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ORIGINAL COMMUNICATION

How Yawning Switches the Default-Mode Network to the Attentional Network by Activating the Cerebrospinal Fluid Flow

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Yawning is a behavior to which little research has been devoted. However, its purpose has not yet been demonstrated and remains controversial. In this article, we propose a new theory involving the brain network that is functional during the resting state, that is, the default mode network. When this network is active, yawning manifests a process of switching to the attentional system through its capacity to increase circulation of cerebrospinal fluid (CSF), thereby increasing clearance of somnogenic factors (prostaglandin D(2), adenosine, and others) accumulating in the cerebrospinal fluid. Clin. Anat. 27:201–209, 2014. © 2013 Wiley Periodicals, Inc.

Key words: yawning; arousal; sleep; adenosine; default mode network; cerebrospinal fluid

INTRODUCTION

Provine writes in his most recent book: "The hydraulic brain message produced by coughing, sneezing, yawning, and other acts may produce unappreciated secondary behavioral consequences, including alterations of attention, mood, or state of arousal" (Provine, 2012). We propose to develop this concept concerning yawning.

Yawning is a stereotyped and often repetitive motor act characterized by gaping of the mouth accompanied by a long inspiration of breath, a brief acme, and then a short expiration of breath. Simultaneous stretching and yawning is known as pandiculation, which is not merely a simple opening of the mouth but a complex, coordinated movement bringing together a flexion followed by an extension of the neck and a wide dilatation of the pharyngolarynx with strong stretching of the diaphragm and antigravity muscles (Provine, 1986, 2005). Yawning is observed in cold-blooded and warm-blooded vertebrates, from reptiles with rudimentary "archaic" brains to human primates, in water, air, and land environments. Ethologists agree that almost all vertebrates yawn. Yawning is morphologically similar in reptiles, birds, mammals, and fish (Baenninger, 1987; Walusinski and Deputte, 2004). These behaviors may be ancestral vestiges maintained throughout evolution with little variation, bearing witness to the early phylogenetic origins of yawning. Like any phylogenetically old behavior, yawning can be observed early in ontogeny, that is, at 12 weeks of fetal life (Walusinski, 2012).

Yawning is involuntary and only humans seem capable of altering its occurrence for cultural or social reasons. It is highly stereotypical because no environmental input changes the sequence of movements. Behavioral and neurophysiological studies provide converging evidence that yawning occurs preferentially during rest, periods of drowsiness and awakening or is associated with hunger and satiety. The frequency of yawning has a distinctive circadian distribution and occurs most frequently before and after sleep, that is, during periods of lower levels of vigilance and alertness. Furthermore, the yawning rate correlates with the individual's subjective feeling of drowsiness and adjusts to individual circadian rhythms (Baenninger et al., 1996; Provine, 2005; Giganti et al., 2010).

Nevertheless, the purpose of this behavior remains controversial. As outlined by Guggisberg et al.: "The existing scientific literature on yawning is

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characterized by a relative abundance of theoretical considerations and hypotheses which contrasts with a scarcity of experimental data." But should we be satisfied with their conclusion? "The argument that from an evolutionary perspective, yawns must have a 'primitive' physiological function arises from imprecise reasoning" (Guggisberg et al., 2010, 2011). Concerning the most recent theories, the findings of Gallup et al. are consistent with a brain-cooling hypothesis, whereas Thompson links cortisol levels with yawning episodes (Thompson, 2011; Gallup and Eldakar, 2012). Bertolucci suggests that yawning and pandiculation might have an auto-regulatory role regarding the locomotor system, that is, to maintain the animal's ability to express coordinated and integrated movement by regularly restoring and resetting the structural and functional equilibrium of the myofascial system (Bertolucci, 2011). In any case, it is certain that yawning opens the Eustachian tube, inflating the lungs and thus spreading the surfactant of the alveoli; it also signals drowsiness and boredom (Baenninger, 1997). Robert Provine asks with humor: "Does the flamboyant act of yawning, spontaneous or contagious, serve a function? Or is it much ado about nothing?" but concludes: "Yawning is a response to and facilitator of change in behavioral or physiological state" (Provine, 2012). In their landmark 1963 study, Ferrari et al. concluded, "Stretching and yawning are two physiological acts that might be considered as an effort of the body to delay the onset of sleep and a mechanism to reinforce wakefulness after sleep." Inspired by these ideas, we want to highlight how yawning, a daily behavior, may be the visible aspect of a homeostatic process during the shift between the default-mode network (DMN) and the attentional network. This process may involve the cerebrospinal fluid (CSF) clearance of a somnogenic purine nucleoside, adenosine.

