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Review article

Apical drive—A cellular mechanism of dreaming?

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ABSTRACT

Dreams are internally generated experiences that occur independently of current sensory input. Here we argue, based on cortical anatomy and function, that dream experiences are tightly related to the workings of a specific part of cortical pyramidal neurons, the apical integration zone (AIZ). The AIZ receives and processes contextual information from diverse sources and could constitute a major switch point for transitioning from externally to internally generated experiences such as dreams. We propose that during dreams the output of certain pyramidal neurons is mainly driven by input into the AIZ. We call this mode of functioning “apical drive”. Our hypothesis is based on the evidence that the cholinergic and adrenergic arousal systems, which show different dynamics between waking, slow wave sleep, and rapid eye movement sleep, have specific effects on the AIZ. We suggest that apical drive may also contribute to waking experiences, such as mental imagery. Future studies, investigating the different modes of apical function and their regulation during sleep and wakefulness are likely to be richly rewarded.

1. Introduction

‘Dreaming is one of the most interesting and most wondrous phenomena of brain physiology’ (Ramón y Cajal, 1908: 87).

The transition to sleep brings about a crucial shift in the way that we relate to our surroundings. While during wakefulness, our experiences are strongly influenced by our current environment, upon falling asleep we gradually cease to perceive external stimuli and to act upon them. This sensory and motor disconnection is a defining feature of sleep across species. Its reversible nature distinguishes it from coma, as sensory stimuli readily wake up the sleeper, provided they are strong, sudden, or salient enough. Occasionally, an ambient sound like a ringing alarm clock may be incorporated into the content of a dream, but this appears to be the exception rather than the rule, as it is notoriously difficult to influence dream content experimentally using sensory

stimuli (Dement and Wolpert, 1958). Despite this striking *disconnection from the environment*, during sleep conscious experiences are generated in a variety of forms, ranging from abstract thoughts to ‘immersive spatiotemporal hallucinations’ that characterize typical dreams (Windt, 2015). Because of the sensory disconnection, however, these experiences are largely *independent of current external input* and thus *internally generated*.

Through which mechanisms are the neurons underlying dream experiences activated during dreaming sleep? What drives the neurons that generate the content of dreams? Several hypotheses and theories have tried to account for the mechanisms and function of dreaming (for review, see Nir and Tononi, 2010). Some of them assume that dreams are akin to perception, in that they originate in low-level sensory areas and are secondarily interpreted or contextualized by higher-order brain areas. Allan Hobson’s activation-input-modulation model for instance, is paradigmatic of such bottom-up theories (Hobson et al., 2000; Hobson

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and Pace-Schott, 2002; Hobson, 2009). In its initial version, it postulated that dreams are generated by signals from the brainstem (ponto-geniculo-occipital waves) that excite visual cortices and are then processed and synthesized by higher-order brain areas. In contrast, top-down models assume that dreams are more like imagination, starting from abstract thoughts, concepts, or even unconscious wishes, which are secondarily enriched with sensory percepts (Nir and Tononi, 2010). The present paper proposes, for the first time, a specific cellular mechanism that could account for such a top-down component of dreams.

More specifically, we propose that a key component of the mechanism lies in the fact that cortical pyramidal neurons have two functional compartments with distinct inputs (Larkum, 2013; Aru et al., 2020). Fig. 1 shows a sketch of layer 5 pyramidal (L5p) neurons whose cell bodies lie in layer 5, but whose dendrites span across all cortical layers. The basal dendrites mainly collect their inputs from layers 4–6 and feed relatively directly into the soma. This is the somatic integration zone, which is tightly coupled to the axon initial segment where the cell’s output arises, in the form of axonal action potentials. The main input to the soma conveys a stream of current sensory information about the external world. The other integration zone can be found where the thick apical trunk branches into an apical tuft of thinner dendritic branches, around cortical layer 1 of the cortex; this is the apical integration zone (AIZ) (Fig. 1), which is also the apical calcium spike initiation zone (Larkum et al., 1999, 2009; Larkum, 2013). The AIZ integrates input targeting the part of the pyramidal cell near the cortical surface, which has been called “the apical compartment” (Larkum, 2013; Aru et al., 2020) or the “distal compartment” (Suzuki and Larkum, 2020). Convergent evidence indicates that the apical compartment collects information from a variety of sources that can be used to interpret the “meaning” and significance of the current, feedforward sensory input to the soma (Larkum, 2013; Phillips et al., 2015; Aru et al., 2020). This input to the apical compartment includes contextual information from surrounding areas and other sensory modalities, as well as internally generated and stored information, e.g. from semantic memory. Much of this information to the apical compartment comes from higher cortical areas (cortical feedback), from higher order thalamic nuclei, and from the limbic system (Larkum, 2013; Aru et al., 2019). AIZ integrates that input, so that it can be propagated to the somatic integration zone in certain brain states (Fig. 1).

Here we propose a specific neurobiological mechanism for how cortical neurons are activated during dreams: we suggest that the drive does not come in feed-forward fashion as in wakefulness, but rather from internal sources activating the AIZ (Fig. 1). Our proposal is that the very same neurons that take part in encoding and representing the world during wakefulness are activated during dreams. However, the means of

activation is different: during wakefulness neurons are mainly activated through their basal synapses, whereas during dreaming, due to the specific neuromodulatory milieu, the main drive comes from the AIZ (Fig. 1). We call this proposed mode of activation “apical drive”.

First, we outline the neurophysiology (Section 2) and the main phenomenological features (Section 3) of dreaming. We then offer a brief overview of previous work on the properties and functions of the AIZ and show how it could be related to sleep and dreaming (Section 4). Next, we provide some simple anatomical and functional grounds suggesting that activation of the cell via its AIZ is involved in dreaming (Section 5). As the cholinergic and adrenergic neuromodulatory systems play leading roles in regulating behavioural states, we review evidence showing that they have strong effects on apical function (Section 6). We discuss how “apical drive” can explain dream characteristics (Section 7) and how it can contribute to awake cognition, including the role of “apical drive” in hallucinations (Section 8). Finally, we discuss some of the many unresolved issues that arise and conclude that they merit further investigation.

2. Neurophysiology of sleep and dreaming

Using electrophysiological recordings, including electroencephalography (EEG), electromyography (EMG), and electro-oculography (EOG), one can distinguish three main behavioral states: wakefulness, rapid eye movement (REM) sleep, and Non-REM (NREM) sleep (Fig. 2A). Each sleep state has a characteristic neuromodulatory profile. As can be seen in Table 1 and Fig. 2C, cholinergic modulation is conspicuously high during REM sleep, while adrenergic modulation is low. This neuromodulatory milieu has specific effects on the computations performed by the brain. Here we suggest a specific cellular mechanism resulting from high levels of acetylcholine (ACh) or other, similarly-acting metabotropic agonists, combined with low levels of noradrenaline (NA), which might underlie the enigmatic phenomenon of dreaming. More generally, we make the case that internally generated experience relies on specific neural mechanisms that are regulated by arousal systems. In this section we will first briefly summarize the work from the last few decades that has shed light on the neural processes associated with dreaming.

While dreaming was initially thought to occur exclusively during REM sleep (Aserinsky and Kleitman, 1953), subsequent studies showed that dreaming and REM sleep can be experimentally dissociated by pharmacological manipulation (Oudiette et al., 2012) and in patients with brain lesions (Solms, 1997, 2000). In addition, it is now well established that dreaming often occurs also in NREM sleep, although less frequently and with qualitative differences (see Table 1). Especially in

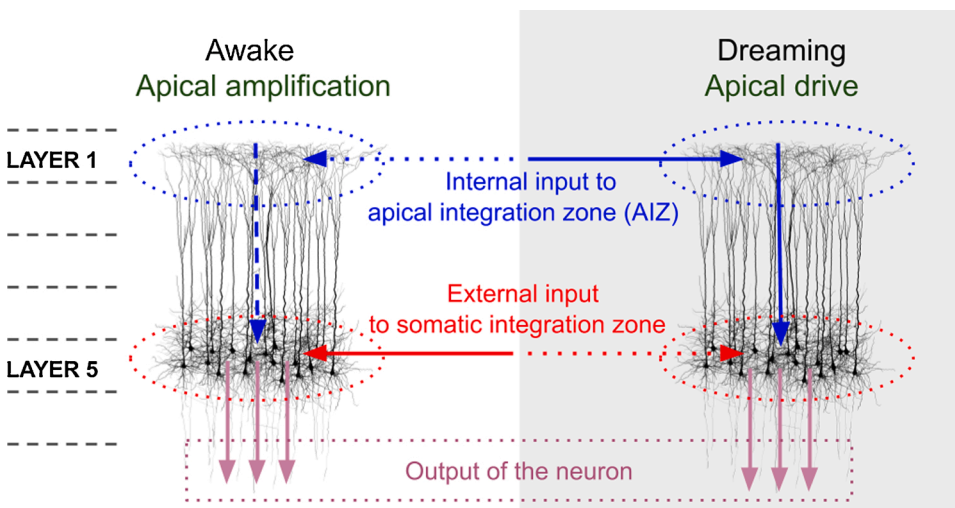


Fig. 1. A cellular hypothesis for dream generation. Neurons involved in the perception of external input when awake are driven by internal input when dreaming. This internal input targets the apical integration zone (AIZ) of layer 5 (L5) pyramidal neurons (blue dotted ovals). External input mainly targets the somatic integration zone (red dotted ovals). When awake the response to external input (continuous red arrow) can be amplified by apical input (dashed blue arrow), which increases the salience of external inputs that are relevant in the current context as signaled by the apical input. During dreaming internal input (continuous blue arrow) can activate an apical dendritic mechanism that enables it to drive the neuron’s output, consisting of action potentials in the axon (violet arrows), and that output is interpreted (by downstream circuits) as conveying information about the external world (external input) even though it does not.

