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Yawning: Thompson Cortisol Hypothesis Discussed

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Abstract

Yawning is a scientific conundrum that has baffled scientists for decades. Whilst the origin and mechanism of yawning may be understood, its presence and frequency in a number of neurological disorders is not clearly understood. The Thompson Cortisol Hypothesis (2011) proposes a link between yawning and blood cortisol levels because of the known association between cortisol (and its elevation in levels) and other states such as fatigue, stress, and importantly, a number of neurological disorders such as multiple sclerosis and stroke. Investigation to support this hypothesis is underway.

Introduction

Yawning is often attributed to boredom and fatigue and is described as a simultaneous inhalation of air often accompanied by stretching (pandiculation) followed by exhalation of breath (Thompson, 2010). The act of yawning is a phylogenetically ancient behaviour with early onset, recognisable by the end of the third trimester in prenatal human development (Provine, 2005). However, it is become such an important subject of investigation in recent years because of the potential contribution it may make to our understanding of neurological disorders (Thompson, 2006). This is because of the commonality between neurological disorders, fatigue, and more recently with cortisol levels (Thompson, 2011).

The Thompson Cortisol Hypothesis (Thompson, 2011) is potentially important as it may serve as a diagnostic tool for early signs of underlying untoward neurological sequelae and development of disorders. Many conditions have been associated with frequent yawning including psychosis (Askenasy, 1989), cardiac tamponade (Krantz, et al., 2004), and multiple sclerosis (Postert, et al., 1996). The physiological role of yawning is still not fully understood and its functional significance is not clear. Askenasy (1989) proposed that the yawn is an arousal reflex to reverse brain hypoxia. Although hypoxia is related to oxygen levels, the underlying explanation here is that yawning is a reflex with the aim to reverse drowsiness and to maintain a level of alertness that is needed for wakeful activities.

More current research has developed this idea showing that yawning provides transient increases in arousal in conditions of low vigilance (Cattaneo, et al., 2006). This is possibly due to stretching of the lungs (and the intercostal muscles) which leads to feelings of awakeness (Provine, 1986). Stretching of these muscles requires special control systems such as the locus coeruleus, paraventricular nucleus of the hypothalamus, and the reticular activating system (Walusinski, 2007). Association has been made to wake and sleep patterns (Giganti, et al., 2007). Findings of higher yawn frequency at waking decline with age because of changes in circadian and homeostatic control over sleep and wakefulness (Giganti, et al., 2007).

While yawning appears to be universal, contagious yawning does not happen in all individuals. Many researchers explain yawning in terms of social cues that serve to synchronise group behaviour (Deputte, 1994; Daquin, Micallef, & Blin, 2001); Prasad (2008) explained contagious yawning in terms of an atavistic trait presenting as a vestigial reflex that previously served to coordinate aggressive social behaviour. The act of contagious yawning has initiated research into the mirror-neuron system (MNS) (Cooper, et al., 2001; Schurmann, et al., 2005) that is activated when people observe others. While others (Platek, et al., 2003) have explained this phenomenon with mental attribution theory, ie an inferential model that imparts empathy to others who share similar mental states.

Interestingly, hemiplegic patients have displayed movement of their paralysed arm while yawning, termed parakinesia brachialis oscitans by Walunsinski (2010). While the aetiology of this is unclear in stroke patients, this phenomenon disappears as the patient regains control over the hemiplegic limb. Topper, Mull, and Nacimiento, (2003) suggest the possibility of an emotional motor system to explain these movements in hemiplegic limbs during yawning though seems unconvincing.

Research into multiple sclerosis suggests that yawning is triggered by rises in brain and/or body temperature and may act as a cooling mechanism. Accordingly, increases in blood flow resulting from a yawn removes hyperthermic blood from the face and head, while introducing cooler blood from the lungs and extremities (Gallup, & Gallup, 2008). Abnormal thermoregulation has been found in both stroke and

multiple sclerosis patients who display excessive yawning (Postert, et al., 1996; Marino, 2009; Sung, Lee, & Chu, 2009; Gallup, Gallup, & Gallup, 2010a).

Thompson Cortisol Hypothesis

Cortisol levels may be directly or indirectly, associated with yawn frequency. Yawning, fatigue, stress, cortisol levels, and neurological disorders are all linked in some way. For example, fatigue is often present after onset of disorders and may give rise to yawning episodes. The link between fatigue and yawning is known; the link between thermoregulation and yawning has been proposed; and the instances of involuntary arm-raising in the parakinesia brachialis oscitans in stroke patients has been evidenced. There is also the known link between elevated blood cortisol levels and fatigue, and between cortisol levels and stress. Therefore, Thompson (2011) has proposed that cortisol levels may be elevated during yawning because excessive yawning is implicated in a number of untoward neurological disorders. Thus, yawning, as a warning of an underlying neurological disorder, may give rise to elevated cortisol levels.

Discussion

There are established links between yawning and various states as well as between cortisol and fatigue and stress. These will be explored here.

Yawning and fatigue

Extensive evidence links yawning to levels of arousal and sleepiness, for instance, yawn frequency was increased by up to 70% in participants when faced with a television test pattern for 30 minutes (Provine, 2005) while children often manifest drowsiness through excessive yawning (Walusinski, Neau, & Bogousslavsky, 2010). Askenasy (1989) brings together boredom, arousal and fatigue in association with yawning: Boredom occurs when the main source of stimulation in a person's environment no longer sustains their attention, by content or form. At this moment, the mind has to make an effort to maintain contact with the environment. Boredom induces drowsiness by stimulating the sleep generating system and when associated with fatigue the fatigue potentiates the drowsiness-inducing effect. Drowsiness has been suggested as the most common stimulus of the yawn (Askenasy, 1989, p. 611).

The most common cause of frequent and repeated yawning has been described as sleep debt (Walusinski, 2009). In humans, the observed decrease in yawning frequency during the ages of 31-40 weeks is explained through the development of homeostatic control of sleep and wakefulness while in non-primates, yawning frequency is higher before sleep than after, and has been linked to the rest-activity cycle. Greco, Baenninger, and Govern (1993) asked volunteers to record their yawning activity over a period of a week and found that yawns occurred most frequently an hour after arising from sleep and during the last hour before retiring to bed. Over 60% of recorded yawns were found to occur during lectures and studying, car driving and television watching. These activities require minimal interaction and are in line with tasks that encourage minimal arousal. The opposite was reported during activities of a faster and more interactive nature such as cooking, cleaning, washing, and taking part in conversation. Only 6-8% of yawns occurred during these tasks. These data support the notion that yawning sub-serves arousal and implicates higher brain activation following yawn occurrences (Kasuya, et al., 2005).

Yawning has been used in various accident prevention campaigns focusing on yawning as a vital sign of the possibility of falling asleep involuntarily (Walusinski, et al., 2010). Abtahi, Hariri, and Shirmohammadi (2011) considered possible methods for detecting driver drowsiness based on yawning action to prevent road accidents.

Zilli, Gigantic, and Uga (2008) conducted a study aimed at gaining knowledge related to sleep/wake transitions and time of day in the assumption that this relation reflects the time course of sleepiness. Since aging modifies sleep-wake and tiredness rhythms, they compared older individuals with young adults expecting to see yawn frequency and time course vary with age. They found both groups yawn most frequently following sleep and just before sleep although these peaks were earlier in both the morning and evening for the older sample which was in line with their earlier sleeping patterns. Older adults yawned less frequently in general than younger adults and morning peaks were shorter, and early afternoon peaks were displayed which were not apparent in the younger group. Zilli and coleagues (2008) attributed their findings to wake-sleep and sleep-wake transitions as yawning episodes were in line with when such transitions were about to take place, including early afternoon bouts for the aged group due to the increased tendency to 'nap'. These findings are also in line with yawning being associated with arousal levels and feelings of fatigue.

Empirically, it appears that yawning is associated with transitions between wakefulness and sleep and different levels of arousal. Greco, Baenninger, and Govern (1993) explain increases in yawn frequency during activities such as driving and lecture

attendance due to the easy way relaxation and keen attention alternates during these tasks. However, interestingly, it appears that yawning is not as strongly correlated in distribution when looking at tiredness or sleep-deprivation (Greco, Baenninger, & Govern, 1993), suggesting that yawning is a stronger indicator of fatigue. Of note here is that fatigue is different to sleep deprivation and does not only occur due to lack of sleep, instead it is a state of being and a symptom of various disorders including stroke and multiple sclerosis.

Cortisol levels and fatigue

Cortisol has been strongly linked to fatigue with cortisol treatments shown to increase feelings of vigour in both patients and healthy subjects (Tops, et al., 2006). Disproportionate low levels of corticosteroids have been reported in clinical populations including asthenia, fatigue, and depression. Corticosteroid treatment was effective when treating chronic fatigue syndrome (CFS) as well as increasing feelings of well-being. Nater and colleagues (2008) found hypo-cortisolism in a sample of CFS patients and suggested that increased activation in the immune system due to a lack of cortisol leads patients to feel fatigued. Various cortisol hormones have been found to affect mood; glucocorticoids can cause sleepiness due to increased arousal and activation (Fadeev, Gitel, & Melnichenko, 2001); elevated endogenous cortisol can also cause insomnia and arousal, and low cortisol levels have been found in atypical depression (Fries, et al., 2005).

Various clinical trials have indicated that a range of syndromes in which fatigue is a symptom, such as post-traumatic stress disorder, CFS, and fibromyalgia are linked to low levels of adrenal corticosteroid cortisol (Fries, et al., 2005; Van Den Eede, et al., 2007; Nater, et al., 2008). However, this has not always been found to be the case (Crofford, et al., 2004; Di Giorgio et al., 2005). When looking at non-clinical populations, cortisol also appears to be linked to fatigue especially in association with burnout and vital exhaustion (Melamed, et al., 2006; Ter Wolbeek, et al., 2007). In contrast, the alexithymia trait, characterised by fatigue and low vigour, is associated with low cortisol levels (Tops, et al., 2006).

Findings by Lindeberg and colleagues (2008) suggest that cortisol is related to fatigue before disease onset as low waking cortisol and flattened decline in daytime secretion was linked to exhaustion in healthy individuals, suggesting changes prior to disease onset. However, in contrast, Rubin and colleagues (2005), examining elective surgery patients, pre-operation and at 6-months post-surgery, found that cortisol levels differed after post-operative fatigue had developed. Whilst the authors found no associations with low levels of cortisol they found patients to display higher levels of cortisol post-operation. Rubin and colleagues (2005) concluded that studies reporting low cortisol levels in patients are often conducted with chronically ill patients suggesting that low cortisol levels may develop after long-term illness.

Typically, cortisol levels are highest following waking - cortisol awakening response or 'CAR'. At CAR, cortisol concentration can increase from between 50-60% and then proceed to decline throughout the day normally reaching its lowest concentration around midnight (Kumari, et al., 2009). Evidence suggests that low levels of morning cortisol may lead to symptoms of fatigue in non-clinical populations. Healthy women have been shown to complain of fatigue and muscular pain when displaying low morning cortisol levels (Tops, et al., 2006). A directional link was suggested as previous day fatigue did not associate with decreased cortisol secretion the following morning; however, low levels of morning cortisol was predictive of fatigue later in the day (Adam, et al., 2006).

Kumari and colleagues (2009) conducted the first longitudinal epidemiological study measuring cortisol secretion and fatigue in a large community based population. Cortisol levels were taken over a day together with levels of fatigue over a 2.5 year period. Results supported Adam and colleagues (2006) findings that low cortisol is indicative of new-onset fatigue while previous fatigue did not coincide with future changes in cortisol levels. Interestingly, the study took into consideration a variety of possible confounding variables including gender, age, medication, and health conditions and found that low cortisol levels leading to fatigue were independent of all covariates. The authors concluded that low levels of cortisol are associated with future onset of fatigue. Contradicting Rubin and colleagues (2005), they advocated cortisol levels to be aetiological, or occur early in the genesis of fatigue, increasing the risk of future onset (Kumari, et al., 2009).

The lack of effect of previous fatigue on cortisol levels was explained by the suggestion that both the biological and psychological consequences of fatigue may serve to alleviate fatigue hypo-cortisolism (Kumari, et al., 2009). As the study failed to find pre-existing fatigue episodes effecting cortisol levels, it is possible that fatigue symptomatology may be the result of the disorder rather than as a direct result of fatigue. These findings tend to support those of other studies that found cortisol levels occurring with fatigue, and those that found fatigue as a factor in affecting the onset of certain neurological disorders such as CFS (Werbel, & Ober, 1993; Ter Wolbeek, et al., 2007).

Observations from Tops and colleagues (2006) found oral cortisol treatment, when used on a healthy female sample, to increase levels of vigour and decrease levels of fatigue. Findings were based on prior and post-treatment self-reports and were compared with a placebo condition. However, the largest effects where noted in less than optimal conditions, for instance, when already fatigued. Here participants were asked to complete a task and then asked to report on their mood. After the task, participants reported increased levels of fatigue and this is when the largest effects of cortisol treatment were recorded between the groups. This may indicate that any cortisol effects may be stronger and more noticeable in challenging times or during illness.

Nater and colleagues (2008) also found hypo-cortisolism in a sample of CFS patients suggesting that low cortisol levels result in increased activation of the immune system leading patients to feel fatigued. Data shows that cortisol levels are linked to fatigue onset (Kumari, et al., 2009; Adam, et al., 2006), and a history of unexplained fatigue precedes the development of CFS which implies a continuum between fatigue in the healthy population and fatigue-related illnesses (Kumari, et al., 2009). Not all research has found predicative ability in cortisol to future fatigue and some have shown hypo-cortisolism to coincide with better health (Kumari, et al., 2009). The research on cortisol levels and fatigue are vast; however, there is inconsistency in findings. While most report cortisol alterations as the initiating factor, a few report alterations as likely to occur after symptom onset. The type of alteration is also controversial; Crofford and colleagues (2004) found increased activity in fibromyalgia, while patients with CFS showed low activity. They suggested that elevated levels of cortisol could be due to loss of resiliency of the hypothalamic-pituitary-adrenal (HPA) axis, and being unable to return to baseline after periods of pre-longed stress.

Cortisol and stress

Researchers have used chronic stress to explain hypo-cortisolism (Fries, et al., 2005), with such patterns being indicative of pathology or disease severity, predicting mortality in clinical populations (Sephton, Kraemer, & Spiegel, 2000). Out of 9 confounding factors in a large scale cortisol study, stress, smoking, early waking, and cardiovascular disease medications showed a connection to cortisol levels (Kumari, et al., 2009). Low cortisol levels have been linked to an array of disorders, many of which appear to be stress-related (Clauw & Crofford, 2003). This led to investigation into a possible common physiological pathway for hypo-cortisolism development emphasising alterations and reduced responsiveness in HPA axis activity.

Clauw and Crofford (2003) found that hypo-cortisolism can be caused by different types of HPA axis alterations (although alterations do not appear to be population specific), with different alterations emerging in patients within the same clinical population (Fries, et al., 2005). Such changes can be due to various dysfunctions: (1) reduced biosynthesis in releasing hormones, as well as decreased receptor stimulation; (2) hyper-secretion of any secretagogue with down-regulation of the target receptors; and (3) glucocorticoids increased sensitivity to negative feedback causing a decrease in free cortisol and/or in cortisol resistance (Heim, Ehlert, & Hellhammer, 2000).

It is well established that stressors including infection, trauma and mental stress result in HPA axis activation which serves to produce cortisol. In response to stressful stimuli the HPA axis leads to increases in peripheral cortisol production. Cortisol helps to provide energetic resources needed when faced with stressors while also helping to modulate and contain other physiological stress response components; hence, the ability to affect physiological changes encompassing most of the main organ systems (Adam, & Kumari, 2009). Short-term HPA activations are necessary for efficient everyday functioning; however, excessive or chronic activation has been associated with detrimental health outcomes with research implementing the HPA axis in the development of a variety of both clinical and sub-clinical conditions.

Hellhammer and Wade (1993) put forward a developmental model for hypo-cortisolism based on stress-related disorder patients and their display of hypo-cortisolism symtomatolgy including fatigue, pain and stress-sensitivity. They explain hypo-cortisolism through stress time course with a change from hyper- to hypo-cortisolism in the HPA axis activity. Hence, during times of stress, our HPA activity is hyper-reactive. Once the stress period ceases, there is over-compensation and the activity becomes attenuated and lower than non-stressed individuals.

Numerous studies support such over-adjustment explanations; for instance, Houshyar and colleagues (2003) found rats following a period of continued morphine use displayed elevated levels of corticosterone during withdrawal which was followed by a continuous drop in levels. The authors also found that administration of dexamethasone suppressed the stress response indicating increased pituitary glucocorticoid negative feedback. Fries and colleagues (2005) concluded that the primary mechanism behind hypo-cortisolemic stress

responses is enhanced pituitary sensitivity to glucocorticoid negative feedback as indicated by cortisol super-suppression. Research indicates that stress-related hypo-cortisolism is often displayed alongside increased catecholamine concentrations; and hypo-cortisolism may be due to reduced inhibitory cortisol feedback on catecholamine release resulting in stress-related disorders (Fries, et al., 2005).

Hormone glucocorticoid acts to regulate cytokine production from the immune system as a response to stress. In doing so, low cortisol levels may result in an over-reactive immune system in terms of inflammatory responses. Suggestion is of a preliminarily nature due to the uncertainty of the literature in this area with some researchers gaining data that are not consistent with the suggestion of a co- relationship (Fries, et al., 2005).

Beneficial effects of hypo-cortisolism have also been put forward. Hypo-cortisol conditions have shown a significantly higher link to underlying infections indicating increased activity to prepare the immune system for possible reoccurrence. Van Hoof, Cluydts, and De Meirleir (2003) found fatigue symptomatology as serving to promote subsequent recuperation through energy conservation. Elderly participants with hypo-cortisolaemia displayed a lower allostatic load comparable to younger participants despite reporting higher stress levels (McEwen, 2000). The term allostatic load was coined by McEwen and Stellar (McEwen, 2000) and is defined as the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress. As allostatic load is indicative of increased mortality rates, hypo-cortisolism acts as a protective mechanism against high allostatic load. Such beneficial effects serve as a possible reason as to why cortisol alterations are common in an array of disorders.

Many cortisol studies tend to be conducted over short periods and some studies analyse cortisol samples that have been gathered over a single day, meaning that significant findings may be situational rather than trait founded (Hellhammer, et al., 2007); although with large samples, large bias seems doubtful. Many studies also regularly use self-report methodology and as with any self-report measures, compliance should be considered as a possible bias. Participants may not always comply with research instruction, such as at times to gather saliva samples. The time that samples are taken is crucial, as waking time rather than clock time, has been found to make a difference between a significant effect being obtained (Adam, & Kumari, 2009). If taken incorrectly, it may significantly skew data analyses and interpretation. Self-report measures require self-perception of individual health and healthcare interventions meaning that fatigue, as perceived by subjects, may not correspond to fatigue as it exists in stress-related illnesses.

Cortisol measures, such as those based on average urinary measures have also come under scrutiny (Seeman, et al., 2002), as opposed to preferred methods based on the diurnal cortisol rhythm. This view sees deviations from typical diurnal cortisol rhythm as indicative of environmental influences on the HPA axis and the role of the HPA axis in disease processes (Adam, & Kumari, 2009). In addition, cortisol studies are often offered in the form of epidemiological research. While typically consisting of large sample sizes and benefiting from covariate control and ascertaining associations, even larger samples may be needed to be sufficient for looking at naturally occurring disease states within the population (Adam, & Kumari, 2009).

Salivary cortisol recordings have been found to produce more pronounced cortisol responses than serum samples (Aardal-Eeiksson, Karlberg, & Holm, 1998). In addition, Jerjes and colleagues (2006) suggest that 24-hour urinary total cortisol metabolite (TCM) excretion may provide a more reliable reading of cortisol detection than urinary free cortisol (UFC) in 24 hour samples. However, in spite of this, a study using UFC (Di Giorgio, et al., 2005) found differences in cortisol activity between CFS patients and controls whereas a study using TCM found no differences (Jerjes, et al., 2006). Such discrepancies highlight the importance of different sampling measures and measures need to be considered in relation to their sensitivity in detecting cortisol alterations.

Stroke

The link between yawning and stroke patients is becoming increasingly documented in case reports of parakinesia brachialis oscitans, and neurological pathways associated with yawning. The possibility of a yawning centre located at the lower brainstem being involved in the neural substrate of yawning was hypothesised in a study evaluating 5 brainstem stroke patients who presented with frequent pathological yawning (Cattaneo, et al., 2007). Excessive yawning was found to be the first symptom displayed following stroke which would persist for anything from a few hours to a few days after initial onset. All patients involved in this study displayed gait ataxia which continued for weeks. Some of the patients also displayed symptoms such as hemiparesis, vertigo, nystagmus and dysmetria. All patients displayed acute or sub-acute ischemic lesions involving invariably a paramedian region in the upper pons and ponto-mesencephalic junction. This led to the

conclusion that patients displaying excessive yawning and gait ataxia are associated with lesions of the paramedian upper pons and ponto-mesencephalic junction (Cataneo, et al., 2007). While this suggests that excessive yawning following brainstem lesions may be the result of activation of a putative yawning centre resulting from supra-nuclear control, the exact mechanism of the yawning is unclear. Importantly, this study suggests that pathological yawning can be an early sign of brain stem infarction (Thompson, 2010).

A further study (Singer, et al., 2007) evidenced the hypothalamus, especially the paraventricular nucleus (PVN), as playing a pivotal role in yawning elicitation (Goessler, et al., 2005; Argiolas, & Melis, 1998). This may explain why lower brainstem ischemia can lead to pathological yawning (Cattaneo, et al., 2006; 2007) as neurons are sent from the PVN to brainstem structures. Singer and colleagues (2007) reported on seven patients who experienced pathological yawning following acute middle cerebral artery stroke. They determined that excessive yawning can also be a result of lesions in cortical or subcortical areas which physiologically control diencephalic yawning centres.

Findings suggest that the middle cerebral artery (MCA) plays a part in the anatomical structure of yawning which proves interesting as the hypothalamus and brainstem are not supplied by the MCA. Singer and colleagues (2007) suggest that such findings could be due to MCA lesions releasing the PVN from neocortical control mechanisms, leading to PVN increased activity. This possible explanation presumes existing neocortical control mechanisms connected to the PVN as well as making no suggestion as to whether this phenomenon is a result of reduction in the cortical structures inhibitory input or due to an increase in excitatory input (Singer, et al., 2007).

Temporal lobe epileptic seizures have also led to excessive yawning (Muchnik, et al., 2003; Yankovsky, Andermann, & Dubeau, 2006) and attention is drawn to the vast amounts of research that has linked neocortical areas to the phenomenon of contagious yawning (Platek, Mohamed, & Gallup, 2005; Schurmann, et al., 2005). Cases of parakinesia brachialis oscitans (PBO) have been documented for many years but the term was created in 2005 by Walusinski (2007). In a clinical case publication by Walusinski and colleagues (2010), 6 case reports of patients who had displayed PBO post-stroke were reported. From their observations, they attempt to delineate a pathophysiological explanation for the occurrence of PBO implicating two main locations: middle cerebral artery (MCA) territory (lending support to the the findings of Bladin and Berkovic, 1984), and the pontomedullary region (supporting the findings of Louwerse, 1998, and also Topper, Mull, and Nacimiento, 2003).

Following extensive brain imaging evaluation, Walusinski and colleagues (2010) concluded that PBO requires a lesion in the internal capsule, in turn affecting an inhibitory pathway which liberates certain subcortical structures responsible for coordinating yawn inspiration and quadrupedal locomotion motor control (Walusinski, 2007). Believing that the brain follows an organisational structure (MacLean, 1985), with each functional level gaining in complexity and functionality, means that if any of these structures are disrupted, as is the case in certain stroke localisations, phylogenetically primitive functions may become liberated that are normally inhibited by a more sophisticated structure (Lapresle, 1986). Topper, Mull, and Nacimiento (2003) reported on 3 patients following stroke and concluded that the raising of the paralysed arm is the display of an automatic motor pattern that is usually inhibited in the presence of intact corticobulbar fibres that when damaged, this automatic motor pattern appears in a stereotyped fashion. Displayed motions of this sort are only present until voluntary limb movements are restored.

Explanation for repetitive yawning often witnessed in stroke patients supposes that through yawning arousal, mechanisms are stimulated that allows recovery movement in the arm. Arousal stimulation occurs via activation of the PVN of the hypothalamus, locus coeruleus and reticular activating system (Walusinski, 2007). It is suggested that yawning is an outward homeostatic mechanism triggered by similar subcortical structures and regulated by the same neurotransmitters that relate to body temperature, breathing, locomotion and vigilance (Walusinksi, 2007). Through the study of stroke as well as bilateral anterior opercular syndrome patients, a distinction between automatic and voluntary pathways seem to be demonstrated. While the patients suffer from facial/arm paralysis and are unable to conduct any voluntary acts of these parts, emotional expression such as blinking, laughing and physiological yawning remain possible as does the movement of the extremities while yawning (Walusinski, 2009).

Meenakshisundaram and colleagues (2010) conducted an observational study of 75 stroke patients to describe the associated movements of hemiplegic limbs during yawning. They found that 80% of the patients displayed such movements. A similar figure was found by Mulley (1982). The authors explained limb movements as a result of the movement of the diaphragm while yawning, enabling the paralyzed arm to receive motor stimulation from the lateral reticular nucleus of the medulla which is involved in ventilation

and locomotion in animals (Meenakshisundaram, et al., 2010). Important data is available showing cases of pathological yawning prior to injury which suggests that yawning may be an indicator of underlying problems. A case report speculated that a woman experiencing excessive spontaneous yawning months prior to the development of a bulbar/pseudobulbar palsy due to amyotrophic lateral sclerosis, was caused by dysfunction of the upper motor neurons losing their inhibitory influence on the brainstem and lower motor neurons (Williams, 2000). Cattaneo and colleagues (2006) also reported on two case studies of patients who suffered from brainstem ischemia, both reporting cases of excessive yawning prior to neurological symptoms becoming apparent.

An hypothesis has linked thermoregulation to yawning, explaining the functionality of yawning is to act as a cooling mechanism (Gallup, & Gallup, 2008). If this is to be the case, patients with central nervous system injury (Dietrich, & Bramlett, 2007) and brain-injured patients (Soukup, et al., 2002) both display excessive brain temperature. Also lesions within the central nervous system may also develop in areas which affect thermoregulatory control such as the hypothalamus (Marino, 2009). Temperature fluctuation is normally due to infection fever and is a common finding in stroke patients; 20-40% will suffer from fever (Sung, Lee, & Chu, 2009). Furthermore, it has been reported that stroke can induce mild elevations in body temperatures as well as animals showing spontaneous increases in body temperature following stroke. Sung, Lee, and Chu (2009) found that stroke resulting in destruction of the brainstem, directly and significantly influences body temperature. This could be a possibility as to why excessive yawning is implicated as a symptom in stroke patients.

During an ischaemic or haemorrhagic stroke, deficits in vigilance occur that are accompanied yawning episodes regardless of whether the patient is conscious or not; although, in coma states, yawning can be a serious prognostic sign (Walusinski, 2009). The evidence suggests that the occurrence of yawning during stroke signifies cortical, subcortical circuitry and brainstem damage. In ischaemic cases this usually occurs with hemiplegia and normally indicates pyramidal tract lesions while the extrapyramidal pathways remain intact. Cases of parakinesia brachialis oscitans are suggested to be the course of cortical control disruption resulting in connected neurological structures retrieving their ancestral functions that would otherwise have been inhibited by the cerebral structures (Walusinski, 2009). Stroke studies have possibly been the most useful in providing both an explanation and the neurological pathways of yawning; however, there still exists ambiguity within the literature (Thompson, 2010).

Multiple sclerosis

It has been well documented that temperature changes can have significant affects on multiple sclerosis (MS) symptoms (Smith & McDonald, 1999; Redford, Kapoor, & Smith, 1997). An estimated 60-80% of MS patients experience temporary worsening of clinical signs and neurological symptoms with heat exposure (Davis, et al. 2010). While heat worsens, cooling can improve negative symptoms. Sensitivity to temperature can be extreme and very small changes can have profound effects (Baker, 2011), as little as 0.5?C can make a difference (Davis, et al., 2010). Such effects are due to temperature influences over sodium channels on current necessary for depolarisation of the axon; increases in temperature diminish the depolarising current, decreases have the opposite effect (Smith, & McDonald, 1999). The hypothalamus has been linked to the neural network of yawning and lesions particularly in this area have been suggested as impairing the homeostatic control of body temperature in individuals with MS and may increase atypical fluctuations in body temperature (Davis, et al., 2010).

Ample evidence exists relating yawning to temperature change, with yawns occurring before, after and during instances of abnormal thermoregulation, heat stress, and hyperthermia (Gallup, & Gallup, 2008). Also pharmacological treatments are hypothermic for mania, where brain temperature falls, and thermogenic in depression, where brain temperature rises. Such pharmacological treatment has been found to suppress or induce yawning respectively (Prasad, 2008). It is suggested that yawning may serve as a compensatory brain cooling mechanism when regulatory mechanisms fail to operate favourably helping to maintain optimal levels of mental efficiency (Thompson, 2010). Likewise nasal breathing, which pre-cools arterial blood to the brain, and forehead cooling, has been shown to block yawning (Gallup & Gallup, 2007). Studies on animals have also shown yawning incidences to rise as ambient temperature rises.

Repetitive yawning is associated with a number of diseases linked with heat stress and abnormal thermoregulation (Gallup & Gallup, 2008), including MS (Postert et al., 1996). As well as thermoregulation dysfunction it is not uncommon for MS patients to have impaired sweat gland function (Davis et al., 2005) contributing to increases in body temperature. Another striking point is that MS patients report worsening of symptoms during daytime heat whilst experiencing symptom relief following external cooling such as cold

baths, head, neck and body cooling through cold packs (Gallup, & Gallup, 2007).

Excessive yawning witnessed in MS patients has also been explained in anatomical terms. Postert and colleagues (1996) reported on a multiple sclerosis patient who displayed excessive yawning during an MS episode. Following various testing it was concluded that yawning has anatomical aspects putting forward the suggestion that inflammatory affection of the brain stem in MS patients may cause the phenomenon of excessive yawning. They described excessive yawning as a symptom of brain stem localisation in multiple sclerosis. These thermoregulation associations alongside frequent yawning witnessed in MS patients support the hypothesis of yawning as a cooling mechanism (Gallup, & Gallup, 2008).

As thermoregulatory dysfunction affects sleep it is not surprising that sleep problems are also a common symptom experienced by multiple sclerosis patients (Gallup et al., 2010b). A following suggestion is that yawning, sleep and thermoregulation are connected and indeed yawning and thermoregulation follow a circadian pattern with particular regard to prior and post sleep (Provine et al., 1987). Findings suggest that excessive yawning may not necessarily be related to sleep disorders but rather may be indicative of thermoregulatory dysfunction (Thompson, 2010).

Fatigue is a symptom commonly seen in MS patients and it can often be disabling (Bamer, et al., 2008; Merlino, et al., 2009). According to reports up to 90% of MS patients experience fatigue (Brass, et al., 2010). Fatigue is different to sleepiness in that there can be no desire to sleep when laying down to rest and is aggravated by thermal stress and humidity. It normally occurs early in the morning and is progressive through the day, often reported as one of their worst symptoms (Brass, et al., 2010).

Excessive daytime sleepiness and fatigue can easily be confused. Daytime sleepiness may be the result of insufficient sleep or an underlying sleep disorder. Chervin (2000) found that 57% of obstructive sleep apnoea patients reported problems of fatigue in spite of objective evidence of 'sleepiness'. Likewise, MS patients with sleepiness would often complain of fatigue (Kaynak, et al., 2006). This indicates the importance of appropriate evaluation of MS patients complaining of fatigue to ensure that any possible sleep disorders are ruled out first (Brass, et al., 2010).

Due to such discrepancies, Mills and Young (2007) attempted to define the term of fatigue in MS patients. They found that all MS patients reported fatigue which was associated with motor paresis, inability to maintain mental function in task completion and lack of desire to complete or partake in tasks, a strong desire to rest (72% reported the need for rest without sleep compared to 49% with sleep), and daily occurrence normally following a circadian rhythm. Also, the data gathered also found 47.8% of patients reported excessive yawning which did not just occur during episodes of fatigue. Appearing to support the thermoregulation hypothesis, patients reported sweating when fatigued and heat was found to be the most dominant contributing factor to fatigue onset. However patients made a clear distinction between humid heat which worsened fatigue as opposed to dry heat encountered abroad which could sometimes improve severity of symptoms (Mill, & Young, 2007).

Evidence for cortisol and yawning

While research on a direct link between cortisol and yawning is scarce, some older studies have examined the effects of drug-induced or drug-inhibited yawning and hormonal activation. Current studies acknowledge and refer to such relationships but most of the research found is based on animal samples and dated predominately between the 50s and 90s. In 1964, a link between ACTH and the induction of stretching-yawning behaviour was published (Anias-Calderon, Verdugo-Diaz, & Drucker-Colin, 2004), while a link between dexamethasone and yawning behaviour in animals has been suggested, concluding that dopaminergic and cholinergic are distinctly altered by dexamethasone in yawning behaviour (Hipolide, et al., 1999).

A study published in 2004 provides compelling support for the Thompson (2011) Cortisol Hypothesis. The authors found that following adrenalectomy in rats both spontaneous and apomorphine-induced yawning stopped while treatment of dexamethasone reverted this effect (Anias-Calderon, Verdugo-Diaz, & Drucker-Colin, 2004). This was explained by the fall in blood corticosterone levels that follow adrenalectomy as well as the changes in function, structure and glucocorticoid receptor levels which in turn can affect activity of the paraventricular nucleus, an important structure involved in yawning behaviour (Anias-Calderon et al, 2004).

Furthermore, the paper provides support for the reduction of corticosterone levels as a yawn suppressor as dexamethasone treatment restored yawning behaviour. Although this effect was dose dependant with no effect gained for 1mg/kg administration, all other doses of 5, 10 and 20mg/kg showed significant restoration in yawning behaviour. The authors concluded that the adrenal glands have an important role in yawning frequency; while there are probably several altering factors which may impact on yawning, results still point to the important role of

adrenal glands and glucocorticoids in the control of yawning (Anias-Calderon Verdugo-Diaz, & Drucker-Colin, 2004).

Conclusions

Stress, fatigue and disorders

Considerable evidence has been provided from epidemiologic studies for a link between traumatic events and fatigue symptomatology (Asmundson, Wright, & Stein, 2004; Raphael, Janal, & Nayak, 2004). The trauma of stroke and MS in relation to diagnosis, the illness, and change of lifestyle often lead to worsening of symptoms and stress (Brown, et al., 2006; Capes, et al., 2001). As an individual's response to stress includes HPA axis activation in seems reasonable to suggest that differing cortisol levels may elicit propensity to yawn in these patients which is particularly noticeable in episodes of disease aggravation. Excessive yawning is more common in episodes of MS and in the acute stage of stroke, with yawning becoming attenuated with remission possibly because of diminishing cortisol levels as stress periods weaken.

A link between dysfunctional cortisol levels and MS has been suggested due to pro-inflammatory cytokines, which are increased in MS patients, acting on the HPA axis leading in turn to increased levels of cortisol (Mohr, & Pelletier, 2006). A link between stressful life events and worsening of MS symptoms has been consistent with the degeneration of MS evolving over time as does the development of stress. Mohr and Pelletier (2006) suggest that this intermittent progression over time for both MS disease development and stress shows how the two may be associated as they both have an onset, a period of continual presence and a resolution stage. Individuals with MS have reported periods of stress that provoke attacks or worsen their clinical state. Elevated dopamine levels found in MS patients (Barkhatova, et al., 1998) further illuminates the involvement of stress mechanisms in MS disease development. In accordance with these findings, evidence showed psychological distress to worsen MS fatigue (Mills, & Young, 2007). Likewise, Wei & Lightman (1997) noted that there was increased activation of the HPA axis in inflammatory diseases perhaps acting as a protective mechanism against an excessive immune response. This shows how fatigue and stress worsen MS symptoms as well as showing increased levels of cortisol during such times; excessive yawning is at its most apparent in these patients during onset of symptoms.

Hypoglycaemia in diabetics can often display repeated yawning (Walusinski, et al., 2010). The adrenal stress hormones, adrenalin, and cortisol, are critically involved (Plonk, Bivens, & Feldman, 1974). In fact, most hypoglycaemic symptoms are caused not by low blood sugar per se, but by an over-reaction of adrenalin and cortisol discharge which make up part of the body's defence system against falling blood sugar levels (Plonk, et al., 1974). O'Neill and colleagues (1991) found blood glucose and cortisol levels to be linked suggesting that hyperglycaemia in stroke patients reflects changes in circulating levels of stress hormones, particularly cortisol, glucagon, and insulin (O'Neill et al., 1991). However, not all researchers have found differences in cortisol levels between clinical and non-clinical populations (Jerjes, et al., 2006).

Stroke

Investigations have lead to establishing increased cortisol levels and failure of dexamethasone control over cortisol suppression following acute stroke (Fassbender, et al., 1994). Of high importance is the damaging effects that increased cortisol concentrations have been known to have on functional outcome (Olsson, 1990). Research looking at links between cortisol and fatigue uncovered strong associations between cortisol, smoking and alcohol intake, these factors were found to be more powerful than the association between fatigue and cortisol (Badrick, Kirschbaum, & Kumari, 2007; Badrick, et al., 2008). Smoking and drinking are well known risk factors in stroke. This suggests that life-style factors prior to stroke may affect cortisol levels and increase the likelihood of future strokes. Some stroke patients may already have pre-existing higher levels of cortisol before injury.

Confusion and disorientation are commonly experienced states in stroke patients and hypercortisolism is commonly reported in patients suffering from such states. These states may be linked to influencing levels of arousal which also serve to influence the display of excessive yawning in patients. The observed dissociation in rhythmicity between ACTH and cortisol levels has been examined in relation to the possible effect of cytokines on HPA axis functions. Interleukin, a form of cytokine, is of a higher plasma concentration following stroke and is also responsible for increases in cortisol release (Johansson, et al., 1997; 2000).

Cortisol levels have been associated with stroke severity and short-term mortality following stroke. The activity of the natriuretic peptide (NP) system has also been associated with poor outcome. Makikallio and

colleagues (2007) investigated the interrelations of these two systems on the effects of hormonal activation in the acute phase following ischaemic stroke. They found cortisol levels to be increased showing a relationship with prognosis; the higher the levels of cortisol recorded the poorer the patient outcome. They concluded that the synergy of increased levels of cortisol and NP system activity were prognostically unfavourable (Makikallio, et al., 2007). Furthermore yawning has been evidenced as both a poor (Lehmann, 1979; Mulley 1982) and good prognostic indicator (Braunwald, et al, 1987). Perhaps increased cortisol levels indicate poor prognostic outcome and these high levels may serve to elicit yawning and following yawns, cortisol levels may drop which may help improve prognostic outcome.

By interfering with neuroendocrine disturbances we may be able to lessen both brain damage and neuropsychiatric disturbance (Johansson, et al., 1997) as hypercortisolism is associated with cognitive impairment and later depression in patients. It has been shown that hypercortisolism impairs immune system function and this may explain why it is often able to predict functional outcome following stroke (Johansson, et al., 1997). Cytokine antagonists can directly or indirectly reduce cortisol levels and therefore, perhaps reduce the extent of brain damage (Johansson et al., 1997). If cortisol is linked to yawning, yawning may serve as a warning of underlying neurological problems (Thompson, 2010). Through persisting release of hormones, the disease course may be modulated and disease development prevented or at least delayed.

Multiple sclerosis

HPA axis hypo- and hyper-activity alterations have also been displayed in people suffering from fatigue and MS (Grasser, et al., 1996). However, more consistent findings have displayed a stronger trend towards hyper-activity (Fassbender, et al., 1998; Heesen, et al., 2002). These findings tend to support those of animal studies in which higher cortisol levels were present in animals exposed to chronic inflammatory stress. Michelson and colleagues (1994) also found significantly higher levels of cortisol in MS patients when compared to matched controls. Many studies have found a link between MS and depression (Ferini-Strambi, 2011); and depression and anxiety were found to have a high positive predictive value regarding fatigue symptomatology in MS patients (Iriarte, Subira, & De Castro, 2000). Both of these conditions are established in their links with cortisol. Such high fatigue prevalence in MS alongside evidence of atypical cortisol levels provides strong support for a possible link with pathological yawning.

Barkhatova and colleagues (1998) found disturbances in neurotransmitter metabolism in MS patients which they suggested may be directly associated to the pathogenetic mechanisms of the disease. Many investigators agree that the neurotransmitters dopamine, acetylcholine, serotonin, gamma-aminobutyric acid and the hormones oxytocin, adreno-corticotrophic hormone (and others), as well as nitric oxide, may modulate yawning (Singer, et al., 2007). Hence, a multiform pathogenesis is suggested by some, which may also influence and alter altered cortisol activity (Michelson, et al., 1994; Wei, & Lightman, 1997; Barkhatova, et al., 1998) and excessive yawning (Singer, et al., 2007).

Studies have also looked at cytokine levels which have been found to decrease cortisol levels in healthy individuals (Lee, et al., 2010). There is the possibility of pro-inflammatory cytokines that have a strong influence on the cortisol releasing hormone (Fassbender, et al., 1994). These cytokines are released in relapses of MS; increased cortisol levels are also apparent during relapse which is when yawn frequency is at its highest.

Interestingly, the use of interferons (IFN) to treat MS patients has been seen alongside elevations in serum cortisol levels (Pende, et al., 1990) which might suggest that the therapeutic responses following treatment may actually be a secondary effect due to elevation of serum cortisol. However, some studies have reported no significant increases in cortisol levels following treatment (Reder, & Lowy, 1992).

ACTH stimulates secretion of cortisol and ACTH has been known to elicit yawning (together with stretching behaviour) in animals (Lobo, et al., 1990). Likewise, surges in ACTH and cortisol levels before waking and at night are in line with increases of human yawning behaviour displayed at such times. Appealing data is reported by Sandyk (1998) who found MS patients to respond to pulsed electromagnetic (alternating electrical current) treatment, creating a surge of ACTH activity, with uncontrollable bouts of yawning and pandiculation which ceased after magnetic field exposure was stopped. This is supported by Gallup and Gallup (2008) who state that yawning may actually help relieve MS symptoms, Sandyk (1998) found that those patients displaying yawning and pendiculation behaviour also reported the most significant degree of symptom improvement following treatment. These effects noted by Sandyk (1998) of ACTH on yawning were only found in female subjects. Altered ACTH activity resulting in aberrant regulation of cortisol further supports the possibility that cortisol levels influences yawning.

Neurotransmitters and neurology

Dopaminergic receptors may be involved in yawning as they are in Parkinson's disease and schizophrenia (Corio, 1990; Armbruster, 2009). It has been suggested that elevated levels of cortisol may decrease serotonin levels leading to depressive states (Dinan, 1994); and treatment of selective serotonin reuptake inhibitors (SSRI) have been well documented in conjunction with the side-effects of excessive yawning (Gutierrez-Alvarez, 2007). The effects of acute SSRI administration has been seen in healthy subjects through resulting HPA axis stimulation and increases in salivary cortisol levels (Harmer, et al., 2003). Additional links have been made between cortisol secretion and SSRIs (Tucker, et al., 2004); and between serotonin and excessive yawning (Sommet, et al., 2007). Holmgren and colleagues (1992) considered serotonin as a positive modulator that possibly triggers the yawning response. Serotonin has been reported in diminished states in MS patients (Davidson, et al., 1977), and in stroke patients (Gao, et al., 2008).

Thermoregulation

Heat stress has been accepted as causing premature fatigue not only in MS patients but also in healthy populations (Gilbert, et al., 2004), while thermoregulatory dysfunction and fatigue have been linked to excessive yawning (Gallup, & Gallup, 2010a). Research on two healthy individuals with excessive yawning found that both reported their yawning episodes to coincide with thermoregulatory factors (Gallup, et al., 2010a). One noted a significant drop in body temperature following the episodes while both found that attacks were relieved and/or postponed through cooling.

Perhaps unsurprisingly, the endocrine system has been found to be involved in many aspects of thermoregulation (Gale, 1973). Hypothermic lambs display low plasma cortisol while dexamethasone treatment is shown to prevent hypothermic body temperatures (Clarke, Heasman, & Symonds, 1998). The combined action of corticosteroids and catecholamines appear to be involved in the control of regulatory heat production in animal studies (Werner, & Vens-Cappell, 1985). However, it has also been found that cortisol levels did not significantly alter during the course of a 30 minute run in human subjects despite body temperature rises (Kraemer, et al., 1989).

There is increasing evidence of yawning as an indicator of thermoregulatory dysfunction; and if thermoregulation is related to cortisol levels, since yawn frequency increases during times of heat stress, then cortisol levels and yawning may indeed be linked.

Circadian rhythms

Yawning occurs most frequently during the first hour after waking and the last hour before sleep. This is in line with body temperature peaks, occurring in the evenings before sleep, then cooling during sleep, curving again to a rise just before waking. Both such rhythms are in synergy showing increased yawning when body temperature is highest in the morning and evening (Gallup, et al., 2010b). However, cortisol circadian rhythms peak after waking and reach a lower point at night. Hence, there is a discrepancy between increased and decreased cortisol levels. Perhaps yawning is able to influence cortisol levels in terms of regulating cortisol in these circumstances. This would support the suggestion that yawning may be an indicator of underlying disease pathology as research shows hyperactivity (Crofford, et al., 2004; Di Giorgio, et al., 2005) and hypoactivity (Tops, et al., 2006; Nater, et al., 2008) can be linked to disease symptomatology. Suggestion here is that yawning increases in frequency during both these instances to attempt to stabilise cortisol levels.

New research

It is clear that diurnal changes, yawning and cortisol can be key elements in disease onset and prognosis and are in need of further investigation. The meaning and relevance of the major elements of the diurnal cortisol rhythm are still unclear (Adam, & Kumari, 2009). Research regarding circadian patterns could also aim to determine if cortisol and yawning rhythms are still evident in the clinical population, for example, in FMS and CFS patients. Assessment involving more continuous measures of cortisol levels may provide information that is of a more broad relevance to health in the general population.

Findings from studies suggest that cortisol treatment may convey protective and therapeutic effects in some patient groups (Schuder, 2005) and even provide symptom relief in other clinical groups following yawning. Data may even show that cortisol and yawning can serve as useful diagnostic tool for identifying thermoregulatory problems or underlying disorders.

New work is underway by Author 1 at the Psychology Research Centre, Bournemouth University, to determine if cortisol levels are intimately linked with yawning episodes. It is hoped that findings will support Thompson's (2011) Cortisol Hypothesis both in healthy groups as well as in diagnosed clinical populations. Potentially, this link may provide a useful indicator of underlying pathology and the link between neurological disorders that presently remains rather unclear.

References

1. ARDAL-ERIKSSON, E., KARLBERG, B. E., & HOLM, A. C., 1998. Salivary cortisol - an alternative to serum cortisol determinations in dynamic functions tests. Clinical Chemistry and Laboratory Medicine, 36(4), 215-222.

2. ABTAHI, S., HARIRI, B., & SHIRMOHAMMADI, S., 2011. Driver Drowsiness Monitoring Based on Yawning Detection, Proc. IEEE International Instrumentation and Measurement Technology Conference, Binjiang (Hangzhou), China, May 10-12, 2011.

3. ADAM, E. K., HAWKLEY, L. C., KUDIELKA, B. M., & CACIOPPO, J. T., 2006. Day-to-day dynamics of experience-cortisol associations in a population-based sample of older adults. Proceedings of the National Academy of Sciences of the U.S.A., 103, 1708-17063.

4. ADAM, E. K., & KUMARI, M., 2009. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology, 34, 1423-1436.

5. ANIAS-CALDERON, J., VERDUGO-DIAZ, L., & DRUCKER-COLIN, R., 2004. Adrenalectomy and dexamethasone replacement on yawning behaviour. Behavioural Brain Research, 154, 255-259. 6. ASKENASY, J. J. M., 1989. Is yawning an arousal defense reflex Journal of Psychology, 123, 609-621.

7. ASMUNDSON, G. J., WRIGHT, K. D., & STEIN, M. B., 2004. Pain and PTSD symptoms in female veterans. European Journal of Pain, 8, 345-350.

8. ARMBRUSTER, D., MUELLER, A., MOSER, D. A., LESCH, K. P., BROCKE, B., & KIRSCHBAUM, C., 2009. Interaction effect of D4 dopamine receptor gene and serotonin transporter promoter polymorphism on the cortisol stress response. Behavioural Neuroscience, 123(6), 1288-1295.

9. BADRICK, E., BOBAK, M., BRITTON, A., KIRSCHBAUM, C., MARMOT, M., & KUMARI, M., 2008. Alcohol and cortisol secretion in an ageing cohort. Journal of Clinical Endocrinology & Metabolism, 93, 750-757.

10. BADRICK, E., KIRSCHBAUM, C., KUMARI, M., 2007. Smoking status and salivary cortisol secretion. Journal of Clinical Endocrinology & Metabolism, 92, 819-824.

11. BAKER, D. G., 2011. Multiple sclerosis and thermoregulatory dysfunction. Journal of Applied Physiology, 92, 1779-1780.

12. BAMER, A. M., JOHNSON, K. L., AMTMANN, D., & KRAFT, G. H., 2008. Prevalence of sleep problems in individuals with multiple sclerosis. Multiple Sclerosis, 14(8), 1127-1130.

13. BARKHATOVA, V. P., ZAVALISHIN, I. A., ASKAROVA, L. S., SHAVRATSKII, V. K., & DEMINA, E. G., 1998. Changes in neurotransmitters in multiple sclerosis. Neuroscience & Behavioural Physiology, 28(4), 341-344.

14. BRASS, S. D., DUQUETTE, P., PROULX-THERRIEN, J., & AUERBACH, S., 2010. Sleep disorder in patients with multiple sclerosis. Sleep Medicine Reviews, 14, 121-129.

15. BRAUNWALD, E., ISSELBACHER, K. J., PETERSDORF, R. G., WILSON, J. D., MARTIN, J. B., & FAUCI, A. S., 1987. Harrisons principles of internal medicine, 11th ed., New York: McGraw-Hill.

16. BROWN, R. F., TENNANT, C. C., SHARROCK, M., HODGKINSON, S., & POLLARD, J. D., 2006. Relationship between stress and relapse in multiple sclerosis: Part 1. Multiple Sclerosis, 12(4), 453-64.

17. CAPES, S. E., HUNT, D., MALMBERG, K., PATHAK, P., & GERSTEIN, H. C., 2001. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. Stroke, 32(10), 2426-2432.

18. CATTANEO, L., CUCURACHI, L., CHIERICI, E., & PAVESI, G., 2006. Pathological yawning as a presenting symptom of brain stem ischaemia in two patients. Journal of Neurology, Neurosurgery & Psychiatry, 77, 98-100.

19. CATTANEO, L., CHIERICI, E., CUCURACHI, L., & PAVESI, G., 2007. Pathological yawning in brainstem stroke. Clinical Neurophysiology, 118, 2821-2821.

20. CHERVIN, R. D., 2000. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest, 118(2), 372-379.

21. CLARKE, I., HEASMAN, L., & SYMONDS, M. E., 1998. Influence of maternal dexamethasone administration on thermoregulation in lambs delivered by caesarean section. Journal of Endocrinology, 156, 307-314.

22. CLAUW, D. J., & CROFFORD, L. J., 2003. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Practice and Research Clinical Rheumatology, 17(4), 685-701.

23. COIRO, V., VOLPI, R., CAPRETTI, L., SPERONI, G., BIANCONI, L., CAVAZZINI, U., MARCATO, A., BUONANNO, G., CAIAZZA, A., & CHIODERA, P., 1990. 5-HT1-, but not 5-HT2-serotonergic, M1-, M2-muscarinic cholinergic or dopaminergic response mediate the ACTH/cortisol response to metoclopramide in man. Hormone Research, 33(6), 233-238.

24. COOPER, G., TINDALL-FORD, S., CHANDLER, P., & SWELLER, J., 2001. Learning by imagining.

25. Journal of Experimental Psychology: Applied, 7, 68-82.

26. CROFFORD, L. J., YOUNG, E. A., ENGLEBERG, N. C., KORSZUN, A., BRUCKSCH, C. B., McCLURE, L. A., BROWN, M. B., & DEMITRACK, M. A., 2004. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain, Behaviour & Immunity, 18, 314-325.
27. DAQUIN, O., MICALLEF, J., & BLIN, O., 2001. Yawning. Sleep Medicine Review, 5, 299-322.
28. DAVIDSON, D., PULLAR, I. A., MAWDSLEY, C., KINLOCH, N., & YATES, C. M., 1977. Monoamine metabolites in cerebrospinal fluid in multiple sclerosis. Journal of Neurosurgery & Psychiatry, 40, 714-745.
29. DAVIS, S. L., WILSON, T. E., WHITE, A. T., & FROHMAN, E. M., 2010. Thermoregulation in multiple sclerosis. Journal of Applied Physiology, 109, 1531-1537.
30. DAVIS, S. L., WILSON, T. E., VENER, J. M., CRANDALL, C. G., PETAJAN, J. H., & WHITE, A. T., 2005. Pilocarpine induced sweat gland function in individuals with multiple sclerosis. Journal of Applied Physiology, 98, 1740-1744.
31. DEPUTTE, B. L., 1994. Ethological study of yawning in primates. 1. Quantitative analysis and study of causation in two species of old world monkeys. Ethology, 98, 221-245.
32. DIETRICH, W. D., & BRAMLETT, H. M., 2007. Hypothermia and central nervous system injury. Progress in Brain Research, 162, 201-217.
33. DI GIORGIO, A., HUDSON, M., JERJES, W., & CLEARE, A., 2005. 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. Psychosomatic Medicine, 67, 433-440.
34. DINAN, T. G., 1994. Glucocorticoids and the genesis of depressive illness. A psychological model. British Journal of Psychiatry, 164, 365-371.
35. FASSBENDER, K., SCHMIDT, R., MOSSNER, R., DAFFERTSHOFER, M., & HENNERICI, M., 1994. Pattern of Activation of the Hypothalamic-Pituitary-Adrenal Axis in Acute Stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke; a Journal of Cerebral Circulation, 25(6), 1105-1108.
36. FASSBENDER, K., SCHMIDT, R., MOSSNER, R., KISCHKA, U., KUHNEN, J., SCHWARTZ, A., & HENNERICI, M., 1998. Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: association with cerebral inflammation. Archives of Neurology, 55, 66-72.
37. FADEEV, V., GITEL, E. P., & MELNICHENKO, G. A., 2001. The diurnal rhythm of adrenocorticotrophic hormone secretion in the assessment of the adequacy of replacement therapy in primary chronic adrenal failure. Neuroscience & Behavioural Physiology, 31, 237-242.
38. FERINI-STRAMBI, L., 2011. Sleep disorders in multiple sclerosis. Handbook of Clinical Neuroscience, 99, 1139-1149.
39. FRIES, E., HESSE, J., HELLHAMMER, J., & HELLHAMMER, D. H., 2005. A new view on hypocortisolism. Psychoneuroendocrinology, 30, 1010-1016.
40. GALE, C. C., 1973. Neuroendocrine aspects of thermoregulation. Annual Review of Physiology, 35, 391-430.
41. GALLUP, A. C., & GALLUP, Jr G. G., 2007. Yawning as a brain cooling mechanism: nasal breathing and forehead cooling diminish the incidence of contagious yawning. Evolutionary Psychology, 5, 92-101.
42. GALLUP, A. C., & GALLUP, Jr G. G., 2008. Yawning and thermoregulation. Physiology and Behaviour, 95, 10-16.
43. GALLUP, G., GALLUP, Jr. GALLUP, C., 2010a. Excessive yawning and thermoregulation: two case histories of chronic, debilitating bouts yawning. Sleep Breath, 14, 157-159.
44. GALLUP, A.C., GORDON, G., GALLUP Jr., CONCETTA, F., 2010b. Yawning, sleep, and symptom relief in patients with multiple sclerosis. Sleep Medicine, 11, 329-330.
45. GAO, H-Q, ZHU, H-Y, ZHANG, Y-Q, & WANG, L-X., 2008. Reduction of cerebrospinal fluid and plasma serotonin in patients with post-stroke depression: A preliminary report. Clinical and Investigative Medicine, 31(6), 351-356.
46. GIGANTI, F., HAYES, M. J., CIONI, G., & SALZARULO, P., 2007. Yawning frequency and distribution in preterm and near term infants assessed throughout 24-h recordings. Infant Behaviour Development, 30,641-647.
47. GILBERT, S.S., VAN DEN HEUVEL, C. J., FERGUSON, S. A., & DAWSON, D., 2004. Thermoregulation as a sleep signalling system. Sleep Medicine, 8, 81-93.
48. GRASSER, A., MOLLER, A., BACKMUND, A., YASSOURIDIS, A., & HOLSBOER, F., 1996. Heterogeneity of hypothalamic-pituitary-adrenal system response to a combined dexamethasone-CRH test in multiple sclerosis. Experimental and Clinical Endocrinology, 104, 31-37.
49. GRECO, M., BAENNINGER, R., & GOVERN, J., 1993. On the context of yawning: when where, and why Psychological Record, 43, 175-183.
50. GUTI'RREZ-'LVAREZ, A. M., 2007. Do your patients suffer from excessive yawning. Acta Psychiatrica Scandinavica, 115, 80-82.
51. HARMER, C. J., BHAGWAGAR, Z., SHELLEY, N.,

& COWEN, P. J., 2003. Contrasting effects of citalopram and reboxetine on waking salivary cortisol. Psychopharmacology, 167(1), 112-114.
52. HEIM, C., EHLERT, U., & HELLHAMMER, D. H., 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology, 25, 1-35.
53. HELLHAMMER, J., & WADE, S., 1993. Endocrine correlates of stress vulnerability. Psychotherapy and Psychsomatics, 60, 8-17.
54. HELLHAMMER, J., FRIES, E., SCHWEISTHAL, O. W., SCHLOTZ, W., STONE, A. A., & HAGEMANN, D., 2007. Several daily measurements are necessary to reliable assess the cortisol rise after awakening: state- and trait components. Psychoneuroendocrinology, 32, 80-86.
55. HEESEN, C., GOLD, S. M., RAJI, A., WIEDEMANN, K., & SCHULZ, K. H., 2002. Cognitive impairment correlates with hypothalamo-pituitary-adrenal axis dysregulation in multiple sclerosis. Psychoneuroendocrinology, 27, 505-517.
56. HIPOLIDE, D. C., LOBO, L. L., DE MEDEIROS, B. N., & TUFIK, S., 1999. Treatment with dexamethasone alters yawning behaviour induced by cholinergic but not dopaminergic agonist. Physiology and Behaviour, 65, 829-832.
57. HOLMGREN, B., URBA-HOLMGREN, R., LEON, B., & UGARTE, A., 1992. Age-dependent changes in serotoninergic modulation of yawning in the rat. Pharmacology Biochemistry and Behaviour, 43, 483-486.
58. HOUSHYAR, H., GOMEZ, F., MANALO, S., BHARGAVA, A., & DALLMAN, M. F., 2003. Intermittent morphine administration induces dependence and is a chronic stress in rats. Neuropsychopharmacology, 28, 1960-1972.
59. IRIARTE, J., SUBIRA, M. L., & DE CASTRO, P., 2000. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. Multiple Sclerosis, 6, 124-130.
60. JERJES, W. K., TAYLOR, N. F., PETERS, T. J., WESSELY, S., & CLEARE, A. J., 2006. Urinary cortisol and metabolite excretion in chronic fatigue syndrome. Psychosomatic Medicine, 68, 578-582.
61. JOHANSSON, A., OLSSON, T., CARLBERG, B., KARLSSON, K., & FARGERLUND, M., 1997. Hypercortisolism after stroke partly cytokine-mediated Journal of Neurological Sciences, 147, 43-47.
62. JOHANSSON, A., AHREN, B., NASMAN, B., CARLSTORM, K., & OLSSON, T., 2000. Cortisol axis abnormalities early after stroke relationships to cytokines and leptin. Journal of Internal Medicine, 247, 179-187.
63. KASUYA, Y., MURAKARNI, T., OSHIRNA, T., & DOHI, S., 2005. Does yawning represent a transient arousal-shift during intravenous induction of general anesthesia Anesthesia and Analgesia, 101(2), 382-384.
64. KAYNAK, H., ALTINTAS, A., KAYNAK, D., UYANIK, O., SAIP, S., AGAOGLU, J., ONDER, G., & SIVA, A., 2006. Fatigue and sleep disturbance in multiple sclerosis. European Journal of Neurology, 13(12), 1333-1339.
65. KRAEMER, R. R., BLAIR, S., KRAEMER, G. R., & CASTRACANE, V. D., 1989. Effects of treadmill running on plasma beta-endorphin, corticoctropin, and cortisol levels in male and female 10k runners. European Journal of Applied Physiology and Occupational Physiology, 58(8), 845-851.
66. KRANTZ, M. J., LEE, J. K., & SPODICK, D. H., 2004. Repetitive Yawning Associated with Cardiac Tamponade. American Journal of Cardiology, 94, 701-702.
67. KUMARI, M., BADRICK, E., CHANDOLA, T., ADAM, E.K., STAFFORD, M., MARMOT, M. G., KIRSCHBAUM, C., & KIVIMAKI, M., 2009. Cortisol secretion and fatigue: Associations in a community based cohort, Psychoneuroendocrinology, 34, 1476-1485.
68. LAPRESLE, J., 1986. Palatal myoclonus. Advances in Neurology, 43, 265-273.LEE., J. B., SHIN, Y. O., MIN, Y. K., & YANG, H. M., 2010. The effect of Oligonal intake on cortisol and related cytokines in healthy young men. Nutrition Research and Practice, 4(3), 203-207.
69. LEHMANN, H. E., 1979. Yawning: A homeostatic reflex and its psychological significance. Bulletin of the Menninger Clinic, 43, 123-136.
70. LINDEBERG, S. I., EEK, F., LINDBLADH, E., OSTERGREN, P. O., HANSEN, A. M., & KARLSON, B., 2008. Exhaustion measured by the SF-36 vitality scale is associated with a flattened diurnal cortisol profile. Psychoneuroendocrinology, 33, 471-477.
71. LOBO, L. L. NEUMANN, B. G., EIDMAN, D. S., & TUFIK, S., 1990. Effects of REM sleep deprivation of ACTH-induced yawning. Pharmacology, 40(3), 174-178.
72. LOUWERSE, E., 1998. Forced yawning as a pseudobulbar sign in amyotrophic lateral sclerosis. Journal Neuroscience Research, supplement, 392.MacLEAN, P., 1985. Evolutionary psychiatry and the triune brain. Psychological Medicine, 15, 219-221.
73. MAKIKALLIO, A., KORPELANINEN, J., MAKIKALLIO, T., TULPPO, M., VUOLTEENAHO, O., SOTANIEMI, K., HUIKURI, H., & MYLLYLA, V., 2007. Neurohormonal activation in ischemic stroke: Effects of acute phase disturbances on long-term mortality.

Current Neurovascular Research, 4, 170-175.
74. MARINO, F. E., 2009. Heat reactions in multiple sclerosis: An overlooked paradigm in the study of comparative fatigue. International Journal of Hyperthermia, 25(1), 34-40.
75. McEwen B. S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology, 22(2): 108-24
76. MEENAKSHISUNDARAM, R., THIRUMALAIKOLUNDUSUBRAMANIAN, P., WALUSINSKI, P., MUTHUSUNDARI, A., & SWENI, S., 2010. Associated movements in hemiplegic limbs during yawning. Frontiers of Neurology & Neuroscience, 28, 134-139.
77. MELAMED, S., SHIROM, A., TOKER, S., BERLINER, S., & SHAPIRA, I., 2006. Burnout and risk of cardiovascular disease: evidence, possible causal paths and promising research directions. Psychological Bulletin, 132, 327-353.
78. MERLINO, G., FRATTICCI, L., LENCHIG, C., VALENTE, M., CARGNELUTTI, D., PICELLO, M., SERAFINI, A., DOLSO, P., & GIGLI, G. L., 2009. Prevalence of poor sleep among patients with multiple sclerosis: an independent predictor of mental and physical status. Sleep Medicine, 10(1), 26-34.
79. MICHELSON, D., STONE, L., GALLIVEN, E., MAGIAKOU, M. A., CHROUSOS, G. P., STERNBERG, E. M. & GOLD, P. W., 1994. Multiple sclerosis is associated with alterations in hypothalamic-pituitary-adrenal axis function. Journal of Clinical Neuroendocrinology and Metabolism, 79(3), 848-853.
80. MILLS, R. J., & YOUNG, C. A., 2007. A medical definition of fatigue in multiple sclerosis. An International Journal of Medicine, 101, 49-60.
81. MOHR, D. C., & PELLETIER, D., 2006. A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis. Brain, