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Critical review

Systems

Staying awake: top-down systems control of sleep

HW Steenland*

Abstract

Introduction

Since the dawn of the Industrial Revolution and Thomas Edison's improvements on the light bulb, we have often had no real excuse to sleep, but to say 'I am sleepy'. Caffeine and sensory stimulation are the most common methods to forestall sleep. However, the primary reason that people choose to put off sleep is that they are preoccupied with a superseding interest. There are two major situations, which appear to dictate whether or not we sacrifice sleep, and these include the anticipation of a reward and the anticipation of punishment. Because these situations do not necessarily involve ongoing sensory or pharmacological stimulation, the origin of this influence may precipitate from the executive functions of the cortex. This review examines the potential role of the prefrontal cortex as a candidate for top-down systems control over sleep propensity. It is postulated that top-down systems control over sleep may be accomplished through interaction with the sleep switch in combination with activation of the ascending arousal system. The intention here is to generate discussion, interest and a potential theoretical framework from which to examine neurophysiological mechanisms.

Conclusion

We should be mindful that a comprehensive account for how we forego sleep will require an explanation of how a single abstract concept (such as the anticipation of money or punishment) can seed a cascade of goal-directed processes which can take acute precedence over sleep homeostasis.

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Introduction

The two-process model of sleep regulation and threshold control

The two-process model of sleep regulation developed by Borbély[1,2] is one of the most well-recognised models to explain the interaction between circadian processes and sleep homeostasis. The architecture of this model consists of a sinusoidal circadian process and a parallel skewed sine-wave sleep process (Figure 1). The circadian process (process C) is defined by cyclic oscillations in sleep propensity and is largely independent of the sleep–wake cycle. A concrete example of process C is the cyclical change in body temperature that occurs throughout the day[3]. By contrast, process S (sleep) represents the homeostatic sleep need that builds up during the day and gradually declines throughout subsequent sleep. A direct metric of process S appears to be slow-wave activity (SWA), which consists of the sum of the signal power (~0.5–4.5 Hz band) recorded from cortical electroencephalogram or local field potentials[2]. SWA also appears to reflect sleep depth and sleep intensity[4]. Just as process S gradually declines after the initiation of sleep, so does SWA[5–7]. Consistently, sleep deprivation results in a rebound of SWA in proportion to the duration of prior wakefulness[8–10]. Finally, naps taken later in the day, as compared to earlier in the day, have a larger propensity of SWA[11,12], corroborating that process S builds up throughout a day of wakefulness. The two-process model did not completely explain how 'decisions' to remain awake can control or antagonise sleep onset, other than to postulate that a threshold termed 'H' could limit process S[13] (Figure 1). According to Borbély et al.[13], when we are sleep deprived by external situations (e.g. socialising), the 'H' threshold is raised. Conceptually, this fits with the model of sleep propensity of Johns. However, Johns[14,15] also included a secondary wake drive, which is partially under volitional control and would account for how one could willingly forego sleep. For the sake of forestalling terminological confusion, and an unnecessary re-conceptualisation of the two-process model of sleep, the term 'top-down systems control' or 'TDSC' will be used to denote neural systems that could raise the threshold 'H' of the two-process model, possibly through influence of the ascending arousal, corticothalamic, circadian and sleep switch circuits, consequently changing sleep propensity (Figure 1). Moreover, for this early conceptualisation, it is not necessary to view TDSC as a tonic 'drive', but as an available mechanism recruited to help maintain wakefulness under particular situations. Experimentally, the impact of volition on sleep onset can be appreciated from studies using the maintenance of wakefulness test, whereby simply switching the instruction to stay awake as opposed to falling asleep yields a longer sleep latency[16,17]. To understand how real-life situations, such as the anticipation of reward or the anticipation of punishment could change sleep propensity, we should first examine briefly what is being restored by sleep homeostasis.

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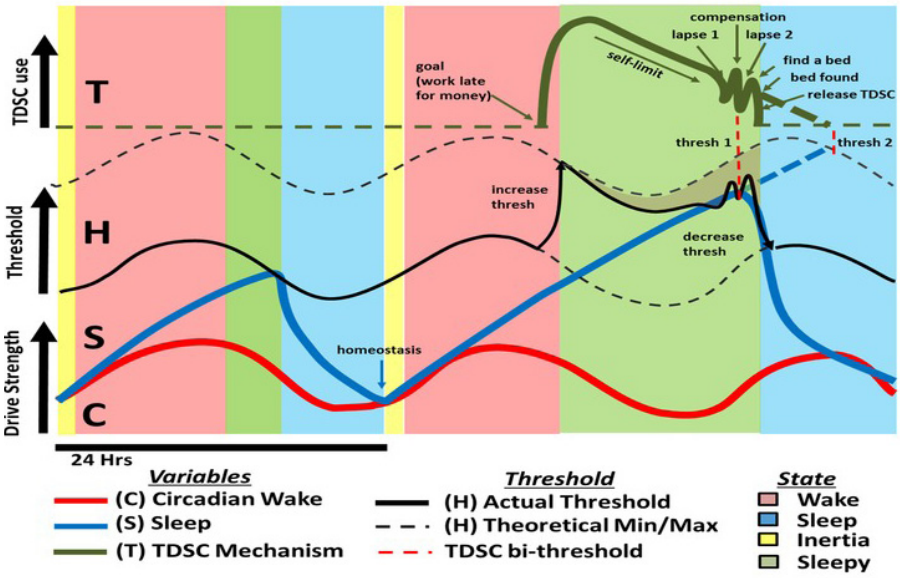