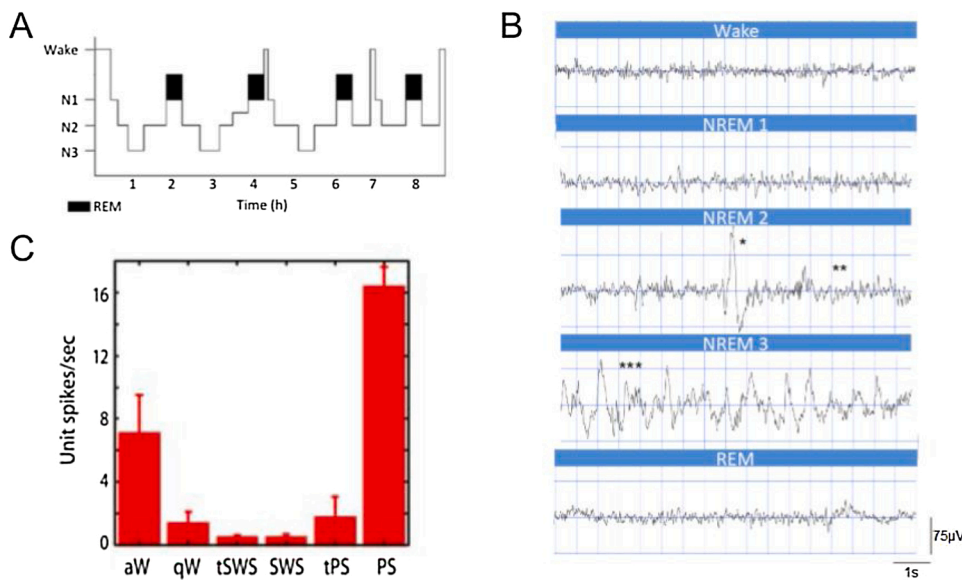


Fig. 2. Basic facts about sleep stages and neural activity of acetylcholine neurons. A. Hypnogram showing the distribution of sleep stages across a typical night of sleep in humans. B. EEG traces from different sleep phases. Non-REM (NREM) sleep in humans is subdivided into three stages in which the EEG is dominated by progressively slower frequencies: N1, a transitional stage in which the fast EEG of wakefulness starts to slow; N2, accounting for about 50 % of sleep in adults, characterized by K-complexes (marked with *) and spindles (**); and N3, also called ‘slow wave sleep’ (SWS) or ‘deep sleep’, in which at least 20 % of the page contains high-amplitude slow waves (***). REM sleep is characterized by rapid eye movements and high-frequency, low amplitude (desynchronized) EEG activity. C. Figure from Lee et al. (2005) showing that the average firing rate of labelled acetylcholine (ACh) neurons (n = 5) in the basal forebrain projecting to the neocortex were more than twice as high during REM sleep (here called “PS, paradoxical sleep”) than in quiet or active wakefulness (qW, aW), (transition to) slow wave sleep (tSWS and SWS) or transition to REM sleep / paradoxical sleep (tPS). Data from some of the labelled ACh neurons showed an even larger increase in firing rate (up to 11 times higher) during REM sleep compared to quiet wakefulness. Panel C copyright 2005 Society for Neuroscience.

Table 1
Physiological and psychological features, and neuromodulatory milieu, during wakefulness, NREM sleep, and REM sleep.

	Wakefulness	NREM sleep	REM sleep
EEG	Rapid, desynchronized	Slow, synchronized High-amplitude slow waves and spindles	Rapid, desynchronized
EOG	Eye movements	No eye movements	Rapid eye movements
EMG	High muscle tone	Intermediate muscle tone	Muscular atonia
Conscious experiences	Awake conscious experiences, including, perceptions, thoughts, and feelings.	Variable, ranging from the absence of consciousness to complex ‘hallucinatory’ experiences. Generally shorter, less vivid, more conceptual compared to REM sleep dreams. In late phases of sleep, sometimes indistinguishable from REM sleep dreams.	Vivid, internally generated story-like experiences.
<i>Neuromodulators</i>			
Acetylcholine	High	Low	Very High
Noradrenaline	High	Low	Low
Serotonin	High	Low	Low
Histamine	High	Low	Low
Dopamine	High	(Medium/High)	(Medium/High?)
Hypocretin	High	Very low	Low

the late phases of sleep, NREM dreams can sometimes be indistinguishable from REM dreams (Monroe et al., 1965; Antrobus et al., 1995).

Different types of evidence have converged to suggest that EEG slow

waves, one of the hallmarks of NREM sleep, or the neuromodulatory conditions underlying slow waves, interfere with the generation of conscious experiences, including dreams. At the neuronal level, slow waves reflect the bi-stability of cortical neurons and circuits between periods of depolarization and increased neuronal firing (up-state, on-period) and periods of hyperpolarization and neuronal silence (down-state, off-period) (Steriade et al., 2001), each lasting a few hundred milliseconds. Off-periods associated with slow waves have been shown to interfere with causal relations between different brain regions and to lead to a breakdown in cortico-cortical connectivity (Massimini et al., 2005; Pigorini et al., 2015; Arena et al., 2020). Slow waves are not uniformly distributed over the cortical surface as previously assumed, but can occur locally, as a function of learning and prior experience (reviewed in Bernardi and Siclari, 2019). While initially thought to be restricted to NREM sleep, recent studies have shown that local slow waves can occur also in wakefulness, although with a smaller amplitude (Vyazovskiy et al., 2011; Hung et al., 2013; Bernardi et al., 2015), as well as in REM sleep (Funk et al., 2016; Baird et al., 2018; Bernardi et al., 2019). A large study employing EEG recordings and serial awakenings has recently shown that low frequency activity (spectral power in the 1–4 Hz range) is negatively associated with dreaming in both NREM and REM sleep (Siclari et al., 2017), especially when the slow activity occurs in posterior brain regions grouped under the name of ‘posterior hot zone’, comprising the medial and lateral occipital lobe, extending to the precuneus and posterior cingulate gyrus (Siclari and Tononi, 2017; Siclari et al. 2018; for discussion see Koch et al., 2016; Boly et al., 2017; Storm et al., 2017; see also Odegaard et al., 2017 and Wong et al., 2019 for critical viewpoints). Dreams are also more likely to be reported when sleep spindles display a faster frequency in the posterior hot zone (Siclari et al., 2018). Faster spindle frequency has been related to relative thalamic depolarization and longer slow wave up-states, which are typically observed in NREM sleep late in the night, when NREM dreams can be just as long and vivid as REM dreams. Finally, successful recall of the content of the dream in NREM sleep appears to be favored by microarousals and associated events, including the so-called type I slow waves /K-complexes (Siclari et al., 2018).

Taken together, previous work has suggested that a key neural correlate of dreaming in both REM and NREM sleep is the reduction in slow wave activity in the posterior hot zone (Siclari et al., 2017). The same areas and neurons have also been proposed to be the key correlates of awake conscious experience (Koch et al., 2016).

3. Phenomenology of dreams

3.1. Dream experiences have a true perceptual quality and are associated with activation of the same brain areas as perceptual experiences when awake

In the present paper we take the view that dream reports can be taken at face value, provided that carefully designed experimental protocols are used (Windt, 2015; Revonsuo, 2000; Valli and Revonsuo, 2009; Nir and Tononi, 2010; Siclari et al., 2017, 2018; Siclari and Tononi, 2017).

One of the perhaps most remarkable aspects of dream experiences is that they have a truly perceptual quality. Dreams are not mere wake-like thoughts or vague impressions, but, instead, contain vivid representations of objects, people, places, sounds and voices. These experiences are, strictly speaking, hallucinations - 'perceptions of something that is not present' - yet the 'perception' itself is real and is experienced as being virtually identical to waking perception. Again, this seems to support the idea that the very same neurons mediate waking and dreaming experiences, simply their mode of activation is different. This similarity is supported by content analysis studies, showing that the modality of perceptual experiences in dreams closely mirrors waking experiences in terms of frequency, with almost 100 % of dreams being visual, followed by auditory, somatosensory, gustatory and tactile experiences (Snyder, 1970). In line with these observations, visual areas are functionally and hemodynamically just as active during REM sleep (a stage in which the most vivid dreaming occurs), as in wakefulness (Maquet, 2000; Schwartz and Maquet, 2002). Importantly, EEG activation of the posterior hot zone distinguishes dreaming sleep from unconsciousness in both REM and NREM sleep (Siclari et al., 2017, 2018), suggesting that these regions are part of a core network mediating dream experiences, irrespective of sleep stage. Activation of the posterior hot zone has also been shown to correlate with the perceptual as opposed to thought-like quality of dream ratings (Siclari et al., 2017). In addition, within the posterior hot zone, localized activations have been related to broad categories of dream content, including faces, spatial setting and perceived speech. These activations closely match brain areas involved in the perception of the same contents during wakefulness (Siclari et al., 2017). Functional magnetic resonance imaging activity in visual areas has been used to successfully decode dream contents at sleep onset with a classifier that had previously been trained while awake subjects viewed movies (Horikawa et al., 2013), further corroborating the correspondence of perceptual substrates between sleep and wakefulness.

3.2. Similar to waking perceptions, dream perceptions can be associated with corresponding motor behaviors

During sleep, motor output is largely suppressed. In REM sleep, this suppression is brought about by brainstem neurons that synapse on inhibitory interneurons in the anterior spinal cord (Ehrminger et al., 2016; Valencia Garcia et al., 2017). However, there are exceptional conditions characterized by motor behaviors during sleep, which can give insight into the dream state. These conditions include parasomnias (sleepwalking in NREM sleep, and REM sleep behavior disorder in REM sleep), in which patients enact their dreams and perform goal-directed movements aimed at dreamed objects or people (Schenck et al., 1986; Oudiette et al., 2012; Siclari et al., 2020), and lucid dreaming, a state in which the dreamer is aware of the fact that he or she is dreaming and is able to communicate with the examiner via a pre-established code of eye movements. Lucid dreamers can visually track moving targets in their

dreams, and in doing so perform smooth pursuit eye movements that are strictly dependent on perception in wakefulness (LaBerge et al., 2018a). These observations suggest that apical drive can operate not only to generate perception-like experiences, but also motor reactions to these experiences, provided that motor output becomes possible (either through lucidity and resulting control of eye movements or loss of motor suppression).

