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Review article

Yawning—Its anatomy, chemistry, role, and pathological considerations

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ABSTRACT

Yawning is a clinical sign of the activity of various supra- and infratentorial brain regions including the putative brainstem motor pattern, hypothalamic paraventricular nucleus, probably the insula and limbic structures that are interconnected via a fiber network. This interaction can be seen in analogy to other cerebral functions arising from a network or zone such as language. Within this network, yawning fulfills its function in a stereotype, reflex-like manner; a phylogenetically old function, preserved across species barriers, with the purpose of arousal, communication, and maybe other functions including respiration. Abnormal yawning with ≥3 yawns/15 min without obvious cause arises from lesions of brain areas involved in the yawning zone, its trajectories causing a disconnection syndrome, or from alteration of network activity by physical or metabolic etiologies including medication.

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; AChR, acetylcholine receptor; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Ca^{2+}, a calcium ion; CA1, cornu ammonis area 1, a region in the hippocampus anatomy; CO_2, carbon dioxide; CSF, cerebrospinal fluid; CT, computed tomography; D1 receptor, dopamine receptor D_1, (D1R); D2 receptor, dopamine receptor D_2, (D2R); D3 receptor, dopamine receptor D_3, (D3R); D4 receptor, dopamine receptor D_4, (D4R); EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; G protein, guanine nucleotide-binding protein; K^+, a potassium ion; L-DOPA, levodopa or L-3,4-dihydroxyphenylalanine; MS, multiple sclerosis; MSH, melanocyte-stimulating hormone; NADPH, nicotinamide adenine dinucleotide phosphate; NIHSS, National Institutes of Health Stroke Scale; NMDA, N-Methyl-D-aspartic acid; NO, nitric oxide; NOS, nitric oxide synthase; pO_2, Partial pressure of Oxygen; PD, Parkinson's disease; O_2, oxygen, by molecular formula (O_2); pIFG, posterior inferior frontal gyrus; PVN, paraventricular nucleus; RAS, reticular activating system; REM, Rapid eye movement sleep, a phase of sleep; RLS, Restless legs syndrome; RT-PCR, Reverse transcription polymerase chain reaction; STS, superior temporal sulcus; TSH, thyroidea stimulating hormone; T2, T2-weighted magnetic resonance imaging; vmPFC, ventromedial prefrontal cortex; 5-HT1A receptor, G protein-coupled receptor that binds serotonin (5-HT) and mediates inhibitory neurotransmission; 5-HT2C receptor, G protein-coupled receptor that binds serotonin (5-HT) and mediates excitatory neurotransmission; 5-HT6 receptor, another G protein-coupled receptor that binds serotonin (5-HT) and mediates excitatory neurotransmission.

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1. Introduction: what is a yawn

Physiological yawning, i.e. yawning without a cause in healthy individuals, is a ubiquitous phenomenon that can be observed across species barriers at least in most mammals (Fig. 1A, B) if not in most classes of vertebrates (for detailed review of published observations see e.g. Baenninger, 1997). Yawns consist of a typical sequence of respiratory phases such as long inspiration, brief peak or acme, and rapid expiration, accompanied by a coordinated motor pattern including opening of the jaw, closure of the eyes, contraction of facial muscles and sometimes stretching of trunk, neck and arms. Changes in autonomic function frequently accompany yawning (in more detail e.g. Baenninger, 1997). Yawning can be modulated in its frequency by operant conditioning, better so in animals such as monkeys (Louboungou and Anderson, 1987; Anderson and Wunderlich, 1988) but also in humans (Baenninger, 1997). Its visible action pattern – that is the coordinated repiratory and motor behavior – has been described as stereotyped or reflex-like (Lehmann, 1979; Provine, 1986), because once elicited it cannot be completely suppressed. However, its appearance can be modulated as well, e.g. by inhibiting opening of the jaw (Fig. 1C) and suppressing facial and thoracic innervation (Goessler et al., 2005). Yawning is termed pathological, abnormal, or excessive if it is spontaneous, more frequent than generally perceived as normal, compulsive, and not triggered by appropriate stimuli including fatigue or boredom. Chasm (Latin for gap, cavity, cleft as reviewed in lay and medical dictionaries by Heusner, 1946) as a synonym is *per se* descriptive, but rather used in abnormal than physiological conditions. No consensus definition exists concerning the frequency of yawns. Descriptions vary between 2 and 30 yawns per 10 min (Singer et al., 2007; Cattaneo et al., 2006). We recently adopted the abnormal yawning frequency to $\geq$3 yawns/15 min to decrease the likelihood that 2 subsequent, accidental yawns were counted as one episode with abnormal yawning (Krestel et al., 2015). Abnormal yawning seems to be a rare neurobiological phenomenon. Its cause in humans is unknown, but it can be observed in a variety of medical conditions that will be covered in more detail later on.

2. Anatomy of yawning

2.1. Hypotheses regarding the neuroanatomical location of the yawning center

The neuroanatomical location of the motor pattern that orchestrates yawning in humans is not known, respectively has not been experimentally proven. However, from early analyses of malformed infants who lacked a telencephalon but in whom a yawn-stretch act could be observed, it was concluded that if a yawn center exists, “it is to be found in the medulla oblongata in the immediate vicinity of the respiratory and vasomotor centers” (Fig. 2A; Heusner, 1946). This statement was deduced from two earlier accounts. The first described an anencephalic female who survived 3 months and in whom – postmortally – the medulla spinalis & oblongata, pons and mesencephalon were seemingly well developed (Gamper, 1926). The telencephalon was missing and the most cranial brain tissue was a severely malformed diencephalon. A certain residual function of the hypothalamus could not be excluded because the *substantia grisea centralis* behind the 3rd ventricle contained well-formed neuronal nests – however without resemblance to known neuronal nuclei. As this child showed phase switches between sleep and wake, a fully developed yawn-stretch act and no yawning nor stretching during sleep – hence a seemingly normal yawning behavior –, Gamper concluded that the yawn-stretch center is a subcortical mechanism and should be located in the *substantia grisea centralis* or

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periaqueductal grey (Fig. 2B) but might well be influenced by the telencephalon [in healthy subjects]. The second noteworthy account was by Catel and Krauspe (1930) who observed yawning in a seven days surviving female anencephalus. The nervous system was apparently well developed up to the area around the trigeminal nerve in the ponto-mesencephalic transition, however, the pyramidal tract and parts of ventral pons were missing or largely rudimentary. Cranial nerves XII to V, including their nuclei were well formed. The rudimentary diencephalon consisted of irregularly formed non-coherent cellular conglomerates, cysts and plexus-like structures. A very immature optic tract originated from 2 of these cellular conglomerates, which hence must have been parts of the thalamus. However, no further anatomical details could be delineated in this brain part. An intact connection to the medulla oblongata was not found. More cranial (i.e. forebrain) venous plexus, mesenchymal cysts, partly isolated cavities and dispersed cell nests, reminding of rudimentary basal ganglia, were found (Catel and Krauspe, 1930). In more recent publications, Askenasy (1989) located the yawning center "at the level of the reticular brainstem close to the reticular activating system" (RAS) and substantiated his suggestion by case reports of patients in whom the corticobulbar pathways were interrupted e.g. by tumors and who were tetraplegic but could yawn. The RAS is composed of several neuronal circuits connecting the brainstem to the cortex. The most caudal circuits are located in the midbrain reticular formation and in mesencephalic and pontine nuclei. Thus, according to today's knowledge, Ashkenasy's yawning center would reside somewhere in the midbrain (Fig. 2A). Third, it was proposed that the yawning center is located among pontomedullary central pattern generators (Walusinski, 2006; Fig. 2A). Central pattern generators are neuronal circuits in the medulla and subserve innate, repetitive motor behaviors that are essential for survival such as cough, swallowing, breathing (e.g. Marder and Rehm, 2005). Walusinski (2006) suggested that the yawning motor pattern recruits control systems including the locus coeruleus and the paraventricular nucleus.

2.2. Hypothalamic paraventricular nucleus controls brainstem yawning center

In principle, the central nervous system is composed of a "primary" and "secondary neuron". For efferent systems this frequently means that the "first neuron" (or network, frequently located in the supratentorial brain) exerts some control over the "second neuron" (or network, frequently located in the infratentorial central nervous system). This central nervous system organization is sometimes also called top-down control. In regard to yawning, the paraventricular nucleus (PVN) in the hypothalamus (Fig. 3) is frequently regarded as the supratentorial control of the yawning center in the brainstem. This leads us to a frequently cited study in anesthetized rats, in which stereotyped yawning could be elicited by chemical or electrical stimulation of the PVN in the hypothalamus (Sato-Suzuki et al., 1998). The study proposed that parvocellular oxytocinergic neurons in the PVN projecting to the lower brainstem mediate the yawning response and that nitric oxide is an important player. This concept had already been suggested elsewhere (see e.g. Argiolas and Melis, 1998, in 3.1. Basic model). As the PVN might be involved in yawning not only in rodents but also in humans, based on conservation of the act of yawning across species barriers at least in mammals, we would like to review its neuroanatomy including its connections to other brain areas and the brainstem nuclei. In humans, the anterior part of the hypothalamus contains neuronal nuclei of which the most important are the preoptical, supraoptical and the paraventricular nuclei (Fig. 3). The PVN contains neurosecretory magnocellular and parvocellular neurons as well as centrally projecting (i.e. to other brain regions) neurons. Magnocellular neurosecretory neurons are known for their production and transport of oxytocin and

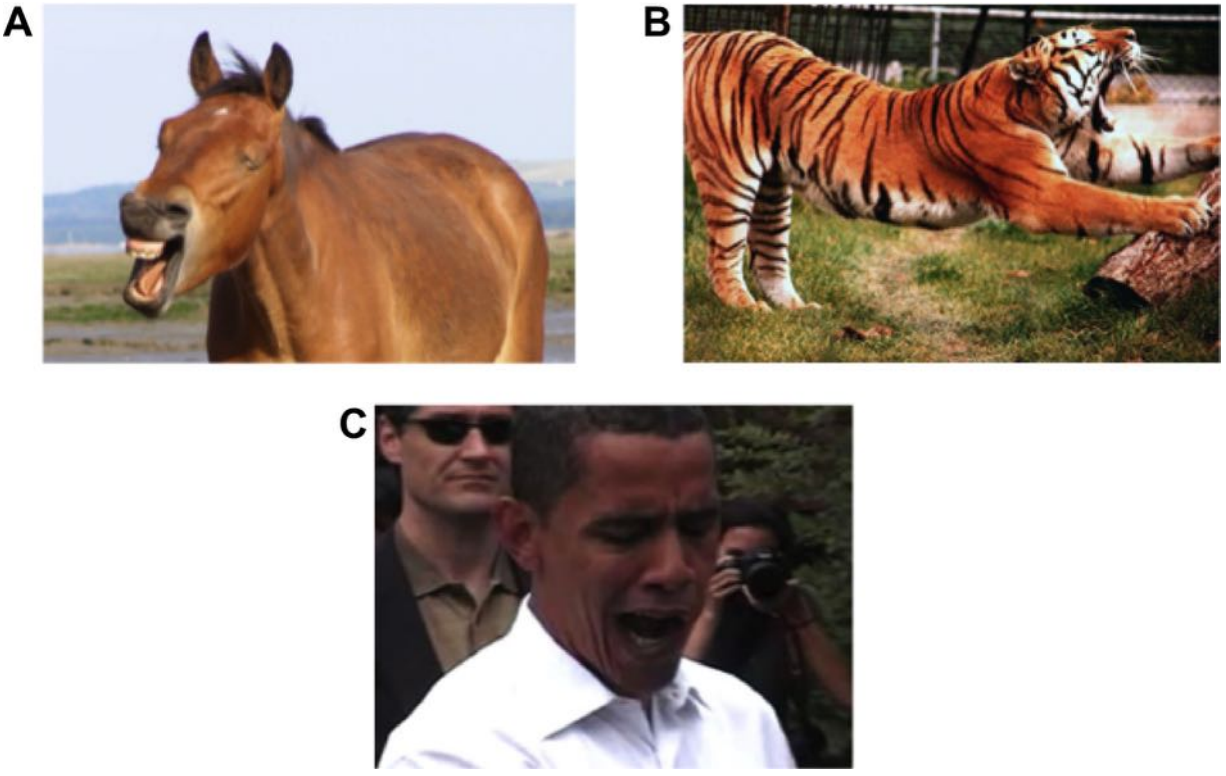

Fig. 1. Physiological yawning. This is an ubiquitous phenomenon across species barriers at least in mammals; here depicted in a horse (A) and a tiger (B). Yawning cannot be completely suppressed, once elicited. However, its appearance can be modulated to certain extent e.g. by (partially) inhibited opening of the jaw (C).