Figure 1: The two-process model of sleep regulation with modulation by TDSC. The circadian process C (red line) oscillates throughout the day providing wakefulness drive. Process S (blue line) slowly builds up during the day until it reaches a threshold (solid black line) at which point sleep is likely. This typically occurs during the falling phase of body temperature. TDSC (green line) can only be applied during wakefulness and has the capacity to postpone sleep onset when cued or turned on for particular situations. However, this resource is self-limiting since its optimal functioning is dependent on restitution from sleeping itself. This self-limit ensures that the process cannot continue indefinitely and that sleep will eventually be reached. The recognition that one should sleep, in spite of our goals, may be related to the experience of sleepiness (lapse 1 and 2) and the approach to threshold 1. Before cognitive function degrades too far, it is advantageous to redirect one's goals to find a safe place to sleep. In the event that our goals are not refocused, TDSC will run down (thresh 2), sleep pressure will rise and we may fall asleep (e.g. driving home from work) without realising the cues of sleepiness. In the present model, TDSC raises the threshold of the two-process model. However, the self-limiting properties of TDSC gradually return this threshold to normal so that sleep will eventually occur. Figure adapted from [2] with permission from Elsevier.

Homeostatic balance

The determinants of homeostatic SWA appear to be related to two factors. The first factor is composed of synaptic potentiation and the corresponding molecular changes that occur, simply by being awake[18]. The second factor appears to be use dependent and can drive local increases in SWA over specific areas of the brain that have been involved in the learning process[19–21]. Whether the quantity of SWA (or homeostatic pressure) is related to the build-up of extracellular metabolites (e.g. glutamate[22], adenosine[23]) or metabolic clearance[24], saturated synaptic plasticity[25,26], memory reactivation[27,28] (response to cellular stress[29]) or some other yet unidentified process is beyond the scope of this review. For the sake of argument and simplicity, the term 'homeostatic balance' will be used to refer to as a state of recovered sleep. It is assumed that this balance is necessary for optimal daily function and to prevent us from simply collapsing into slumber. For a complete explanation of sleep as a homeostatic entity, we need to take a step further and explain the mechanisms through which the 'H' threshold can be raised. The TDSC hypothesis makes the tentative assumption that a distributed neural system rather than a local metabolic process is responsible for raising the 'H' threshold in order to postpone sleep onset when one needs to avoid danger or achieve particular goals. Moreover, the TDSC over sleep homeostasis should be constrained by its own local homeostatic reserve, and it is to this concept that we now turn. The review to follow discusses the top-down systems control of sleep.

Theoretical constraints of TDSC: a brief comparison to breathing

When volitionally holding our breath, we typically cease when we still have about three-fourths of oxygen left[30,31]. This occurs well before fainting, yet psychologically we feel we are nearly out of reserve[30,31]. Thus, there appears to be two major system thresholds. The first threshold appears to be related to maximal psychological discomfort and drives behavioural activation, which consists of the refocusing of attention to get the required resource before the reserve runs out (Figure 1). The second threshold is metabolic and consists of a full inability to execute action (i.e. fainting), because the very action to restore homeostatic balance requires a homeostatic reserve.

Given that sleep is homeostatically regulated, it is possible that a similar bi-threshold process is imposed on TDSC. For example, one could maintain wakefulness and performance, with TDSC for several hours past one's typical sleep time, with the goal of acquiring money (e.g. first night of shift work). Consistently, it has been shown that wakefulness and performance can be maintained at baseline during a vigilance task when monetary incentives are given even after 36 h of sleep deprivation[32]. Moreover, simply providing the subject with knowledge of their performance is

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sufficient to reduce reaction time impairments with sleep deprivation[33]. When sufficient performance deficits or lapses in attention occur in spite of TDSC, this could represent a first threshold (Figure 1) and might provide a cue to the subject to find a safe place to sleep. As a person is pushed further from their homeostatic set-point with continued wakefulness, the effectiveness of the TDSC system may decline sufficiently, reaching a second threshold, at which point the subject may not recognise cues related to sleepiness and therefore lapse unexpectedly into sleep (analogous to fainting). Consistently, with extended sleep deprivation, monetary incentives are insufficient at restoring performance on an auditory vigilance task, and subjects may nod off to sleep during the task[32], suggesting that the threshold for systems failure (threshold 2) may have been nearly reached. In summary, it appears that homeostatic sleep pressure enforces two thresholds on TDSC: the first threshold accounts for behavioural activation (redirecting ones goals to go to bed) and compensatory effort and is cued by the feeling of sleepiness, while the second threshold accounts for systems failure as a result of the TDSC mechanism requiring local homeostatic balance of its system components.

What cues could trigger compensatory TDSC to maintain performance or redirect behaviour?