3.3. Dreams are associated with reduced reflective consciousness, bizarreness, high emotionality and amnesia

Despite these similarities with waking perception, dreams also display some striking differences. With the rare exception of lucid dreaming, dreaming individuals almost never realize that they are lying in a bed sleeping, but instead find themselves immersed in a dream plot, which they take for real. This false belief is even more surprising when one considers the numerous inconsistencies, uncertainties, and temporal discontinuities that characterize many dreams. Indeed, physically impossible or highly unlikely events can occur in dreams, yet only rarely and temporarily lead to puzzlement or insight into the fact that one is dreaming. It has been suggested that the reduced reflective consciousness and impaired ability to judge may result from relative deactivation of frontal and parietal associative areas that distinguishes REM sleep from wakefulness (Schwartz and Maquet, 2002). Dreams are often highly emotional and frequently negatively toned, consistent with increased activation of limbic and paralimbic areas (Schwartz and Maquet, 2002). Finally, memory for the dream and within the dream is greatly altered. Unless immediately recorded, most dreams are rapidly forgotten and only a small and salient minority of dream experiences makes it into long-term memory (Nir and Tononi, 2010).

Despite a good correspondence between our dreaming and waking lives (during dreams we often encounter familiar people and places, and have preoccupations that are similar to the ones of our waking lives), dreams are almost never the exact replay of waking life episodes (Schwartz, 2003). Instead, elements of waking life are transformed and appear in unusual combinations in dreams. Studies evaluating which elements of waking events appear in dreams have shown that many dreams can be traced back to events occurring during the day preceding the dream – a phenomenon referred to as day-residue effect (de Saint-Denys, 1867; Nielsen and Powell, 1992). Some studies have also provided evidence for a dream-lag effect, that is, another temporal peak of integration of elements from events occurring about a week before the dream (Nielsen and Powell, 1992; Van Rijn et al., 2015; van Rijn et al., 2018). It remains open whether it is specific to certain types of events (Vallat et al., 2017; Veloce et al., 2019) and sleep stages (Blagrove et al., 2011).

In summary, dreams are internally generated experiences that are independent of current, external sensory stimuli, occurring while one is largely disconnected from the environment on both the sensory and the motor side. Dreams often have a vivid perceptual quality, similar to waking experiences, and are associated with activation of perceptual areas corresponding to specific dream contents. Motor reactions to dream perceptions can occur in particular conditions (lucid dreaming, parasomnia) and appear to be congruent with these perceptual experiences. Features distinguishing dreams from waking cognition include reduced reflective consciousness, bizarreness, high emotionality, and partial memory impairments. In the current work we will outline and discuss to which extent these characteristics of dreaming can be explained by apical drive.

4. Three modes of apical functioning

4.1. Apical integration zone and its function

In vitro work on individual layer 5 pyramidal (L5p) cells has revealed the existence of an apical zone of integration (AIZ) that mediates

interactions between feedforward information and internal contextual information from diverse sources (e.g. Larkum et al., 1999, 2004, 2009; Harnett et al., 2013; Larkum, 2013; Major et al., 2013) (Fig. 1). Evidence shows that AIZ sends signals to the somatic integration zone (Fig. 1), but the communication also goes in the other direction: action potentials back-propagate from soma to the AIZ (Larkum et al., 1999; Larkum, 2013). These back-propagating action potentials lower the threshold for activating the AIZ. When the AIZ is activated at the time of this back-propagation, large dendritic calcium spikes are generated that cause burst firing of somatic action potentials. This process is called back-propagation-activated calcium spike firing or BAC firing (Larkum et al., 1999; Larkum, 2013). So far, the main focus of theoretical investigations into the relevance of AIZ in cognitive functions has been on one specific type of interaction between the AIZ and the soma - apical amplification (Phillips, 2017; Phillips et al., 2016). In the present work we suggest that the interactions between the soma and the AIZ have distinct functional modes in different behavioral states. In particular, we propose that in contrast to normal awake behaviour, in which apical amplification is the main mode of functioning, dreams are characterized by apical drive and dreamless sleep by apical isolation. Below, we describe each of these functional modes.

4.2. Apical amplification as a cellular mechanism for contextual modulation

Neurophysiological and psychophysical evidence shows contextual modulation to be widespread in neocortex (Lamme, 2004; Gilbert and Sigman, 2007; Gilbert and Li, 2013). That evidence supports a rigorous, mathematically specified, theory of cortical function in which contextual fields are explicitly distinguished from receptive fields (Phillips et al., 1995; Kay et al., 1998; Kay and Phillips, 2011). This form of contextual modulation cannot be identified with the elementary arithmetic operators, such as multiplication and division, but can be identified with the effects of input to the AIZ in L5p neurons (Kay and Phillips, 2020). Basal inputs to cortical pyramidal cells in perceptual regions convey information that more or less directly reflects external, sensory information. Inputs to the AIZ arise from a diverse variety of internal sources including higher cortical regions, higher-order thalamus, limbic regions, and the amygdala (Larkum, 2013). Those inputs provide the context for interpreting current information about the external world arriving at the basal dendrites. By amplifying or attenuating transmission of that external input, the apical input to the AIZ helps to disambiguate and interpret its meaning (reviewed in Phillips et al., 2015; Phillips, 2017).

Evidence from a wide variety of methodologies suggests that apical amplification provides a cellular mechanism for contextual modulation, thus involving it in a wide range of cognitive functions and their disorders (Phillips et al., 2015). For example, in perception apical amplification could be the cellular basis of contextual disambiguation, where one and the same stimulus is perceived differently in different contexts. More generally, apical amplification is a potential mechanism for the context-dependence of our thoughts and actions (e.g. a knife could be a tool for buttering or cutting, a way to turn a screw, or a weapon). Similarly, one could think of selective attention as working through apical amplification: if one is looking for her child in a crowd, the neurons representing this child can be pre-activated via the AIZ. Other cognitive functions in which apical amplification is implicated include cognitive control, and the flexible selection and coordination of behavioral action (Phillips et al., 2015).

4.3. Apical drive as a mechanism for expressing information from internal sources

Given the importance of contextual modulation to many cognitive functions, and the evidence relating that to apical amplification, the amplifying response to concurrent basal depolarization has been the

main apical function emphasized so far (e.g. Spratling and Johnson, 2006; Phillips et al., 2015, 2016; Wibrall et al., 2017; Takahashi et al., 2016). We now argue that apical function can be related to sleep and dreaming if two other possible modes of apical function are also considered, i.e. *apical drive*, and *apical isolation*. As shown in Fig. 3, our working hypothesis is that apical amplification is the predominant mode of apical function in perceptual cortical regions when awake, that apical isolation is the predominant mode during slow wave sleep when dreaming is mostly absent or qualitatively reduced, and that apical drive is the predominant mode when dreaming in REM sleep. Sections 5 and 6 of the paper will describe apical drive in more detail. Here it is sufficient to say that these three modes are tightly related and are all based on the same principles as described in 3.1. Apical drive can be seen as a very sensitive version of apical amplification, where the activation of AIZ can trigger axonal action potential output from the cell (Larkum et al., 1999; Suzuki and Larkum, 2020). This conclusion suggests that apical drive might also be observed under wakefulness, a topic that will be taken up in section 8.

4.4. Apical isolation as a mechanism for suppressing the effect of apical input on spiking

Though the focus of this paper is on apical drive during dreams, a brief outline of the concept of *apical isolation* is also needed. As depicted in Fig. 3, during apical isolation the AIZ might be activated, but this activation neither strongly modulates nor drives somatic spiking. In other words, the AIZ is largely isolated from the processes happening at the soma. Such isolation might be the state of affairs during some parts of NREM sleep. For example it has been observed that during spindle-rich NREM sleep, the activity of the AIZ is increased, while this increase is not seen at the cell somata (Seibt et al., 2017). Another evidence for apical isolation comes from the state of general anesthesia where even a strong activation of the AIZ has essentially no effect on somatic activity (Suzuki and Larkum, 2020). As anesthesia is similar to dreamless sleep in the sense that there is no conscious experience, it is reasonable to suggest that such a state might also happen during certain phases of NREM sleep. Suzuki and Larkum (2020) showed that the effect of AIZ on soma is controlled by metabotropic ACh and glutamate receptors: Blocking these receptors blocked the effect of AIZ on somatic spiking. A similar mechanism is likely to cause apical isolation also during SWS. Taken together, apical isolation is a state where there is active dendritic processing independently of spiking activity of these cells. It is worth noting that this state of activation might be crucial for systems memory consolidation (Seibt et al., 2017; Klinzing et al., 2019).