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antidiuretic hormone via their axons (supraopticohypophyseal tract) to the posterior pituitary gland where these peptide-hormones are secreted and exert their neuro-endocrinological function such as oxytocin does in regulating menorrhea, contractions of the pregnant uterus, milk secretion from female *mammae* and trust behavior (Kosfeld et al., 2005). Via releasing and possibly inhibitory hormones, parvocellular neurosecretory neurons indirectly regulate the production of hormones in the anterior pituitary gland such as growth hormone, gonadotropins, TSH, and ACTH etc. Finally, the PVN contains interneurons and populations of neurons including parvocellular, oxytocinergic neurons that project to other brain regions. One of these projections probably occurs via the medial forebrain bundle to structures in the brainstem implicated in regulation of respiratory, cardiovascular and autonomic functions including the *locus coeruleus*, solitary nucleus, ventrolateral medulla, the motor nucleus of the vagal nerve and via synapsing to further motor nuclei such as the ones of the trigeminal, facial and hypoglossal nerve (Duus, 1995). Especially the ventrolateral medulla contains a cluster of interneurons – named Pre-Bötzinger complex – that seems to be essential for the generation of respiratory rhythms in mammals (Smith et al., 1991). The exact mechanism of rhythm generation and transmission to motor nuclei such as the phrenic nerve (C1-C4) innervating the diaphragm remains controversial (Rybak et al., 2007; Abdala et al., 2009). Further neuronal effector centers involved in yawning are the motor nuclei of cranial nerves V, VII, IX, XI [and XII, more in animals?], and nerves innervating accessory respiratory muscles (Goessler et al., 2005). Additional data, generated in animals, about the intranuclear organization of the PVN and its projections is presented here, as it might be of relevance to better understand the neuroanatomical basis of yawning. Cells in the parvo- and magnocellular division of the PVN

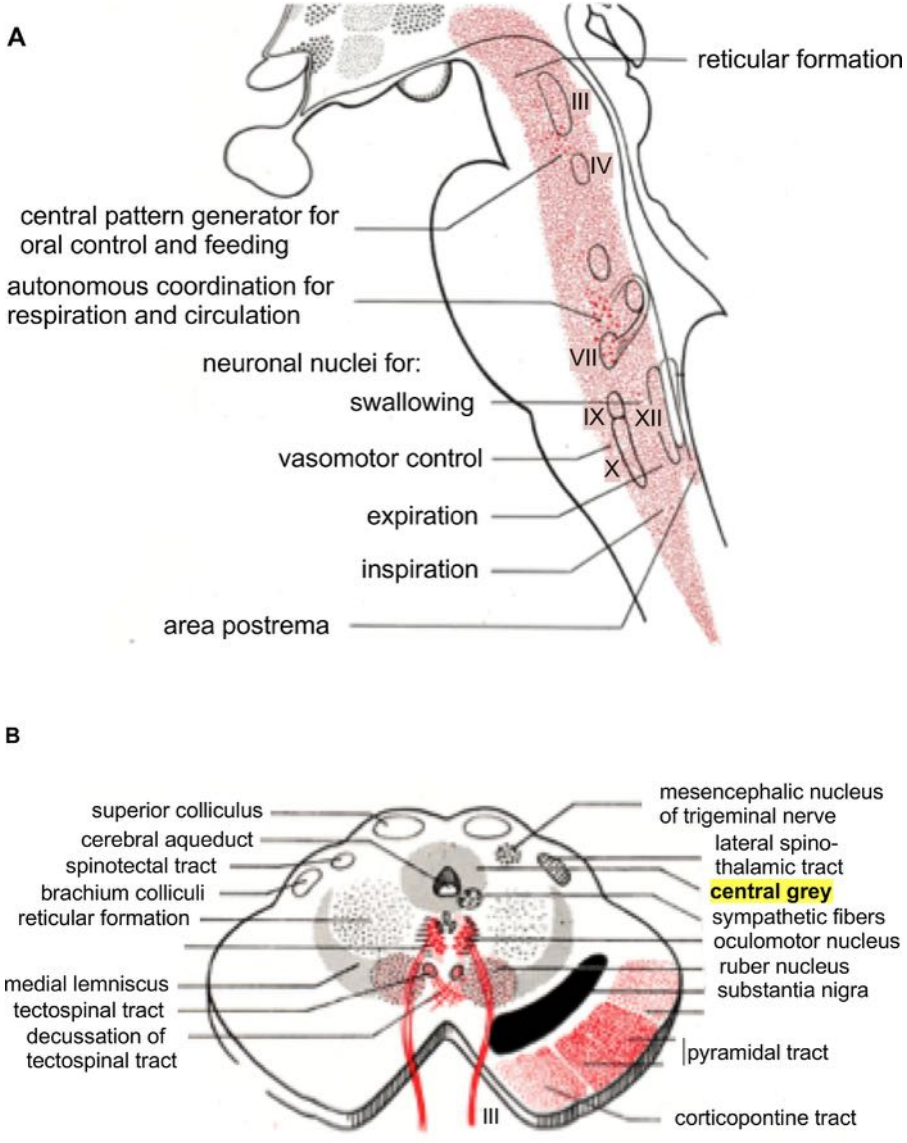

Fig. 2. Hypotheses regarding the neuroanatomical location of the yawning motor center. A) Shows a sagittal section of the brainstem, rostrally including the hypothalamus and the pituitary gland (Duus, 1995). Heusner (1946) proposed that the yawning motor center is located in the vicinity of respiratory and vasomotor centers in the *medulla oblongata*. Askenasy (1989) located the yawning center close to the reticular activating system (RAS), whose most caudal circuits would today reside in the midbrain and upper pons. Third, some authors believe that the yawning center exists among pontomedullary, central pattern generators for cough, swallowing, breathing. B) Shows an axial section through the mesencephalon including the aqueduct and central gray (Duus, 1995). Gamper (1926) deduced the location of the yawning center from studies of malformed kids with missing telencephalon to a subcortical location in the brainstem within the central or periaqueductal gray (highlighted). III, oculomotor nerve; IV, trochlear nerve; VII facial nerve; IX, glossopharyngeal nerve; X, vagus nerve; XII, hypoglossal nerve.

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have axons that branch sometimes – so called axon collaterals. Several axon collaterals of parvocellular neurons ramify locally and appear to contact dendrites of cells in both the parvo- and magnocellular division. This evidence suggests one possibility how the output of parvo- and magnocellular neurons might be integrated (Swanson and Sawchenko, 1983, and references therein) and could be important in regard to the hypothesis that cells in the parvocellular division [only] mediate the controlling effects on yawning (see 3.3. oxytocin network). In addition, magnocellular neurons seem to communicate by gap junctions. The predominant projection to the brainstem is the so called paraventriculo-spinal pathway, discovered in 1975, that was originally described to directly connect the PVN and other hypothalamic areas with preganglionic cell groups of both the parasympathetic and sympathetic divisions of the autonomic nervous system in the dorsal vagal complex and thoracic spinal cord, respectively. Subsequent work by several groups added more detail to its course. In cow and rat, fibers originating in the PVN descend initially through the median forebrain bundle and then, after passing between *substantia nigra* and red nucleus, continue through ventrolateral parts of the reticular formation to enter the dorsolateral funiculus of the spinal cord. In the pons, fibers leave this pathway to innervate the parabrachial nucleus and the *locus coeruleus*, while in the medulla, some fibers arch dorsally to innervate the dorsal motor nucleus of the vagal nerve and the *nucleus tractus solitarius*. In addition, a second pathway descends through the central gray and appears to innervate the *Edinger Westphal* nucleus, *locus coeruleus*, and perhaps the central gray (*substantia grisea centralis*), as well (Swanson and Sawchenko, 1983 and references therein). This detailed description also contains reported fibers to neuronal networks suggested to home the putative yawning motor pattern including the central or peri-aqueductal grey (Gamper, 1926), the midbrain reticular formation near the reticular activating system (Askenasy, 1989), and the ponto-medullary brainstem near the reticular formation (Walusinski, 2006).

2.3. Trajectories projecting to the PVN

Most of neural afferents to the PVN origin from a rather small number of cell groups in the brainstem, hypothalamus, and limbic regions of the telencephalon. The brainstem sends noradrenergic and adrenergic fibers to the PVN, which form one of the most dense catecholamine terminal fields in the brain. Mainly noradrenergic fibers project from A2 [noradrenergic] (and C2 [adrenergic]) cell groups of the *nucleus tractus solitarius* and from the A6 group of *locus coeruleus* to the parvocellular division, and from A1 (and C1) cell groups of the ventral medulla (located dorsal to but not within the lateral reticular nucleus) to both the parvo- and magnocellular division (Swanson and Sawchenko, 1983 and references therein). Sparse serotoninergic afferents reach the PVN mainly from mesencephalic raphe nuclei. The hypothalamus projects to the PVN from the anterior and lateral hypothalamic area, the ventromedial and dorsomedial nucleus, and the preoptic area which all end in the parvocellular division. Only projections from the dorsomedial nucleus and the median preoptic nucleus appear to end in the magnocellular division, as well. The suprachiasmatic nucleus, which receives direct input from the retina, projects to the parvocellular part. ACTH immunoreactive fibers are found in the parvocellular divison and in the magnocellular division where oxytocinergic cells are concentrated. These projections arise from immunoreactive neurons in and near the arcuate nucleus of the hypothalamus. Because β-endorphin has been co-localized within many ACTH-stained neurons, β-endorphin-containing fibers also reach the PVN (Swanson and Sawchenko, 1983 and references therein). The telencephalon may influence PVN activity, but rather through its limbic system. There is as yet no evidence for direct projections from neocortical areas to the PVN. Retrograde transport studies in the rat suggest that the lateral nucleus of the septal region, the amygdala (medial nucleus), and the hippocampus (specifically the ventral part of the subiculum) project to the PVN. However, these results do not seem to be without controversy (see Swanson and Sawchenko, 1983 and references therein). Other sources support [oxytocinergic] connections between the hippocampus, tuberomammillary bodies, and the PVN (e.g. Walusinski, 2006; Argiolas and Gessa, 1991). The bed nucleus of the stria terminalis may present one additional route by which the limbic region may influence parvocellular and oxytocinergic magnocellular neurons in the PVN (Swanson and Sawchenko, 1983 and references therein). Future work should be directed into validating the biochemical nature of fibers to the putative yawning motor pattern, given the fact that circa 30 different putative neurotransmitters have been identified in cell bodies or in presumed terminals within the PVN (Swanson and Sawchenko, 1983).