Sleepiness is often described as a propensity to fall asleep as can be measured by the multiple sleep latencies test (MSLT)[34], but also see Johns[14]. Sleepiness in humans is accompanied by behavioural micro-sleeps or a slowing of responsiveness, behavioural lapses[35,36] and interoceptive changes such as slow eyelid closure, droopy eyes, head nodding and changes in facial tone[36–39]. From the electrophysiological perspective, performance deficits may correspond to cortical micro-sleeps, which consist of a brief slowing (for 3–15 s) of cortical EEG into the theta range[40–44]. The psychomotor vigilance task is one of the most well-used methods to assess micro-sleeps in humans. It consists of measuring reaction times as subjects get progressively sleepy, and because of its nearly negligible learning curve, performance can be assessed without the worry of learning effects confounding interpretations (for an extensive review see[45]). Probably the most important with respect to TDSC is the finding that compensatory effort is engaged in vigilance tasks[32], possibly owing to ongoing error monitoring. In addition, attentional lapses have been found to occur coincident with deactivations of the anterior and prefrontal cortical network[36,46], while attentional recovery was found to involve inferior-frontal and temporal-parietal cortex activity[46]. Thus, in a natural environment (as opposed to the monotony of driving a car), micro-sleeps and their behavioural and psychological consequences may be sufficient to cue the brain that the first threshold has been surpassed so as either to apply more effort or reorient one's goals to seek a safe and comfortable shelter for rest and possibly sleep. In part, this might explain why tests of subjective/situational sleepiness do not accurately predict the latency to sleep in a monotonous environment[47,48]. However, subjective ratings of sleepiness do predictably co-vary with circadian cycles[49,50], increase with sleep deprivation[50–52] and the accumulation of frontal-cortical theta rhythms (4–8 Hz)[52]. Thus, subjective sleepiness may reflect a forewarning system to find an optimal place to sleep rather than precisely predicting sleep propensity. Furthermore, in accordance with the bi-threshold postulate (above), as we are moved dangerously further from homeostatic set-point, it would be expected that the number of cues related to subjective sleepiness increases; however the further we are from this set-point, the less likely the nervous system will react to these cues since TDSC may itself require sleep homeostasis. In summary, a variety of cues (behavioural and psychological) may provide us with important feedback regarding subjective sleepiness while we are engaged in goal-directed activity on a background of homeostatic sleep pressure.

The architecture of the sleep system and points of potential TDSC

A large body of evidence implicates the ventrolateral preoptic area (VLPO) as a putative sleep switch for transitioning from wakefulness to slow-wave sleep by shutting down the ascending arousal system. For a detailed review of this literature, the reader is directed elsewhere[53–55]. There are several ways in which the VLPO could be antagonised. The most well-developed idea is that the ascending arousal system is activated through orexinergic inputs, the net effect of which would be inhibition of the VLPO[54,56]. Indeed, the link between orexin in feeding and behavioural arousal might explain why we fall asleep after a meal[56]. Interestingly, simply shifting a meal schedule so that food is presented during the natural sleep time of rats is sufficient for their sleep–wake cycle to switch so they sleep during the opposite photoperiod (rats become diurnal)[57,58], implicating that alternative homeostatic drives could shape sleep onset.

Similar to the VLPO, there is also evidence that the median preoptic nucleus (MnPO) may act as a sleep switch. For example, the MnPO sends inhibitory input to the ascending arousal system[59,60] and is sensitive to homeostatic sleep pressure[61,62]. Additionally, inhibition of the MnPO can produce prolonged wakefulness in rats[59] while activation can increase NREM sleep[59]. Finally, the MnPO neurons increase their activity in response to sleep pressure while

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the VLPO may help regulate sleep depth[62]. If the cortex needs to communicate homeostatic sleep pressure with the VLPO and MnPO, it has yet to be discovered[63].

In addition to antagonising the sleep switch, activating the ascending arousal system could maintain wakefulness in its own right. The ascending arousal system comprises a host of neuromodulatory systems which terminate throughout the brain and are thought to help maintain the cortex[64] and thalamus[65] in an activated state. This system includes the locus coeruleus (norepinephrine releasing), dorsal Raphé (serotonin releasing), tuberomammillary nucleus (histamine releasing), ventral tegmental area (VTA) (dopamine releasing), laterodorsal tegmentum (acetylcholine releasing), pedunculopontine tegmentum (acetylcholine releasing), basal forebrain (acetylcholine releasing), perifornical lateral hypothalamus (orexin releasing) (Figure 2) and a more recent candidate, the ventral periaqueductal grey (vPAG) (dopamine releasing)[66]. TDSC may also need to activate the thalamus, to prevent a sleep-like bursting mode. Consistently, there is evidence for this type of top-down thalamic activation through metabotropic glutamate receptors[67]. Alternative system-level explanations may exist, such as the maintenance of cortical effective connectivity[68], but the exploration of this is beyond the scope of the current review.

The prefrontal cortex (PFC) is one likely candidate for TDSC of the sleep system for several reasons. (i) It is the only cerebral cortical region to be highly interconnected with nearly every aspect of the ascending arousal system in both monkeys and rodents (see below) and is involved in the anticipation of reward and punishment. (ii) The PFC is one of the brain regions most susceptible to sleep deprivation[69]. This sensitivity could provide the brain with early cues of impeding system failure and could trigger goal redirection to a safe place to sleep. (iii) The PFC is thought to be one of the major originating sites for SWA which spreads as a travelling wave from anterior to posterior sites of the brain[70]. (iv) Removal of the frontal cortex as well as other cortical regions has minimal effects on cycling between states of wake, non-rapid eye movement (NREM) and rapid eye movement (REM) sleep[71,72]. Thus, the PFC appears non-essential for regular sleep–wake generation, but may be engaged to antagonise sleep depending on the goal that the situation demands. The sections to follow will discuss the anatomical connectivity of the PFC with the ascending arousal system and studies which implicate the role of the PFC in modulating arousal in both primates and rodents.

