Current Biology Dispatches

Memory Processing: Ripples in the Resting Brain

Matthew P. Walker¹ and Edwin M. Robertson^{2,*}

¹Department of Psychology, University of California Berkeley, CA 94720, USA ²Institute of Neuroscience and Psychology, Glasgow, G12 8QB, UK *Correspondence: edwin.robertson@glasgow.ac.uk http://dx.doi.org/10.1016/j.cub.2016.02.028

Recent work has shown that, during sleep, a functional circuit is created amidst a general breakdown in connectivity following fast-frequency bursts of brain activity. The findings question the unconscious nature of deep sleep, and provide an explanation for its contribution to memory processing.

Our minds are constantly processing events from our past [1]. Even during sleep, and perhaps preferentially so, these off-line processes continue, helping to ensure the long-term retention of memories. New findings by Kaplan *et al.* [2], published recently in *Current Biology*, reveal how deep sleep may create the brain network necessary for such memory consolidation.

Non-rapid eye movement (NREM) sleep, often considered a dreamless, non-conscious state, is replete with a diverse array of coordinated electrical events. These range from some of the slowest frequency oscillations to some of the fastest. One such oscillation is the fast-frequency (100-200 Hz) ripple, lasting approximately 200 milliseconds. Ripples are generated within the hippocampus and coincide with slow oscillations and sleep spindles within the cortex, which together have been linked with memory consolidation. Hippocampal ripples increase in number after intensive learning, and this increase predicts the success of memory consolidation, measured by post-sleep retention. Moreover, disrupting ripples will prevent consolidation and result in forgetting (for example [3,4]). Identifying the large-scale brain networks affected by hippocampal ripple events may therefore bring us a step closer to understanding how memories are modified off-line, and with it, insights into the nature of information processing during deep sleep.

Using a technically sophisticated design, Kaplan *et al.* [2] combined functional magnetic resonance imaging (fMRI) with the physiological recording of ripples from electrodes within the hippocampus. For the monkeys to tolerate the confines of a functional imaging scanner, they were anaesthetized using drugs that have only a negligible affect upon the cerebrovascular response to brain activity. With this design, the authors were able to identify the emergence of large-scale networks following a hippocampal ripple.

Ripples did not give rise to a vast number of functionally connected networks within the brain. Nor were ripples associated with a restricted, local circuit of activity. Instead, ripples evoked a tightly correlated pattern of activity throughout regions of the so-called default mode network (DMN) [2]. The DMN includes areas of the parietal, prefrontal and medial temporal lobe regions (including the hippocampus). One mental ability that engages the DMN is autobiographical memory; both the recollection of past experience (retrospective memory), and the imagining of future events (prospective memory) [5]. It was coupled activity within this DMN that emerged during these ripple bursts, and only during ripples. Other hippocampal events, such as lower frequency sigma or gamma oscillations, had no effect upon the DMN. Thus, ripples were unique in creating a long-ranging functional network, one that is associated with recalling specific episodes from the past, or predicting events in the future.

Earlier work using fMRI has shown that hippocampal ripples are associated with a widespread pattern of activation across almost every area of the cortex [6]. By contrast, the findings of Kaplan *et al.* [2] focused upon the temporally coupled relationship of spontaneous brain activity, which is a measure of functional connectivity, and how this changed across a network following ripple events. Together, these studies establish that ripple events lead to widespread activation of isolated, functionally independent areas of the cerebral cortex while there also emerges a functional pattern of connectivity in a well-described brain network — the DMN.

Human fMRI studies have similarly described a breakdown in the functional connectivity of the brain during deep NREM sleep, shifting into smaller, independent circuits [7]. Furthermore, artificially stimulating the brain during deep NREM sleep using transcranial magnetic stimulation (TMS) results in a wave of excitation that progresses a far smaller distance compared to wakefulness [8]. Although deep NREM sleep may have a general signature of decreased functional connectivity, the work of Kaplan et al. [2] suggests that connectivity may be frequently restored within the DMN during each ripple event (Figure 1).

Assessments of network connectivity during different brain states, such as those by Kaplan et al. [2], may offer new insights into the off-line processing of information. For example, during deep NREM sleep, some brain regions become modularized and independent of one another, relative to wakefulness (Figure 1). This important change in the functionality of networks may explain how memories that interfere and interact over wakefulness are processed independently over sleep [1,9,10]. When two memories are learnt in quick succession, they can interfere with one another. As a result, one of the memories can be prevented from undergoing consolidation across wakefulness [11]. By contrast, both memories are successfully consolidated over sleep [11]. Appreciating that brain networks become more functionally independent of one another during sleep provides a mechanism for understanding



Current Biology Dispatches



Figure 1. Functional connectivity during sleep.

(A) Brain circuits are functionally connected (thick lines) during wakefulness. (B) These become disconnected (thin lines) during deep NREM sleep. (C) However, functional connectivity is restored within a specific circuit, the default mode network (DMN), following a high frequency oscillation, or ripple, generated by the hippocampus.

how the interaction between memory systems is prevented, which allows each individual memory to be consolidated independently.