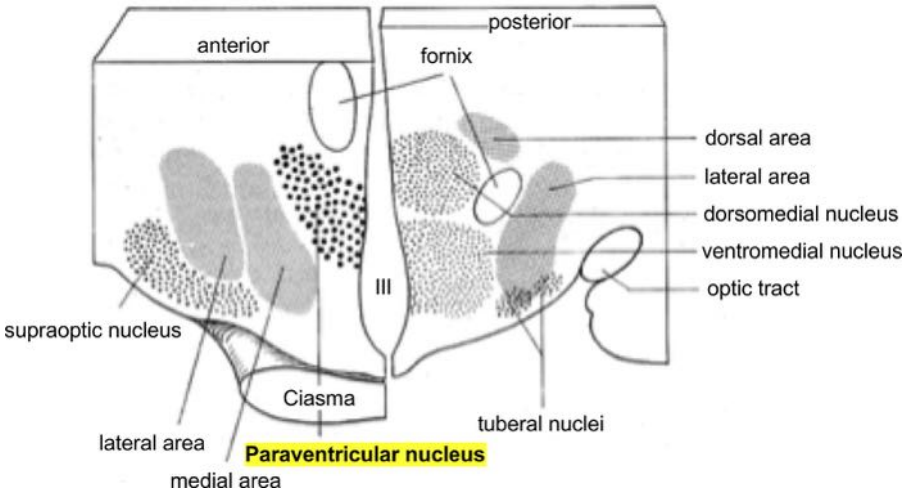

Fig. 3. Supratentorial control of the yawning center in the brainstem. Shown is a coronal brain section through the 3rd (III) ventricle and the surrounding hypothalamus (Duus, 1995). Shown are also various nuclei within the hypothalamus. Note the paraventricular nucleus (highlighted, PVN) on the more anterior or rostral, right, brain section (according to neuroradiological convention). Electrical and/or chemical stimulation of the PVN can experimentally elicit yawning. A similar PVN function in humans is deduced from the preserved yawn-stretch across species barriers in mammals.

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3. Neurochemistry of yawning

3.1. Basic model with yawning as oxytocinergic behavior

A lot of work has been invested into elucidating the neurochemistry involved in yawning. The subsequently presented overview centers on a model, proposed by a group that contributed significantly to this field and also integrated work of many others (Argiolas and Melis, 1998). Their model is extended and updated with unmentioned and more recent findings. The basic model suggests that oxytocinergic neurons originating in the PVN of the hypothalamus and projecting to extra-hypothalamic brain areas mediate the expression of yawning in animals in many but not all circumstances. Activation of neurons in the PVN by dopamine receptor agonists, excitatory amino acids, and oxytocin results in yawning, while their inhibition by e.g. opioids prevents the behavioral response. Dopamine receptor agonists bind mainly to D2 receptors and oxytocin to uterine-type oxytocinergic receptors and this leads to activation of [omega-conotoxin-sensitive] N-type Ca^{2+} channels via [pertussis toxin-sensitive] G_0/G_q proteins and subsequently to calcium influx. To a minor extent, Ca^{2+} is released from intracellular stores via the Phosphoinositid-Phospholipase C (PLC) pathway. Excitatory neurotransmitters including glutamate and N-Methyl-D-aspartic acid (NMDA), but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), were originally suggested to activate NMDA receptors, which are coupled to Ca^{2+} channels. This was confirmed by subsequent agonist-antagonist studies showing that NMDA-induced yawning was antagonized by (+)-MK-801, a selective antagonist of NMDA receptors, but not by omega-conotoxin, a potent blocker of N-type Ca^{2+} channels (Succu et al., 1998), and it is therefore likely that NMDA receptors mediate Ca^{2+} influx themselves. Increased cytoplasmic Ca^{2+} concentration in oxytocinergic neurons activates nitric oxide synthase (NOS) to produce nitric oxide (NO) that is suggested to act as intracellular messenger. The mechanism by which NO activates oxytocinergic transmission is not known. Guanylate cyclase, one favored target of NO, seemed then not involved. The inhibitory effect of opioids such as morphine on yawning induced by dopamine D2 receptor agonists, oxytocin, or NMDA is apparently mediated by μ-type morphine receptors since the morphine effect is blocked by the prior administration of the respective antagonist naloxone. In addition, a very potent agonist acting at kappa opioid receptors is ineffective in eliciting yawning. Signal transmission from extra – to intracellular may be mediated by decreased intracellular Ca^{2+} and reduced NOS activity, as less NOS metabolites were measured by *in vivo* microdialysis in the PVN after administration of morphine. The link between μ-receptor activation and decreased intracellular Ca^{2+} was stated as unknown by Argiolas and Melis (1998), but is probably due to closure of voltage-gated Ca^{2+} channels (e.g. Schroeder et al., 1991). Finally, it was suggested that the PVN is apparently not involved in yawning induced by 5-HT_{2C} agonists or ACTH/MSH. It was further proposed that the latter compounds act at sites located [prior to or] after oxytocinergic neurons, but there exist probably additional neuronal pathways that influence yawning. This was also proposed for cholinergic, noradrenergic & GABA-ergic systems involved in yawning (Argiolas and Melis, 1998).

3.2. Dopaminergic modulation of the basic model

The PVN receives dopaminergic afferents, which was concluded from the presence of dopaminergic fibers in the vicinity of parvo- and magnocellular neurons of the PVN and from dopaminergic boutons synapsing on magnocellular neurons. The origin of these fibers was not precisely located but the ventral tegmental area was suggested (Buijs et al., 1984). The basic model by Agriolas et al. suggested that the dopaminergic effect of yawning is mediated by postsynaptic dopamine D2 but not D1 receptors. The postsynaptic site of dopamine receptor activation was later confirmed (Collins and Eguibar, 2010). Recently, the dopamine D2 receptor was questioned and the dopamine D3 receptor was suggested instead. This was based on agonist-antagonist studies in rats (Collins and Woods, 2008; Collins et al., 2008; Baladi et al., 2010). The same group went on to propose specific roles for the D3 and D2 receptor in dopamine agonist-induced yawning (Collins and Eguibar, 2010). Other experimental data (again in rats) did not support a major role of dopamine D3 and D4 receptors, but of D2 receptors in dopamine agonist-induced yawning (Depoortère et al., 2009; Sanna et al., 2012a). There is evidence that the D2 receptor still might play a role in dopamine agonist-induced yawning. This comes from treatment of humans with Parkinson's disease (PD). In these patients, apomorphine, a relatively non-selective dopamine receptor agonist, with possibly slightly higher affinity for D2-like dopamine receptors, is used to test dopaminergic responsiveness or intermittently treat parkinsonian motor fluctuations. Yawning was quite commonly observed after apomorphine administration (Frankel et al., 1990; O'Sullivan et al., 1999 and references therein). Four major dopaminergic pathways have been described in mammalian brain. These are the mesocortical and –limbic pathways with their dopamine-producing somata in the ventral tegmental area, the nigrostriatal pathway and the tuberoinfundibular pathway with its dopamine-containing somata in the hypothalamus. To what extent the nigrostriatal system is involved in yawning, remains to be answered. However, microinjection of nanogram amounts of apomorphine and other dopamine D2 agonists into the PVN but not in the striatum of rats induced yawning (Melis et al., 1987). Apart from possible involvement of several receptor subtypes in yawning, dopamine receptors seem to underlie diurnal variations in sensitivity, since yawning, induced with identical doses of apomorphine, could be elicited more frequently in the morning than in the evening in healthy men (Lal et al., 2000). Dopamine-agonist induced yawning can be modulated by other transmitters. These include nicotine (Tizabi et al., 1999; Brown et al., 2006), adenosine (Rimondini et al., 1998), endocannabinoids (Beltramo et al., 2000; Nakamura-Palacios et al., 2002), and noradrenaline (Sawchenko and Swanson, 1981; Nowak et al., 2006). A dense catecholaminergic innervation was shown to synapse on PVN neurons (e.g. Swanson et al., 1981). Of interest is also the modulatory effect of dexamethasone, since yawning has been postulated – amongst others- as a signal for stress (see Communication hypothesis, below). Dexamethasone modulated (increased as single and decreased as repeated administration) pilocarpine- but not apomorphine-induced yawning in rats (Hipólide et al., 1999).

3.3. Oxytocin network extending to supra- and infratentorial brain

Oxytocin immunoreactivity is found in magnocellular (e.g. Buijs, 1978; Hatakeyama et al., 1996) and in parvocellular neurons (e.g. Buijs et al., 1978). The presence of NOS, indicated by positive NADPH diaphorase staining, colocalizes with oxytocinergic magnocellular neurons (e.g. Sánchez et al., 1994) and is also found in the rostral part of the PVN where rather parvocellular neurons reside (e.g. Sato-Suzuki et al., 1998). However, a direct co-localization of NOS and oxytocin in parvocellular neurons escaped our literature review. The type of oxytocineric PVN neuron involved in yawning has not been unequivocally proven, but reports of recent years favor parvocellular neurons (see e.g. Sato-Suzuki et al., 1998; Kita et al., 2006). Neuroanatomically, both

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parvo- and magnocellular neurons were shown to have extrahypothalamic projections. Oxytocin-containing fibers from magnocellular PVN neurons were traced to the dorsal/ventral hippocampus, amygdala, substantia nigra, central gray, *nucleus tractus solitarius*, and *nucleus ambiguus* in rats. In contrast to projections to rostral brain areas, far more oxytocin- than vasopressin-containing fibers were found in the medulla oblongata (and spinal cord) (Buijs, 1978). The author even suggested that some of the bi- and multipolar PVN cells may project to the neurohypophysis, as well as to extrahypothalamic areas and added that it is not precisely known whether all of these extrahypothalamic fibers are axons or whether some might be "dendrites with a receptive function" (Buijs, 1978). In contrast, retrograde double-labeling studies from another group indicated that hypothalamic projections to the brainstem or spinal cord do not, for the most part, arise as collaterals from magnocellular PVN cells that also project to the posterior pituitary gland (reviewed in Sawchenko and Swanson, 1982). Their retrograde labeling studies found roughly 10 times more cells in the parvo- than magnocelluar disvision of the PVN that contained a retrograde tracer (injected into the dorsal motor nucleus of the vagus and nucleus of the solitary tract) and were immunoreactive for oxytocin (Sawchenko and Swanson, 1982). In a follow-up study – by injecting a retrograde tracer into the dorsal vagal complex and thoracic spinal cord and staining the PVN immunocytochemically against oxytocin and vasopressin – fibers within the paraventriculo-spinal pathway could be identified that originated predominantly from oxytocinergic cells, located in the parvo- and magnocellular division of the PVN but more frequently in the medial and lateral parvocellular division (Swanson and Sawchenko, 1983). However, only 20% of retrogradely labeled cells stained positive for either oxytocin or vasopressin suggesting that additional cell types contributed to this tract. Interestingly, additional 5% of cells containing the retrograde tracer stained immunocytochemically positive for tyrosine hydroxylase (suggested by the authors to be dopaminergic), somatostatin, and met-enkephalin. Apart from this tract connecting the PVN with preganglionic cells of parasympathetic and sympathetic divisions of the autonomic nervous system, no statement was made about the nature of fibers that branch from the paraventriculo-spinal pathway to putative neuronal networks containing the yawning motor pattern. Still, fibers from magnocellular PVN cells also project to the vicinity of putative cardiovascular and respiratory nuclei. Several experimental studies in rats showed that electrical or chemical stimulation of the parvocellular division of the PVN affected yawning (e.g. Sato-Suzuki et al., 1998; Kita et al., 2000). However, the PVN is so small in these animals and even if targeting was precise, it cannot be excluded that magnocellular neurons in the vicinity are excited as well. Therefore, the issue might not be finally settled which type of PVN neuron is involved in yawning control. The hippocampus was repetitively implicated in yawning as oxytocin injections into it induced yawning (e.g. Argiolas and Gessa, 1991). These observations might reflect an indirect effect using the PVN as sort of relay station, as hippocampal-hypothalamic oxytocinergic projections were shown to exist. Similarily, oxytocin may induce yawning if injected not only in the PVN and hippocampus, but also in other brain areas, such as the ventral tegmental area and the posterior nucleus of the amygdala that, like the hippocampus, receive oxytocinergic projections from the PVN (Sanna et al., 2012b). Oxytocin seems to act as neurotransmitter in the brainstem as iontophoretically applied oxytocin is able to change the firing rate of some neurons in the dorsal medulla and oxytocin is released in Ca^{2+} dependent manner from tissue slices of medulla upon potassium application (Swanson and Sawchenko, 1983). The putative link between the action of NO as intracellular messenger and oxytocinergic transmission in yawning is still missing.

3.4. N-Methyl-D-aspartic acid (NMDA) and gamma-Aminobutyric acid (GABA)

A correlation between NMDA-induced yawning and NOS in the PVN was suggested. First, NMDA-induced yawning in freely moving conscious rats could be blocked by a NOS inhibitor (Melis et al., 1994a). Second, rats that had been rendered diabetic and impaired in their NMDA-induced yawning response by streptozotocin treatment were injected adenoviruses carrying a gene for neuronal NOS into the PVN. This could restore NMDA-induced yawning (Zheng et al., 2007). Excitatory (glutamatergic) amino acid activation is rather mediated via NMDA- thanAMPA receptors, as administration of NMDA but not AMPA into the PVN induced yawning (Melis et al., 1994b; Collins and Eguibar, 2010). Yawning induced by injection of a NO-releasing compound or glutamate into the medial parvocellular PVN of anesthetized rats was paralleled in its effect by injection of cyanide, a mitochondrial cytochrome c oxidase inhibitor. This led to the suggestion that the medial parvocellular division is sensitive to chemical hypoxia or ischemia and even contains an oxygen sensor that causes yawning (Kita et al., 2000; see also 4.1. Respiratory hypothesis). GABA may also modulate yawning by affecting NOS activity. Injection of GABA-A (muscimol) but not GABA-B (baclofen) receptor agonists into the PVN reduced yawning induced by apomorphine, NMDA, and oxytocin and was paralleled by a decrease in NOS metabolites as measured in a paraventricular microdialysate (Melis and Argiolas, 2002). However, this effect is controversal (see Doger et al., 1989).

3.5. Endogenous opioids

Enkephalins, being endogenous opioids, are found in magnocellular and parvocellular PVN divisions, and the paraventriculo-hypophyseal tract may also contain enkephalins (Swanson and Sawchenko, 1983). Yawning is a prevalent sign of the opiate withdrawal syndrome in human opiate addicts (O'Brien, 1996; reviewed in Argiolas and Melis, 1998). Adenosine and opiate systems were shown to modulate each other, resulting in a withdrawal syndrome including yawning, if rats – physically made dependent with adenosine agonists – were challenged with adenosine antagonists, or if adenosine antagonists were given to morphine pre-treated rats (Coupar and Tran, 2001). Intracellular phosphorylation, converting the opioid receptor into a constitutively active form, plays a role in the opiate withdrawal syndrome in dogs. Administration of a protein kinase C inhibitor, prior to rendering dogs opioid dependent, attenuated acute symptoms, if withdrawal was induced (Freye and Levy, 2005).

3.6. Serotonergic yawning

Serotonin (5-HT) 2C receptor agonists are effective at inducing yawning in rats and humans, which can be blocked by 5-HT2C antagonists. Stimulation of 5-HT1A receptors can also block dopamine induced yawning (Argiolas and Melis, 1998). The relationship between serotonin and yawning is however not straightforward in rats: 5-HT2C receptor agonists do not induce yawning when they are directly injected into the PVN; 5-HT2C receptor antagonists do not prevent dopamine/oxytocin induced yawning and 5-HT2C mediated yawning is not prevented by oxytocin receptor antagonists but by NOS inhibitors, when given into lateral ventricles (Argiolas and Melis, 1998). In addition, 5-HT6 receptors play a role in the control of yawning, as respective antagonists could increase the number of yawns (Sleight et al., 1998), but not in continuous treatment for seven days (Marcos et al., 2008). In humans, yawning was reported as side effect during treatment with selective serotonin reuptake inhibitors such as

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paroxetine (Harada, 2006), escitalopram (dosage reduction terminated yawning) (Gutiérrez-Alvarez, 2007), the combined serotonin and norepinephrine reuptake inhibitor Duloxetine (De Las Cuevas and Sanz, 2007) and with venlafaxine, a reuptake- inhibitor of serotonin, norepinephrine and weakly dopamine (Chen and Lu, 2009). Its site of action was proposed to lay outside the PVN and we recently proposed that the insula might be the long sought-after brain region for serotonin-mediated yawning (see also 5.1.1. Anterior circulation stroke; Krestel et al., 2015).

3.7. Acetylcholine and noradrenaline

Cholinergic or −mimetic drugs such as the acetylcholine esterase inhibitor physiostigmine and the muscarinic receptor agonist pilocarpine can induce yawning in rodents. This effect seems to be mediated by M1- and M2 subtypes of muscarinic acetylcholine receptors (AChR) as the muscarinic receptor antagonists atropine and scopolamine, but not nicotinic AChR antagonists prevented yawning induced by ACTH, dopaminergic agonists, and oxytocin (Argiolas and Melis, 1998). It is not known at which neuroanatomical site acetylcholine and its agonists affect yawning. Possibilities include modulation of the PVN afferents, efferents and at somata of PVN neurons themselves. Lesion studies suggested a central role of septo-hippocampal cholinergic neurons in the induction of cholinergic yawning, but it remained unclear which trajectories reached the brainstem to induce the yawning motor pattern (Collins and Eguibar, 2010). The above mentioned observation that muscarinic receptor antagonists prevented yawning induced by above mentioned transmitters and hormones suggests that modulation takes place at the level of PVN efferents or directly in the brainstem. Indeed, muscarinic AChR subtypes M1-M5 have been found in pons and medulla of rats with biochemical methods (Wei et al., 1994). Even the nucleus tractus solitarius (Endoh, 2007; patch clamp experiments) and the rostral ventrolateral medulla (Kumar et al., 2009; quantitative RT-PCR) were shown to express M_2 type muscarinic AChR in rat. The proof however is still missing whether cholinergic trajectories from the PVN to brainstem exist that may directly induce yawning. On the other hand, as intense bidirectional noradrenergic projections between the parvocellular division and the brainstem (locus coeruleus, nucleus tractus solitaries, dosal vagal complex) exist (e.g. Sawchenko and Swanson, 1981), adrenergic modulation of yawning via direct PVN brainstem projections seems possible.

3.8. Adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormones

Adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormones (MSH) can induce a stretching-yawning syndrome that was considered different from the classic yawning syndrome (induced e.g. by dopamine agonists or oxytocin), because the behavior starts only 20 to 30 min after intraventricular injection and lasts for hours. Some evidence concerning the neuroanatomical site of action comes from a study in which injection of ACTH into the peri- [not para-] ventricular area around the 3rd ventricle could induce yawning and be blocked by prior installation of a melanocortin 4 receptor antagonist. However, yawning could not be elicited by injection into CA1 area of hippocampus, caudate nucleus or preoptic area (Argiolas et al., 2000). The involvement of PVN – brainstem projections in ACTH/MSH induced yawning remains controversial. It shows in some instances analogies to dopamine or oxytocin-induced yawning such as prevention of yawning by omega-conotoxin and NOS inhibitors and hypophysectomy. On the other hand ACTH/MSH induced yawning is not prevented by PVN lesions nor by dopamine or oxytocin receptor antagonists (reviewed in Argiolas and Gessa, 1991). Therefore, both possibilities- i.e. involvement and detouring the PVN in yawning – seem possible.

4. Potential roles of yawning

4.1. Respiratory hypothesis

Besides unraveling the neuroanatomical and chemical blueprint of yawning, it has always been of interest to understand its role in biology and why it has been evolutionary conserved. One of the earlier and still widely held beliefs is that yawning is due to changes in respiratory function or brain perfusion (with oxygen), respectively. The respiratory hypothesis dates back to Johannes de Gorter (1689–1762), a prolific Dutch author who, in his book "*De Perspiratione insensibili*", attributed yawning "*to a need for faster blood circulation and to cerebral anemia*". More recently, H. Russell's monograph from 1891, which is one of the earliest and most extensive printed excerpts about yawning in the English language, suggests such physiological power for yawning. Herein, yawning is an automatic impulse caused by bad air in the lungs, designed by nature as a gymnastic and intended both to awaken respiratory organs into activity and to effect a stimulation of the brain through increased activity of the circulation (Russell, 1891). Although this concept has been frequently attacked and seems to date the least experimentally validated hypothesis about the purpose of yawning, it is still not without favor among clinicians. Often cited together is the theory that yawning is caused by anemia or insufficient perfusion of the brain. One of its early protagonists was Valentin Dumpert who suggested that yawning is not only caused by anemia or poor brain circulation, but in addition a tendency to defend impaired consciousness is required [For him the yawn-stretch act was an elementary indirect vascular reflex ("elementarer indirekter Gefässreflex, dem das ganze Blutgefässsystem unterstellt ist")] that controlled all blood vessels (Dumpert, 1921). Hence, the two theories together can be formulated these days as the hypothesis of an impact of (cerebral) hypoxemia or hypercapnia on yawning frequency and duration. Observations in favor of this hypothesis have been multiple such as: i) Enhancement of venous backflow to the heart and activation of the parasympathetic nervous system with dilation of arterioles and bronchioli during yawns results in increased respiratory elimination of carbon dioxide and uptake of oxygen (reviewed in Askenasy, 1989). ii) Deep inspiration removed atelectasis that accumulated during 2 h of normal ventilation in excised rat lungs by a single large inflation and was assumed to parallel the in vivo situation with shallow breathing and subsequent yawning (Thet et al., 1979). iii) Brain hypoperfusion by stepwise reduction of arterial blood pressure triggered yawning and decrease in pO2 and EEG frequency (Karasawa et al., 1982). iv) Experimentally induced chemical hypoxia by local injection of cyanide, a mitochondrial cytochrome c oxidase inhibitor, into the parvocellular part of the PVN elicited yawning in anesthetized rats, prompting the authors to suggest that this area contains an oxygen sensor (Kita et al., 2000). Indeed, current understanding of candidates in the carotid body – supposed to register oxygen fluctuations in blood – include NADPH oxidases generating reactive oxygen species in O_2 dependent manner, oxygen-regulated plasmalemmal K^+ channels, and cytochrome c oxidases which can respond with depolarization of mitochondrial membranes and Ca^{2+} release (Kummer and Yamamoto, 2002). However, the currently favored model for oxygen sensing in the carotid body is inhibition of O_2 sensitive K^+ channels in glomus cells with subsequent depolarisation, Ca^{2+} entry, and transmitter release activating afferent nerve fibers (López-Barneo et al., 2008). Evidence against the respiratory hypothesis include observations of yawns – mouth movements, grimaces, tongue protrusions – as early as in human and rodent

fetuses (Van Woerden et al., 1988; Sherer et al., 1991; Walusinski, 2010). Although fetuses require oxygen and must expel carbon dioxide, they clearly do not use the pulmonary respiration mechanism. Fetal mouth movements, grimacing and stretching might be the exercise of a motor pattern by which neonates are able to produce normally integrated yawns within minutes after being born. Second, a study in young, healthy students in whom neither yawning rate and/or duration was altered by breathing gas mixtures with higher than normal levels of CO_2 (3 or 5%) or 100% O_2, although both affected breathing rate. Physical exercise sufficient to double breathing rate had no effect on yawning, too. The authors concluded that altered partial pressures of O_2 and CO_2 in blood did not affect yawning (Provine et al., 1987). However, the report does not mention any measurements of blood gas partial pressures (neither transcutaneous nor arterial). Third, periods of apnea are not followed by compensatory yawning after breathing is resumed (reviewed in Baenninger, 1997). The measurements, recorded by one of us using digital oxymetric monitoring, show a light drop of oxygen saturation immediately after a yawn (unpublished data). The conclusion seems to be that fluctuations in partial pressure of oxygen or carbon dioxide do not seem to be a driving force for yawning in humans. Still, to fully exclude the respiratory hypothesis, the study by Provine et al. (1987) should probably be repeated with measurements of O_2 and CO_2 partial pressures.