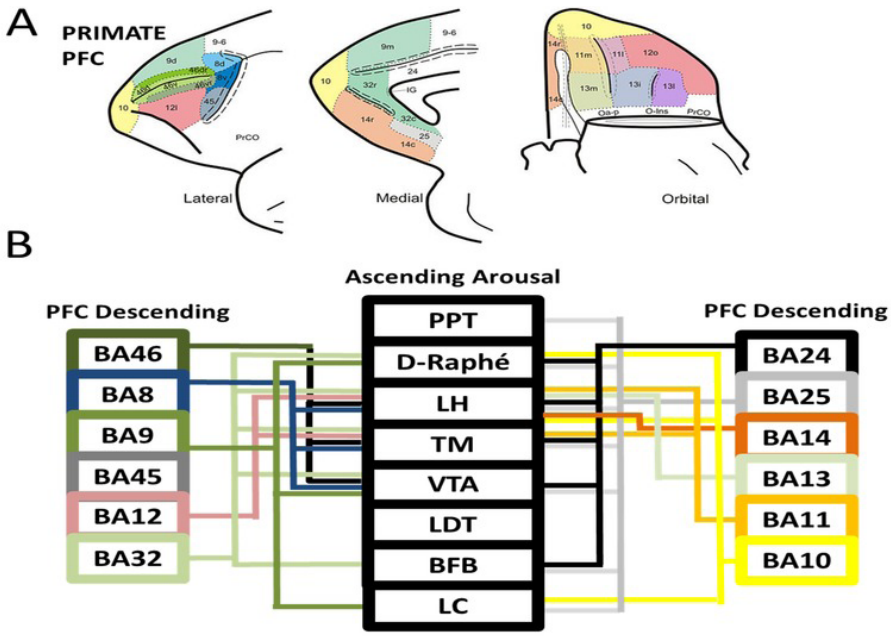

Figure 2: Reciprocal connectivity between the primate brain prefrontal cortex (PFC) and the ascending arousal system. **(B)** Broadmann's areas for the PFC of the primate (Cebus Monkey), including lateral, medial and orbital regions. Figure from [160] is reproduced with permission from *BioMed Central*. Colours refer to different prefrontal areas. **(B)** Descending projections from the PFC of the primate to the ascending arousal system. Colours denote relationships with **(A)** and BA refers to Broadmann's area.

Primate PFC and evidence for the top-down control of arousal

Anatomical connection studies

The subdivisions of the human PFC include the ventromedial prefrontal cortex (VMPFC) and the dorsolateral prefrontal cortex (DLPFC) and will be referenced according to Broadmann's areas (BA) to help equate data across studies and avoid regional confusion (Figure 2A). From the studies examined here, BAs were estimated based on Talairach coordinates provided from each research article.

The primate PFC not only receives input from the ascending arousal system but also influences the ascending arousal system in a top-down fashion. While an account of the top-down connectivity patterns from the primate PFC has not been completely worked out, several trends seem to be emerging (Figure 2B). The most consistent and robust connectivity originat-

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ing from the PFC (BA8, BA9, BA46, BA14, BA32, BA24, BA11, BA13 and BA10) appears to be directed to the lateral hypothalamus[73-76]. The connection from BA32 onto the lateral hypothalamus has been identified to be excitatory as evidenced by asymmetric synapses[77]. The connections of the PFC (BA8, BA46, BA14, BA32, BA24, BA11 and BA13) to the tuberomammillary hypothalamus also appear consistent and robust[75,76]. The PFC consistently and sparsely sends projections to the VTA (BA8, BA46, BA14, BA24, BA25 and BA32)[76,78], but this connection is absent from the orbital region BA11[78]; moreover, it is still unclear whether PFC terminals connect in direct apposition with dopaminergic neurons[78]. Efferent connectivity to the basal forebrain has been identified for more orbital and medial aspects of the PFC (BA32, BA25 and BA11)[76,79], but this connection appears absent to the lateral aspects of the PFC (BA8, BA9 and BA46)[75]. Known connections to the dorsal Raphé originate from the medial and lateral PFC regions (BA32, BA24, BA25 and BA9)[76,80] but not orbital regions (BA11)[80]. A similar pattern emerges with medial and lateral PFC connections (BA24, BA25 and BA9) to the locus coeruleus[76,80], again orbital frontal cortex, is not connected (BA11)[80]. Interestingly, other areas of cortex, including inferior temporal, parietal association and somatosensory, were also not interconnected with the dorsal Raphé or locus coeruleus. To my knowledge, there is only one report of connectivity to the pedunculopontine tegmentum originating from the medial PFC (BA25)[76]; however, there is no report of connectivity with the laterodorsal tegmentum, which is a site of termination in the rodent (see below). Finally, the primate PFC does not appear to connect with either the suprachiasmatic nucleus (SCN)[74] or VLPO; however, this apparent lack of connectivity may be a consequence of restricted and small areas of injection and the use of anterograde tracers in an otherwise large primate cortex. Retrograde tracer experiments may need to be conducted from the SCN and VLPO to determine definitively if these areas receive input from the primate cortex.

Functional studies

The grey matter volumes of the human VMPFC (BA11) correlate negatively with subjective estimates of daytime sleepiness[81], and activation of the medial orbitofrontal cortex (BA10/11) is linked with subjective reports of mental fatigue[82] and even contagious yawning (BA11)[83]. In addition, among other brain regions including the thalamus, the frontal pole (BA10) of the PFC was found to become deactivated during behavioural micro-sleeps in a monotonous visuomotor task[84]. Most interesting was that the micro-sleep theta rhythm power was highly correlated with deactivation in the frontal pole (BA10) and frontal-orbital cortex (BA47). Finally, BA10 is one of a few prefrontal regions which appear to be activated when transitioning from sleep to wakefulness, implicating its latent activation in sleep inertia[85]. Taken together, based on the limited evidence, it will be of interest to investigate the possible role of BA10/11 as a putative cortical subjective sleep sensor.

