



Sleep homeostasis, habits and habituation

Vladyslav V Vyazovskiy^{1,2}, Mark E Walton³, Stuart N Peirson²
 and David M Bannerman^{2,3}

The importance of sleep for behavioural performance during waking is long-established, but the underlying reasons and mechanisms remain elusive. Waking and sleep are associated with changes in the levels of GluA1 AMPAR subunit in synaptic membranes, while studies using genetically-modified mice have identified an important role for GluA1-dependent synaptic plasticity in a non-associative form of memory that underlies short-term habituation to recently experienced stimuli. Here we posit that sleep may play a role in dishabituation, which restores attentional capacity and maximises the readiness of the animal for learning and goal-directed behaviour during subsequent wakefulness. Furthermore we suggest that sleep disturbance may fundamentally change the nature of behaviour, making it more model-free and habitual as a result of reduced attentional capacity.

Addresses

¹Department of Physiology, Anatomy and Genetics, University of Oxford, Parks Road, Oxford, OX1 3PT, United Kingdom

²Sleep and Circadian Neuroscience Institute, Oxford Molecular Pathology Institute, Sir William Dunn School of Pathology, South Parks Road, Oxford OX1 3RE, United Kingdom

³Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, United Kingdom

Corresponding author: Vyazovskiy, Vladyslav V
 (vladyslav.vyazovskiy@dpag.ox.ac.uk)

Current Opinion in Neurobiology 2017, **44**:202–211

This review comes from a themed issue on **Neurobiology of sleep**

Edited by **Yang Dan** and **Thomas Kilduff**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 30th May 2017

<http://dx.doi.org/10.1016/j.conb.2017.05.002>

0959-4388/© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Over one hundred years of research has suggested that sleep and circadian rhythms play an important role in learning and memory. Several hypotheses have been put forward to explain how sleep benefits learning, and why disrupted or mistimed sleep and sleep deprivation might affect cognitive function [1,2]. It has been proposed that sleep facilitates incorporation of memory traces into permanent storage [3], benefits learning through global synaptic down-selection [4], or both [5]. In recent years substantial progress has been made with respect to

understanding the neurobiological mechanisms underlying learning and memory, in particular with regard to the role of glutamate receptors and synaptic plasticity. Concomitantly, the molecular and synaptic changes that occur during wake, sleep and sleep deprivation have been investigated in detail. Given these recent advances, and given the central importance of glutamate receptors and synaptic plasticity in the relationship between sleep and memory, a view shared by various theories [1,4,6], our aim here is to re-evaluate the relationship between sleep and memory in the light of these recent findings.

Homeostatic and circadian regulation of sleep

The neural processes associated with sensory processing, motor functions and learning involve intense synaptic and spiking activity, which are computationally and metabolically demanding [7,8]. Not surprisingly, staying awake for extended periods of time leads to substantial wake-dependent changes in cortical and subcortical network activity [9[•],10[•],11[•]], which likely contribute to well-known behavioural deficits after sleep deprivation or disruption [12–14]. It has therefore been suggested that prolonged wakefulness needs to be off-set by periods of recovery during which metabolic balance and network function must be restored [13,15]. Such opposing effects of waking and sleep on brain activity and behaviour may be described conceptually within a framework of homeostatic regulation [16].

Sleep homeostasis is a ubiquitous phenomenon found in many animal species, suggesting that it underscores some fundamental, essential function [16,17]. According to this framework, sleep pressure (reflected in the dynamics of a hypothetical ‘Process S’) increases as a function of time spent awake and decreases with sleep. Like an hourglass, the levels of Process S indicate the time passed awake or asleep and denote how likely we are to be awake or asleep at any given moment. The best characterized physiological indicator of sleep-wake history is the level of cortical EEG slow-wave activity (SWA, EEG power between 0.5 and 4.0 Hz) during NREM sleep [18,19], reviewed in Ref. [20]. In mammals, sleep SWA is high in early sleep and after sleep deprivation, when sleep pressure is increased physiologically, and decreases progressively to reach low levels in late sleep [21–23]. The dynamics of SWA across the period of sleep have been linked to the levels of synchronisation within cortical networks and neuronal excitability [13,24,25], although the role of subcortical neuromodulation cannot be ruled out [26].

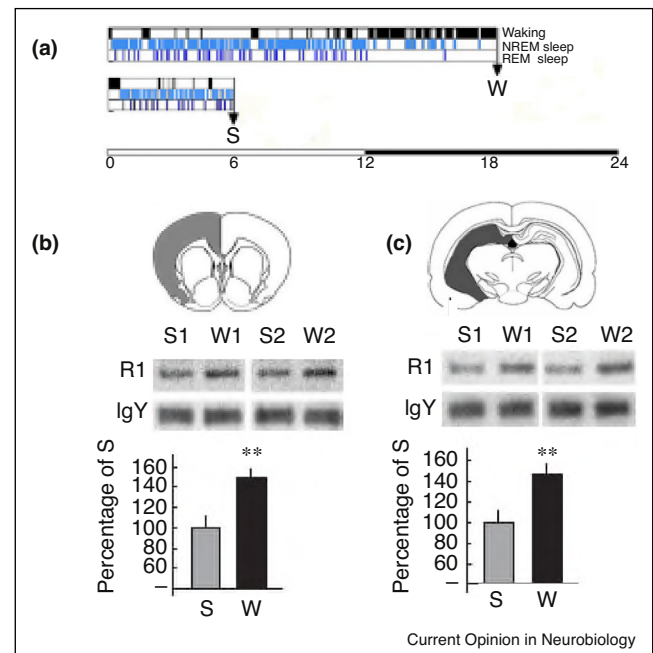
Importantly, sleep homeostasis is not the only process that is involved in the regulation of waking and sleep across the 24-hour day. It is now well established that Process S undergoes a powerful influence from another process—the circadian rhythm (referred to as Process C), which links daily variations in a wide range of physiological variables with the occurrence of waking and sleep [27,28]. This circadian process is the product of the circadian clock—an intracellular mechanism based upon the rhythmic expression and negative feedback of a number of clock genes and their protein products. In mammals, the master circadian pacemaker is located in the hypothalamic suprachiasmatic nuclei (SCN), which regulates peripheral clocks found in cells and tissues throughout the body [29]. According to our current understanding, the homeostatic process interacts with a circadian drive for arousal, which prevents sleep from occurring at inappropriate times and thus benefits waking functions [16]. Although several studies have implicated the circadian system in the regulation of synaptic plasticity, learning and memory [30,31], it is possible that changes in sleep may provide the primary mechanism by which circadian rhythms influence these processes.

Synaptic homeostasis: molecular correlates

Important insights into the mechanisms underlying sleep regulation have been obtained from a series of molecular studies where the effects of waking and sleep on gene expression in the brain have been investigated. These studies showed that several hundred genes were expressed differentially between day and night, or varied between sleep and wake regardless of time of day [32–35]. Importantly, it was revealed that different functional categories of genes in the brain were selectively associated with wakefulness and sleep. Being asleep was associated with differential expression of genes primarily involved in protein synthesis and membrane trafficking. Genes up-regulated after waking included molecules involved in energy homeostasis, a number of transcription factors, clock-related genes, heat-shock proteins, genes related to activity-dependent neural plasticity, and glutamatergic neurotransmission-related genes. These findings suggested that at least some of the well-known cognitive deficits incurred after sleep loss may arise from changes in synaptic machinery, and specifically changes associated with excitatory glutamatergic signalling and synaptic plasticity.