BRAIN HOMEOSTASIS: A BRIEF OVERVIEW

On one hand, survival depends on the maintenance of the body's physiology within an optimal homeostatic range; one the other, the principal function of the central nervous system (CNS) is to adapt an organism's behavior to changes in the environment. These statements underscore the need for brain homeostasis, including the regulation of synapse elimination, neurogenesis, and neuronal surveillance. Homeostasis, the maintenance of optimal internal conditions, is achieved through a complex set of physiological and behavioral responses to external and internal stimuli. Body temperature, blood pressure, and nutrient and energy levels all have precise homeostatic ranges. When the internal milieu is challenged, physiological responses are initiated to defend the homeostatic range. The ultradian wake-sleep cycle, a cerebral function by and for the brain, is the basic temporal module of physiological regulation underlying the behavioral continuum and responds also to CNS homeostatic processes. Indeed, it has been posited that a critical function of sleep is synaptic renormalization following a net increase in synaptic strength during waking periods (Born and Feld, 2012; Vyazovskiy and Tobler, 2012).

AROUSAL AND ATTENTION, REST, AND SLEEPINESS

Maintaining attention for more than a few seconds is essential for mastering everyday life. Sustaining attention is a multicomponent, nonunitary mental faculty, involving a mixture of sustained/recurrent processes subserving task-set/arousal maintenance and transient processes subserving the target-driven reorienting of attention. For this purpose, the brain is organized into a collection of specialized functional networks that flexibly interact to support various cognitive functions like the unrivaled human attentional control. On one hand, the facility with which humans perform and shift among a wide variety of cognitive tasks seems to indicate a mechanism for entering into a task-dependent mode. On the other, a set of brain regions, namely, the DMN, is active when the mind is not engaged in specific behavioral tasks (vigilant attention) or during sleep onset. This network has low activity during focused attention on the external environment.

ATTENTIONAL NETWORKS

Central to many behavioral functions, attention is one of the oldest and most pivotal issues in psychological science. William James (1842–1910) was the first to write about its multiplicity (James, 1894). Cortical and subcortical networks mediate different aspects of attention. Without the modulatory influence of subcortical areas, the brain would not attend effectively. On the basis of detailed neuroanatomical, electrophysiological, and neurochemical studies in animals, as well as human neuroimaging data, researchers have identified large-scale cortical–subcortical circuits, including feedback loops and reentrant connections, that subserve different aspects of attention and working memory. Subcortical circuits, such as the fronto-striato-thalamo-cortical loops have been found to play an important role. The right dorsolateral prefrontal cortex (DLPFC) acts in an executive capacity, monitoring performance or arousal levels and regulating them accordingly, in conjunction with the anterior cingulate cortex (ACC) or other midline frontal structures. The right inferior parietal region participates equally in both endogenous and exogenous alerting. The left hemisphere has been associated with linking temporal and spatial information, and the specific presentation of warning signals. The pulvinar, superior colliculus, superior parietal lobe, temporoparietal junction, superior temporal lobe, and frontal eye fields are activated as an orienting network. Authors have proposed a conflict-monitoring model suggesting that the ACC engages the DLPFC, which might be mediated by the locus coeruleus and dopaminergic sites in the ventral tegmental area. These findings suggest that the DLPFC might support