5. Anatomical and functional arguments suggest that dreams could arise from apical drive in neocortical pyramidal cells

5.1. Direct empirical support for apical drive

There is direct experimental evidence showing that the activation of AIZ can affect perception and hence be a suitable candidate for generating dreams. In a sensory detection task, Takahashi et al. (2016) demonstrated that manipulation of the AIZ of L5p cells affects the behavioral report of the animal. In this experiment, mice learned to detect weak whisker stimuli of different intensities i.e. sometimes at, sometimes below, sometimes above the detection threshold. This allowed the researchers to demonstrate that the activity of AIZ was well correlated with the animal's behavioral "report" of (i.e. its response to) its sensory perception. In addition, signals from AIZ could predict the behavioral hits and misses of threshold stimuli. Most importantly, directly influencing the AIZ through pharmacological intervention or optogenetics had a measurable influence on the detection behavior of the animal; in particular, optogenetic activation of the AIZ led to false alarms. In other words, artificially activating the AIZ caused the animal to respond as if a whisker stimulus would have been present. Hence, it

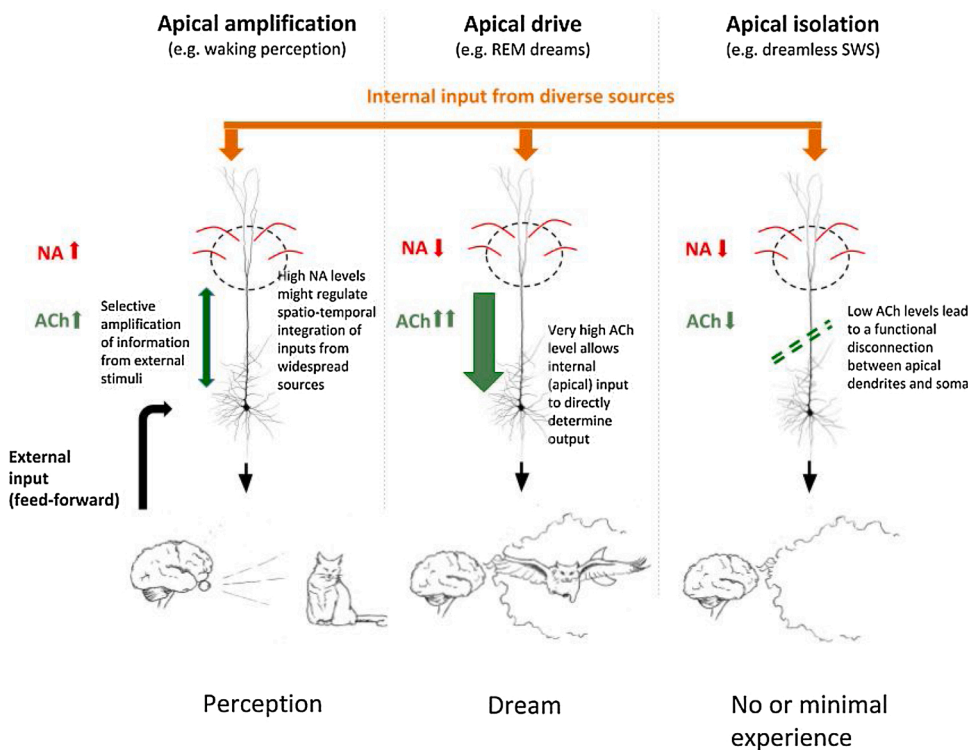


Fig. 3. The proposed role of acetylcholine (ACh) and noradrenaline (NA) during wakefulness, dreams and dreamless sleep. ACh regulates transmission of information from the apical integration zone to the soma, facilitating apical drive. NA regulates the extent of spatio-temporal summation of input to the apical dendrites. During both quiet and active wakefulness, apical input amplifies the transmission of relevant information. During dreams, apical drive transforms contextual guidance into self-fulfilling prophecies. During dreamless sleep, both NA and ACh are low so neurons are in the “apical isolation” mode.

might have been that the animal “dreamt up” a stimulus that was not there, causing a vivid illusion, just like humans have been shown to do when expecting a stimulus that in reality is not there on the screen (Aru and Bachmann, 2017; Aru et al., 2018). This research offers strong support for the claim that input to AIZ can activate the cells and can lead to the animal reporting the presence of a sensory signal. Hence, AIZ activation could in principle lead to perceptual experiences including dreams.

Recently, Suzuki and Larkum (2020) went a step further in dissecting the mechanisms of apical drive. The authors optogenetically stimulated the AIZ of L5p cells, thus in effect generating an artificial ‘apical drive’, and measured the effects of this perturbation on the activity at the soma of the same cells while varying the state of consciousness of the animal. In the awake state, stimulation of AIZ had a large effect on the soma and could drive high frequency firing of the neurons. However, various anesthetics made this effect disappear: the same optogenetic stimulation of the AIZ did not propagate to the soma under anesthesia. Hence, under anesthesia apical drive was not effective. This situation, where the AIZ is activated but this activation is not propagated to the soma, corresponds to “apical isolation” (Fig. 3, right), a state seen in NREM sleep (Seibt et al., 2017). Accordingly, the situation where strong activation of AIZ leads to neuronal output corresponds to apical drive. As in the experiments of Suzuki and Larkum (2020) such apical drive was artificially elicited during wakefulness, it is in principle possible that apical drive could also be occurring in the awake state (see section 8).

Suzuki and Larkum (2020) went on to study the processes underlying apical drive: which mechanisms are responsible for this blocking of the drive from AIZ to soma? One of the main results was that blocking the muscarinic ACh (mACh) receptors led to a breakdown of the ability of AIZ to drive the firing of the cells. Hence, ACh seems to play a key role during apical drive, which would fit with our idea that apical drive is the predominant mode during REM sleep when cholinergic modulation is at its peak.

Taken together, recent rodent work demonstrates that 1) apical drive can lead the animal to report that it perceived a stimulus that was in fact not there (Takahashi et al., 2016), and 2) one of the key mechanisms

supporting apical drive is cholinergic neuromodulation (Suzuki and Larkum, 2020). These findings motivate us to look closer at how neuromodulators control the workings of AIZ (Section 6).

5.2. Anatomical arguments

As mentioned on several occasions, the input to AIZ comes from various internal sources (Larkum, 2013). Feedback from higher cortical areas, for example from the frontal and parietal cortices, is known to target the AIZ and layer 6 of the same column (Markov et al., 2014; Harris et al., 2018). During REM the activity of limbic and paralimbic areas, including the amygdala, anterior cingulate cortex, and insula, is higher than in wakefulness (Maquet et al., 1996; Nofzinger et al., 1997). These areas are the prime candidates for the sources of apical drive during dreams, as indeed these areas send projections to AIZ (Amaral et al., 2003; Leinweber et al., 2017). Also the hippocampus is known to project to layer 1 of certain cortical areas (Yamawaki et al., 2019), and perirhinal cortex projects to AIZ (Doron et al., 2019). Finally, higher order thalamic nuclei, such as the pulvinar, and the intralaminar nuclei, also send their projections to AIZ (Jones, 2012; Larkum, 2013). All these areas are in a position to potentially drive the pyramidal neurons during dreaming and hence are the main suspects for the internal sources of dreaming.

5.3. Arguments based on Bayesian brain theory

It might be worth considering the possible computational role of the inputs to AIZ and soma. One important insight that has a long history is that the external world cannot be directly sensed, but rather has to be inferred by the brain (Kant, 1781; von Helmholtz, 1860; Russell, 1912; Hohwy, 2013). Accordingly, conceptions of neocortex as performing probabilistic inference in what is known as a ‘Bayesian’ manner have become highly prominent (e.g. Rao and Ballard, 1999; Knill and Pouget, 2004; Körding, 2007; Lee and Mumford, 2003; Friston, 2012). Within this framework one can think of the somatic integration zone as collecting “data” and the AIZ as providing the prior or the “hypothesis”

about these data (Aru et al., 2020). The computations happening within the L5p cells could be understood as “testing” the hypothesis on these data (Siegel et al., 2000; Kay et al., 2019). During dreaming, instead of being tested against external data, internal hypotheses become self-fulfilling prophecies that directly activate pyramidal cells by themselves (see also Hobson and Friston, 2012).

6. The combination of high cholinergic and low adrenergic arousal favor dreaming

6.1. Arousal and cognition when awake depend on the combined effects of cholinergic and adrenergic systems

Several sub-cortical nuclei regulate the state of arousal and the excitability of neocortical pyramidal cells (Hobson, 2009; Brown et al., 2012; Zaghera and McCormick, 2014). To a first approximation, the bewildering intricacies of this regulation can be simplified by focusing on the activity of the cholinergic and adrenergic systems, although other neuromodulators such as serotonin, histamine, and dopamine also play important roles (Table 1). We will in the following focus on the effects of ACh and NA as their effect on the AIZ has been extensively studied (but see Nichols, 2016 for the effects serotonin and psychedelic drugs on the AIZ).

As outlined above, both the cholinergic and adrenergic systems are tonically active when awake, though with important phasic fluctuations (e.g. Brown et al., 2012; McGinley et al., 2015; Reimer et al., 2016). During NREM sleep, the activity of both the cholinergic and the adrenergic system is low, whereas during REM sleep cholinergic arousal reaches its highest levels (Fig. 2C) while adrenergic activity reduces even further (Table 1; Lee et al., 2005; Vazquez and Baghdoyan, 2001; Datta, 2010; Saper et al., 2010; Takahashi et al., 2010).

Temporary phasic fluctuations of cholinergic and adrenergic modulation have a major role in regulating cognitive functions when awake. Cholinergic modulation is particularly crucial to attention (Sarter, 2009; Sarter and Kim, 2015; Hasselmo and Sarter, 2011; Schmitz and Duncan, 2018). Adrenergic modulation is proposed to have a major role in regulating many cognitive functions, including contextual effects in perception, attention, and cognitive control (Mather et al., 2015; Phillips et al., 2016) and the executive functions of the prefrontal cortex (PFC) (Robbins and Arnsten, 2009). Cholinergic modulation tends to activate limbic regions while deactivating PFC regions (Hobson et al., 2000).

Though some previous reviews have focused only on the cognitive functions of either cholinergic (e.g. Sarter et al., 2009; Schmitz and Duncan, 2018) or adrenergic modulation (e.g. Robbins and Arnsten, 2009; Phillips et al., 2015, 2016), cognition when awake depends profoundly on both arousal systems (McGinley et al., 2015; Reimer et al., 2016; Shine, 2019). The combined effects of ACh and NA when awake may be complementary such that slow fluctuations of arousal are mainly due to ACh, whereas faster fluctuations are mainly due to NA (Reimer et al., 2016). Shine (2019) argues that the main effect of cholinergic modulation on cognition is to segregate activities into distinct subsets, whereas the main function of adrenergic modulation is to integrate distinct activities into coherent wholes.