Consistent with this notion, synaptic levels of glutamate receptor subunits, including the GluA1 AMPAR subunit (also known as GluR-A or GluR1, encoded by the *Gria1* gene), exhibit a pronounced daily variation as a function of sleep-wake history [36,37]. For example, it has been shown that if rats were sacrificed after periods of sustained wakefulness or sleep deprivation then GluA1-containing AMPAR levels in synaptoneurosomes in cortex and hippocampus were considerably higher than in a group

Figure 1



GluA1 levels in synaptoneurosomes from the neocortex and the hippocampus are higher after wakefulness as compared to sleep. **(a)** Hypnograms from two individual rats. The white and black bars indicate the light and dark period, respectively. The time of sacrifice is indicated by an arrow (S: after sleep; W: after wakefulness). **(b)** Representative immunoblots (1 and 2 represent two different samples) and quantification of the density of GluA1-containing AMPARs in the neocortex. Values are mean \pm SEM ($n = 9$ rats), W values are expressed as 100% \pm SEM of average S values. IgY was used as loading control. **, $p < 0.01$ (paired t-test). **(c)** Synaptoneurosomes (sn) were prepared from the entire left hippocampus of each rat ($n = 9$, same animals as in **(b)**). Values are mean \pm SEM ($n = 9$ rats/group). **, $p < 0.01$ (paired t-test). Adapted from Ref. [36].

of animals that were sacrificed after periods of sleep (Figure 1). The GluA1 subunit plays an essential role in the trafficking of AMPARs into the post-synaptic membrane and thus supports and maintains synaptic plasticity [38–40], including short-term potentiation (STP) and certain forms of long-term potentiation (LTP) [41–44]. This is consistent with the proposal that wakefulness is associated with a net increase in synaptic strength, as manifested by increased levels of glutamate receptors in brain areas like the hippocampus and cortex [4]. In turn, according to this view, sleep is associated with synaptic renormalisation, manifested as a decrease in GluA1-containing AMPAR levels back down to baseline levels [4]. So what are the behavioural consequences of these diurnal changes in glutamate receptor subunit expression and plasticity at cortical and hippocampal synapses.

Synaptic plasticity and memory

Historically, the relationship between synaptic plasticity and memory has been almost exclusively considered in

terms of encoding associative, long-term memories. NMDAR-dependent long-term potentiation (LTP) is the dominant cellular model of synaptic plasticity in learning and memory, and the idea that LTP-like processes, in brain areas such as the hippocampus, underlie the acquisition and storage of associative long-term memories has predominated [45]. Nevertheless, despite this widespread belief and the general acceptance of a hippocampal LTP/associative memory hypothesis, the evidence in support of this theory is equivocal at best [46–48].

On the other hand, there is increasingly strong evidence that glutamate receptors and synaptic plasticity may underlie a very different kind of memory trace. For example, *Gria1*^{−/−} mice with a global, constitutive knockout of the GluA1 AMPAR subunit, exhibit a robust and selective deficit in a non-associative form of short-term memory that underlies short-term habituation to recently experienced stimuli. In marked contrast, these mice are perfectly able to acquire associative, long-term memory tasks, including the Morris watermaze, just as well as their wild-type littermates [49,50**] (see Box 1, Figure 2). Habituation describes the decline in the tendency to respond or attend to stimuli that have become familiar as a result of prior exposure. Recent studies with *Gria1*^{−/−} mice demonstrate two forms of habituation: a GluA1-dependent, short-term habituation and a GluA1-independent, long-term habituation [50**]. Thus, evidence suggests that GluA1-dependent plasticity underlies the short-lasting sense of familiarity for recently experienced stimuli such that the attention paid to these stimuli is reduced [51].

Synaptic plasticity, sleep and dishabituation

The relevance of these behavioural findings in *Gria1*^{−/−} mice for understanding the functional role of sleep is brought into focus by the diurnal wake-sleep dependent rhythm in the synaptic expression of glutamate receptor subunits, including GluA1 [36,37]. The involvement of GluA1-dependent synaptic plasticity in encoding familiarity for recently experienced stimuli may be reflected in the accumulation of GluA1 subunits in the post-synaptic membranes of hippocampal and cortical neurons during waking experience [40]. Thus, the increase in synaptic GluA1 after prolonged periods of wakefulness may reflect on-going habituation, leading to a reduction in attention. Importantly, this particular kind of GluA1-dependent memory is not permanent, and the sense of familiarity that it supports (and the concomitant reduction in attention) is not lasting. Indeed, we suggest that this sense of familiarity may be diminished after restorative sleep [4]. Thus, an intriguing possibility is that restoration of attentional performance (*i.e.* dishabituation) is the behavioural endpoint of the network renormalisation that occurs during sleep [52], and glutamatergic plasticity plays an important role in this process. It remains to be determined

Box 1 Synaptic plasticity and habituation—studies in *Gria1*^{−/−} mice

Studies using genetically modified mice in which GluA1 has been selectively ablated provide important information on the function of synaptic plasticity of glutamatergic neurotransmission in learning and memory. *Gria1*^{−/−} mice are able to acquire associative, long-term spatial memory tasks, including the Morris watermaze, just as well as their wild-type littermates. There is no impairment in these animals when learning the spatial location of a fixed, hidden escape platform, or when learning which arms of a spatial radial maze task are always associated with food, and which arms are unrewarded (the spatial reference memory version of the task). In marked contrast, *Gria1*^{−/−} mice exhibit a robust and selective deficit in a non-associative form of short-term memory that underlies short-term habituation to recently experienced stimuli (see Figure 2).

For example, when a wild-type mouse is placed in a novel environment it will initially exhibit high levels of exploration and activity which then reduces over time as the environmental cues become familiar (*i.e.* as the animal habituates). *Gria1*^{−/−} mice habituate more slowly to a novel environment and hence their exploration levels remain elevated for much longer and hence they appear hyperactive. Habituation can also be studied by allowing an animal to explore a novel object for a period of time, before then giving the animal a choice between exploring the same (now familiar) object again or exploring a different, novel object. Normally, animals will be less interested in, and pay less attention to, the object that they have already encountered, and so will choose to explore the novel object. This demonstrates that this form of habituation is stimulus-specific (*i.e.* it does not reflect a generalised reduction in attention to all stimuli), and it is a highly adaptive response that frees up attention for more useful, novel experiences. *Gria1*^{−/−} mice fail to habituate to recently presented stimuli like objects and so they keep exploring and paying attention to stimuli that wild-type mice would have already started to ignore. Thus, *Gria1*^{−/−} mice show less preference for the novel object over the familiar object. Similarly, in the spatial domain, whereas wild-type mice will show a preference for the novel arm of a Y-maze (compared to arms that they have recently experienced during a sample trial), *Gria1*^{−/−} mice again fail to exhibit a novelty preference, demonstrating equal levels of exploration for novel and familiar arms, indicating a deficit in habituation to spatial cues.

