevent input of visual information, neural activity becomes biased toward the region of visual cortex corresponding to the non-deprived eye, and this is further enhanced by a period of sleep. This effect is promoted by reactivation of potentiated pathways during sleep, as blocking NMDA receptors or the synthesis of related downstream proteins during a post-learning sleep period negates the

consolidation of this plasticity. Further, phosphorylation of AMPA receptors is found only in animals allowed to sleep after monocular deprivation [22]. In humans, the blockade of NMDA or AMPA receptors during an eight-hour period of nocturnal, post-learning sleep likewise abolishes typical sleep-dependent improvements in visual discrimination learning [21]. Moreover, sleep deprivation, which is known to impair learning, has been shown to negatively alter glutamate receptor activation and protein cascades necessary for LTP [19,26]. This work highlights the importance of sleep for glutamatergic receptor signaling that maintains plasticity initiated during a waking period, without which learning would be impeded.

As others have pointed out, the oscillatory activity that occurs during sleep is similar to that supporting induction of LTP [19]. This may make sleep-related oscillations ideal for the reactivation of potentiated synapses. NREM sleep in particular has been the focus of many studies on this matter [27,28,29]. Indeed, some studies have found that under anesthesia or during waking, synapses previously strengthened by LTP are more likely to generate slow oscillatory up states and spindle activity [30,31]. Further, there is a reciprocal relationship between spindle activity and glutamatergic receptors, such that NMDA inputs mediate spindle activity [13], and stimulation of spindle activity in the cortex influences NMDA receptors and Ca^{2+}, leading to the induction of LTP [29]. Consistently, neural electrical stimulation during *in vitro* imitations of the electrophysiological states that characterize SWS, including the combination of up states and down states, facilitates LTP and is blocked by NMDA or AMPA antagonists [28]. *In vivo* applications of slow oscillatory activity (0.75 Hz) during NREM sleep following the learning of word-pairs not only increases SWS, slow oscillatory power, and slow spindle power, but also results in better memory for the learned word-pairs compared to a control condition. Such effects are specific to slow oscillations, as theta frequency stimulation does not produce these results [27]. This evidence suggests a close relationship between the electrical activity of NREM sleep and activation of glutamate receptors that contribute to learning, providing evidence for the role of NREM sleep in reactivation and maintenance of LTP.

REM sleep is also implicated in LTP reprocessing. During REM sleep, but not NREM sleep, proteins necessary for the long-term maintenance of already established LTP, such as cAMP (cyclic adenosine monophosphate) and CREB (cAMP-response element binding protein), are activated at higher levels compared to a period of wakefulness, a process not found in mice genetically altered to lack memory consolidation abilities [19,32]. Antagonists acting on specific subunits of NMDA receptors also increase gamma activity during REM sleep [33]. This finding is interesting given that theta and gamma oscillations, which are synchronized within regions of the hippocampus during REM sleep with periodic bursts of synchrony across areas, are proposed to play a role in memory processing and transfer during sleep [20]. Theta and gamma oscillations are also temporally associated between hemispheres during REM, which may be particularly important for neural processes given that recovery sleep following REM deprivation produces a rebound and intensification of gamma synchronization between the left and right frontopolar and dorsolateral regions of the frontal lobe [34]. Importantly, stimulation in the gamma range across the corpus callosum initiates a short-lived potentiation that is blocked with NMDA antagonists, implicating this oscillatory connection between hemispheres during REM sleep as another mechanism for the sleep-associated maintenance of plasticity in neural circuits [34,35].

As some of the most interesting evidence for neuronal replay during sleep, hippocampal place cells that were activated during spatial learning during a waking period are sequentially reactivated

on a compressed timescale during subsequent NREM and on a timescale comparable to learning during subsequent REM [36,37]. Important to the discussion here, replay is associated with sharp wave ripples in the hippocampus during NREM sleep, and theta activity during REM sleep. Given that these electrical markers of sleep have been correlated with memory improvements [38,39], such replay is proposed to reflect a mechanism of memory consolidation through an exchange in communication between the hippocampus and cortex [18,40].