6.2. High cholinergic arousal enables apical drive

Both in vitro and in vivo work provides evidence that both cholinergic and adrenergic systems have important effects on apical function. Immunostaining for acetyltransferase in rats indicates that the densities of ACh axons and varicosities is highest in layer 1 (Mechawar et al., 2000). As expected based on that, in vitro intracellular recordings show that release of ACh profoundly and selectively regulates the electrical excitability of AIZ in rodent L5p neurons (Williams and Fletcher, 2019). Release of ACh transforms apical dendritic integration in L5p neurons such that apical depolarization alone can powerfully drive somatic

action potential output (See Figs. 1D and 3 G in Williams and Fletcher, 2019). This enhancement of apical excitability was shown to be specific to the depolarization of the AIZ because ACh release did not alter response to direct depolarization of the soma (Williams and Fletcher, 2019). These effects were shown to be mediated by the muscarinic ACh receptor-dependent enhancement of dendritic calcium channel activity in the AIZ, and to last for more than a second following only a 4 millisecond release of ACh. These results agree well with that muscarinic ACh receptors are essential for REM sleep (Niwa et al., 2018) and converging evidence that ACh is important for dreaming (LaBerge et al., 2018b; Singh and Gupta, 2019).

Cholinergic activation of nicotinic ACh receptors also leads to inhibition of the inhibitory neurogliaform (NGF) cells in the supragranular layers of the neocortex. NGF cells profoundly dampen electrogenesis in the AIZ of L5p neurons, so, in addition to enhancing the effects of apical depolarization on somatic action potential output, ACh also disinhibits input to the AIZ (Pérez-Garci et al., 2006; Palmer et al., 2012; Brombas et al., 2014; Letzkus et al., 2015).

As described above, one key finding from the recent work of Suzuki and Larkum (2020) is that muscarinic ACh receptor antagonists abolished apical drive. When muscarinic ACh receptor antagonists were applied in the awake cortex in vivo, the activation of AIZ did not lead to somatic action potentials. This research demonstrates that muscarinic ACh receptors causally contribute to apical drive.

Taken together, ACh strongly facilitates apical drive. The facts that 1) ACh is at its highest activity during REM (Lee et al., 2005; Vazquez and Baghdoyan, 2001), when most of the vivid dreams occur, and that 2) muscarinic ACh receptor agonists facilitate (Williams and Fletcher, 2019) and antagonists block (Suzuki and Larkum, 2020) apical drive, are key pillars for the present proposal regarding the cellular mechanisms of dreams.

6.3. Low adrenergic arousal and spatio-temporal summation at apical dendrites

The large effects of adrenergic arousal on AIZ and its ionic mechanisms have been reviewed in depth previously (Phillips et al., 2016). To understand some of the ionic mechanisms involved, it is necessary to know about the hyperpolarization activated *h-current* (I_h) conducted by cation channels of the HCN-type, which are particularly dense in the distal apical dendrites, including the AIZ (Williams and Stuart, 2000; Berger et al., 2001; Lörincz et al., 2002; Kole et al., 2006; Harnett et al., 2015). I_h selectively reduces spatio-temporal summation in the distal apical dendrites, while having little effect on basal dendritic integration (Major et al., 2013). This means that when I_h is larger, the AIZ will be relatively less influenced by inputs that are further from it in space and effects on AIZ will decay quicker over time, hence reducing the ability of AIZ to amplify basal input.

Crucially, there is evidence for two opposing effects of NA on HCN channels and thus on I_h . While some evidence suggests that adrenergic arousal reduces I_h (Carr et al., 2007; Barth et al., 2008; Dembrow and Johnston, 2014; Wang et al., 2007), other data suggest that noradrenaline can enhance I_h (Pedarzani and Storm, 1995; Storm et al., 2000).

These two possibilities have quite different effects relative to the hypothesis presented here. If adrenergic arousal closes HCN-channels and reduces I_h , one would expect that during REM sleep and dreaming, when adrenergic arousal is low (Table 1), I_h increases. This would reduce the effect of apical drive on the soma by a large shunting effect of open dendritic HCN channels, which attenuates the effect of ACh and apical drive (i.e. the depolarizing, apical drive is reduced because ions “leak” through open HCN channels). This inference is supported by data from rat PFC pyramidal cells (Barth et al., 2008) and by experiments using two-photon dendritic Ca^{2+} imaging and in-vivo whole-cell and extracellular recordings in awake mice (Labarrera et al., 2018).

In contrast, if noradrenaline opens HCN-channels (Pedarzani and

Storm, 1995; Storm et al., 2000), dendritic HCN channels would be less open during REM sleep and dreaming when NA is low. This would reduce their shunting effect and increase the spatio-temporal summation on AIZ, so that apical drive should more strongly affect the soma, in agreement with our proposed mechanism of dreaming. (See also Discussion, paragraph 9.2.1.2.)

6.4. Overview of cholinergic and adrenergic regulation of apical function

Our hypotheses regarding the regulation of apical function by arousal systems is summarized in Fig. 3. It illustrates three main conclusions. 1. The cholinergic and adrenergic arousal systems, which regulate transitions between waking and different sleep stages both have large effects on apical function in L5p cells. 2. Apical depolarization in those cells is sufficient to generate somatic action potentials given adequate cholinergic arousal, such as during REM sleep dreaming. 3. When cholinergic and adrenergic arousal are combined, as in the awake state, apical depolarization guides the probabilistic inferences made from sensory data by amplifying signals that are either probable or highly informative in the current context. However, even during wakefulness, the levels of cholinergic and adrenergic arousal are not constant (e.g. Brown et al., 2012; McGinley et al., 2015; Reimer et al., 2016). This raises the possibility that subtle phasic changes in those arousal systems, when awake, regulate apical function so that it approaches the idealised modes of apical function sketched in Section 4 and Fig. 3 to greater or lesser degrees. In particular, we suggest that apical drive can also happen during wakefulness (see Section 8).

7. Apical drive and dreaming

7.1. Apical drive and dream characteristics

Our proposal, which takes into account the distinct effects of ACh and NA on apical function, can help explain several phenomenological aspects of typical REM sleep dreams (Table 2). First, we propose that in the presence of high ACh levels, internal input into the AIZ directly drives pyramidal cell output. This accounts for the fact that dreams are experiences that are *generated internally*, without influence of current external stimuli.

Second, we hypothesize that the same pyramidal neurons involved in the perception of external stimuli during wakefulness are involved in dreams. However, instead of being activated by external sensory stimulation through inputs to the soma, during dreams, pyramidal neurons are activated mainly by internal information through apical drive (Fig. 3). The fact that the same sensory neurons are activated during dreaming and perception can explain why dreams have a *vivid perceptual quality*, similar to waking perception, and is consistent with the observation that perceptual contents in dreams activate the same areas as corresponding contents during wakefulness (Siclari et al., 2017).

Third, as explained in Section 6.3, low adrenergic arousal changes spatio-temporal summation in the apical tuft. According to one hypothesis (See Section 6.3), low adrenergic arousal reduces and according to the other hypothesis it enhances spatio-temporal summation. In either case, this implies that during dreaming the inputs impinging on the AIZ will be *relatively different* from the inputs that affect AIZ when awake. There is not yet much empirical evidence about which types of inputs are spatially closer to the AIZ and which ones are more distal (Cruikshank et al., 2012; Yamawaki et al., 2019), but in principle it is possible that inputs from certain structures (e.g. limbic and paralimbic areas) project to locations closer or further away to AIZ than other structures (e.g. higher cortical areas). Such limbic projection patterns, together with the effect of low NA that changes the relative strength of inputs during REM sleep, might explain the emotional content of dreams.

Finally, our hypothesis can also help explain why dreams may contain features that differ from waking perceptions. Most agree that dreams are flagrantly ‘psychotic’ in that they tend to include experiences

Table 2
Apical drive and dream characteristics.

Features of REM sleep experiences	Description	Possible underlying mechanism at cellular level
Internal generation of dream experiences	Dreams are internally generated experiences, independent of sensory input.	In the presence of high ACh levels, ‘internal’ input into the AIZ directly drives pyramidal output/firing.
Perceptual quality of dream experiences	Dreams are like vivid ‘hallucinations’, with a perceptual quality that is similar to waking experiences.	The same pyramidal neurons that mediate perceptions during wakefulness are activated during dreams, only the way they are activated differ. Instead of being activated by external sensory stimulation through inputs close to the soma, like during wakefulness, during dreams, they are activated by internal information transmitted to the soma through apical drive.
Bizarreness of experiences and hyperassociativity	Dreams can contain incongruities (for example unusual associations or physically impossible events), they represent a hyperassociative state, in which seemingly disparate or only loosely related contents become connected in one single dream scene.	In dreams, the content of the experience does not reflect the exact properties of external stimuli, like in waking perception, but instead the way information is organized ‘internally’ and transmitted to apical dendrites. Increased spatiotemporal summation and influence of more distal inputs arriving at the apical dendrite (possibly favoured by low NA) may explain hyper-associativity.

that are hallucinatory and delusional (e.g. Hobson, 2009; Walker, 2017). According to our hypothesis, *bizarre or incongruent elements* (unlikely associations) can occur because in dreams, the content of the experience does not predominantly reflect the properties of current external stimuli, like in waking perception, but instead the way information is organized ‘internally’ and transmitted to the apical compartment of pyramidal cells. In addition, if the low noradrenaline levels in REM sleep lead to an increased spatiotemporal summation of different inputs arriving at the apical dendrite, as suggested by some experimental work (Pedarzani and Storm, 1995; Storm et al., 2000), then this may help explain why REM sleep dreams represent such a rich ‘hyperassociative’ state, in which seemingly disparate or only loosely related concepts or objects become connected in one single dream scene. Apical drive may therefore help explain (probably in conjunction with other mechanisms; Solms, 1997; Nichols, 2016) how incongruence can come about during dreams and may also provide insights about the function of dreams (Fig. 4).

A long-standing idea in neuroscience is that the brain learns an internal model of the world (Conant and Ross Ashby, 1970; Gregory, 1980; Friston, 2010) (Fig. 4, middle). This model is built up through learning and plasticity based on waking experiences and it might be adjusted during sleep (Hinton et al., 1995). In this internal model there are parts (subspaces) that are never visited during wakefulness, i.e. they are never directly experienced. An insight from recent advances in machine learning is that in order to better generalize to the environment, it is beneficial to explore these unvisited subspaces (in machine learning terms, this is known as “generative replay” (Shin et al., 2017; Hoel, 2020; Stoianov et al., 2020; van de Ven et al., 2020)). It is possible that

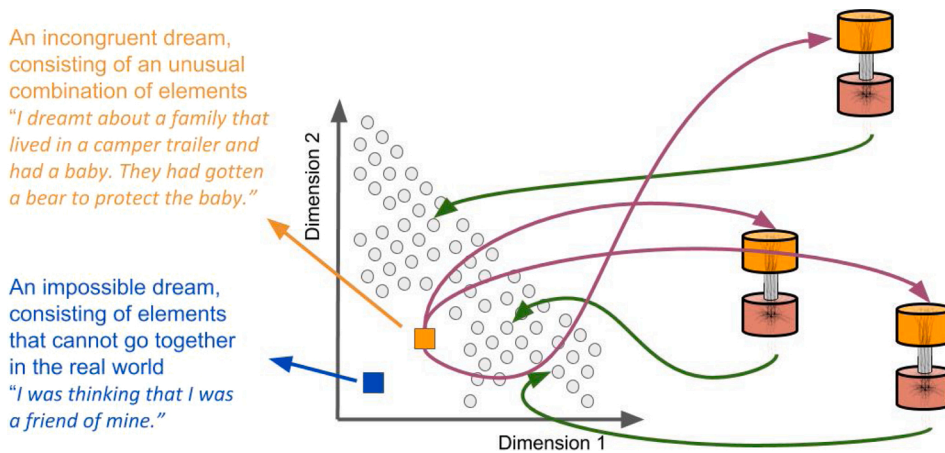


Fig. 4. Apical drive might reflect exploration in the internal model and generate bizarre dreams. In the middle a simplified internal model is depicted (simplified, as it only contains two dimensions). The gray circles represent experiences that are sorted along these dimensions. During wakefulness the three pyramidal neurons on the right all belong to different experiences (green arrows) and thus to different points of the internal model.

The orange square is a point in the internal model that has never been directly experienced during wakefulness. However, during dreaming this data point is sampled, and this sampling leads, through feedback connections (purple), to the activation of the apical compartments of the L5p neurons. This apical drive leads to a dream experience that is incongruent.

The blue square is a point in the internal model that is even further away from the subspace visited in wakefulness; exploring it during sleep leads to a dream of something “impossible”. On the left there are examples of both incongruent and “impossible” dreams, obtained from adults in a standardized experimental setting from REM sleep.

dreams reflect this exploration, where a point in this internal model is activated and, via feedback connections to cortex, drives the AIZ of L5p cells (Fig. 4, purple lines). It might be that in wakefulness these L5p cells have never participated in a joint experience; hence, apical drive assembles a dream experience that consists of incongruent elements. Thus, apical drive potentially sheds light on the nature and function of dreams: they are samples from the internal model that help to generalize to the external world. This idea is related to several other proposals about the function of dreaming (Hobson et al., 2014; Hoel, 2020) and seems compatible with various ideas in the field (Revonsuo, 2000; Valli and Revonsuo, 2009; Nir and Tononi, 2010; Windt, 2015). Other mechanisms, including the relative frontal deactivation that has been documented in REM sleep compared to wakefulness (Braun et al., 1997; Maquet, 1997), may play a role in the reduced reflective consciousness and lack of insight with respect to the bizarre elements in dreams.

8. Apical drive in the awake brain: a mechanism for internally generated cognition

8.1. Apical drive when awake

Though this paper is primarily concerned with dreaming, the possibility of apical drive as a mode of apical function has implications for our understanding of the waking state, because perceiving and thinking when awake may share some neural substrates with dreaming (Perogamvros et al., 2017; Siclari et al., 2017). In particular, it has been suggested that dreaming shares functional and neuronal similarities with mental imagery (Nir and Tononi, 2010). Could then mental imagery and some other processes during wakefulness also depend on apical drive? Are there conditions under which apical drive may be useful when awake? How are transitions between different modes of apical function regulated when awake? What prevents apical drive from occurring if inappropriate when awake?

There are many psychological phenomena that might be due to activation of neurons in perceptual regions by input from internal sources when awake. One is amodal completion in normal perception. Amodal completion uses internal knowledge to fill-in sensory data that is missing, but under the strict control of data that is present (Pessoa et al., 1998; van Lier and Gerbino, 2015). Other phenomena include thinking in visual, verbal, and other modalities, as in visual short-term

memory for example (Phillips, 1974, 1983; Postle, 2015). Many other psychological phenomena depend on information from internal sources rather than from current sensory input, including synaesthesia, day-dreams, fantasies, and delusions (McKellar, 1957), so some of those may also involve apical drive when awake.

During wakefulness there are circumstances where internally generated predictions can dominate perception. For example, it has been demonstrated that if humans expect certain stimuli, they perceive them even when there is objectively no stimulus on the screen (Aru and Bachmann, 2017; Aru et al., 2018). In such cases, strong predictions might overrule bottom-up perception. As the region of the display where the subjects perceive the expected stimuli was objectively empty, it is possible that apical drive is the main mechanism for generating the illusory content experienced by the participants.

One mental process that is likely to rely on apical drive is “mental imagery” (Kosslyn, 1988; Farah, 1989; Pearson, 2019). Mental imagery is the prime example of internally generated perception during wakefulness. Recent work has demonstrated that during mental imagery the visual cortical areas are activated in a similar fashion as during perception, only that this activation flows backward, from higher to lower cortical areas (Dentico et al., 2014; Dijkstra et al., 2019). Similar top-down activation has been observed during associative memory recall (Linde-Domingo et al., 2019). The present work suggests that one mechanism of this top-down activation might be apical drive.

Apical drive in perceptual regions when awake would only be appropriate under special circumstances, however, so how could apical drive be prevented when inappropriate? The far stronger adrenergic tone or lower cholinergic tone when awake than when dreaming may reduce the probability of the cell being driven by apical input alone. We will discuss these possibilities in section 9.2.1.

8.2. Apical drive and hallucinations

Dreams have often been compared with psychotic hallucinations because both are internally generated perceptual experiences. The study of hallucinations in schizophrenia has long suggested that they are in some ways an instantiation of what is expected (Arieti, 1974), and that this instantiation involves activation of perceptual regions (Hugdahl, 2015). Hoffman (2010) suggests that psychotic verbal hallucinations may be due to ‘episodic states of heightened auditory expectancy’. He

distinguishes the expectancy from its perceptual consequences in two very different ways. First, he notes that it is suggested by patient's experiential reports. Patients in whom repetitive transcranial magnetic stimulation over temporo-parietal regions is used to suppress the 'voices' that they hear, report a feeling that there is a voice "out there" even though they cannot hear it. Second, he notes that there is selective activation in the left anterior insula, the right middle temporal cortex, and other regions concerned with emotional valence immediately prior to activation of the temporo-parietal areas assumed to instantiate the hallucination. Hoffman (2010) concludes that verbal hallucinations are due to 'heightened auditory attention' that facilitates activation in perceptual regions via top-down connections. The potential overlap between this conclusion and our hypothesis concerning dreaming is obvious if the 'heightening' is interpreted as implying the conversion of apical amplification into apical drive. As Hoffman notes, such studies of psychiatric patients do not prove that heightened auditory attention actually causes hallucination experiences, but they do justify deeper study of that possibility.

It has been proposed that many of the cognitive impairments that occur in schizophrenia arise from reduced sensitivity to context (e.g. Uhlhaas and Silverstein, 2005; Silverstein, 2010, 2016; Silverstein and Keane, 2011). Computational modeling of L5p cells has now related such impairments to apical function and risk genes for schizophrenia by showing that many of these genes could affect context-sensitivity via their direct effects on apical function (Mäki-Marttunen et al., 2019). A Bayesian interpretation of the positive symptoms of schizophrenia (Fletcher and Frith, 2009; Sterzer et al., 2018; Corlett et al., 2019) is highly compatible with the hypotheses presented here, because it suggests that when internal information is used to drive cells in perceptual regions, that 'perceiving' becomes believing. For example, patients with auditory hallucinations are more prone to have illusory auditory experiences that are driven by expectations (Powers et al., 2017). During these auditory experiences of objectively non-existent stimuli, one can measure increased activity in their auditory cortex (Powers et al., 2017), which might be evoked by apical drive.

9. Discussion

9.1. Summary of the argument

Dreams are a prime example of internally generated conscious experiences. During dreaming, there is a disconnection from the environment, but vivid experiences nevertheless occur. The key question we sought to answer was the following: if there is sensory disconnection, then how are the neurons involved in the dream experience activated? We propose that this happens through the internal input into the apical integration zone (Figs. 1 and 3), a processing mode we named "apical drive". We reviewed the evidence for apical drive. In particular, it seems that apical drive is enabled by high levels of ACh, which is at the peak during REM sleep, and that the key properties of apical drive are able to explain some key characteristics of dreaming.

Dreaming is experiencing while asleep. When asleep, our senses do not generate percepts. Rather, sensory-like experiences are generated from internal sources. Anatomical and physiological studies show that pyramidal cells in modality-specific and multimodal perceptual regions of neocortex receive highly specific information from the senses via their basal dendrites and information from diverse internal sources via their apical dendrites. These internal sources include higher cortical regions, higher-order thalamus, the limbic system, amygdala, and claustrum (Larkum, 2013). We suggest that during dreaming, conscious experiences are mainly generated through input from internal sources via the apical dendrites of pyramidal cells.

Much remains to be learned concerning apical function and its regulation by cholinergic, adrenergic, and other systems during awake consciousness, sleep and dreaming. We next turn to two main unresolved issues regarding our hypothesis.

9.2. Two questions about the role of ACh in dreaming

There seem at first glance to be at least two important unresolved questions and possible weak points of our core hypothesis: (1) Why does the ACh-dependent apical drive not cause dreaming also in the wake state, when the level of ACh release in the neocortex is also high? (2) Why does dreaming often occur also during the NREM/SWS state, when the level of ACh release in the neocortex is low? Here we discuss these issues.

9.2.1. Why does apical drive not cause dreaming also in the wake state, when ACh release is high?

According to our core hypothesis, dreaming is caused by apical drive promoted by high levels of ACh during REM sleep. But it is well known that there is high ACh release in the wake state (Table 1), so why does not this also cause similar dream experiences when we are awake?

9.2.1.1. *Acetylcholine (ACh) release in cortex is much higher in REM sleep than in wake.* Although many review articles and textbooks simply state that ACh in the cortex is "high" in both wake and REM sleep, and "low" in NREM sleep, there is strong evidence that ACh release in the cortex is actually far higher in REM sleep than in the wake state(s), although this is often not explicitly mentioned. In particular, Lee et al. (2005) recorded basal forebrain cholinergic neurons combined with EEG across the sleep-wake cycle in rats, labeling individual neurons for immunohistochemical identification. Their data show that the spike frequency of identified ACh basal forebrain neurons that project to the neocortex was much higher in REM sleep than in wakefulness (Fig. 2C).

Thus, it seems likely that the very high ACh release during REM sleep strongly upregulates the apical ion channels underlying the ACh-dependent dendritic plateau potentials described by (Williams and Fletcher, 2019): i.e. intrinsically generated, prolonged depolarizations, lasting from tens to hundreds of milliseconds in response to brief depolarizations. These plateaus are likely to boost synaptic input to the apical tuft, thus promoting apical drive. According to our hypothesis, this favors dreaming. In contrast, during wake, when ACh is considerably lower (Fig. 2C) and, hence, the internally triggered, ACh-dependent apical plateau potentials are probably weaker, the apical input alone may be insufficient to dominate the cells' spike output.

Furthermore, the larger ACh release during REM sleep is also likely to cause stronger cholinergic disinhibition of the apical tuft and AIZ of pyramidal cells, by cholinergic inhibition of the inhibitory neurogliaform (NGF) cells targeting the tuft in Layer 1. Thus, Brombas et al. (2014) found that application of ACh induced a long-lasting inhibition of active firing of NGF cells. This would be expected to weaken the "blanket" of inhibition by NGF cells (Karnani et al., 2014), which tends to suppress apical activity. Thus, the increased ACh during REM sleep is likely to further promote apical drive. Disinhibition of the apical tuft may also be mediated by VIP interneurons suppressing the inhibitory activity of NGF- or somatostatin (SOM)-expressing dendrite-targeting interneurons (Jackson et al., 2016).

Taken together, these arguments lead to the expectation that the apical dendrites of pyramidal neurons will become more excitable in REM than in the awake state because of ACh-promoted dendritic disinhibition and ACh-dependent dendritic plateau potentials. These may be key factors for explaining why we often dream in REM sleep, but not in the wake state.

9.2.1.2. *Noradrenaline (NA).* In addition, or alternatively: the far higher level of NA in wakefulness than in REM and NREM sleep (Table 1), may differentially affect both synaptic input and intrinsic, ionic conductances in pyramidal cells. Acting via α receptors (α AR), NA may suppress excitatory synapses during wake, preferentially in Layer 1, where NA fibers are most dense (Audet et al., 1988). This may selectively weaken the excitatory apical input (Boehm, 1999; Jiménez-Rivera

et al., 2012; Ohshima et al., 2017), thus preventing apical input from alone driving the cell in the wake state. Thus, high NA suppressing apical input may help explain why we do not dream in the wake state. Nevertheless, apical input may still cause apical amplification, boosting feed-forward, sensory input in the wake state (Larkum, 2013; Phillips, 2017; Takahashi et al., 2016), even if the apical input is normally not strong enough to drive the cell alone.

During wake, NA may also, via α ARs, suppress the inward HCN current (I_h) preferentially in L1 (Arnsten et al., 2012; Barth et al., 2008), where the densities of both NA terminals (Audet et al., 1988) and pyramidal cell HCN channels are highest (Magee, 1999; Luthi and McCormick, 1998; Berger et al., 2001; Lörincz et al., 2002; Kole et al., 2006; Harnett et al., 2015). On one hand, this loss of apical I_h would reduce the total depolarizing current and rebound excitation in the distal dendrites during wake, which might thus reduce the apical drive, and hence reduce dreaming. If so, also postsynaptic α ARs may help preventing apical drive and dreaming during wake. On the other hand, by reducing I_h , α ARs may also counteract the reduced dendritic input resistance caused by open HCN channels, as outlined above (6.3), and this effect may dominate. If so, α ARs, may thus reduce the shunting by HCN channels of inward currents underlying plateau potentials (Williams and Fletcher, 2019). However, if NA mainly works via β ARs, both the depolarizing and shunting effects of I_h might be selectively enhanced, since β ARs can boost I_h (Pedarzani and Storm, 1995; Storm et al., 2000; DiFrancesco and Borer, 2007) – i.e. opposite to I_h suppression via α ARs. Recent evidence indicates that the boosting of I_h via β ARs dominates in neocortical layer 5 pyramidal cells (Hagger-Vaughan et al., 2017; Klaus et al., 2017; Hagger-Vaughan and Storm, unpublished data). Since NA and hence β AR activation is low during REM sleep, the resulting I_h reduction would then reduce shunting, which may promote apical drive and dreaming, supporting our proposed mechanism of dreaming, as outlined above (6.3). In contrast, during wake, when β ARs are activated, the resulting boosting of I_h will tend to shunt the plateau and may prevent apical drive and dreaming during wake perception. Whether α AR- or β AR-mediated effects on the apical I_h dominate in vivo remains to be determined, and may possibly also differ between neocortical areas, layers, cell subtypes, and/or degrees of arousal or attention. The effects of NA on pyramidal cell computations will also depend on other factors, but it seems more likely that the fundamental role of NA is fairly uniform across areas, layers, cell types, and wake states.

Thus, the combination of high ACh and NA during wakefulness may put the pyramidal cells into a state that allows external sensory information to dominate our awake experiences, whereas the apical drive is allowed to dominate during REM or NREM dreams when NA alone (REM) or both ACh and NA (NREM) levels are low (Table 1; Fig. 3). In addition, there is evidence that several other somato-dendritic K^+ channels (GIRK, SK, 2 P, Kv etc.) are altered by neuromodulators that change substantially between wake and sleep states (Nicoll, 1988; Pedarzani and Storm, 1993; Storm et al., 2000; Vogalis et al., 2003; Hu et al., 2007; Hu et al., 2009; Hoffman et al., 1997; Cai et al., 2004). Thus, it is ultimately a quantitative question exactly which mechanisms will dominate in each state, area, layer, and cell type. Although it is beyond the scope of this paper to exhaustively discuss the roles of various channels and receptors, this discussion illustrates that there are at least some potential mechanisms that may explain why the ACh-dependent apical drive allows dreaming during REM sleep but does not cause dreaming also in the wake state.

9.2.1.3. Dopamine (DA). Dopamine (DA) has been implicated in sleep regulation, dreaming, and dream recall by several authors (e.g. Gottesmann, 2002; De Gennaro et al., 2016; Solms, 1997, 2000). DA release is known to be high in wakefulness, in particular in prefrontal cortex (Table 1; Miller et al., 1983; Trulson and Preussler, 1984; Maloney et al., 2002), and some studies suggest that DA release is higher in REM than in

NREM sleep (Léna et al., 2005), but others reported little difference between wake and sleep states (Miller et al., 1983; Trulson and Preussler, 1984). DA may be important for forebrain mechanisms underlying dreaming and hallucinations (Solms, 1997, 2000). At the cellular level, DA can differentially affect both intrinsic conductances and synaptic transmission. For example, DA acting via D1 receptors and cyclic AMP may (like NA via β ARs;) enhance I_h and its depolarizing and shunting effects (Pedarzani and Storm, 1993; Storm et al., 2000). If DA release is higher in REM, the resulting I_h increase may then enhance depolarization, which may then promote apical drive and dreaming, or enhance shunting, which may reduce apical drive. The overall effects of DA will also depend on other factors. Thus, it is difficult at this point to predict whether DA contributes to apical drive during REM sleep, because there is diverging evidence regarding the DA levels in different parts of the cortex (Table 1), and DA may trigger mechanisms that may promote or weaken apical drive. However, the roles of DA may be complex; a main role may be to contribute to forebrain mechanisms underlying the specific input to L1, which according to our hypothesis provides the main content of dreams (Solms, 1997, 2000). This is distinct from the apical drive dendritic mechanisms, which determine whether the L1 input reaches the soma of L5p cells and becomes expressed in their spike output, hence contributing to dream experiences.

9.2.2. How does dreaming occur during NREM?

Why does dreaming often occur also during NREM/SWS, when the overall level of ACh release in the neocortex is low (Table 1) according to the available evidence (Lee et al., 2005; Vazquez and Baghdoyan, 2001)? There are several possible causes; here we discuss a few of them.