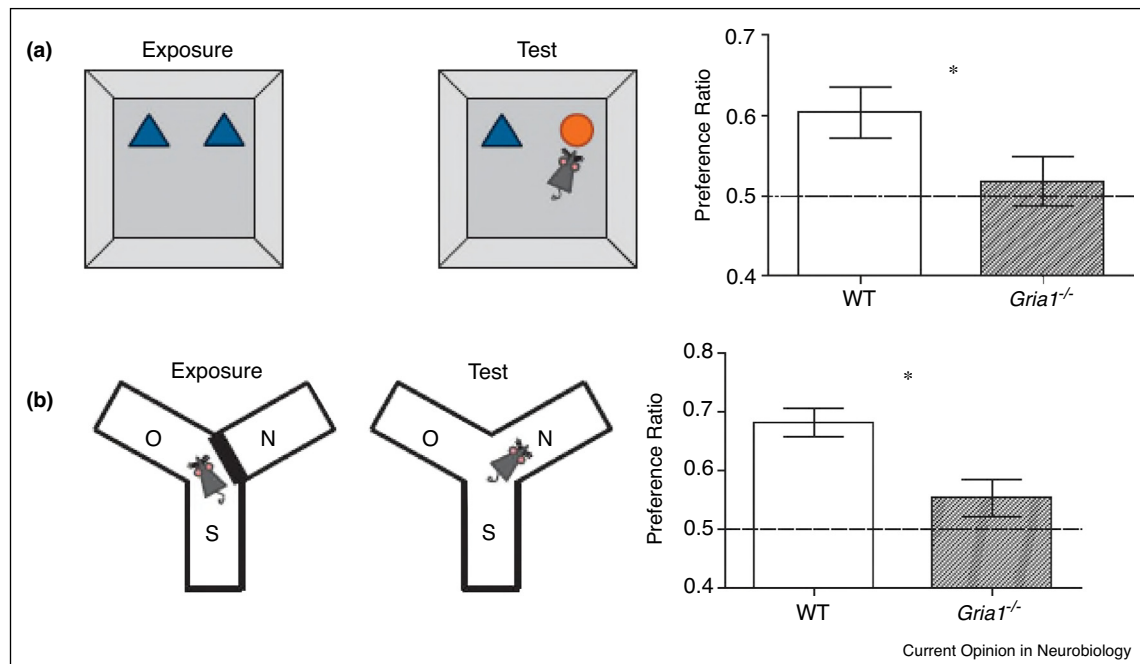
Interestingly, a similar pattern of behavioural results has been seen with mice that lack the GluN2A subunit of the NMDAR (also known as NR2A, encoded by the gene *Grin2a*), at least as far as they have been tested thus far [86]. Notably the GluN2A subunit exhibits similar daily variation with sleep-wake history as the GluA1 subunit [36**].

whether sleep merely passively provides an opportunistic process for dishabituation by providing a period of reduced sensory input, allowing the memory traces underlying short-term familiarity to decay, thus resulting in the restoration of attentional capacity, or whether sleep includes an active process (or processes) that leads to the restoration of attention.

Sleep disturbance and attentional deficits

According to this framework, a failure to engage such dishabituation processes could result in persistently low levels of attentional capacity. It is important to note that GluA1-dependent habituation is stimulus specific and does not result in a generalised reduction in attention to all stimuli (as noted in Box 1). However, according to well-established models of habituation, for example,

Figure 2



Gria1^{-/-} mice display impaired short-term habituation. **(a)** Left: the design of the novel object recognition task. Mice were exposed to two copies of an object for 10 min, and then after a 2-min interval they were allowed to explore a duplicate of the familiar object and a novel object for 5 min. Right: *Gria1*^{-/-} mice display impaired short-term habituation on the novel object recognition test. The times spent exploring the novel object during the test phase are shown as a ratio of the total time spent exploring both objects. The dashed line at 0.5 indicates chance performance. Error bars indicate \pm s.e.m. **(b)** *Gria1*^{-/-} mice display impaired short-term habituation on the spatial novelty preference test. During a 5-min Exposure phase (left panel), mice were allowed to explore two arms of a 3-arm, Perspex Y-maze surrounded by distal extra-maze cues. After a 1-min delay, the mice were returned to the maze for the Test phase (2-min duration), during which they were now able to explore freely all three maze arms, including the previously unvisited (novel) arm (centre panel). Wild-type (WT) mice exhibit a preference for the previously unvisited (Novel) arm over the two familiar arms to which they have previously been exposed (Start and Other). *Gria1*^{-/-} mice did not show a significant preference for the novel arm. Ratio of time spent in the novel versus other arm (\pm s.e.m.). * $p < 0.05$ difference between groups. Adapted from Ref. [51].

Wagner's Sometimes Opponent Process (SOP) model; [53], stimuli are considered to consist of multiple 'elements.' These elements could be considered as the fundamental units that together comprise the various features of a stimulus (*i.e.* together they represent the visual, tactile, auditory, olfactory and taste components of a given stimulus). Different stimuli (particularly in the same stimulus domain) will therefore likely have a proportion of their elements in common. In other words, there will be some overlap in terms of the elements that comprise certain stimuli. In Wagner's SOP model, habituation is considered to occur at the level of individual elements (although it also seems likely that habituation may occur at various different levels of stimulus organisation). Therefore, over a prolonged period of wakefulness, and with exposure to numerous stimuli, there will be a gradual increase in the habituation to elements of many stimuli. Given that there is a degree of overlap in the elements that comprise one stimulus to the next, ongoing stimulus-specific habituation will eventually lead to an overall stimulus-independent, decrease in attentional

performance, as the total number of elements that have become habituated gradually increases across waking experience. Thus, extended periods of wakefulness will result in reduced attention, whereas sleep provides recovery such that high levels of attention are once again possible during the next waking period.

A related possibility is that reduced attentional performance after sleep deprivation is associated with the intrusion of sleep-like patterns of neuronal activity into the awake state [54]. Indeed, several studies have shown that cortical OFF-periods or slow waves are common during waking, especially during quiet states, but also even during active behaviours [9[•],12,55–59]. It seems not unlikely that the occurrence of sleep-like cortical states during waking could lead to attentional deficits, inasmuch as the networks supporting a specific behaviour are experiencing a down-state, although direct evidence supporting this notion is still limited [12,60,61]. At the same time, the occurrence of neuronal down-states during waking, associated with lowered spiking and synaptic

activity, is likely associated with reduced metabolic requirements, or could reflect a shortage of energy substrates [62].

More generally, the changes in network activity and neuronal excitability across sleep/wake cycles have potentially important implications for energy homeostasis in the brain [4,7]. It has been shown in humans and animals that cerebral metabolic rates are increased after sleep deprivation or spontaneous wakefulness [15,63]. Furthermore, after prolonged periods of wakefulness, it may become progressively harder to engage with stimuli when it is required to do so. Under normal circumstances, the more often or the longer a stimulus is presented, the less and less attention is paid to that stimulus. However, if it then becomes necessary to pay attention to a habituated stimulus (or to a stimulus that contains a high proportion of habituated elements), then the attentional mechanisms or working memory processes will need to overcome or override (and thus effectively work against) that ongoing habituation process. Thus it will be cognitively, and potentially metabolically, more demanding, to sustain attention to a habituated stimulus. The occurrence of network OFF-periods during sleep deprivation may reflect cortical states, during which the capacity to sustain metabolically-demanding processes, such as paying attention, is reduced. On the other hand, the increase in synaptic GluA1 after prolonged periods of wakefulness, leading to habituation, may result in it being progressively harder to pay attention to relevant stimuli when required. We posit that network renormalisation during sleep [64], leading to dishabituation, may reduce the energetic costs of paying attention to stimuli and thus help maintain a viable energy balance in the brain.

The notion that sleep disturbance or deprivation might lead to deficits in attention is well established [52,65,66]. For example, numerous studies, both in humans and rodents, have demonstrated that sleep disruption most reliably leads to performance impairments in tasks requiring sustained attention [67–69,70**]. The consequences of such attentional disruption for cognitive performance following sleep disruption are likely to be many and varied, but may include an impaired ability to acquire new information. Consistently, sleep deprivation in mice during the light period, when animals are typically asleep, leads to impaired performance in the novel object recognition task, while sleep deprivation performed in the dark period is not effective [71,72]. Time of day, arousal state and preceding sleep-wake history may contribute to these effects. An inability to attend to the appropriate stimuli at the appropriate times will impede the ability to form new associations and thus to form new longer-term memories, consistent with existing evidence that sleep disturbance or deprivation can disrupt new learning [1]. Furthermore, reduced attentional capacity may also impact on planned behaviour, particularly in situations in which it is

necessary to perform computationally demanding searches for appropriate retrieval cues (either externally or internally) relevant to achieve a future, distant goal [73].

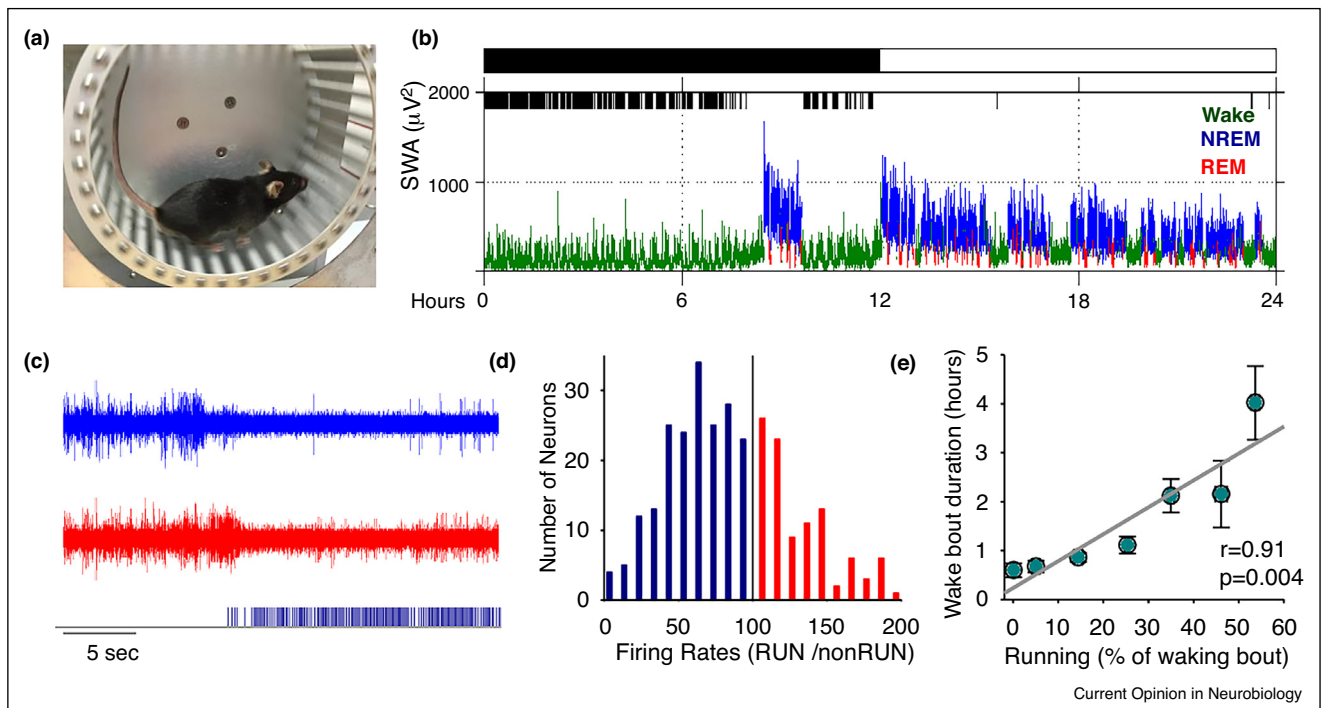
Sleep disturbance changes the nature of behaviour

A further consideration, which may, in part, result from this reduced ability to pay attention (although the two ideas are not wholly dependent on each other), is that sleep disruption may produce a more fundamental change in the nature of behaviour. Broadly speaking, behaviour and the sorts of responses that are made can be categorised into two distinct types. These are often described as goal-directed versus habit-like (or habitual) behaviours (which are computationally related to model-based versus model-free reinforcement learning respectively; see Box 2). It is generally considered that early on when learning a new task, behaviour is predominantly goal-directed, requiring high levels of attention that can be metabolically demanding [74]. However, if responses and outcomes are predictable and these associations have been acquired, then responding becomes more automatic: it requires less attention and is computationally and possibly therefore metabolically, less demanding. Indeed, the switch from goal-directed responding to habit-like behaviour is generally considered as an adaptive response to free up attentional resources for other things once associative learning is at asymptote and the environment is relatively predictable [75,76].

Box 2 Habits, goals and implications for neuropsychiatric disorders

Sleep disturbance may result in a shift away from goal-directed, model-based cognition and behaviour to a more model-free, habit like state. This may have important clinical implications. For example, there is an increasing realisation that sleep disturbance and altered sleep EEG oscillations may be important and common symptoms in several neuropsychiatric disorders, including depression and schizophrenia [2,87–90], although the underlying mechanisms and the functional relevance of these observations have remained unclear. Furthermore, sleep disturbances may exacerbate or even precipitate certain other symptoms associated with these disorders. We posit that sleep disruption may exacerbate neuropsychiatric symptoms like delusions by shifting individuals to more model-free forms of behaviour and cognition. A number of authors have made the link between the propensity for model-free, habit-like behaviour and the tenacity and persistence of delusions, such that aberrant thoughts and beliefs are resistant to re-evaluation, in the same way that habitual instrumental responding is resistant to re-evaluation [91,92]. Consistent with this possibility, several studies have now demonstrated increased model-free, habit-like behaviour in schizophrenic patients in experimental situations [93*,94]. This shift could result in a failure to re-evaluate aberrant thoughts or beliefs appropriately, hence exacerbating the tenacity and persistence of existing delusions in these patients. This account provides a potential mechanism by which sleep disruption might precipitate or exacerbate psychosis in at risk individuals. This notion is also consistent with the observation that delusions are more likely to persist during sleep deprivation in patients with depression [95].

Figure 3



Stereotypic wheel running is associated with reduced cortical neuronal activity and longer wakefulness. **(a)** A photograph of an individual mouse running on a wheel, as used in this study. **(b)** Representative 24-hour profile of EEG slow-wave activity (SWA, 0.5–4 Hz) in one individual mouse. 4-s values of SWA are color-coded according to a vigilance state. The black and white bars indicate 12-h dark and 12-h light period, respectively. Raster plot above the SWA profile during the dark period represents running-wheel activity. **(c)** Two multiunit activity (MUA) traces recorded from the primary motor cortex in the same animal with corresponding running-wheel-activity (bottom), each vertical bar represents a single wheel rung count. Note a substantial reduction of MUA upon the onset of running. **(d)** The distribution of all putative single units recorded in $n = 11$ mice as a function of the ratio of their average firing rates during running (RUN) and non-running waking (nonRUN). Note that a smaller proportion of neurons increase firing during wheel running (red), while the majority decrease firing rates during running (blue). **(e)** The relationship between the proportion of time spent running during a period of spontaneous waking and the duration of the corresponding waking period. Mean values ($n = 11$ mice). Note that a higher proportion of running is associated with longer average waking periods. Parts of the figure adapted from Ref. [9**].

However, the converse may also be true. Namely, that if attentional resources are limited (*e.g.* as a consequence of sleep disruption/disturbance), then it is much more likely that a model-free/habit-based form of behaviour will predominate over a model-based, goal-directed behaviour which requires high levels of attentional control and higher metabolic resources. Indeed, in everyday life there are numerous examples that reduced attention can increase the chances of performing unwanted habits instead of intended actions [77]. Furthermore, it is increasingly recognised that rather than there existing a simple serial relationship whereby goal-directed, model based behaviours always precede habit-like, model-free responding, organisms are often likely to have access to both forms of behaviour and can rapidly and readily switch between the two, given different environmental circumstances such as changes in stress and arousal [78,79**,80]. Given the importance of circadian rhythms and sleep deprivation over motivated behaviours (*e.g.* [81]), it seems plausible that sleep disturbance will fundamentally change the nature of behaviour, making

responding more model-free and habitual as a result of reducing attentional capacity.

Potentially consistent with this account, we have recently demonstrated an important relationship between the nature of behaviour during waking experience and sleep pressure (Figure 3). Typically, waking has often been thought of as a homogenous process, which is associated with a continuous, progressive increase in sleep pressure, largely irrespective of the nature of ongoing behaviour or activities. However, we recently showed that automatic, stereotypical wheel running behaviour in mice was associated with a marked reduction in neural activity in the motor and somatosensory cortex [9]. Furthermore, increased engagement with this low attention/low cost automatic, stereotypical behaviour was also associated with a substantially increased capacity to stay awake and an attenuated increase in neuronal excitability across the waking period [9,82]. Although the psychological processes which determine wheel running in rodents are not clear, this finding might suggest that waking

dominated by automatic, model-free behaviours may have a lower 'cost' with respect to accumulation of sleep need. Thus, while reduced sleep may favour model-free behaviour, conversely engaging in model-free behaviours may reduce sleep requirement.

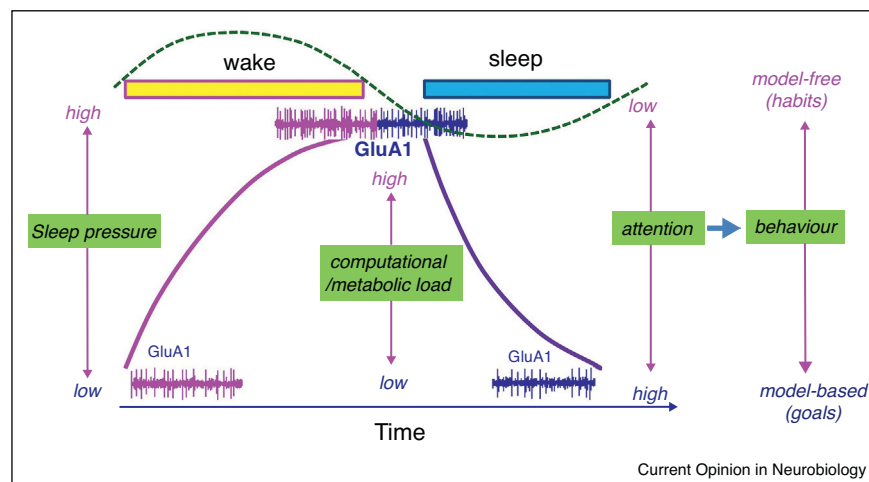
The mechanisms underlying the proposed effects of prolonged wakefulness on wake behaviours remain to be determined but may implicate the occurrence of local neuronal OFF-states within relevant cerebral networks. Sleep has properties of a local process whereby those networks which have been especially active during waking, or underwent the strongest plastic modifications, may require more intense sleep [4,13,83]. Interestingly, a recent study showed that merely increasing network spiking activity irrespective of ongoing vigilance state or behaviour does not result in the homeostatic response during subsequent sleep [84]. By the same token, it is possible that habitual behaviours, which are not associated with any new associative learning and can proceed with reduced levels of attention, may be associated with a reduced accumulation of sleep need. Whether the occurrence of OFF periods is merely a marker of energy deficit incurred during intense synaptic activity and plasticity, a consequence of reduced levels of arousal promoting neuromodulators, or an active process contributing to online renormalisation of network function remains to be determined.

If, as predicted, sleep disruption shifts behaviour to favour more model-free strategies, this may also, in part, explain the significance of sleep disturbance for various neuropsychiatric disorders (Box 2). Furthermore, a reduced ability to adopt a model-based approach following sleep disruption could be considered analogous, at least in part, to more recent ideas about the role of sleep in memory consolidation which suggest that its key role is to facilitate the extraction and/or utilisation of the 'gist' from a memory, enabling the creation of a schema or world-view [1,5]. Both scenarios suggest that sleep disturbance would lead to a reduction in model-based engagement with the world. This could manifest as either a failure to overcome innate or learned biases or through shallower search through prospective decision trees (*e.g.* [85]). It is important to note, however, that the psychological and neurobiological mechanisms leading to this reduction in model-based behaviours may be quite different according to these two distinct accounts.

Conclusions

Here we have briefly reviewed evidence which suggests that synaptic homeostasis of GluA1-containing AMPA receptors may provide a mechanism for dishabituation and the restoration of attentional capacity during sleep, maximising the readiness of the animal for behaviour during subsequent periods of wakefulness (Figure 4). Attentional deficits following sleep disruption could

Figure 4



Sleep restores attentional performance through dishabituation: the role of glutamatergic plasticity. Prolonged wakefulness is associated with increased levels of GluA1 subunit of AMPA receptors, increased neuronal excitability and synchronization, resulting in a brain state which is metabolically expensive and suboptimal for attentional processing. Studies using genetically modified mice have identified an important role for GluA1-dependent synaptic plasticity in a non-associative form of short-term memory that underlies short-term habituation to recently experienced stimuli. Prolonged wakefulness or disrupted sleep are associated with a progressive shift from model-based, goal-directed behaviours to model-free, habitual behaviours. It is reflected in a progressively increased difficulty to engage with stimuli and maintain them at the forefront of attention, which is associated with high computational/metabolic cost. Circadian process may partially restore attentional performance, thereby benefiting learning. Network renormalisation during sleep, including removal of AMPA receptors, may reduce the energetic costs of paying attention to stimuli and thus help maintain the energy balance in the brain. Failure to engage such dishabituation processes will result in persistently low levels of attentional capacity. Thus, extended periods of wakefulness will result in reduced attention, whereas sleep provides recovery such that high levels of attention are once again possible during the next waking period.

contribute to many of the learning and memory deficits reported previously in the literature. Furthermore, an inability to maintain high levels of attention appropriately (e.g. after sleep deprivation) may also shift cognition and behaviour towards more automatic, model-free, habit-like forms which require low attentional capacity, and away from more goal-directed, model based processing which requires high levels of attention. This may also have important implications for understanding the significance of sleep disruption in neuropsychiatric disorders.

Conflict of interest statement

Nothing declared.

Acknowledgements

Supported by: Wellcome Trust Strategic Award098461/Z/12/Z (VVV, DMB, SNP), MRC NIRC MR/L003635/1 (VVV), Wellcome Trust Senior Research Fellowship087736 (DMB) and Wellcome Trust Senior Research Fellowship202831/Z/16/Z (MEW). We thank Dr PL Oliver for comments on the manuscript.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Rasch B, Born J: **About sleep's role in memory.** *Physiol. Rev.* 2013, **93**:681-766.
2. Wulff K, Gatti S, Wettstein JG, Foster RG: **Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease.** *Nat. Rev. Neurosci.* 2010, **11**:589-599.
3. Diekelmann S, Born J: **The memory function of sleep.** *Nat. Rev. Neurosci.* 2010, **11**:114-126.
4. Tononi G, Cirelli C: **Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration.** *Neuron* 2014, **81**:12-34.
5. Feld GB, Born J: **Sculpting memory during sleep: concurrent consolidation and forgetting.** *Curr. Opin. Neurobiol.* 2017, **44**:20-27.
6. Stickgold R: **Parsing the role of sleep in memory processing.** *Curr. Opin. Neurobiol.* 2013, **23**:847-853.
7. Harris JJ, Jolivet R, Attwell D: **Synaptic energy use and supply.** *Neuron* 2012, **75**:762-777.
8. Attwell D, Gibb A: **Neuroenergetics and the kinetic design of excitatory synapses.** *Nat. Rev. Neurosci.* 2005, **6**:841-849.
9. Fisher SP, Cui N, McKillop LE, Gemignani J, Bannerman DM, Oliver PL, Peirson SN, Vyazovskiy VV: **Stereotypic wheel running decreases cortical activity in mice.** *Nat. Commun.* 2016, **7**:13138.
10. Miyawaki H, Diba K: **Regulation of hippocampal firing by network oscillations during sleep.** *Curr. Biol.* 2016, **26**:893-902.
11. Bellesi M, Tononi G, Cirelli C, Serra PA: **Region-specific dissociation between cortical noradrenaline levels and the sleep/wake cycle.** *Sleep* 2016, **39**:143-154.
12. Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, Tononi G: **Local sleep in awake rats.** *Nature* 2011, **472**:443-447.
13. Vyazovskiy VV, Harris KD: **Sleep and the single neuron: the role of global slow oscillations in individual cell rest.** *Nat. Rev. Neurosci.* 2013, **14**:443-451.
14. Van Dongen HP, Belenky G, Krueger JM: **A local, bottom-up perspective on sleep deprivation and neurobehavioral performance.** *Curr. Top. Med. Chem.* 2011, **11**:2414-2422.
15. Vyazovskiy VV, Cirelli C, Tononi G, Tobler I: **Cortical metabolic rates as measured by 2-deoxyglucose-uptake are increased after waking and decreased after sleep in mice.** *Brain Res. Bull.* 2008, **75**:591-597.
16. Borbely AA, Daan S, Wirz-Justice A, Deboer T: **The two-process model of sleep regulation: a reappraisal.** *J. Sleep Res.* 2016, **25**:131-143.
17. Tobler I: **Phylogeny of sleep regulation.** In *Principles and Practice of Sleep Medicine*. Edited by Kryger M, Roth T, Dement W. W. B. Saunders; 2005.
18. Borbely AA: **A two process model of sleep regulation.** *Hum. Neurobiol.* 1982, **1**:195-204.
19. Daan S, Beersma DG, Borbely AA: **Timing of human sleep: recovery process gated by a circadian pacemaker.** *Am. J. Physiol.* 1984, **246**:R161-R183.
20. Borbely AA, Achermann P: In *Homeostasis of Human Sleep and Models of Sleep Regulation*, 3rd edn. Edited by Kryger MH, Roth T, Dement WC. Philadelphia: W.B. Saunders; 2000.
21. Franken P, Chollet D, Tafti M: **The homeostatic regulation of sleep need is under genetic control.** *J. Neurosci.* 2001, **21**:2610-2621.
22. Tobler I, Borbely AA: **Sleep EEG in the rat as a function of prior waking.** *Electroencephalogr. Clin. Neurophysiol.* 1986, **64**:74-76.
23. Vyazovskiy VV, Achermann P, Tobler I: **Sleep homeostasis in the rat in the light and dark period.** *Brain Res. Bull.* 2007, **74**:37-44.
24. Vyazovskiy VV, Cirelli C, Tononi G: **Electrophysiological correlates of sleep homeostasis in freely behaving rats.** *Prog. Brain Res.* 2011, **193**:17-38.
25. Harris KD, Thiele A: **Cortical state and attention.** *Nat. Rev. Neurosci.* 2011, **12**:509-523.
26. Anaclet C, Pedersen NP, Ferrari LL, Venner A, Bass CE, Arrigoni E, Fuller PM: **Basal forebrain control of wakefulness and cortical rhythms.** *Nat. Commun.* 2015, **6**:8744.
27. Bass J, Takahashi JS: **Circadian integration of metabolism and energetics.** *Science* 2010, **330**:1349-1354.
28. Fisher SP, Foster RG, Peirson SN: **The circadian control of sleep.** *Handb. Exp. Pharmacol.* 2013:157-183.
29. Dibner C, Schibler U, Albrecht U: **The mammalian circadian timing system: organization and coordination of central and peripheral clocks.** *Annu. Rev. Physiol.* 2010, **72**:517-549.
30. Frank MG, Cantera R: **Sleep, clocks, and synaptic plasticity.** *Trends Neurosci.* 2014, **37**:491-501.
31. Fernandez F, Lu D, Ha P, Costacurta P, Chavez R, Heller HC, Ruby NF: **Dysrhythmia in the suprachiasmatic nucleus inhibits memory processing.** *Science* 2014, **346**:854-857.

This study performed in arrhythmic hamsters highlights the importance of suprachiasmatic nucleus and related circuitry in the effects of disrupted circadian rhythmicity on cognitive performance.

32. Mackiewicz M, Naidoo N, Zimmerman JE, Pack AI: **Molecular mechanisms of sleep and wakefulness.** *Ann. N. Y. Acad. Sci.* 2008, **1129**:335-349.
 33. Cirelli C, Gutierrez CM, Tononi G: **Extensive and divergent effects of sleep and wakefulness on brain gene expression.** *Neuron* 2004, **41**:35-43.
 34. Terao A, Steininger TL, Hyder K, Apte-Deshpande A, Ding J, Rishipathak D, Davis RW, Heller HC, Kilduff TS: **Differential increase in the expression of heat shock protein family members during sleep deprivation and during sleep.** *Neuroscience* 2003, **116**:187-200.
 35. Thompson CL, Wisor JP, Lee CK, Pathak SD, Gerashchenko D, Smith KA, Fischer SR, Kuan CL, Sunkin SM, Ng LL *et al.*: **Molecular and anatomical signatures of sleep deprivation in the mouse brain.** *Front. Neurosci.* 2010, **4**:165.
 36. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G: **Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep.** *Nat. Neurosci.* 2008, **11**:200-208.
- This study reports that synaptic levels of glutamate receptor subunits, including the GluA1 AMPAR subunit, exhibit a pronounced daily variation as a function of preceding sleep-wake history. Specifically, it has been shown that if rats were sacrificed after periods of wakefulness then the levels of expression of GluA1 in post-synaptic membranes in cortex and hippocampus were considerably higher than after periods of sleep.
37. Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, Huganir RL: **Homer1a drives homeostatic scaling-down of excitatory synapses during sleep.** *Science* 2017, **355**:511-515.
 38. Malenka RC, Bear MF: **LTP and LTD: an embarrassment of riches.** *Neuron* 2004, **44**:5-21.
 39. Collingridge GL, Isaac JT, Wang YT: **Receptor trafficking and synaptic plasticity.** *Nat. Rev. Neurosci.* 2004, **5**:952-962.
 40. Kessels HW, Malinow R: **Synaptic AMPA receptor plasticity and behavior.** *Neuron* 2009, **61**:340-350.
 41. Hoffman DA, Sprengel R, Sakmann B: **Molecular dissection of hippocampal theta-burst pairing potentiation.** *Proc. Natl. Acad. Sci. U. S. A.* 2002, **99**:7740-7745.
 42. Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, Kaiser KM, Koster HJ, Borchardt T, Worley P *et al.*: **Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning.** *Science* 1999, **284**:1805-1811.
 43. Romberg C, Raffel J, Martin L, Sprengel R, Seeburg PH, Rawlins JN, Bannerman DM, Paulsen O: **Induction and expression of GluA1 (GluR-A)-independent LTP in the hippocampus.** *Eur. J. Neurosci.* 2009, **29**:1141-1152.
 44. Erickson MA, Maramba LA, Lisman J: **A single brief burst induces GluR1-dependent associative short-term potentiation: a potential mechanism for short-term memory.** *J. Cogn. Neurosci.* 2010, **22**:2530-2540.
 45. Martin SJ, Grimwood PD, Morris RG: **Synaptic plasticity and memory: an evaluation of the hypothesis.** *Annu. Rev. Neurosci.* 2000, **23**:649-711.
 46. Bannerman DM, Rawlins JN, Good MA: **The drugs don't work-or do they? Pharmacological and transgenic studies of the contribution of NMDA and GluR-A-containing AMPA receptors to hippocampal-dependent memory.** *Psychopharmacology (Berl)* 2006, **188**:552-566.
 47. Bannerman DM, Sprengel R, Sanderson DJ, McHugh SB, Rawlins JN, Monyer H, Seeburg PH: **Hippocampal synaptic plasticity, spatial memory and anxiety.** *Nat. Rev. Neurosci.* 2014, **15**:181-192.
 48. Bannerman DM, Bus T, Taylor A, Sanderson DJ, Schwarz I, Jensen V, Hvalby O, Rawlins JN, Seeburg PH, Sprengel R: **Dissecting spatial knowledge from spatial choice by hippocampal NMDA receptor deletion.** *Nat. Neurosci.* 2012, **15**:1153-1159.
 49. Sanderson DJ, Sprengel R, Seeburg PH, Bannerman DM: **Deletion of the GluA1 AMPA receptor subunit alters the expression of short-term memory.** *Learn. Mem.* 2011, **18**:128-131.
 50. Sanderson DJ, Good MA, Skelton K, Sprengel R, Seeburg PH, Rawlins JN, Bannerman DM: **Enhanced long-term and impaired short-term spatial memory in GluA1 AMPA receptor subunit knockout mice: evidence for a dual-process memory model.** *Learn. Mem.* 2009, **16**:379-386.
- This study reports that GluA1 deletion disrupts a rapidly induced, short-lasting form of hippocampal synaptic plasticity and prevents formation of hippocampus-dependent, short-term spatial memory, but at the same time enhances long-term spatial memory.
51. Barkus C, Sanderson DJ, Rawlins JN, Walton ME, Harrison PJ, Bannerman DM: **What causes aberrant salience in schizophrenia? A role for impaired short-term habituation and the GR1A1 (GluA1) AMPA receptor subunit.** *Mol. Psychiatry* 2014, **19**:1060-1070.
 52. Kirszenblat L, Van Swinderen B: **The yin and yang of sleep and attention.** *Trends Neurosci.* 2015, **38**:776-786.
 53. Wagner AR: **SOP: a model of automatic memory processing in animal behaviour.** In *Information Processing in Animals: Memory Mechanisms*. Edited by Spear NE, Miller RR. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1981:5-47.
 54. Krueger JM, Huang YH, Rector DM, Buysse DJ: **Sleep: a synchrony of cell activity-driven small network states.** *Eur. J. Neurosci.* 2013, **38**:2199-2209.
 55. Hromadka T, Zador AM, DeWeese MR: **Up states are rare in awake auditory cortex.** *J. Neurophysiol.* 2013, **109**:1989-1995.
 56. Abasolo D, Simons S, Morgado da Silva R, Tononi G, Vyazovskiy VV: **Lempel-Ziv complexity of cortical activity during sleep and waking in rats.** *J. Neurophysiol.* 2015, **113**:2742-2752.
 57. McGinley MJ, Vinck M, Reimer J, Batista-Brito R, Zagha E, Cadwell CR, Tolias AS, Cardin JA, McCormick DA: **Waking state: rapid variations modulate neural and behavioral responses.** *Neuron* 2015, **87**:1143-1161.
 58. Polack PO, Friedman J, Golshani P: **Cellular mechanisms of brain state-dependent gain modulation in visual cortex.** *Nat. Neurosci.* 2013, **16**:1331-1339.
 59. Slater JD, Chelaru MI, Hansen BJ, Beaman C, Kalamangalam G, Tandon N, Dragoi V: **Focal changes to human electrocorticography with drowsiness: a novel measure of local sleep.** *J. Neurosychiatry Clin. Neurosci.* 2017 <http://dx.doi.org/10.1176/appi.neuropsych.16060120>. in press.
 60. Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, Panksepp J: **Sleep as a fundamental property of neuronal assemblies.** *Nat. Rev. Neurosci.* 2008, **9**:910-919.
 61. Engel TA, Steinmetz NA, Gieselmann MA, Thiele A, Moore T, Boahen K: **Selective modulation of cortical state during spatial attention.** *Science* 2016, **354**:1140-1144.
 62. Vyazovskiy VV, Tobler I, Cirelli C, Tononi G: **Author's reply to cerebral metabolism and sleep homeostasis: a comment on Vyazovskiy, et al.** *Brain Res. Bull.* 2009, **80**:443-445.
 63. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, Varga M, Baldwin P, Selbie S, Belenky G, Herscovitch P: **Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study.** *Brain* 1997, **120**(Pt. 7):1173-1197.
 64. Watson BO, Levenstein D, Greene JP, Gelinas JN, Buzsaki G: **Network homeostasis and state dynamics of neocortical sleep.** *Neuron* 2016, **90**:839-852.
- Comprehensive analysis of the dynamics of cortical neuronal activity suggests that 'homeostatic' role of sleep may consist in 'homogenizing' the distribution of firing rates among cortical neurons, through differential effects on slow-spiking and fast-spiking neurons.
65. Killgore WD: **Effects of sleep deprivation on cognition.** *Prog. Brain Res.* 2010, **185**:105-129.
 66. Goel N, Rao H, Durmer JS, Dinges DF: **Neurocognitive consequences of sleep deprivation.** *Semin. Neurol.* 2009, **29**:320-339.