It is important to note that another hypothesis regarding sleep and neural plasticity, the Synaptic Homeostasis Hypothesis [41,42], proposes that sleep generally downscales the potentiation of synapses that has accumulated over a period wakefulness, thus maintaining neural stability [42]. This hypothesis puts particular emphasis on SWS and slow oscillations, which are seen to increase after waking, and decrease after sleep [42]. While seemingly at odds with the studies discussed thus far, which show that sleep processes help maintain LTP, others have suggested that synaptic downscaling and maintenance may both occur during SWS, depending on how the plasticity relates to different types of learning [22], and how it may develop in different neural pathways that differ in their requirements for plasticity [28].

As Cadonic and Albensi [3] point out, abnormal NMDA receptor signaling also likely plays a role in pathology, such that hypo- and hyperactivation has been associated with Schizophrenia and Alzheimer's disease, respectively. Not surprisingly, evidence additionally indicates oscillatory activity, and sleep, in the etiology of such diseases. Wamsley and colleagues [43] have demonstrated that Schizophrenia patients display a reduction in the number and density of sleep spindles during a period of sleep following motor task learning, which is associated with a reduction in motor performance following sleep compared to controls. High-frequency (> 20 Hz) oscillatory power is also increased during sleep in Schizophrenic and depressed patients compared to healthy individuals [44]. While these studies do not clarify exact causal relationships, they reaffirm the role of sleep in brain plasticity and cognitive functioning, and may provide clues to developing treatments.

Ample research points toward sleep as a crucial contributor to neural plasticity and learning. The dynamic neurophysiology of sleep provides an optimum milieu for the reactivation of recently potentiated synapses and transfer of information to cortical stores, with alterations of this environment linked to pathology. Given the foregoing discussion, Cadonic and Albensi [3] are accurate to champion the further investigation of plasticity-related receptors and oscillations in future memory research, but the addition of sleep to this endeavor will greatly expand the progress we can make to ultimately understanding how we remember and learn.

Conflict of Interest

All the authors declare to have no conflict of interest.

References

1. Roediger HL. (1980) Memory metaphors in cognitive psychology. *Mem Cogn* 8: 231-246.
2. Hebb DO. (1949) *The organization of behaviour.* New York: Wiley.
3. Cadonic C, Albensi BC. (2014) Oscillations and NMDA receptors: Their interplay create memories. *AIMS Neurosci* 1: 52-64.
4. Bliss TVP, Lomo T. (1973) Long-lasting potentiation of synaptic transmission in dentate area of

anesthetized rabbit following stimulation of perforant path. *J Physiol Lond* 232: 331-356.
5. Bliss TVP, Collingridge GL. (1993) A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature* 361: 31-39.
6. Dingledine R, Borges K, Bowie D, et al. (1999) The glutamate receptor ion channels. *Pharmacol Rev* 51: 7-61.
7. Lisman J, Yasuda R, Raghavachari S. (2012) Mechanisms of CaMKII action in long-term potentiation. *Nature Rev Neurosci* 13: 169-181.
8. Lynch MA. (2004) Long-term potentiation and memory. *Physiol Rev* 84: 87-136.
9. Whitlock JR, Heynen AJ, Shuler MG, et al. (2006) Learning induces long-term potentiation in the hippocampus. *Science* 313: 1093-1097.
10. Morris RG, Anderson E, Lynch GS, et al. (1986) Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. *Nature* 319: 774-776.
11. Klimesch W. (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Res Rev* 29: 169-195.
12. Hanslmayr S, Staudigl T. (2014) How brain oscillations form memories—A processing based perspective on oscillatory subsequent memory effects. *NeuroImage* 85: 648-655.
13. Jacobsen RB, Ulrich D, Huguenard JR. (2001) GABA(B) and NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. *J Neurophysiol* 86: 1365-1375.
14. Korotkova T, Fuchs EC, Ponomarenko A, et al. (2010) NMDA receptor ablation on parvalbumin-positive interneurons impairs hippocampal synchrony, spatial representations, and working memory. *Neuron* 68: 557-569.
15. Klimesch W. (1996) Memory processes, brain oscillations and EEG synchronization. *Int J Psychophysiol* 24: 61-100.
16. Hanslmayr S, Spitzer B, Bauml KH. (2009) Brain oscillations dissociate between semantic and nonsemantic encoding of episodic memories. *Cereb Cortex* 19: 1631-1640.
17. Rechtschaffen A, Kales A. (1968) *A manual of standardized terminology, techniques and scoring system for sleep stages in human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, University of California.
18. Stickgold R, Hobson JA, Fosse R, et al. (2001) Sleep, learning, and dreams: Off-line memory reprocessing. *Science* 294: 1052-1057.
19. Abel T, Havekes R, Saletin JM, et al. (2013) Sleep, plasticity and memory from molecules to whole-brain networks. *Curr Biol* 23: R774-R788.
20. Montgomery SM, Sirota A, Buzsaki G. (2008) Theta and gamma coordination of hippocampal networks during waking and rapid eye movement sleep. *J Neurosci* 28: 6731-6741.
21. Gais S, Rasch B, Wagner U, et al. (2008) Visual-procedural memory consolidation during sleep blocked by glutamatergic receptor antagonists. *J Neurosci* 28: 5513-5518.
22. Aton SJ, Seibt J, Dumoulin M, et al. (2009) Mechanisms of sleep-dependent consolidation of cortical plasticity. *Neuron* 61: 454-466.
23. Shimizu E, Tang YP, Rampon C, et al. (2000) NMDA receptor-dependent synaptic reinforcement as a crucial process for memory consolidation. *Science* 290: 1170-1174.
24. Fonseca R, Nagerl UV, Bonhoeffer T. (2006) Neuronal activity determines the protein synthesis dependence of long-term potentiation. *Nature Neuro* 9: 478-480.
25. Frey U, Morris RGM. (1998) Synaptic tagging: Implications for late maintenance of hippocampal long-term potentiation. *TINS* 21: 181-188.