While a broad decrease in functional connectivity may explain the independent consolidation of memories between memory systems, the re-emergence of a circumscribed functional network described by Kaplan et al. [2] may explain the recognized benefits of sleepdependent consolidation within memory systems. Consolidation leads to the stabilization, enhancement, and reorganization of memories [12]. The replay of neuronal activity from earlier learning occurs during NREM sleep ripples, and those ripples are critical for the stabilization of the memory during sleep [4]. The findings of Kaplan et al. [2] demonstrate that ripples, and presumably the replay that takes place during them, create a functional network of memory processing within areas of the DMN (Figure 1) [2]. Neuronal replay in the hippocampus may therefore drive replay within other parts of the DMN, and with it, the plastic changes underlying memory consolidation.

There are, however, potential problems with this interpretation. Hippocampal replay has been shown to drive replay in the visual cortex, which lies outside the DMN. This sensory region ought not to be functionally connected to the hippocampus during ripples, and therefore not associated with replay events [13]. Whilst the DMN is certainly important for memory processing, such findings make clear that it is not the only circuit that makes a contribution to memory processing, including during ripples. The dialogue between prefrontal cortex and hippocampus is also central to many aspects of sleep-dependent memory processing [14]; yet, there was no functional circuit identified between the hippocampus and prefrontal cortex during ripple events in the study by Kaplan *et al.* [2].

It is possible that the impact of ripples on functional brain connectivity was underestimated in the new study [2]. potentially because of the anaesthetized state of the animals. Alternatively, other oscillatory events during NREM sleep, such as slow waves or sleep spindles (for example [15]), or other sleep stages, such as REM, may create networks that are not part of the DMN, but nevertheless complement its contribution to memory processing. Additionally, restricted local circuit activity may contribute to memory processing. One such example is the shaping of ocular dominance columns within the primary visual cortex of cats that occurs during NREM sleep [16]. Similarly, enhanced performance on a visual discrimination task in humans, thought to depend upon local changes within the visual cortex, also occurs across sleep [17]. Changes in these brain areas are not likely to be driven by hippocampal replay because they are not functionally connected to the hippocampus when a ripple, and the associated replay, occurs. Instead, more local mechanisms may be operating. A similar situation appears to exist within the motor system. The primary motor cortex (M1) may not be functionally connected to the hippocampus when

ripple-related replay occurs. Nonetheless, replay within M1 is linked to motor memory consolidation during sleep [18] (for review [12]). Thus, replay may arise from both the intrinsic properties of local neuronal circuits and from the large-scale network activity associated with a particular region.

The discovery that a large-scale functional circuit emerges following ripples [2] may also help to refine our understanding of conscious states. Deep NREM sleep, during which ripples prevail, is thought to reflect a state of unconsciousness for at least two reasons. First, all species showing bi-hemispheric sleep have an attenuated response to the outside world during NREM sleep; a potential result of diminished functional connectivity within the cortex. Second is the presumed absence of information processing due to sensory cues from the outside world not being processed. However, sensory cues presented during NREM sleep reliably enhance the reactivation of memories, improving their consolidation and subsequent retention [19]. The emergence of a rippledependent functional circuit (DMN) associated with memory, as revealed by Kaplan et al. [2], further supports this alternative view of NREM sleep as a time of ongoing information processing. Deep sleep may not, therefore, be the completely unconscious state we once imagined. Instead, it may be better situated within a more dynamic space of consciousness, at a location where internally stored information processing dominates, with the opposite being true of wakefulness. Where REM sleep - the dream state - resides within such a space remains an unresolved question, one that similar such studies may, however, soon put to rest.

REFERENCES

- Robertson, E.M. (2009). From creation to consolidation: a novel framework for memory processing. PLoS Biol. 7, e19.
- Kaplan, R., Adhikari, M.H., Hindriks, R., Mantini, D., Murayama, Y., Logothetis, N.K., and Deco, G. (2016). Hippocampal sharpwave ripples influence selective activation of the default mode network. Curr. Biol. 26, 686–691.
- O'Neill, J., Senior, T.J., Allen, K., Huxter, J.R., and Csicsvari, J. (2008). Reactivation of experience-dependent cell assembly patterns in the hippocampus. Nat. Neurosci. 11, 209–215.

Current Biology Dispatches

- Girardeau, G., Benchenane, K., Wiener, S.I., Buzs ki, G., and Zugaro, M.B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. Nat. Neurosci. *12*, 1222– 1223.
- Schacter, D.L., Addis, D.R., Hassabis, D., Martin, V.C., Spreng, R.N., and Szpunar, K.K. (2012). The future of memory: remembering, imagining, and the brain. Neuron 76, 677–694.
- Logothetis, N.K., Eschenko, O., Murayama, Y., Augath, M., Steudel, T., Evrard, H.C., Besserve, M., and Oeltermann, A. (2012). Hippocampal-cortical interaction during periods of subcortical silence. Nature 491, 547–553.
- Boly, M., Perlbarg, V., Marrelec, G., Schabus, M., Laureys, S., Doyon, J., Pelegrini-Issac, M., Maquet, P., and Benali, H. (2012). Hierarchical clustering of brain activity during human nonrapid eye movement sleep. Proc. Natl. Acad. Sci. USA 109, 5856–5861.
- 8. Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., and Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. Science 309, 2228–2232.