67. Arnal PJ, Sauvet F, Leger D, van Beers P, Bayon V, Bougard C, Rabat A, Millet GY, Chennaoui M: **Benefits of sleep extension on sustained attention and sleep pressure before and during total sleep deprivation and recovery.** *Sleep* 2015, **38**(12):1935-1943.
68. Groeger JA, Stanley N, Deacon S, Dijk DJ: **Dissociating effects of global SWS disruption and healthy aging on waking performance and daytime sleepiness.** *Sleep* 2014, **37**:1127-1142.
69. McCoy JG, Strecker RE: **The cognitive cost of sleep lost.** *Neurobiol. Learn. Mem.* 2011, **96**(4):564-582.
70. Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, Hasan S, von Schantz M, Archer SN, Dijk DJ: **Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase.** *PLoS One* 2012, **7**:e45987.
- This study showed that subjective alertness and sustained attention are more affected by both partial and total sleep deprivation than other cognitive domains and executive functions.
71. Palchykova S, Winsky-Sommerer R, Tobler I: **Sleep deprivation in the dark period does not impair memory in OF1 mice.** *Chronobiol. Int.* 2009, **26**:682-696.
72. Palchykova S, Winsky-Sommerer R, Meerlo P, Durr R, Tobler I: **Sleep deprivation impairs object recognition in mice.** *Neurobiol. Learn. Mem.* 2006, **85**:263-271.
73. Pezzulo G, Rigoli F, Chersi F: **The mixed instrumental controller: using value of information to combine habitual choice and mental simulation.** *Front. Psychol.* 2013, **4**:92.
74. Moradi F, Buracas GT, Buxton RB: **Attention strongly increases oxygen metabolic response to stimulus in primary visual cortex.** *Neuroimage* 2012, **59**:601-607.
75. Daw ND, Niv Y, Dayan P: **Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control.** *Nat. Neurosci.* 2005, **8**:1704-1711.
76. Dolan RJ, Dayan P: **Goals and habits in the brain.** *Neuron* 2013, **80**:312-325.
77. Reason JT: **Actions not as planned: the price of automatised.** In *Aspects of Consciousness*. Edited by Underwood G, Stevens R. Academic Press; 1979:67-89.
78. Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, Costa RM, Sousa N: **Chronic stress causes frontostriatal reorganization and affects decision-making.** *Science* 2009, **325**:621-625.
79. Schwabe L, Wolf OT: **Stress prompts habit behavior in humans.** •• *J. Neurosci.* 2009, **29**:7191-7198.
This study in humans demonstrates that stress promotes habits at the expense of goal-directed performance in humans.
80. Doll BB, Simon DA, Daw ND: **The ubiquity of model-based reinforcement learning.** *Curr. Opin. Neurobiol.* 2012, **22**:1075-1081.
81. Menz MM, Buchel C, Peters J: **Sleep deprivation is associated with attenuated parametric valuation and control signals in the midbrain during value-based decision making.** *J. Neurosci.* 2012, **32**:6937-6946.
82. Vyazovskiy VV, Tobler I: **The temporal structure of behaviour and sleep homeostasis.** *PLoS One* 2012, **7**:e50677.
83. Krueger JM, Frank MG, Wisor JP, Roy S: **Sleep function: toward elucidating an enigma.** *Sleep Med. Rev.* 2016, **28**:42-50.
84. Rodriguez AV, Funk CM, Vyazovskiy VV, Nir Y, Tononi G, Cirelli C: **Why does sleep slow-wave activity increase after extended wake? assessing the effects of increased cortical firing during wake and sleep.** *J. Neurosci.* 2016, **36**:12436-12447.
85. Huys QJ, Eshel N, O'Nions E, Sheridan L, Dayan P, Roiser JP: **Bonsai trees in your head: how the pavlovian system sculpts goal-directed choices by pruning decision trees.** *PLoS Comput. Biol.* 2012, **8**:e1002410.
86. Bannerman DM, Niewoehner B, Lyon L, Romberg C, Schmitt WB, Taylor A, Sanderson DJ, Cottam J, Sprengel R, Seeburg PH et al.: **NMDA receptor subunit NR2A is required for rapidly acquired spatial working memory but not incremental spatial reference memory.** *J. Neurosci.* 2008, **28**:3623-3630.
87. Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM: **Sleep and circadian rhythm disruption in schizophrenia.** *Br. J. Psychiatry* 2012, **200**:308-316.
88. Peterson MJ, Benca RM: **Sleep in mood disorders.** *Psychiatr. Clin. North Am.* 2006, **29**:1009-1032 abstract ix.
89. Sprecher KE, Ferrarelli F, Benca RM: **Sleep and plasticity in schizophrenia.** *Curr. Top. Behav. Neurosci.* 2015, **25**:433-458.
90. Menet JS, Rosbash M: **When brain clocks lose track of time: cause or consequence of neuropsychiatric disorders.** *Curr. Opin. Neurobiol.* 2011, **21**:849-857.
91. Corlett PR, Taylor JR, Wang XJ, Fletcher PC, Krystal JH: **Toward a neurobiology of delusions.** *Prog. Neurobiol.* 2010, **92**:345-369.
92. Corlett PR, Krystal JH, Taylor JR, Fletcher PC: **Why do delusions persist?** *Front. Hum. Neurosci.* 2009, **3**:12.
93. Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW: • **Cortico-striatal control of goal-directed action is impaired in schizophrenia.** *Biol. Psychiatry* 2015, **77**:187-195.
This study suggests that dysfunction of the cortico-striatal circuitry may contribute to the well-known impairment of goal-directed performance in patients with schizophrenia, which is mediated by a deficit in judging the action-outcome association and using this knowledge for making choices.
94. Culbreth AJ, Westbrook A, Daw ND, Botvinick M, Barch DM: **Reduced model-based decision-making in schizophrenia.** *J. Abnorm. Psychol.* 2016, **125**:777-787.
95. Benedetti F, Zanardi R, Colombo C, Smeraldi E: **Worsening of delusional depression after sleep deprivation: case reports.** *J. Psychiatr. Res.* 1999, **33**:69-72.