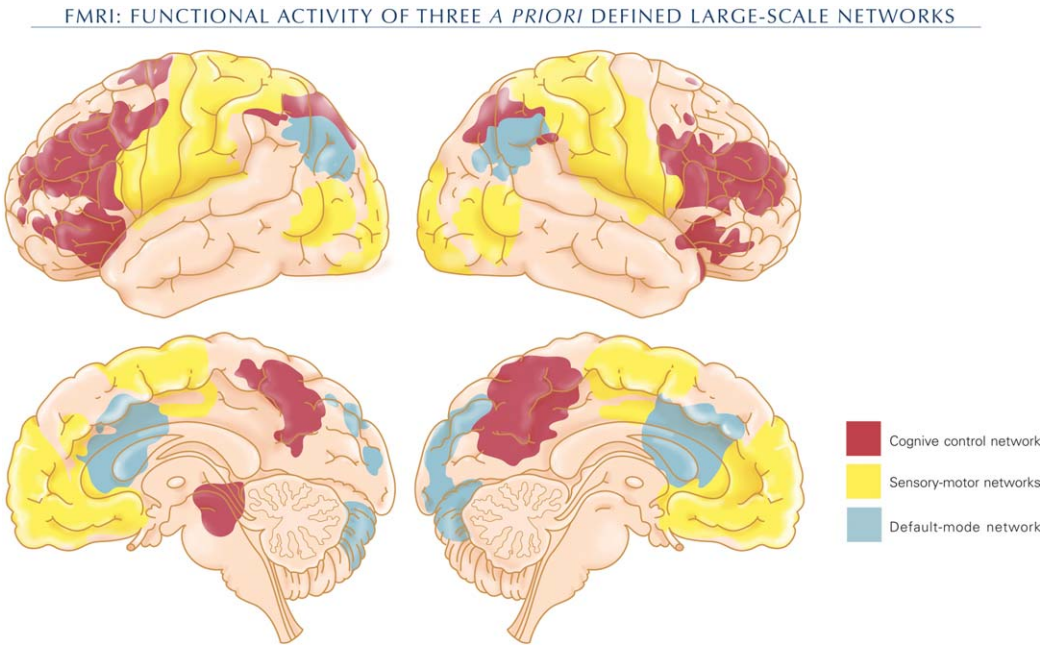

Fig. 1. Circulation of the cerebral fluid (illustration by Hélène Badault for the author).

heteromodal conflict resolution, whereas the ACC could be specific to the resolution of response conflict (Fig. 1). Although disparate modules of attention constitute an important model, the exact nature of these networks and the degree to which they are independent is still not clear (Raz and Buhle, 2006; Zhang et al., 2008; Harris and Thiele, 2011).

THE DEFAULT MODE NETWORK

A set of brain regions has been identified via functional magnetic resonance imaging. These regions are collectively termed the DMN because their pattern of spontaneous physiological activity is detectable during the normal resting state. Areas collectively activated during the default mode state involve a set of midline brain structures, including the ACC and the ventral and dorsal medial prefrontal cortex. Moreover, the precuneus/posterior cingulate cortex plays a pivotal role (Fig. 1) (Raichle et al., 2001; Raichle and Snyder, 2007).

DMN is characterized by high activity when the mind is not engaged in specific behavioral tasks and low activity during focused attention on the external environment. The function of the DMN has been attributed to introspection, self-awareness, and theory of mind judgments, and some of its regions are involved in episodic memory processes. In a word, DMN function postulates its involvement in self-referential processing and thought (i.e., internal mentation, daydreaming, etc.), which is typically in opposition to externally oriented goal-directed cognition. Thus, emerging task-relevant effects clearly support the conclusion that DMN synchronous suppression is functionally important for successful operation of certain cognitive processes, such as focused attention and working memory. Such task-based deactivations show an antagonism with focused attention. This anti-correlated organization appears to be a fundamental property of the CNS. (Dosenbach et al., 2007; Dosenbach et al., 2008; Fox et al., 2009; Anticevic et al., 2012; Tang et al., 2012).