Poudel et al.[86] found that human subjects that are resistant to drowsiness demonstrate corresponding activity in the ACC (BA32), following sleep restriction[86]. It was also reported that there was decreased activity in the frontal (BA9,6)-parietal (BA40,7) attention network of sleep-deprived individuals corresponding most to that of the drowsy individuals. Consistently, in a separate study, subjects who were resistant to deprivation were found to have enhanced frontal (BA6)-parietal (BA7) activations compared to sleep-deprived vulnerable subjects[36]. In the same study, an increase was found in frontal-parietal activity during reaction time lapses when drowsy[36]. Similarly, an increase in frontal (BA45) and parietal (BA3,40,4,5) activation was also seen during behavioural micro-sleeps in a continuous, monotonous visuomotor task, without prior sleep deprivation[84].

The left DLPFC (BA9) and bilateral thalamus may become increasingly active following sleep deprivation when challenged with a complex task, suggesting a compensatory top-down mechanism for sustained attention when sleepy[87]. Consistently, the alertness of sleep-restricted subjects correlates positively with activation of the DLPFC (~BA46) and performance in the n-Back working memory task[88]. Thus, subjects who reported being less sleepy had greater DLPFC activity and better performance on this task[88]. Consistently, a recent study showed that monetary anticipation will first activate the DLPFC followed by activation of the VTA, implicating the DLPFC has a top-down influence over the VTA. A study conducted by Strangman et al.[89] implemented a virtual-reality spatial navigation task during sleep deprivation (~27 h) and found a compensatory increase in DLPFC area BA9 (largest effect size) in conjunction with the temporal regions (BA22, BA22, BA39 and BA37) and the right substantia nigra. Similarly, compensatory recruitment of the PFC (BA46, BA32/8 and BA13/47) has been reported following total sleep deprivation (35 h) while performing a logical reasoning task[90]. Parietal and temporal areas (BA39/40/42 and BA21/22) also showed compensatory activation in this task.

Collectively, the findings implicate the ventromedial and DLPFC in both the maintenance of performance and the resistance to sleep. Based on the human studies, it is hard to tell what could mediate this mechanism since ascending arousal systems are seldom reported in these fMRI studies, possibly owing to the small size of

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these regions of interest. Moreover, the variety of frontal regions activated might indicate the variety of compensatory mechanisms for particular situations.

Based on the human studies reviewed here, a trend seems to be emerging, with area BA10/11 constituting a region for the subjective motoring of the sleepiness state with DLPFC-parietal and DLPFC-temporal regions compensating for sleep deprivation during particular task demands. While prefrontal circuitry of the primate appears to be in place for TDSC, a careful examination of their causal (excitatory vs inhibitory) interaction with the sleep system is necessary.

Rodent medial PFC and evidence for top-down control of arousal

Based on functional and connective similarities, the VMPFC of the primate may be likened to the mPFC of the rodent, while the DLPFC of the primate appears to share only some similarities with the rodent mPFC[91,92]. Three major components of the rodent medial prefrontal cortex (mPFC) include the infralimbic, prelimbic and anterior cingulate cortex (ACC) (Figures 3–5). The current review focuses on these subdivisions in relation to sleep circuitry. For more extensive reviews on rodent mPFC function, the reader is directed elsewhere[91,93].

Infralimbic-arousal pathways

The infralimbic PFC projects to a large portion of the ascending arousal system, including the dorsal Raphé, basal forebrain, laterodorsal tegmentum, lateral hypothalamus, VTA, vPAG and of the three mPFC regions discussed is the only one to connect to the tuberomammillary nucleus[66,94–101] (Figure 3). The infralimbic cortex is also the only cortical structure to interact with the sleep switch (VLPO)[102] and the dorsal aspect of the SCN[102,103], suggesting an interface with circadian and sleep control.

The infralimbic input to the Raphé is thought to be made onto local inhibitory neurons[104,105], suggesting that the mPFC turns the dorsal Raphé off. It has also been found that this connection may be used for modulating controllable stress[106]. Specifically, it was found that blocking this region during training, on a stress paradigm, leads to elevated c-Fos and serotonin output from the dorsal Raphé in the rat. If rats had control over whether or not they were shocked and had their mPFC cortex deactivated, subsequent fear behaviour was comparable to that of animals that were shocked without control over the outcome. Since stress should serve to reduce sleep onset, the connection between infralimbic and Raphé may promote sleep by reducing arousal related to environmental stress; however, interpretive complications might arise due to circulating stress hormones such as cortisol or corticosterone.

The infralimbic cortex is probably most well-known for its involvement in fear extinction memory[107–109] through direct connections with the amygdala[110]. The experience of fear and anxiety are definitely factors that interfere with sleep, so we will briefly review how the infralimbic cortex might influence the amygdala to influence arousal. The amygdala