4.2. Communication hypothesis

The second so-called communication hypothesis is about the purpose of yawning as a communicative tool that serves to synchronize the behavior of a group (Daquin et al., 2001). One of the conclusions in an analysis of a novel by Jean-Paul Sartre about profound boredom gets it to the point: “the yawn is a hole with a difference [. . .] it does not invite filling [. . .] but it is full and expressive” (Bell, 1980). It is generally accepted that yawning signalizes sleepiness. This association is obvious and has been proven as yawning occurs more frequently in mornings and evenings during transitions between activity and sleep (Greco et al., 1993; Baenninger, 1997). Furthermore, it is presumed to signalize lack of interest/boredom, as increased yawning rates were observed in students sitting in a class, in people driving a car or during studying (which is generally but not necessarily believed to be boring; Greco et al., 1993). In addition, more frequent yawning is associated with viewing uninteresting, repetitive stimuli than with viewing interesting stimuli (Provine and Hamernik, 1986). Yawning as a signal for stress or threat/conflict is more established in the animal kingdom (reviewed in Baenninger, 1997). In fact, increased yawning frequency as a signal for stress in humans was reported only once in a survey of students (Greco et al., 1993).

4.2.1. Contagious yawning

Apart from yawning without obvious external trigger, it can be elicited by observing or listening other individuals yawn and by reading or thinking about it. The urge to yawn is often irresistible and only partially suppressible and has hence been termed contagious. Its neuroanatomical substrate has been attempted to be unraveled with functional magnetic resonance imaging (fMRI) in humans. Differences in fMRI-activated brain areas were found among experimental studies. According to the predominantly activated brain region – and results of non-fMRI studies – different theories have been proposed. First, contagious yawning may be mediated by cerebral mechanisms involved in empathy and self-processing because brains of probands observing other people yawn versus laugh were selectively activated in areas that are believed to be involved in processing of empathy (theory of mind) and information about oneself such as the posterior cingulate, precuneus, bilateral thalamus, and parahippocampal gyrus (Platek et al., 2005). The same group also showed that the urge to yawn in probands observing others yawn was amongst others positively correlated with scores of pencil tests for empathy (Platek et al., 2003). Support for this theory came from another group, showing that the ventromedial prefrontal cortex (vmPFC) is selectively activated in fMRI scans of brains of people observing yawn versus cough/gape conditions (Nahab et al., 2009). The vmPFC was shown to be involved in empathic processing (Eslinger, 1998; Shamay-Tsoory et al., 2003), but also in weighing or biasing future choices and minimizing decision-making time (Bechara et al., 1999, 2000; Fellows and Farah, 2007). A different mechanistic hypothesis is that contagious yawning is mediated by a mechanism called action understanding or imitation. This theory was put forward by a study that compared yawning and intransitive orofacial movement conditions. Here, selective fMRI activation was seen in the superior temporal sulcus (STS; Schürmann et al., 2005). Neurons in the STS discharge when an individual observes certain movements but not when the individual performs the corresponding motor actions him-/herself. As one characteristic of mirror neurons is to discharge during perception of a motor action but – as they are motor neurons – also during performance of that action by the individual him-/herself and because STS neurons lack motor neuron properties, they are considered to be strictly related to the mirror neuron system but not part of it (Rizzolatti and Craighero, 2004). The STS is believed to be the area where the action made by another individual is compared with sensory-motor consequences of the same action made by oneself in order to copy a new action or to adjust an action present in one’s motor repertoire to a different action (Iacoboni et al., 2001). Therefore, the unique STS- activation in Schürmann’s study might reflect a [pattern] recognition process of the yawning versus orofacial movement conditions. Taken together, the above-mentioned fMRI studies have in common that their yawning study conditions were based on seeing films or pictures of other subjects and evoked unique activation in brain areas that do not belong to the mirror neuron system. Therefore, the authors univocally concluded that contagious yawning is not related to imitation that is mediated by the mirror neuron system. They rather suggest the cortical release of a stereotypical motor pattern (in particular Schürmann et al., 2005; Nahab et al., 2009). In contrast, investigation of auditory contagious yawning by fMRI showed that yawn sounds not only were effective at eliciting an urge to yawn but yawn sounds with high urge to yawn significantly activated essential parts of the mirror neuron system including right posterior inferior frontal gyrus (pIFG) and posterior superior temporal gyrus (STS; Arnott et al., 2009). How can this controversy about involvement of the mirror neuron system in contagious yawning be explained? First, the stimulus may make a difference, as processing of sound takes place in a different cortical area than processing visual stimuli. However, when it comes to recognition of a stereotypical pattern, acoustically and visually processed information should converge. Here, the mirror neuron system offers the theoretical advantage of containing so called visuo-motor and echo-neurons; cells that discharge upon seeing or hearing a particular action (Rizzolatti and Craighero, 2004) which makes them in principle suitable to recognize different sensory information of one action. On the other hand, fMRI activation in classical mirror neuron areas including the posterior inferior frontal gyrus can be detected in the studies by Schürmann et al. (2005) and Nahab et al. (2009) especially on second examination of those figures in which yawning was compared to a blank screen or white cross on grey screen respectively, and not to orofacial movements or gape/cough conditions. Even the study of Platek et al. (2005) showed figures with fMRI activation in the vicinity of the superior/inferior parietal gyrus – being part of the mirror

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neuron network – if yawning was compared to neutral face conditions and not to laugh. Finally, the studies about visual contagious yawning did not grade the urge to yawn of their probands in response to visual stimuli (exept for Nahab et al. whose probands answered a binary questionnaire whether they yawned while seeing visual stimuli and whether they yawned more when seeing repeated stimuli). Therefore correlations of subjective high-urge-to-yawn feelings with fMRI activity patterns were not reported. In summary, the mirror neuron network can still be involved in the recognition and processing of contagious yawning. The question remains whether contagious yawning is based on imitation, action understanding, empathy, or some "inborn" capacity of the brain. One relative argument against imitation is an observation by Moore (1942) that blind people yawn in response to an audio recording of yawns. How can blind people perform the act of yawning in a correct and recognizable way, if they haven't ever observed it and if it is not a motor pattern belonging to the basic repertoire of the brain? It is therefore suggested that the efferent part of contagious yawning is not elicited by cortical mirror neuron motor areas. Rather the highly stereotypical expression is recognized by the cortex (might it be STS, pIFG or vmPFC) and might activate intermediate control centers including e.g. the insula, hippocampus, and the PVN which then induce execution of the motor program by brainstem structures that coordinate innervation of facial, laryngeal, pharyngeal structures, the diaphragm and accessory respiratory muscles. As mentioned, contagious yawning does not necessarily depend on visual or acoustic input only. Thinking or reading about yawning can be enough to trigger the yawn act (Baenninger and Greco, 1991; Greco et al., 1993; Provine, 1986). The mirror neuron network would be handy to explain this sort of observation in its function as pattern recognition system. The theory of speech evolution is based on a transfer of gestural meaning to abstract sound meaning and on the existence of a common neural substrate for hand/arm and speech gestures, as well as for sound and language processing (Rizzolatti and Craighero, 2004). It was shown that during reading and spontaneous speech without further motor action, mirror neuron areas including the hand motor cortex were activated as well (Meister et al., 2003). Therefore, reading or thinking about yawning might activate brain areas that started evolutionary as motor neurons and have become specialized to recognize, that is to discharge to, the written perception of an action or its retrieval from memory but may not necessarily contribute to the motor performance of that action anymore. The conclusion is that the communication hypothesis can only explain a part of the behavior by great apes, perhaps parrots and other birds, and mammals, but not by reptilians. The sauropsids include reptiles (poikilotherm) and birds (homeotherm). But, in fact, relative brain size varies greatly among sauropsids, with turtles and snakes occupying the low end of the range. All reptiles present a trilaminar cortex in a large dorsal ventricular ridge that protrudes into the ventricle. It is difficult to homologize to anything in mammalian brains. These differences in cerebral architecture probably explain why social processes such as unconscious mimicry like contagious yawning cannot be observed by reptiles or tortoises (Wilkinson et al., 2011).

4.3. Arousal hypothesis

The third major hypothesis favors arousal as the prominent biological purpose of yawning. Supporters of this hypothesis include Ronald Baenninger who recapitulated that "*the thread used to tie all the diverse data and observations together is the basic hypothesis that a major function of yawning is to regulate levels of arousal*" (Baenninger, 1997). For his conclusion, he also reverted to own data such as the study showing significantly increased wrist activity – as measured with wrist monitors – after yawning as an indicator for elevated arousal (Baenninger et al., 1996). While analyzing the biochemistry of yawning, the constellation of neurotransmitters favoring yawning such as serotonin and dopamine suggested to JAskenasy (1989), another protagonist of the arousal hypothesis, that yawning has an "*antisleep effect*". Olivier Walusinski suggested that the yawning-stretch syndrome may be an afferent proprioceptive feedback contributing to one's cerebral body scheme. But he also advocated its contribution to arousal by triggering dissolution of the cerebral network controlling sleep – and especially REM sleep – and facilitating the establishment of a network that controls the wake status (Walusinski, 2006). He adds recently to his theory a more complete explanation by 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 accumulating in the cerebrospinal fluid (Walusinski, 2014). A further pro-arousal argument came from Sato-Suzuki and co-workers who showed that cortical EEG frequency – recorded experimentally with 2 screws from the vertex of anesthetized rats – increased prior to yawns elicited by electrical or chemical stimulation of the PVN and subsequently reversed to slow EEG activity after yawning (Sato-Suzuki et al., 1998). These behavioral and EEG phenomena could be repeated with different stimuli such as orexins (Sato-Suzuki et al., 2002) and histamine (Seki et al., 2002). On the other hand, Guggisberg and co-workers showed in 16 patients who suffered from daytime sleepiness that yawning is triggered by states of low vigilance but does not lead to an arousing effect when compared to the performance of voluntary isolated body movements by the same group of patients. In detail, yawning was preceded by significantly greater delta activity in EEG than voluntary movements, indicating drowsiness before the yawn event. After yawning, power in the delta frequency range was still significantly greater than after a voluntary movement. In addition, mean alpha frequency over central regions increased after isolated movements while it decreased after yawning indicating arousal rather by voluntary body movements (Guggisberg et al., 2007). Other studies investigating the association of yawning with arousal in humans with EEG, skin conductance, or measurements of other autonomic parameters found controversial results (Guggisberg et al., 2010, 2011). In conclusion, yawning correlates with low states of vigilance and is associated with transitions between wake and sleep, periods of exposure to uninteresting repetitive stimuli, or with particular stressful events. The failure to associate yawning with improved vigilance or increased autonomic tone does not preclude yawning to be a clinical sign for particular activity states of those brain regions that are involved in regulation or execution of yawning. If this can be demonstrated in future experiments, the arousal hypothesis may be rephrased as focal brain activity hypothesis.