Oakley and Halligan (2009) have suggested that a deviation from the normal default mode activity might provide a neural signature of hypnosis. Altered activation of the default network has been reported in functional imaging studies of patients with neuropsychiatric disorders such as dementia, schizophrenia, epilepsy, anxiety and depression, autism and attention deficit/hyperactivity disorder (Buckner et al., 2008; Broyd et al., 2009). Unfortunately, none of these studies mention the patients' yawning.

SLEEP AND AROUSAL

During World War I, a pandemic of encephalitis lethargica swept the globe. This presumed viral infection of the brain caused a profound and prolonged state of sleepiness, followed by parkinsonism, in most individuals. An Austrian neurologist, Constantin von Economo (1876–1931), reported that this state of prolonged sleepiness was due to injury to the posterior hypothalamus and rostral midbrain. He also recognized that one group of individuals infected during the same pandemic instead had the opposite problem: a prolonged state of insomnia marked by

salvos of yawning that occurred with lesions of the preoptic area and basal forebrain. Based on his observations, von Economo predicted, with acute foresight, that the region of the hypothalamus near the optic chiasm contains sleep-promoting neurons, whereas the posterior hypothalamus contains neurons that promote wakefulness (von Economo, 1931).

Currently, we know that the ventrolateral preoptic (VLPO) nucleus contains GABAergic and galaninergic neurons that are active during sleep and necessary for normal sleep. The posterior lateral hypothalamus contains hypocretin neurons that are crucial for maintaining normal wakefulness. A model was proposed by Clifford B. Saper in which wake- and sleep-promoting neurons inhibit each other, which results in stable wakefulness and sleep. Curiously, the thalamocortical system is activated in both wakefulness and rapid eye movement (REM) sleep. One key distinction is the activity in distinctive hypothalamic branches of the ascending arousal system. The firing differences in the cholinergic and monoaminergic ascending arousal systems characterize and probably regulate the production of the different behavioral states (Saper et al., 2001, 2005; Fuller et al., 2006; Koike et al., 2011; Larson-Prior et al., 2011).

Domhoff's theory suggests that a neural substrate for dreaming may be based on a subsystem of the waking default network, which is active when the mind is wandering, daydreaming, or simulating past or future events and partially active during REM sleep. The sudden switch to dreamlike thinking, whether at sleep onset, during the drowsiness of a slow morning awakening, or in brief episodes of relaxed waking thought, suggests that the transition to dreaming can be rapid (Domhoff, 2011). When a specific constellation of neural regions is activated in a context where there is no engagement with the external world, it is plausible that, as an On–Off switch, an involuntary behavior serves to rapidly reverse the state toward engagement with the external world. Yawning, a homeostatic process involving circadian variations in vigilance and emotion may be such a behavior. Indeed, yawning manifests a parasympathetic stimulation during the balancing of adrenergic and cholinergic homeostasis in the autonomic nervous system (Jackson et al., 2011).

NEUROPHYSIOLOGY OF YAWNING

Several clinical and pharmacological arguments indicate that yawning involves the hypothalamus, particularly, the paraventricular nucleus (PVN), the brainstem, and the cervical medulla. PVN is an integration centre between the central and peripheral autonomic nervous systems. It is involved in numerous functions ranging from feeding, metabolic balance, blood pressure, and heart rate, to sexual behavior and yawning. In particular, a group of oxytocinergic neurons originating in this nucleus and projecting to extrahypothalamic brain areas (e.g., hippocampus, medulla oblongata, and spinal cord) controls yawning. Oxytocin activates cholinergic neurotransmission in the hippocampus and the reticular formation of the brainstem. Acetylcholine induces yawning by acting as an agonist for the muscarinic receptors of muscles triggered by the motor nuclei of the Vth, VIIth, IXth, Xth, and XIIth cranial nerves, the phrenic nerves (C1–C4) and the motor supply to the intercostal muscles (Argiolas and Melis 1998; Collins and Eguibar, 2010).