9.2.2.1. Spatial/regional differences in neuromodulation. Several lines of evidence indicate that there can be important local differences in neuromodulation among various cortical areas and subareas, within each global brain state such as wake, NREM/SWS or REM sleep. Thus, there may potentially be higher local levels of ACh and NA (and other neuromodulators) in certain parts of the cortex (Munoz and Rudy, 2014; Ballinger et al., 2016), even when the overall cortical levels are low in NREM/SWS (Table 1). This may enable dreaming also during NREM sleep, by promoting apical drive in parts of the cortex, such as the posterior hot zone (Siclari and Tononi, 2017; Siclari et al., 2018). Such a scenario is indirectly supported by Ballinger et al. (2016). In addition, there is accumulating evidence for local sleep in parts of the neocortex during behavioural wakefulness (Murphy et al., 2011; Vyazovskiy et al., 2011; Vyazovskiy and Harris, 2013). Thus (as discussed in section 2), slow waves, which are known to depend on altered neuromodulation such as reduced ACh and NA levels (Table 1), can occur locally during global wakefulness and REM sleep, although usually with smaller amplitude (Vyazovskiy et al., 2011; Hung et al., 2013; Bernardi et al., 2015; Funk et al., 2016; Bernardi et al., 2019). Conversely, during NREM/SWS, there is evidence for local cortical activation, although the overall cortical ACh release is low. Thus, in deep NREM sleep, local EEG desynchronization can be seen simultaneously with SWA in different cortical areas, supporting that locally differentiated neuromodulation can occur (Krueger and Tononi, 2011; Nir et al., 2011; Nobili et al., 2011; Siclari and Tononi, 2017). Furthermore, Siclari et al. (2017) found that both REM and NREM dreaming were associated with locally weaker slow-wave activity in the posterior hot zone. In addition, compared to reports of no experience, dream reports were preceded by fewer, smaller, and shallower slow waves in central and posterior cortical areas, whereas frontal regions showed local, high-frequency "microarousals", suggesting local, intermittent activation of arousal systems during NREM sleep (Siclari et al., 2018). This further supports the idea that there can be substantial local differences in neuromodulation between cortical areas and subareas within each global brain state.

9.2.2.2. Temporal differences in neuromodulation. During NREM sleep, EEG activity has been shown to undergo ultraslow fluctuations in both rodents and humans (Lecci et al., 2017; Parrino et al., 2012; Vanhatalo et al., 2004). This occurs in parallel with fluctuations in pupil diameter, heartbeat, and arousability from sleep, suggesting that they involve different neuromodulator systems (Yuzgec et al., 2018). It is therefore conceivable that in addition to the temporal windows provided by specific NREM sleep events, slower fluctuations of arousal systems may also contribute to modulating apical drive and isolation.

9.2.2.3. Other neuromodulator receptors promoting apical drive. Perhaps not only ACh acting mainly via muscarinic receptors, but also other neuromodulators, acting via other metabotropic receptor types, e.g. metabotropic glutamate receptors, can promote apical drive. Such receptors, if activated during NREM sleep, may turn on some of the same intracellular signalling pathways and ion channels (Nicoll, 1988; Radnikow and Feldmeyer, 2018) that are triggered metabotropically by ACh in REM sleep. There is evidence for this claim, as not only antagonists of metabotropic ACh receptors but also antagonists of metabotropic glutamate receptors are associated with the breakdown of apical drive (Suzuki and Larkum, 2020). Hence, other neuromodulators, acting via other metabotropic receptor types, might lead to apical drive also in NREM sleep, thus enabling dreaming, perhaps via synergistic effects (Hagger-Vaughan and Storm, 2019). This may also be an alternative mechanism for the local reductions of slow waves observed by Siclari et al. (2017), in addition to possible local changes in release of ACh and NA, as discussed above. In conclusion, it seems likely that the combined effects of different inputs that promote NREM apical drive, and local differences in neuromodulation, can at least help explain and possibly fully resolve the second main problem for our hypothesis: how apical drive and dreaming can occur even in NREM sleep, when the overall ACh level is low.

9.2.3. ACh and dreaming: summary

From the above it seems that increased release of ACh in the cortex is not a sufficient factor for dreaming to happen. The main effect of ACh is likely to enable signal propagation from the apical compartment to the soma, so that apical activation can lead to spiking output (Suzuki and Larkum, 2020). However, increased ACh by itself will probably not generate spiking, it is only an enabling factor. To make the neurons fire, there needs to be glutamatergic excitation of the AIZ from elsewhere. Where does this excitation come from? How are dreams generated?

9.3. How experience is generated during dreaming and waking consciousness

9.3.1. Network mechanisms of dreaming

In this work we have proposed a cellular correlate of dreaming. During wakeful consciousness the activation of L5p neurons depends on both input from the environment and the AIZ (Larkum, 2013; Phillips, 2017; Aru et al., 2019, 2020). We have suggested that during dreaming their activation mainly comes from internal sources activating the AIZ. So apical drive is not a fundamentally different processing mode, it is rather akin to an extremely sensitive form of apical amplification that can make the neurons spike even when there is little or even no basal input (Larkum et al., 1999; Suzuki and Larkum, 2020).

According to our hypothesis, during dreaming, there is a shift in the way neurons are activated (Figs. 1 and 3). At lower levels of the sensory hierarchy, the input to the somatic compartment will be weaker, because of sensory disconnection (Funk et al., 2016). At the same time, the internal input to AIZ will be relatively stronger. It is not clear which areas exactly lead to the activation of the AIZ during dreaming, but as noted in section 5.2, there are many areas that are in the position to do so.

However, of course the complex experience of dreaming is not generated by single cells but rather by extended networks of neurons.

When considering the network perspective, it is important to notice that the downstream neurons do not ‘know’ that the L5p cells in sensory areas were activated through apical drive. In other words, these downstream neurons may process this input as if it would come during wakefulness, i.e. representing sensory input. So the process of generating conscious experiences in dreams and awake conscious brains might be similar.

There are of course many theories, models and ideas that try to address the neural basis of conscious experience (e.g. Tononi et al., 2016; Mashour et al., 2020). In parallel with the ideas presented here, a theory of consciousness has been proposed that is directly related to the current ideas. The Dendritic Integration Theory (DIT, Aru et al., 2020) suggests that consciousness is associated with the integration of information streams impinging on the apical and basal compartments of L5p neurons. This integration happens along the apical dendrite and is controlled by the higher order thalamus (Suzuki and Larkum, 2020; Aru et al., 2020). Such dendritic integration couples thalamo-cortical and cortico-cortical loops and leads to complex sustained brain dynamics associated with conscious processing (Aru et al., 2020). Although there are remaining issues to be solved, it seems that our current idea of dream generation may fit with the general concept of DIT, as it simply says that during particular neuromodulatory states the AIZ can drive this process. Thus, our hypothesis may explain why dreams seem so real: dreams use the same machinery for generating experiences, but in contrast to wake consciousness, dreams originate from within.

9.4. Apical drive: experimental predictions and questions

Perhaps it seems premature to propose cellular mechanisms of dreaming. However, the advantage of suggesting specific neurobiological mechanisms is that these ideas can readily be tested by the tools available for modern neuroscience.

If the AIZ of L5p cells is excited optogenetically, the cell bodies are activated during wakefulness, but not during anesthesia (Suzuki and Larkum, 2020). Our hypothesis predicts that the cell bodies will be activated by such optogenetic stimulation during REM sleep. It is both crucial and feasible to test that prediction in the near future. Furthermore, Suzuki and Larkum (2020) found that it was not possible to activate the somata of L2/3 pyramidal cells by depolarizing their AIZ. Hence, a strong prediction of our hypothesis is that apical drive is specific to L5p neurons. This prediction is consistent with the finding that the activity of L2/3 pyramidal cells is decreased during REM sleep (Niethard et al., 2016).

Another key question is where does the drive come from? Research has already shown that various areas target layer 1 (Section 5.2), but the question is, which areas provide the key input during dreaming. In the mouse model it will be virtually impossible to study this during dreaming, but one can ask, which areas provide the apical drive during REM sleep. We suspect that limbic areas, including the perirhinal cortex, play a key role in apical drive. Also, as NA regulates spatiotemporal summation around AIZ, it will be quite central to study which areas project closer to and which project further away from the AIZ of L5p neurons.

In addition, one needs to better understand how apical drive is controlled. We have here discussed the roles of ACh and NA in affecting apical drive, but there could be other ways how it can be regulated. One particularly important class of regulatory mechanisms could come from the inhibitory neurons. Interestingly, different compartments of pyramidal cells are controlled by distinct interneuron classes (Larkum et al., 1999; Larkum, 2013). PV+ neurons act on the soma of pyramidal neurons, while SOM+ neurons inhibit the apical compartment. Yet another type of interneurons, the VIP+ neurons, inhibit the SOM+ neurons, thus their activity disinhibits the apical compartment (Kepecs and Fishell, 2014), and the NGF cells provide another source of inhibition to the AIZ. Together these inhibitory neurons can gate the activity of the L5p neurons so that they either block or facilitate apical drive. Unfortunately,

very little is known about the activation and interplay of these different interneuron types during different sleep stages. Two recent studies using two photon imaging to assess calcium activity have looked at the activity of SOM+ and PV+ interneurons during different sleep phases (Niethard et al., 2016, 2018), but more work needs to be done, especially as it is the VIP+ and NGF cells that are the targets of long-range input (Kepecs and Fishell, 2014; Abs et al., 2018) that we suspect is the main driving force of apical drive.

10. Conclusions

We have presented anatomical and functional arguments suggesting that the activation of neocortical pyramidal cells by depolarization of their AIZ provides a cellular mechanism for dreams. These claims are strongly supported by evidence that cholinergic and adrenergic systems directly affect the AIZ and that this influence depends on the behavioral state. In particular, we have proposed that high cholinergic combined with low adrenergic modulation leads to a cellular state where internal inputs to the AIZ are capable of driving the firing activity of the cell. More generally, we have made the case that internally generated experiences could rely on specific neural mechanisms that are regulated by arousal systems. We conclude that a wide diversity of investigations, using various methodologies, of the different modes of apical function and their regulation when asleep and awake are likely to be richly rewarded.

Author contributions

JFS, JA, and WAP independently came up with the idea of apical drive as a possible dream mechanism. Suggested by JFS, discussions with FS and WAP in Oslo 2019 initiated the paper. FS, WAP, and JFS wrote the first draft. WAP first and JA later coordinated the main writing. JA mainly contributed to sections 1,4,5,7-9, and created Figs. 1 and 4. FS put apical drive into context and outlined how it can explain dream features, mainly contributed to sections 1-3 and 7, Tables 1 and 2, and Fig. 2A-B. WAP mainly contributed to sections 1,4-6,8 and 9. JFS mainly contributed to sections 1,4,6,9 and Table 1, and added Fig. 2C.

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