4.4. Brain-cooling hypothesis

One research group promoted brain cooling as a biological function of yawning. Data of arousal and autonomic activation in humans (Corey et al., 2012) and transient brain temperature peaks around bouts of yawning in rats (Shoup-Knox et al., 2010) were presented as evidence for this hypothesis. Abnormal yawning was suggested to be indicative for thermoregulatory dysfunction, i.e. disorders temporarily associated with abnormal yawning were associated with difficulties in body temperature control (Gallup and Gallup, 2008; Prasad, 2008; Gallup, 2014). It can be agreed upon that (physiological) yawning and tongue protrusion can help in the control of body temperature in species such as felidae or

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canines, which do not exchange heat as effectively via body surface and perspiration as do humans because of their fur. In humans, heat exchange is likely to be more effective at the body surface, promoted by perspiration, than in lungs due to their surface difference. From a neuroanatomical point of view the hypothalamus is believed to be the center for thermoregulation, and the sympathetic nervous system, which controls amongst others sweat glands in skin, has origins in the hypothalamus, as well. In addition, hypothalamic nuclei are believed be one superordinate control system of the yawning motor pattern. Therefore, we rather suggest that neurological diseases or neurotropic medication, affecting input/output or function of the hypothalamus itself, might conjointly affect thermoregulation and yawning behavior. This does not necessarily mean that these 2 mechanisms are causally related and one is performed to serve the other. One needs to take into consideration that a physiologist, Hannu Elo, has shown by calculations that the temperature decreases claimed to occur during yawning are physically impossible (Elo, 2010).

5. Abnormal yawning associated with diseases or medication

Yawning may occur not only because of boredom, drowsiness, or by contagion but also in association with various pathologies. We tried to give a representative review of diseases associated with noticeable yawning, but may not have covered all aspects. Abnormal yawning was termed pathological or excessive in only a few reports. For its definition including frequency, the reader is referred to the introduction. Several reports of noticeable yawning could sometimes be better grouped according to a neurological syndrome of various etiologies. Otherwise, reports were listed according to the respective neurological disease.

5.1. Yawning during and after cerebrovascular insult

5.1.1. Anterior circulation stroke

Anterior circulation stroke with unilateral, supratentorial lesions can be associated with abnormal yawning. In the first report, 3 or more yawns per 15 min were observed in each of 7 patients who presented with acute middle cerebral artery stroke and signs of cortical dysfunction such as aphasia, neglect and gaze palsy. Symptom onset was within 12 h, average NIHSS score was 17 and 1/3 or more of the MCA territory was affected. The authors' conclusion was that supratentorial lesions may release the hypothalamic PVN from neocortical control mechanisms, thereby increasing its activity and leading to excessive yawning. As temporal lobe structures were partially damaged in their patients, they speculated that hippocampal/periamygdalar – hypothalamic connections, shown before to exist, might have been affected (Singer et al., 2007). The second report was about a patient with left internal capsule stroke and right-sided weakness (Upper and lower limb 0/5 and 2/5 respectively), who could not move his arm voluntarily but was able to do so during yawning. The authors speculated that intact non-pyramidal projections from a putative, non-lesioned yawning center in the brainstem might share the common lower motor neuron pathway to innervate brainstem nuclei and spinal cord anterior horn cells. It was not mentioned whether the patient exhibited excessive yawning (Wimalaratna and Capildeo, 1988). Involuntary yawning-associated movements in paralyzed limbs were termed parakinesia brachialis oscitans (Walusinski et al., 2005). They were also observed in a large case series of patients with acute anterior circulation stroke. Interestingly, these yawning-associated movements do not seem to have any prognostic value (Meenakshisundaram et al., 2010). We published a series of 10 patients with acute anterior circulation stroke and $\geq$3 yawns/15 min without obvious cause. We showed that the strongest lesion overlap was in the insula and caudate nucleus (Fig. 4) and that duration of abnormal yawning correlated with clinical stroke severity (NIHSS) and with neuroradiological stroke intensity (inverse apparent diffusion coefficient correlation) in the strategically lesioned brain areas (Krestel et al., 2015). Based on the insula's intense brainstem connections via the cortico-striato-thalamic network and corticobulbar pathways, we suggested following mechanisms upon its lesioning: i) a disconnection syndrome of insular targets including the entorhinal cortex, lateral hypothalamus, or mono-/oligosynaptic trajectories to the Raphe nucleus/nucleus tractus solitarius with (GABA-ergic?) disinhibition of the nearby pre-Bötzinger complex respiratory rhythm generator and cranial nerve nuclei V, VII, IX, X, and XII. ii) A serotonin overspill theory upon partial insular lesioning with activation of the brainstem yawning pattern in analogy to

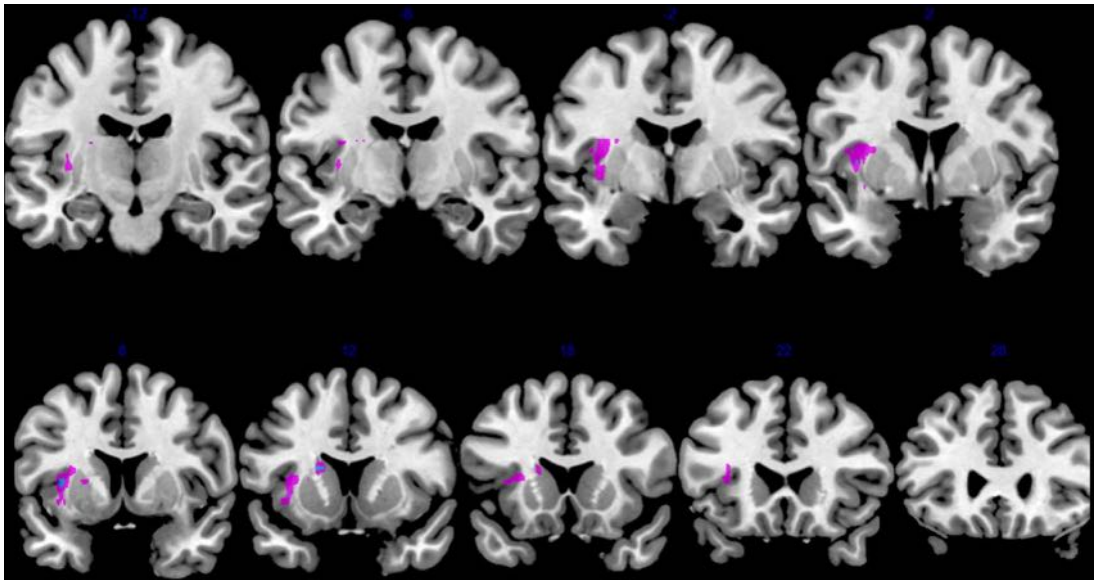

Fig. 4. Hotspots of abnormal yawning. Areas of most intense lesion overlap (purple), depicted in coronal T1-weighted MRI sections, and originating from 10 patients with anterior circulation stroke associated with abnormal yawning. For inter-individual comparisons, images of patients with left-sided lesions were flipped to the contralateral hemisphere. Group-specific lesion overlay plots were created using MRIcroN. For technical details, see Krestel et al. (2015). Unpublished data.

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experimental infusion of serotonin agonists into the insula with gaping in awake rats (Tuerke et al., 2012). Anterior circulation stroke with bilateral supratentorial lesions – termed bilateral anterior opercular syndrome or Foix-Chavany-Marie Syndrome – was associated in several reports with yawning despite paralysis of voluntary facial and pharyngeal innervation. Neuroanatomically, a bilateral lesion of the fronto-parietal operculum is found and an impairment of the proximal corticobulbar tract is implicated. This syndrome arises in its classical and most common form due to cerebrovascular disease, but other causes are also possible such as CNS infections, developmental deficits, and rarely neurodegenerative processes. A reversible form after epileptic seizures is also described (Ghika et al., 2003; Millán et al., 2008; Billeth et al., 2000; Laurent-Vannier et al., 1999).

5.1.2. Posterior circulation stroke

Posterior circulation insults with infratentorial vascular lesions have also been associated with abnormal yawning. In one report, two patients presented with excessive yawning (0.5–3 per min) less than an hour before onset of neurological deficits, consisting of gait ataxia in both cases with additional brachio-facial hemiparesis and internuclear ophthalmoplegiea in the second patient. The first patient had a lacunar paramedian pontine infarction. His yawning frequency decreased rapidly after the insult and disappeared after 3 days together with his neurological deficits. The second patient had an infarction at the ponto-mesencephalic junction due to pseudo-occlusive stenosis of the basilar artery. Her yawning ceased after 1.5 days while deficits persisted (Cattaneo et al., 2006). The authors suggest a denervation hypersensitivity mechanism, consisting of liberation of a putative yawning center in the brainstem from [inhibitory] control of more cranial structures, in analogy to theories about excessive yawning in ALS patients (Williams, 2000) or in a case with hiccups after medullary infarction (Park et al., 2005).

5.2. Locked-in syndromes and yawning

5.2.1. Locked-in syndrome in vascular pathology of the brain

Locked-in syndromes have been associated with yawning. Their etiologies are mainly ischemic brainstem lesions. Accordingly, following reports were found in the literature: Nordgren et al., 1971; Karp and Hurtig, 1974; Krasnianski et al., 2003; Chang et al., 2008. In one report, the origin of the locked-in syndromes was not explicitly mentioned but assumed to be vascular because of acute onset and regression of symptoms (Bauer et al., 1980).

5.2.2. Locked-in syndrome caused by tumor

Yawning has also been reported in locked-in syndrome due to a brainstem tumor (Gschwend, 1977). Here, a patient was admitted to the Neurological University Hospital Berne with tetraplegia including complete voluntary paralysis of all muscles innervated by caudal brainstem nerves. Hence, he could not open his mouth but was able to yawn. Remarkably, the patient could not imitate when somebody yawned in front of him, in other words contagious yawning was not possible. Postmortem studies showed infiltration of ventral pons with destruction of the pyramidal tract and caudal extention to the cerebello-pontine angle. Proximal to the tumor, the oculomotor and trochlear nuclei were intact and therefore the patient could move his eyes. The author concluded that yawning was "motivated" by a center below the pontine lesion and proposed the medulla oblongata and more precisely the Raphe nuclei. This suggestion was traced back on experiments that electrical stimulation of raphe nuclei could elicit sleep in cats (Jouvet et al., 1967). Gschwend associated yawning in his patient with sleepiness, because contagious yawning, implying higher levels of vigilance, was not possible. Therefore, he also cited work about induction of sleepiness by diencephalic electrical stimulation (Hess, 1944) and suggested its effect to be mediated by raphe nuclei, as well. However, sleepiness in cats was in none of the publications (Jouvet, Hess) reported to be accompanied by yawning. Lack of contagious yawning with preservation of spontaneous yawning in Gschwend's patient may be caused by disruption of several control pathways [control of a putative yawning center by the pyramidal tract, hypothalamic, and extrahypothalamic efferents (see 6. Conclusions and perspectives)] leaving a brainstem network akin to its own irregular activity to elicit yawning from time to time.

5.3. Brain tumors

Another report of a brainstem tumor associated with spontaneous yawning was a patient with an hemangioblastoma, verified by biopsy, that was located in ["the lower hall of"] the 4th ventricle and caused autonomic symptoms such as orthostatic hypotension but also spontaneous yawning – probably by increased intracranial pressure (Arai et al., 1986). Brain tumors as a cause of yawning were also recognized earlier: "the occurrence of [excessive] yawning which is essentially an atypical respiratory act, in cases of brain tumor can be explained by irritation of the brain resulting in afferent impulses to the medullary respiratory center which modifies its rhythmic activity" (Nash, 1942).

5.4. Traumatic brain injury

Yawning was mentioned in the context of traumatic brain injury in the following reports. Coma outcome was assessed on the basis of MRI lesion load and presence of clinical sings such as yawning, grasping and chewing in mechanically ventilated patients after cessation of sedation (Weiss et al., 2008). In another work, it was suggested that yawning during hyperventilation in awake patients after recent head injury may serve as a sign of brain damage, especially at the brainstem level (Jurko and Andy, 1975).

5.5. Persistent vegetative state

Patients with persistent vegetative state of different etiologies were also reported to yawn spontaneously. Six months post resuscitation of cardiac arrest, the patient with hypoxic encephalopathy was in a persistent vegetative state being awake and showing spontaneous eye movements, chewing and yawning but no purposeful movement on verbal or visual stimuli (Manish and Veenu, 2007). Yawning was mentioned as one of several symptoms in persistent vegetative state due to traumatic etiology in a German monography (Gerstenbrand, 1967). Intracranial hypertension, whether related to stroke, tumor, or head trauma can be revealed by headaches, impaired vigilance, seizures, and be associated with salvos of yawns. Certain coma scores used in USA take into account the presence of yawning in these situations (Bateman, 2001).

5.6. Epilepsy

An association of yawning with epilepsy has been described in case reports and case series as peri-ictal yawning. Many reports are based on temporary coincidence of symptoms, statistical associations or successful diagnostic treatment trials, respectively. One early publication contained two detailed reports that were associated with epilepsy according to their symptoms. The first patient suffered from occipital headache, compulsive yawning or singultus, accompanied by a reversible sensory cheiro-oral syndrome. The second was a young man with sudden sweating, goose-skin, derealisation symptoms and compulsive yawning. (Penfield and Jasper, 1954). In a later report, 3 children with

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absence epilepsy underwent long term EEG recording. In one of three, a 7-year old child, yawning was significantly more prevalent in pre- and ictal periods compared to the rest of the EEG recording (Goldie and Green, 1961). Subsequently, a patient was reported with attacks of occipital headache and compulsive yawning. Laboratory analyses and cerebral CT were normal. A surface EEG recording showed slight irregularities in occipital channels. However, using sphenoidal electrodes, a generalized paroxysmal pattern was described during one of the patient's attacks. Carbamazepine reduced the frequency of yawning attacks and naloxone, an opioid antagonist, could completely suppress them (Fletcher et al., 1982). The Foix-Chavany-Marie syndrome is again mentioned here (see also 5.1.1. Anterior circulation stroke) because a reversible form was described to exist in epilepsy. It was delineated as a deficit of voluntary control of muscles innervated by nerves V, VI, IX, X, XI with dissociation of automatic patterns such as laughing, crying, yawning, which were still possible (Laurent-Vannier et al., 1999). Two more case reports of yawning and potential epileptic seizures were presented by Muchnik et al. A single episode of a compulsive yawning attack, followed by loss of contact with fixed gaze for 30 s and subsequent confusion and orthograde amnesia was reported in a 95-year old male patient. Cerebral CT showed general cerebral atrophy and bitemporal, irritative EEG activity was found. Carbamazepine 400 mg/d prevented any recurrence of yawning. The second case was a 17-year old woman with insulin-dependent diabetes and repetitive reports of hypoglycemic fainting. Once, she fainted with generalized tonic-clonic convulsions, followed by confusion and compulsive yawning. Valproate was successful in preventing future fainting with convulsions (Muchnik et al., 2003). Then a 61-year old woman with known migraine and bipolar disorder was reported who suffered from attacks of ascending epigastric sensation, compulsive yawning for 30 min, diffuse sweating and subsequent sleepiness several times daily since 2 years. Such an attack could be elicited by photostimulation during an EEG recording that did not show epileptic potentials. However, during subsequent sleep, steep potentials were noted left temporal. After awakening the patient did not remember her attack. Oxcarbamazepine 600 mg/d could suppress recurrence of these attacks within 2 weeks (Medrano et al., 2005). Finally, a 47-year old woman was described, who suffered from treatment-resistant epileptic seizures of various semiologies for many years. In recent years, especially following posturing-type seizures, postictal compulsive yawning is noted. This publication also contains a literature review of epilepsy and yawning (Yankovsky et al., 2006). Peri-ictal yawning was evaluated as lateralizing sign in 97 patients with temporal lobe seizures and was found to occur only in the postictal period after seizures in the non-dominant, right-sided hemisphere (Kuba et al., 2010). Of note is that gelastic seizures, frequently arising from hypothalamic hamartoma with smiling as typical semiological sign of a seizure, have not yet been described to be associated with yawning. Conceivably, a tumor in the PVN's vicinity might activate (by ictal spread) or deafferentiate the PVN and lead to abnormal yawning, but this has not yet been reported in the literature.

5.7. Migraine

Yawning is one of the premonitory symptoms in migraine. Although the brainstem is highly linked to migraine biology, the real driver of attacks might be functional changes in hypothalamic-brainstem connectivity, explaining typical migraine premonitory symptoms such as fatigue and yawning, but also a typical association of attacks to circadian and menstrual cycles, all making the hypothalamus a possible regulating region of migraine attacks (Laurell et al., 2016). Revitalized interest in dopamine as important transmitter in migraine is based, first, on the observation that premonitory symptoms such as yawning, drowsiness, mood changes, irritability, and hyperactivity are exacerbated by dopamine agonists. Second, D1 and D2 dopamine receptors were found in the trigeminocervical complex. Third, dopaminergic projections from the hypothalamus to the trigeminocervical complex and further to the spinal cord exist (reviewed in Akerman and Goadsby, 2007). Based on the analogy that dopamine agonists cause yawning, nausea & blood pressure changes that are similar to some of the premonitory symptoms found in migraine, the dopamine theory of migraine was proposed, originally by Sicuteri (1977). It says that a migrainous brain is hypersensitive to dopamine and subsequent genetic studies implied that polymorphisms in dopamine receptor genes may create this hypersensitivity. Due to this hypersensitivity, dopamine may be one of the triggers that drive a migraine attack. Support for this theory comes from above mentioned neuroanatomical findings and from empirical treatment. Domperidone (20/30 mg), a peripheral D2 receptor antagonist, decreased the duration of an attack by 30%, but only when combined with paracetamol (MacGregor et al., 1993). Domperidone/paracetamol has also been shown to be similarly efficacious as sumatriptan (50 mg) over a 2- and 4-h postdose period (Dowson et al., 2000). One explanation for these results is that dopamine antagonists prevent the nausea accompanying the attack, and then correct the possible hypersensitivity to dopamine in the brain. However, data about involvement of dopamine in migraine pain is less clear than its involvement in premonitory symptoms. For example, dopamine agonists were shown to inhibit neuronal firing in the trigeminocervical complex, but, as mentioned above, it is dopamine antagonists that are clinically effective (Akerman and Goadsby, 2007). Of note is also the following study that migraine patients with restless legs syndrome (RLS) have significantly more frequent (5×) migraine premonitory symptoms including yawning than migraine patients without RLS. The authors conclude that RLS is more common in migraine with premonitory symptoms and suggest a common imbalance of the dopaminergic system in RLS and migraine (Cologno et al., 2008). Functional imaging using positron emission tomography and later fMRI of a migraine patient every day for 30 days in the morning covered 3 complete, untreated migraine attacks and showed that hypothalamic activity increased towards the next migraine attack during the 24 h prior to pain onset. The hypothalamus also showed altered functional coupling with the spinal trigeminal nuclei and the dorsal rostral pons during the preictal day and the pain phase of the native migraine attack, suggesting that the hypothalamus might be a migraine generator and be responsible for premonitory symptoms such as fatigue and yawning, but can also explain a typical association of attacks to circadian and menstrual cycles. (Schulte and May, 2016).

5.8. Neurodegenerative disease

5.8.1. Amyotrophic lateral sclerosis

Excessive yawning has also been reported in neurodegenerative diseases. We would like to begin this section with notes of patients with motor neuron disease or amyotrophic lateral sclerosis (ALS). A 64-year old woman was referred to the doctor with paroxysmal bouts of compulsive yawns occurring 20–30 times in succession seven to ten times a day. Initial neurological examination was normal. Yawning could be suppressed with thioridazine an antagonist to dopamine D2, histamine H1, alpha-adrenergic and other receptors. In the course of nine months, the patient developed dysphagia with bulbar and pseudobulbar clinical signs. Thioridazine was suspended and bouts of yawning reoccurred. Electrophysiological examination showed signs of denervation in all 4 extremities and diagnosis of motor neuron disease was made.

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Her yawning became less evident as her bulbar palsy progressed. The author's interpretation was that yawning may be inhibited in mature humans and the responsible brainstem neurons must be subject to cortical influences that can only be expressed if upper motor neuron pathways are intact. In pseudobulbar palsy, inhibition by upper motor neurons is lost and spontaneous yawning is released. Yawning will disappear with significant malfunction of bulbar nuclei. Therefore, yawning may be a subtle

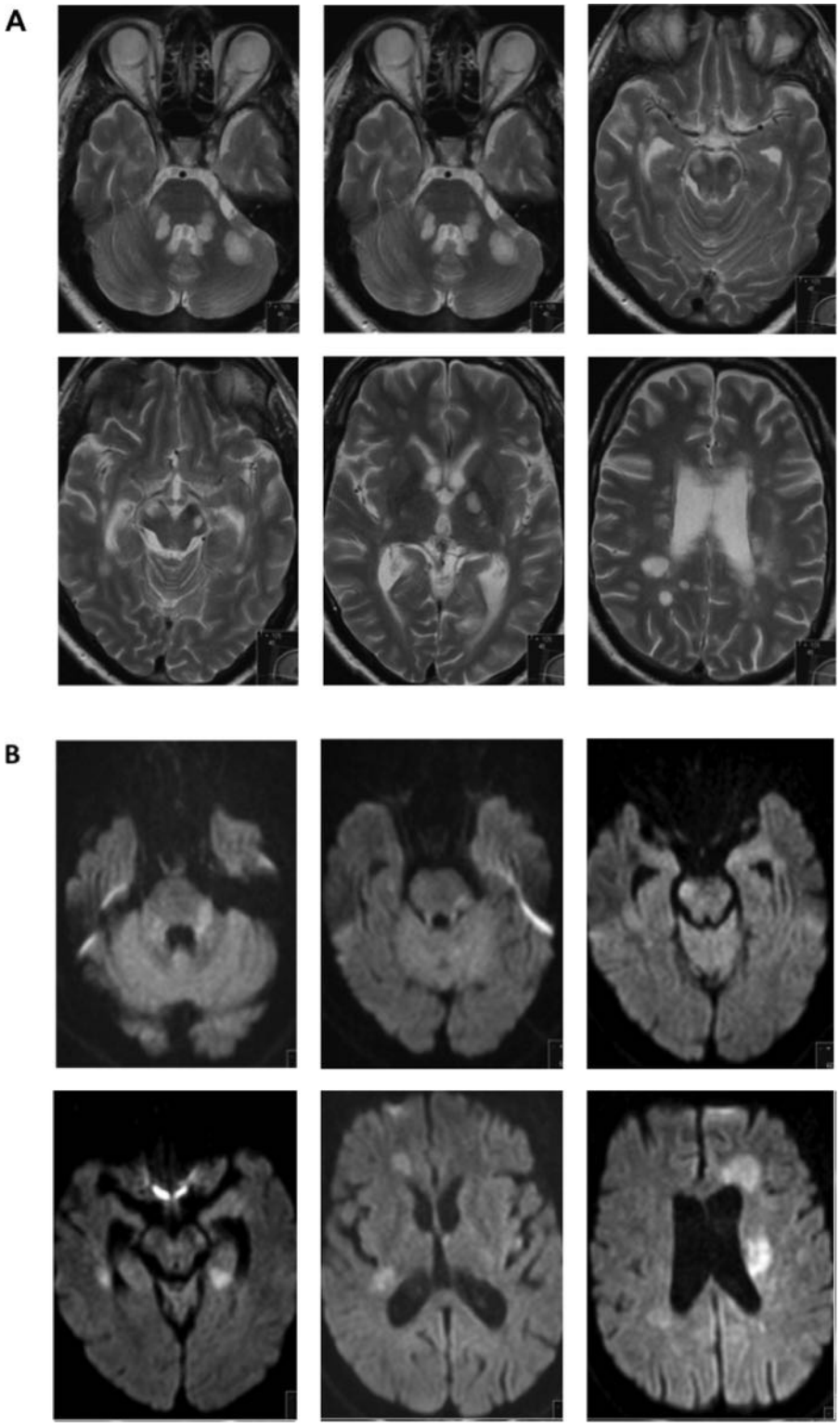

Fig. 5. Axial MRI scans of a patient with relapsing-remitting Multiple Sclerosis. (A) T2-weighted images from caudal to cranial (from upper left to lower right), taken at a time at which the patient was severely physically impaired but did not yawn. (B) Three months later the same patient presented with bouts of highly abnormal yawning (sometimes up to 1 yawn every min) due to a new relapse. Only diffusion-weighted-imaging (DWI) scans could be made due to the patient's restlessness in the scanner. As both T2 and DWI are spin echo sequences, they can be compared to a certain extent. Abnormal yawning was accompanied by new lesions: in left hippocampus, perhaps in the median line of the mesencephalon and the right caudal insula, the corpus of the left caudate nucleus, and in the area of frontal commissural fibers on both hemispheres. Otherwise, an alteration in size and signal intensity of preexisting lesions was seen.

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sign of pseudobulbar palsy (Williams, 2000). The next report refers to 254 patients with ALS who completed a questionnaire on excessive yawning at an internet website. Yawning was reported to be absent in 30%, mild in 30%, moderate in 32% and severe in 9%. No correlation was found between severity of yawning and age, months since diagnosis or the last recorded measurement of forced vital capacity. There was no association between yawning severity and anti-depressant usage. However, there was an association between yawning severity and site of onset. Patients with bulbar onset of disease were more likely (57%) to have moderate or severe yawning than patients with arm onset (42%) or leg onset (31%) (Wicks, 2007). Wicks' observation is supported by the case report of Williams in which the patient had bulbar onset of motor neuron disease, as well. Finally, an article about ALS and yawning by Louwerse ES et al. J Neurosci Res 1998 is occasionally mentioned. However, the article may be not correctly cited as it cannot be found in PubMed or on the homepage of the Journal of Neuroscience Research itself.

5.8.2. Yawning in untreated extrapyramidal disease

Abnormal yawning has also been reported in extrapyramidal disease. We would like to regroup these reports into untreated versus treated hypokinetic movement disorders, i.e. in which abnormal yawning is inherent in the condition or medically promoted. In the untreated condition, the earliest reports about yawning are in the acute encephalitic stage of *encephalitis lethargica* but also in post encephalitic parkinsonian patients (Sicard and Paraf 1921; Mayer, 1921). This was also reported by von Economo (Wimmer, 1924; mentioned in Colosimo and Pontieri, 1999, and reviewed in Evidente et al., 1998). Despite these reports, compulsive or even abnormal yawning is not that frequent in untreated idiopathic [non-encephalitic] Parkinson's disease (PD) patients. In fact, in one publication it was even stated that yawning has not been associated with PD (Goren and Friedman, 1998). This report was followed by several comments including the above mentioned by Colosimo and Pontieri (1999), then by Evidente and Hardy and O'Sullivan et al. which all were published in the same issue of Neurology, 15 1999, pointing to *encephalitis lethargica* with its sequelae and to side effects of dopaminergic therapy.

5.8.3. Yawning in treated extrapyramidal disease

Apart from PD, there is a report about five untreated patients with progressive supranuclear palsy, an atypical Parkinson's syndrome with vertical gaze paralysis and frequent drops, who all exhibited abnormal yawning (1–3 yawns/min). Yawning subsided with administration of dopaminergic medication (L-DOPA + carbidopa or bromocriptin, a D2/D3 receptor agonist; Sandyk, 1987). It is surprising that dopaminergic medication decreased yawning frequency instead of increasing it according to neurochemical and clinical observations (see neurochemistry section above). On the other hand, dopaminergic medication in PD was associated with yawning. Yawning was heralded as early sign for L-DOPA induced ON in PD (Goren and Friedman, 1998). Yawning may also appear while using apomorphine to diagnose dopamine responsiveness or to rescue OFF states in advanced PD patients (Ferraz et al., 1995; Frankel et al., 1990; Bonuccelli et al., 1991; Colosimo et al., 1994; Pahwa et al., 2007). Again, yawning followed subcutaneous apomorphine application in an early double blind placebo controlled study for parkinsonian OFF events. (Dewey et al., 2001) and in a meta review about clinical studies that use apomorphine s.c. to rescue OFF states in advanced PD patients under optimal dopaminergic therapy (Chen and Obering, 2005). Side effects of subcutaneous apomorphine for OFF events despite optimized oral medication in 546 PD patients included dyskinesia, somnolence, hallucination, yawning and injection site bruising and prevented 36% of patients from continuing apomorphine injections (LeWitt et al., 2009).

5.9. Multiple sclerosis

Multiple Sclerosis (MS) could also lead to abnormal yawning, as reported in a patient with left spastic hemiparesis and yawning 4×/min, despite regular and long sleep, which remitted after steroid infusion. MRI showed multiple brainstem lesions [supratentorial lesions were not mentioned]. The authors concluded that brainstem plaques irritated reticular neurons including the RAS and caused yawning. These "irritated" cells (ephaptic coupling? Annotation by this review's authors) send their impulses via intact short interconnections to motor nuclei of cranial nerves involved in yawning (Postert et al., 1996). Abnormal yawning appeared during a relapse in another patient with relapsing-remitting MS concomitantly with new T2-hyperintense, neuroradiological lesions in supratentorial brain including the left hippocampus and caudate nucleus, and the frontal commissure (Fig. 5; unpublished observation).

6. Conclusion and perspectives

A number of important systems and circuits exist in the evolutionary old sector of the human brainstem that are not modifiable by experience and are shared among numerous other species. The innate activity patterns of neurons in these circuits are not subject to mind or reason and frequently regulate basic life processes including breathing, coughing, or swallowing. Physiological yawning takes an intermediate position because it is under partial voluntary control and is switched off during sleep while other basic patterns are not. Several concepts exist concerning the mechanism of yawning. An integration and extension of the networks and brain regions involved in yawning is proposed. The neocortex, limbic system, and thalamus may be involved in external pattern recognition and may be responsible for the contagiousness of yawning, be it via the neuronal system of imitation (mirror neurons), or the system integrating empathy (theory of mind). The yawning network or zone is suggested to consist of parts of cortex, limbic system, hypothalamus, and brainstem. From anatomical malformations and lesion studies there is little doubt that the core yawning center resides in the brainstem. Its proposed functions beyond arousal suggest that the yawning center is not in the vicinity of the RAS with its most caudal circuits in the midbrain reticular formation and in mesencephalic and pontine nuclei, but rather located in the ponto-medullary part of the brainstem near the central pattern generators for respiration and circulation and the motor nuclei of cranial nerves V, VII, IX, XI, implicated in the yawning act. Probably 3 supratentorial pathways fine-tune the innate activity of the brainstem yawning center. Impairment or disconnection of corticobulbar trajectories could explain observed abnormal yawning in Foix-Chavany-Marie syndrome, locked-in syndrome, and bulbar ALS. It remains to be shown whether pyramidal corticobulbar trajectories are part of the yawning network or if thalamo-bulbar motor trajectories are also involved. They run more dorsally in the brainstem close to the central gray and are affected e.g. in emotional facial paralysis. Electrical and chemical stimulation of the PVN with its hypothalamo-pontomedullary trajectories has been shown to affect yawning. Of note is that hypothalamic brain tumors have not been particularly associated with abnormal yawning, nor does yawning typically accompany gelastic seizures that frequently arise from the hypothalamus due to hypothalamic hamartoma. The insula as part of the telencephalic cortex may be a brain region for serotonin-mediated yawning. Inclusion of the insula into the yawning network may explain why peri-ictal yawning is frequently

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seen in temporal lobe epilepsy in which seizure activity may also spread to the insula. A partial loss of function of the insula and its trajectories to the entorhinal cortex, lateral hypothalamus, or mono-/oligosynaptic trajectories to the Raphe nucleus/*nucleus tractus solitarius* by e.g. stroke or demyelinating lesions may affect abnormal yawning, as well. All theories of a top-down control of a brainstem yawning center imply an inhibition-disinhibition concept. Except of the PVN with oxytocin and NO as transmitter at its brainstem synapses, the disinhibition theories in abnormal yawning suggest a dysfunction or loss of GABA-ergic synapses onto the putative brainstem yawning center. Although the neurochemistry at the level of the supratentorial control centers may be fairly well characterized, i.e. which transmitters and molecules elicit or inhibit yawning at the brain rostral to the brainstem, the neurochemistry and synaptic connections at the ponto-medullary brainstem, that is involved in yawning, is not. In order to advance the knowledge on this ancient, stereotype behavior; and shed light on other reflex-like behaviors including coughing, swallowing; the neuroanatomy and – chemistry of yawning at the level of the brainstem has to be much more better understood. Not only the motor pattern but probably also yawning's meaning is preserved across species barriers, i.e. also the observer of yawning from another species may have a similar understanding of what yawning signals. The role of yawning and what it conveys – may be to express sleepiness and arousal, indicate boredom and wellbeing and further messages and functions. The body of reports of abnormal yawning is encompassing. It probably already reflects most of the etiologies of abnormal yawning. Taken together, physiological yawning occurs activity-dependent within intact circuits. Abnormal yawning arises from lesions of brain areas involved in the yawning zone, its trajectories causing a disconnection syndrome, or from physical or metabolic alteration of network activity. An important perspective would be a better understanding of yawning's neuroanatomy and – chemistry at the brainstem level.

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