The activating system consists of neurons located in the midbrain reticular formation (the reticular activating system, RAS) projecting to the thalamus and to the cortex. An intrinsic function of RAS is its participation in responses such that alerting stimuli simultaneously activate thalamocortical systems, as well as postural and locomotor systems, to enable an appropriate behavior (fight vs. flight). The neurons are mostly noradrenergic and particularly concentrated in small nuclei like the locus coeruleus, having widespread projections to forebrain areas and to virtually all brain regions. Locus coeruleus activity varies primarily with the state of vigilance, and has a role in regulating different types of cognitive abilities during alertness. The thalamic nucleus and the PVN belong to a neural loop circuitry sending and receiving histaminergic projections from the tuberomammillary nucleus (TMN), and noradrenergic projections from the locus coeruleus. The basal ganglia, as a rule, are highly interconnected with the pedunculopontine tegmental nucleus (PPN). The motor function of PPN is to control postural muscle tone. It also plays a role in regulating the sleep-wake cycle and is a limbic-motor interface for reward predictions. Taken together, these characteristics suggest that visceral and musculoskeletal sensory pathways are connected to the same subcortical structures involved in arousal and attention mechanisms. From this perspective, yawning triggers the stimulation of the locus coeruleus through feedback from musculoskeletal and visceral sensory inputs. For example, during the powerful contraction caused by yawning, the spindles of the masticatory muscles (masseter, temporalis, pterygoids), which have receptors that respond to stretching, send stimuli via afferent nerves of the Ia category, which are located in the mesencephalic root of the trigeminal nerve (ascending visceral parasympathetic pathway). With the motor neurons of the same muscles, these nerves form a monosynaptic link. This is the basis of the masseteric reflex. These nerves have projections on RAS and the locus coeruleus which are anatomically close to the nucleus of the trigeminal nerve. Through the massive contraction of the masseteric muscles, yawning stimulates those structures responsible for cortical activation (Barbizet, 1958; Walusinski, 2006; Saper, 2013).

CEREBROSPINAL FLUID SYSTEM HOMEOSTASIS AND YAWNING

The clustering of arachnoid villi along the sagittal sinus forms, known as "Pacchioni granulations," were first described in 1705, by the Italian scientist Antonio Pacchioni (1665–1726), as "peculiar wart like excrescences." But he failed to ascribe the right function to them (Brunori et al., 1993; Pacchoni, 1705, 1721). In 1768, Domenico Cotugno (1736–1822)

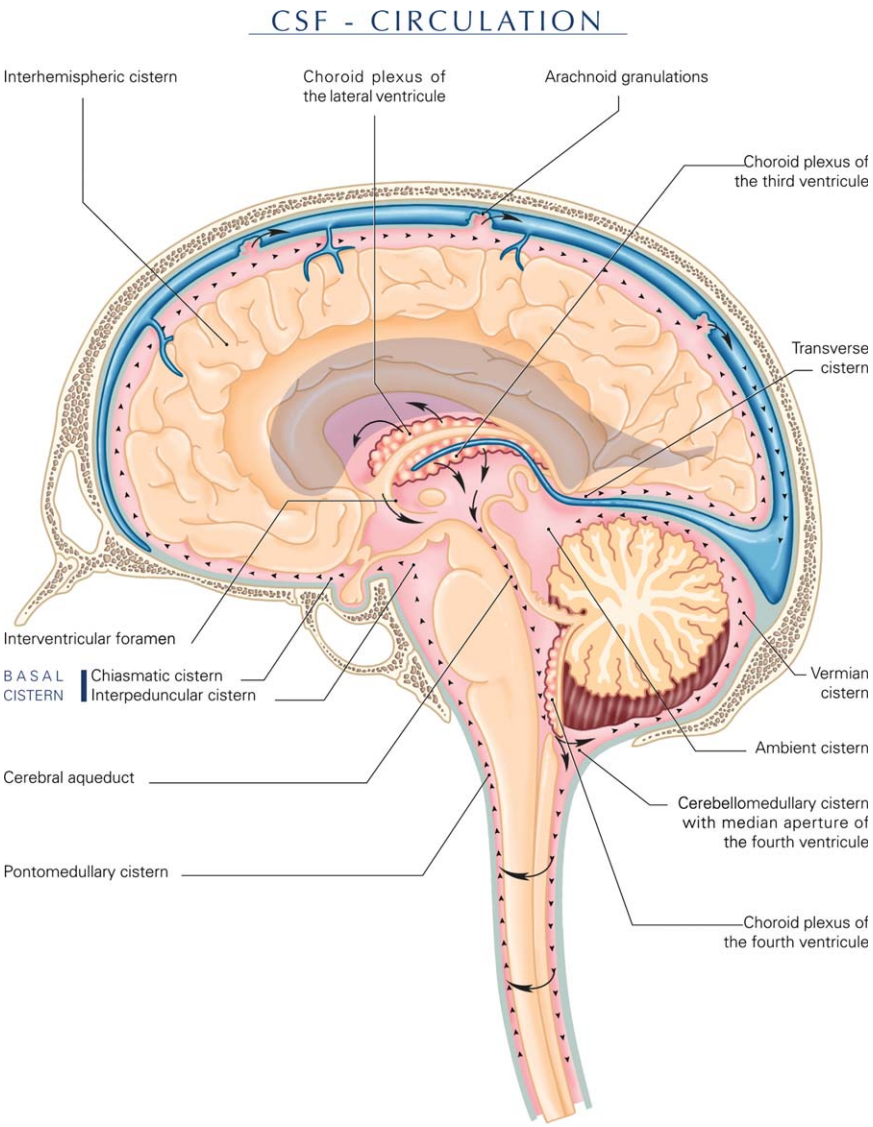

Fig. 2. Functional MRI: schematic localization of the three networks considered (illustration by Hélène Badault for the author).

clearly evoked the presence of fluid surrounding the nervous system and its circulation: "The whole space between the dura mater and the medulla is always filled; not by the medulla which is more turgescent in the living, nor by a water vapour (as this yet obscure substance is suspected of being by noted authors); but by water, similar to that about the heart which the pericardium holds, which fills the ventricles of the brain and the labyrinths of the ear, as well as the other cavities of the body inaccessible to air" (Cotugno, 1768). François Magendie (1783–1855) confirmed this finding in 1825 through comparative observations of animals and humans (Magendie, 1825). However, the initial experimental work on CSF outflow was performed during the landmark study of von Axel Key (1832–1901) and Gustaf Retzius (1842–1919) in 1876. They showed that lymphatic drainage has at least a potentially significant role in the outflow of CSF. A growing body of recent evidence not only suggests the importance of both arachnoid granulations and lymphatic capillaries, but also that transependymal passage plays a role in CSF outflow (Fig. 2) (Magendie, 1825; Key and Retzius, 1876; Woollam, 1957; Stahnisch, 2008).

The sum of the intracranial volumes of brain, blood, and CSF is assumed to be constant. CSF motion is therefore caused by the change of the cerebral blood volume due to the difference between arterial inflow and venous outflow and the movements associated with breathing that cause pressure variations in the ventricular system. Each deep inhalation is followed be an increase in CSF flow rate in the fourth ventricle.

CSF first gains access to drainage sites along the base of the cranium, and as intracranial pressure increases, CSF flow may move to the subarachnoid spaces along the convexity of the brain to absorption sites associated with cranial venous sinuses. Variations in blood volume within the rigid skull are compensated for by displacement of the CSF, brainstem, and spinal cord which act like a piston in the foramen magnum, balancing the intracranial volume. During expiration, increasing intracranial vascular pressure leads to compensatory caudal movement; during inspiration, the pressure decreases and the balancing displacement must occur in the cranial direction (Fig. 2) (Schroth and Klose, 1992; Maier et al, 1994; Kapoor et al. 2008).