- Brown, R.M., and Robertson, E.M. (2007). Off-line processing: reciprocal interactions between declarative and procedural memories. J. Neurosci. 27, 10468–10475.
- Brown, R.M., and Robertson, E.M. (2007). Inducing motor skill improvements with a declarative task. Nat. Neurosci. 10, 148–149.
- Mosha, N., and Robertson, E.M. (2016). Unstable memories create a high-level representation that enables learning transfer. Curr. Biol. 26, 100–105.
- Genzel, L., and Robertson, E.M. (2015). To replay, perchance to consolidate. PLoS Biol. 13, e1002285.
- Ji, D., and Wilson, M.A. (2007). Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat. Neurosci. 10, 100–107.
- Siapas, A.G., and Wilson, M.A. (1998). Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. Neuron 21, 1123– 1128.

- Spoormaker, V.I., Czisch, M., Maquet, P., and Jancke, L. (2011). Large-scale functional brain networks in human non-rapid eye movement sleep: insights from combined electroencephalographic/functional magnetic resonance imaging studies. Phil. Trans. R. Soc. Lond. A 369, 3708–3729.
- Jha, S.K., Jones, B.E., Coleman, T., Steinmetz, N., Law, C.T., Griffin, G., Hawk, J., Dabbish, N., Kalatsky, V.A., and Frank, M.G. (2005). Sleep-dependent plasticity requires cortical activity. J. Neurosci. 25, 9266–9274.
- Walker, M.P., Stickgold, R., Jolesz, F.A., and Yoo, S.S. (2005). The functional anatomy of sleep-dependent visual skill learning. Cerebr. Cortex 15, 1666–1675.
- Ramanathan, D.S., Gulati, T., and Ganguly, K. (2015). Sleep-dependent reactivation of ensembles in motor cortex oromotes skill consolidation. PLoS Biol. 13, e1002263.
- Rasch, B., Buchel, C., Gais, S., and Born, J. (2007). Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 315, 1426–1429.

Translational Control: Selective Upregulation of ECM Components Drives Tumour Growth

Anne E. Willis

MRC Toxicology Unit, Lancaster Rd, Leicester LE1 9HN, UK Correspondence: aew5@leicester.ac.uk http://dx.doi.org/10.1016/j.cub.2016.01.053

A new mechanistic link has been identified between the expression of initiator methionine tRNA and cancer progression, whereby elevated levels of this tRNA specifically drive synthesis of secretome components, resulting in a type II collagen-rich matrix that promotes tumour progression.

Protein synthesis from mRNAs is a highly regulated three-stage process composed of initiation, elongation and termination steps. Global control of mRNA translation makes a considerable contribution to the overall regulation of gene expression [1]. Current data suggest that the initiation stage involving the recruitment of the small ribosomal subunit to the mRNA a process coordinated by the eukaryotic initiation factor (eIF) 4F complex - is the rate-limiting step of translation [2] (Figure 1). Protein synthesis is controlled by regulating the formation of both the eIF4F complex and the ternary complex, which comprises eIF2, GTP and the initiator methionine tRNA (tRNA;^{Met}). Dysregulation of mRNA translation is associated with tumorigenesis and it is

well established that this can occur via increased expression of eIFs [3-5]. More recently, the cellular tRNA composition has also been shown to have dramatic effects on cell growth. For example, it has been demonstrated that increased synthesis of specific proteins, particularly in a tumour cell, is directly related to tRNA content. Thus, tRNAs induced in proliferating cells were shown to have anticodons corresponding to codon usage signatures characteristic of proliferation-related genes [6]. Given the relative abundance of tRNA_i^{Met} [7,8] and the fact that it is necessary for the initiation of the translation of all transcripts (Figures 1 and 2), it could be hypothesised that there would also be message-specific differences in the

requirement for this tRNA, in a similar manner to the requirement of eIFs. An exciting new study published in this issue of *Current Biology* from Clarke *et al.* [9] has now shown that upregulation of tRNA^{Met} promotes tumour growth and angiogenesis. This is due to increased synthesis of subsets of mRNAs that encode part of the secretome and are required for the generation of the extracellular matrix (ECM), including specific types of collagen.

Clark *et al.* [9] demonstrated that immortalised human mammary carcinomaassociated fibroblasts (CAFs), which are known to promote tumour cell growth and angiogenesis, had significantly increased expression of both tRNA^{Met} and tRNA^{IIe}. To investigate this effect further, mouse