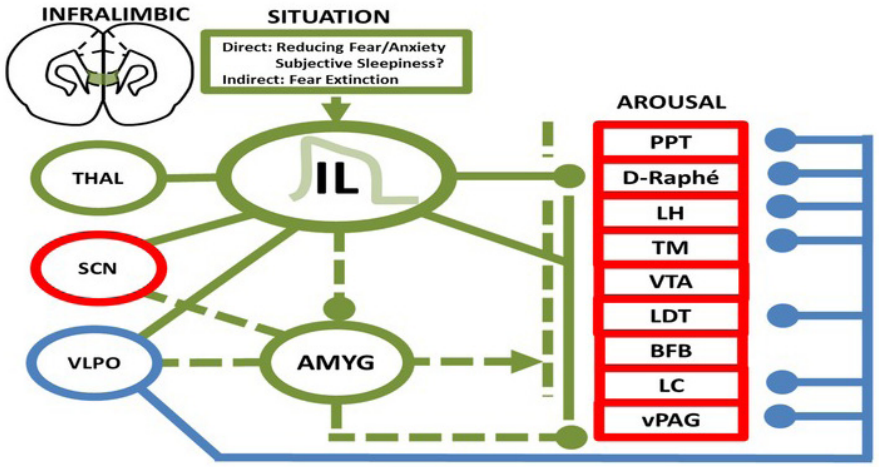

Figure 3: Model of the rodent infralimbic-arousal pathways. Model shows direct (solid lines) and indirect pathways (dashed lines) from the infralimbic cortex (IL) to influence the ascending arousal system (red boxes), thalamus (THAL), VLPO area, SCN and amygdala (AMYG). It is not yet certain whether the direct pathway promotes arousal or simply modulates its tone. The indirect pathway involves inhibition of the amygdala, which should have the effect of reducing arousal and enhancing sleep. The infralimbic influence is self-limiting ('∩' symbol) and only turned on when awake, such that whatever influence it has over arousal will eventually subside. Green connections represent the connections of TDSC. Red colour indicates primary wake-promoting neural components. Blue colour indicates sleep-promoting connections and components. Circular terminals are inhibitory, arrow terminals are excitatory connections and no terminal or flat line means undetermined connection. Abbreviations are as follows: LC, locus coeruleus; TM, tuberomammillary nucleus; BF, basal forebrain; PPT, pedunculopontine tegmentum; LDT, laterodorsal tegmentum; D-Raphé, dorsal Raphé nucleus; LH, lateral hypothalamus; VTA, ventral tegmental area and vPAG is ventral periaqueductal gray. Some connections from VLPO to arousal regions are presumed inhibitory because of the inhibitory cells bodies in the VLPO.

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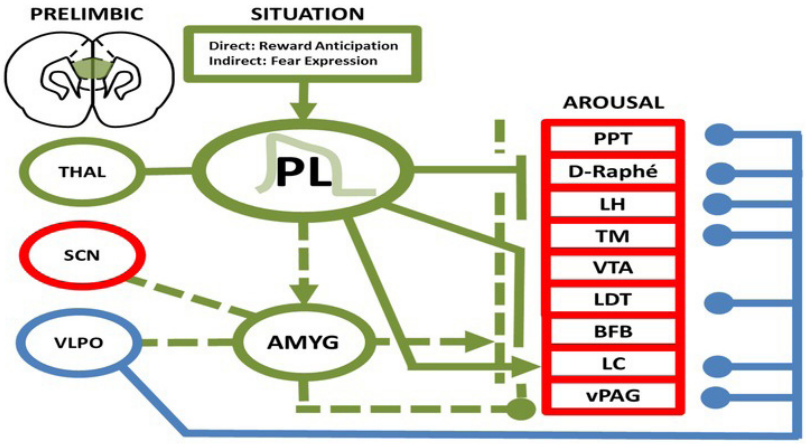

Figure 4: Model of the rodent prelimbic-arousal pathways. Model shows the direct (solid lines) pathway from the ACC to influence the ascending arousal system (red boxes), thalamus, VLPO and SCN and amygdala. The direct pathway appears to have some arousal promoting properties through the locus coeruleus. The ACC influence is self-limiting ('∩' symbol) and only turned on when awake, such that whatever influence it has over arousal will eventually subside. Abbreviations are as follows: LC, locus coeruleus; TM, tuberomammillary nucleus; BF, basal forebrain; PPT, pedunculopontine tegmentum; LDT, laterodorsal tegmentum; D-Raphé, dorsal Raphé nucleus; LH, lateral hypothalamus; VTA, ventral tegmental area and vPAG is ventral periaqueductal gray. Some connections from VLPO to arousal regions are presumed inhibitory because of the inhibitory cells bodies in the VLPO.

is the primary hub which controls the behavioural expression of fear and its memory, including arousal through connection with[111,112] the laterodorsal tegmentum[98], locus coeruleus[113], VTA[114], basal forebrain[115], lateral hypothalamus[116], pedunculopontine tegmentum[117], tuberomammillary nucleus[97] and the vPAG[118,119]. The medial amygdala also sends a direct projection to the VLPO[120] and the SCN[103]. Furthermore, electrical stimulation of the central nucleus of the amygdala has long been known to produce EEG desynchronisation[121–123]. In addition, deactivating the amygdala is sufficient to increase NREM sleep, decrease the latency to sleep and increase cortical power in the low-frequency range, suggesting that the amygdala contributes to an endogenous arousal drive[124,125].

Animals trained in an aversive environment and forced to sleep in the same environment take twice as long (~40 min) to fall asleep, suggesting that the ever-present aversive context can influence sleep onset[126]. Consistently, stress-provoking situations can antagonise sleep onset and produce sleep fragmentation, possibly through activation of the infralimbic cortex, locus coeruleus and amygdala[127]. Most importantly, the VLPO was also activated in this study even when the animal was awake, suggesting a competition between sleep and wake promoting processes. In this experiment, the amygdala was found to be responsible for the increased latency to sleep, and the infralimbic over-activation was found to contribute to sleep fragmentation. Thus, under persistent stressful situations and sleepiness, the amygdala appears to recruit arousal systems which antagonise sleep onset (or VLPO) while the infralimbic cortex antagonises sleep continuity.

In addition to modulating fear extinction, the infralimbic cortex also appears to influence arousal related to food anticipation. When hungry rats are enticed with food, they become behaviourally activated while trying to get the food and have significant anticipatory increases in core temperature[128]. Interestingly, the infralimbic and various arousal-related areas are activated during this enticement as evidenced by Fos immunoreactivity. However, lesion of the infralimbic cortex was found to not only abolish behavioural activation and anticipatory body temperature changes but also block the elevations and Fos activity in the tuberomammillary nucleus, VTA, lateral hypothalamus, dorsal Raphé, laterodorsal tegmentum and substantia innominata of the basal forebrain[128]. This provides an explanation of how energy homeostasis might compete with sleep homeostasis (e.g. being sent to bed without dinner) and underscores the importance that TDSC is defined as situational.

Collectively, the findings reviewed here suggest that the infralimbic cortex regulates arousal through an indirect pathway via the amygdala and a direct pathway through top-down control over the ascending arousal system (Figure 3). The infralimbic cortex may be optimally positioned to integrate subjective sleepiness with fear, hunger, circadian and homeostatic sleep demands.

Prelimbic-arousal pathways

The prelimbic cortex of the mPFC is known to connect to the dorsal Raphé, basal forebrain, laterodorsal tegmentum, lateral hypothalamus, VTA, locus coeruleus and vPAG[66,94,95,98–101,129] (Figure 4); however, there is a scarcity of data examining the influence of the prelimbic cortex on the activation of the ascending arousal system. One study conducted by Jodo et al.[129] found that both electrical and chemical stimulation of the prelimbic cortex of anesthetised rats was sufficient to activate locus coeruleus neurons. Interestingly, the inhibition of the prelimbic cortex was found to decrease locus coeruleus activity,

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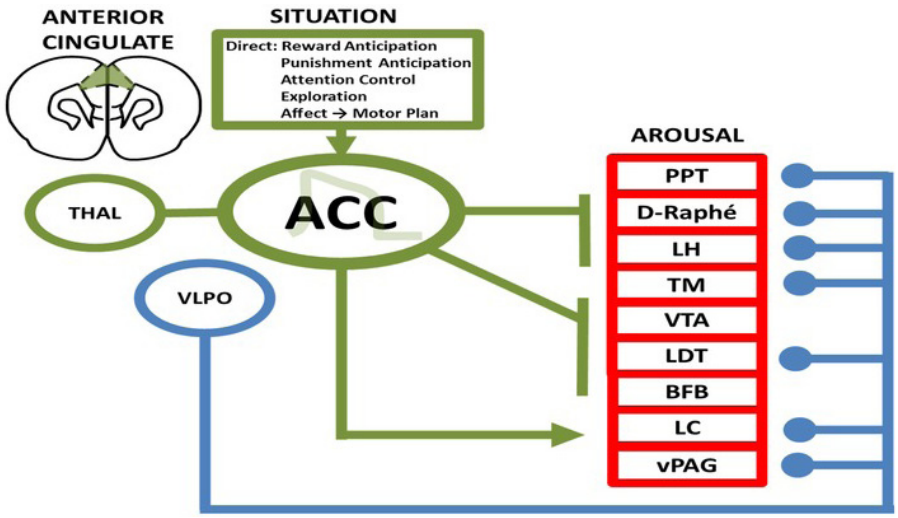

Figure 5: Model of the rodent anterior cingulate-arousal pathways. Model shows direct (solid lines) and indirect pathways (dashed lines) from the prelimbic cortex (PL) to influence the ascending arousal system (red boxes), thalamus, VLPO and SCN and amygdala. The direct pathway appears to have some arousal promoting properties through the locus coeruleus. The indirect pathway involves activation of the amygdala, which should have the effect of increasing arousal and preventing sleep. The prelimbic influence is self-limiting ('∩' symbol) and only turned on when awake, such that whatever influence it has over arousal will eventually subside. Abbreviations are as follows: LC, locus coeruleus; TM, tuberomammillary nucleus; BF, basal forebrain; PPT, pedunculopontine tegmentum; LDT, laterodorsal tegmentum; D-Raphé, dorsal Raphé nucleus; LH, lateral hypothalamus; VTA, ventral tegmental area and vPAG is ventral periaqueductal gray. Some connections from VLPO to arousal regions are presumed inhibitory because of the inhibitory cells bodies in the VLPO.

suggesting that the PFC might contribute a tonic drive to the locus coeruleus. In addition, electrical self-stimulation of the prelimbic cortex is sufficient to produce persistent behavioural activation in rodents[130]. One region activated by such stimulation is the VTA[130]. Consistently, stimulation of the prelimbic cortex activates VTA neurons[131] and alters their bursting activity[132,133], and in many cases inhibition precedes excitation[133,134]. In addition, excitatory prelimbic-VTA responses could be attenuated when orexin-1 antagonists were applied to the VTA during the active, but not the non-active, phase of the animal's diurnal cycle. The result indicates that the endogenous control of the VTA by orexin has diurnal variation. A final indication that the prelimbic cortex may be involved in self-sustaining activity is that single unit activity anticipates reward[135] and punishment[136,137]. At present, there is no rigorous experimental data, showing that rodents can forego sleep in anticipation of a future rewards or punishment; however, one study has shown that animals can be taught to awaken from sleep in order to receive rewards[138], suggesting that foregoing sleep might not be so hard to teach.

The prelimbic cortex is also connected to the amygdala; however, unlike the infralimbic cortex, the prelimbic cortex is known to be partly responsible for fear memory recall and fear expression[137,139] through a facilitatory connection with the basolateral amygdala[110]. As the amygdala is connected with the ascending arousal system, it represents an indirect facilitatory pathway to influence arousal. Thus, under the appropriate context, the prelimbic cortex might modulate arousal through the amygdala to maintain wakefulness.

Anterior cingulate-arousal pathways

The ACC of the mPFC is thought to be involved in a large set of processes, and it is often hard to pin down a singular function. Some of the common functions include pain[140–142], emotion-motor integration[143,144], fear memory[145–147], remote memory[148,149], reward[150,151], and attention and anticipation[147,151]. The ACC has a connectivity pattern to the ascending arousal system similar to that of the prelimbic cortex[94,95,99] and likewise is not connected with SCN, VLPO, tuberomammillary nucleus or the pedunculopontine tegmentum (Figure 5). Similar to the prelimbic cortex, the ACC has been found to increase bursting behaviour of VTA neurons which is often preceded by a brief inhibition[133].

Electrophysiological evidence implicates the ACC in the exploration of novel objects[152,153] and even the exploration of a sexually attractive mate[154]. Novel objects and exploratory environments are a frequent means of sleep depriving an animal because the results of these methods are minimally confounded by stress. Presumably, it's the animal's 'curiosity' that helps maintain the animal's ability to stay awake. It has been recently shown that the ability of animals to maintain wakefulness in a novel environment depends on reciprocal connectivity between the ACC and the locus coeruleus. Indeed, destruction of either the ACC or the locus coeruleus was sufficient to block the exploratory activity of the animal[127], consistent with its role in sustained wakefulness. Given that the concept of 'exploration' or 'curiosity' is somewhat abstract, it is remarkable that such drives could temporarily and substantially antagonise the sleep system. However, it should be noted that a simple offer of money is sufficient for one to stay awake all night.

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The PFC connection to the ascending arousal system is unique

If the entire cerebral cortex had the same direct connections and influence over the ascending arousal system and sleep switch that the PFC has, the potential of the PFC as a candidate for TDSC would lose merit. It has already been mentioned that the rat infralimbic cortex is the only region of the cerebral cortex which has direct efferents to the VLPO and the SCN (above) and to prove this is not the case for primates, retrograde traces need to be injected into these regions. The question remains whether or not other areas of cortex can influence the ascending arousal system. Based on retrograde labelling studies from the areas of interest, it appears that the PFC of rats and monkeys is the only cerebral cortical region to send efferents to the dorsal Raphé[80,101]. A similar case holds true for the locus coeruleus of monkeys and rats with the exception of the insula[80,113]. Consistently, the laterodorsal tegmentum is innervated quite strongly by the PFC but receives no other input from the cerebral cortex of the rat[98,155]. A similar trend holds for tuberomammillary nucleus[97], orexinergic lateral hypothalamus[116] and ventral tegmental nucleus[156] and vPAG[66]. Interestingly, the substantia innominata of the basal forebrain receives input from prefrontal, insular, entorhinal and pyriform cortex in rats[157,158]. By contrast, the nucleus basalis magnocellularis of the basal forebrain is relatively restricted in its cortical input from frontal cortex[158]. In primates, the primary input from the cortex to the nucleus basalis-substantia innominata originates from the orbital frontal cortex and the prepyriform cortex, insula, entorhinal cortex, medial temporal pole and temporal cortex[159]. Thus, with a very few exceptions, the PFC has privileged access to the ascending arousal system in both the primate and rat.

Discussion

The author has referenced some of its own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

Based on these findings in rodents and primates, it appears possible that cortical and limbic (e.g. amygdala) circuits may recruit the ascending arousal system and in some cases interact with the VLPO and SCN to modulate the homeostatic sleep system, so that sleep occurs during time periods both when it is safe and when there are no more goals to be realised. The results of this review implicate that PFC is uniquely positioned to modulate the ascending arousal system. In addition, the infralimbic cortex appears to interact with the SCN, VLPO and various arousal systems directly and indirectly via interaction with the amygdala. Similarly, the ACC and prelimbic cortex appear to modulate the ascending arousal systems for specific situations. The sensitivity of the PFC function to sleep deprivation may provide cues to trigger compensatory effort, which could be related to TDSC. For experimentation purposes, clear tests for the existence of TDSC would involve providing animals or subjects with the option to either sleep (according to circadian schedule) or to become engaged in actions that will result in the acquisition or reward or escape from punishment. Pharmacological or optogenetic manipulations can then be implemented to test the importance of different aspects of the PFC and associated indirect pathways (e.g. amygdala) in the modulation of behavioural activation and sleep propensity.

Conclusion

This review is intended to encourage a conversation on the topic of staying awake, and to compose a cogent and testable framework for exploration of higher-cortical neural systems that could antagonise sleep. It may well turn out that there are better candidates than the PFC to carry out the function of TDSC. However, the finding that the PFC is not related to TDSC would require an explanation for why it is uniquely connected with nearly all systems involved in the control of arousal, sleep switching and circadian rhythms. Finally, we should be mindful that a comprehensive account for how we forego sleep will require an explanation of how a single abstract concept (such as the anticipation of money or punishment) can seed a cascade of goal-directed processes which can take acute precedence over sleep homeostasis.

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Abbreviations list

ACC, anterior cingulate cortex; BA, Broadmann's areas; DLPFC, dorsolateral prefrontal cortex; MPFC medial prefrontal cortex; MSLT, multiple sleep latencies test; NREM, non-rapid eye movement; PFC, potential role of the prefrontal cortex; PFC, prefrontal cortex; REM, rapid eye movement; SWA, slow-wave activity; TDSC, top-down systems control; VLPO, ventrolateral preoptic area; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

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