26. Kopp C, Longordo F, Nicholson JR, et al. (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. *J Neurosci* 26: 12456-12465.
27. Marshall L, Helgadottir H, Molle M, et al. (2006) Boosting slow oscillations during sleep potentiates memory. *Nature* 444: 610-613.
28. Chauvette S, Seigneur J, Timofeev I. (2012) Sleep oscillations in the thalamocortical system induces long-term neuronal plasticity. *Neuron* 75: 1105-1113.
29. Rosanova M, Ulrich D. (2005) Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *J Neurosci* 25: 9398-9405.
30. Timofeev I, Grenier F, Bazhenov M, et al. (2000) Origin of slow cortical oscillations in deafferented cortical slabs. *Cereb Cortex* 10: 1185-1199.
31. Werk CM, Harbour VL, Chapman CA. (2005) Induction of long-term potentiation leads to increased reliability of evoked neocortical spindles *in vivo*. *Neuroscience* 131: 793-800.
32. Luo J, Phan TX, Yang Y, et al. (2013) Increases in camp, MAPK activity, and CREB phosphorylation during REM sleep: Implications for REM sleep and memory consolidation. *J Neurosci* 33: 6460-6468.
33. Kocsis B. (2012) State-dependent increase of cortical gamma activity during REM sleep after selective blockade of NR2B subunit containing NMDA receptors. *Sleep* 35: 1011-1016.
34. Corsi-Cabrera M, Sifuentes-Ortega R, Rosales-Lagarde A, et al. (2014) Enhanced synchronization of gamma activity between frontal lobes during REM sleep as a function of REM sleep deprivation in man. *Exp Brain Res* 232: 1497-1508.
35. Cissé Y, Crochet S, Timofeev I, et al. (2004) Synaptic enhancement induced through callosal pathways in cat association cortex. *J Neurphysiol* 92: 3221-3232
36. Lee AK, Wilson MA. (2002) Memory of sequential experience in the hippocampus during slow wave sleep. *Neuron* 36: 1183-1194.
37. Louie K, Wilson M. (2001) Temporally structured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron* 29: 145-156.
38. Eschenko O, Ramadan W, Mölle M, et al. (2008) Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. *Learn Mem* 15: 222-228.
39. Nishida M, Pearsall J, Buckner RL, et al. (2009) REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb Cortex* 19: 1158-1166.
40. Buzsaki G. (1996) The hippocampo-neocortical dialogue. *Cereb Cortex* 6: 81-92.
41. Tononi G, Cirelli C. (2006) Sleep function and synaptic homeostasis. *Sleep Med Rev* 10: 49-62.
42. Tononi G, Cirelli C. (2014) Sleep and the price of plasticity: From synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* 81: 12-34.
43. Wamsley EJ, Tucker MA, Shinn AK, et al. (2012) Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? *Biol Psychiat* 71: 154-161.
44. Tekell JL, Hoffmann R, Hendrickse W, et al. (2005) High frequency EEG activity during sleep: characteristics in schizophrenia and depression. *Clin EEG Neurosci* 36: 25-35.