Jaw kinematics and inhalation alter intracranial circulation. The consequences of yawn variants involving jaw and airway maneuvers, that is, closed-nose yawn or clenched-teeth yawns, suggested by Provine, or the Valsalva maneuver, commonly used to designate any forced expiratory effort against a closed airway, are the same as for physiological yawning (Provine, 2012). Indeed, all behavior inducing a cervical compression of the jugular immediately increases the CSF pressure. Therefore, wide mouth opening, such as yawning or variants, may have the same effect by stretching the omohyoid muscles and thus squeezing the jugular veins. Hence, Lepp (1982) described jaw kinematics as follows. Jaw movements activate the pterygoid musculovenous pump, located in the upper part of the anterior parapharyngeal space, known as the prestyloid parapharyngeal space. As a result, this pump, also known as the paratubal pump, can impact the mechanism of venous blood flow out of the endocranium, mainly via the plexus venosus foraminis ovalis. The pterygoid cistern, a component of this pump, corresponds to the cavernous part of the pterygoid plexus. It is an extracranial extension of the cavernous sinus and passes through the foramen ovale. It plays an important role as an intermediary station of acceleration for return blood flow from the brain (Bouyssou and Tricoire, 1985; Patra et al., 1988). Lepp (1982) noted that it would be reasonable to consider jaw kinematics together with the lateral pterygoid muscle as a venous trigger, given that they act as the starter for the alternating musculovenous pumping action that takes place in the cavernous part of the pterygoid plexus. This pumping action is particularly efficient during isolated yawning, especially when the mouth reaches its maximum opening. However, Lepp emphasized that yawning itself, and pandiculation even more so, is often merely the initiation of a musculovenous motor chain reaction, which extends to the limbs and the entire skeletal musculature as tonic waves propagated in the rostrocaudal direction to the ends of the fingers and toes. It would thus appear that the large inhalation and maximum opening of the mouth accelerate the circulation of CSF (Nitz et al., 1992).

Research into the hormonal factors that induce sleep has been conducted for nearly 100 years. In 1912, René Legendre (1880–1954) and Henri Piéron (1881–1964) demonstrated the presence of a hypnogenic factor in the CSF, which accumulates during the waking state. They took CSF samples of sleep-deprived dogs and infused them into the brains of normal dogs. The recipient dogs soon fell asleep. Thus, these two authors became the first to demonstrate the presence of endogenous sleep-promoting substances, but did not identify the chemical nature of their sleep substances (Legendre and Pieron, 1912). During the next 90 years, nearly 50 endogenous sleep substances were reported by numerous investigators to be present in the brain, CSF, and other organs and tissues of mammals, although their physiological relevance has remained uncertain in most instances. Nevertheless, concentrations of these molecules in CSF appear to be directly dependent upon their rate of production in the brain. Available evidence indicates prostaglandin PGD(2) as a most plausible candidate. PGD(2) is produced by lipocalin-type PGD synthase localized in the leptomeninges, choroid plexus and oligodendrocytes, and circulates in the CSF as a sleep hormone. During the past several decades, the mechanism of signal transduction has been extensively studied by a number of investigators at the cellular level. These studies indicate that most, if not all hormones, cytokines, and neurotransmitters do not penetrate the cell membrane. Instead, they are bound to specific receptors on the cell surface, and the signals are then transmitted through these receptors via so-called second messengers such as cyclic AMP, Ca2, and so forth. The mechanisms underlying sleep regulation by PGD(2) are somewhat reminiscent of signal transduction mechanisms at the cellular level; namely, PGD(2) is bound to D-type prostanoid receptors on the surface of the meninges, followed by the transduction via the purine nucleoside adenosine through the adenosine A2A receptor, increasing the local extracellular concentration of adenosine in the basal forebrain as a paracrine sleep-promoting molecule. Indeed, this signal is transmitted across the leptomeninges into the brain parenchyma toward the VLPO nucleus of the anterior hypothalamus, which induces sleep. Sleep-promoting neurons in the VLPO send inhibitory signals to suppress the histaminergic neurons in the TMN, which contribute to arousal through histamine H1 receptors. The neural network between VLPO and TMN is considered to play a key role in the regulation of sleep. Although PGD(2) level in CSF affects the action of D-type prostanoid receptors that promote physiological sleep, the regulatory system of PGD(2) clearance from the CSF is not fully understood (Huang et al., 2007, 2011; Urade and Hayaishi, 2011).

Taking into consideration all mechanisms and pathways helping us to understand the significance of CSF outflow, we argue that yawning and pandiculation may accelerate clearance of PGD(2), thus reducing sleepiness. They may also act on other neuromediators that are currently unknown. There have been no studies on the impact of adenosine level on DMN activity but, for example, recent findings highlight the link between astrogliosis, dysfunction of adenosine homeostasis and seizure generation (Tachikawa et al., 2012; Aronica et al., 2013).

Older data that initially seem to contradict our proposal must also be taken into account. Adenosine-mediated effects on sleep-wake cycles are site- and

receptor-dependent. Indeed, in the lateral preoptic area, a region with an abundance of sleep-active neurons, adenosine acting via A1 receptors induces waking by inhibition of sleep-active neurons. On the contrary, adenosine acting via A2A receptors promotes sleep by stimulating sleep-active neurons. Hence, A1 adenosine receptors may exert a negative influence on apomorphine-induced yawning. For example, intracerebroventricular administration of physostigmine to rats induces yawning dose-dependently and a selective A1 receptor agonist (N6-cyclohexyladenosine) reduces the yawning induced. Theophylline or caffeine, two adenosine receptor antagonists, exert an A2 antagonist effect. Hence, it may be possible that blocking the A2 adenosine receptor unmasks the A1 receptor subtype and in turn, elicits inhibition of apomorphine-induced yawning. So, adenosine via the A1 receptor subtype inhibits yawning while adenosine via A2A receptors elicits yawning (Ushijima et al., 1992; Zarrindast et al., 1995a,b; Methippara et al., 2005). Such results point out the need for experimental measurements of PGD(2) levels in the CSF, before, during and after yawning; such data are currently lacking.

TENTATIVE CONCLUSION

Changing between attention levels requires withdrawal from DMN activity and a redeployment to active vigilance by attentional network processing. At present, we know little about the neural processes responsible for this switch and those that initiate the reset between the attentional network and DMN. Such processes must adapt to the contingencies of environmental change and to the consequences for the organism of its own effect and must maintain optimum internal conditions. In the framework of neural networks that govern behaviors, automatic actions such as yawning may constitute a robust "attractor state" in which the resting state neural system (DMN) is readily dislodged and another stable state allowing sustainable attention (attentional network) is engaged.

Our theory takes into account three levels of data, in accordance with Provine and Ferrari's proposal that yawning "might be considered as an effort of the body to delay the onset of sleep and a mechanism to reinforce wakefulness after sleep." Each level is explained by the following:

1. the clinical level: yawning appears when the main source of stimulation in a person's environment no longer sustains his or her attention, by content or by form, that is, yawning appears when DMN is active and sleepiness increases;
2. the network level: yawning disengages DMN to promote the attentional network;
3. the molecular level: yawning accelerates the circulation of the CSF. By this action, the increased clearance of somnogenic substances reduces the propensity toward sleepiness.

In other words, yawning is proposed as a homeostatic process that regulates the level of sleep-inducing molecules and disengages DMN to promote the attentional network. By this proposition, we aim to open up a new avenue for elucidating the interplay between the humoral regulation and the neural network of yawning and its physiological function. We are aware that our hypothesis should be subjected to experimental testing. Hopefully, it provides a foundation on which to base a new class of innovative studies on yawning.

David Horrobin (1939–2003) summarizes this perspective: "The history of science has repeatedly shown that when hypotheses are proposed, it is impossible to predict which will turn out to be revolutionary and which ridiculous. The only safe approach is to let all see the light and to let all be discussed, experimented upon, vindicated or destroyed" (Horrobin, 1976).

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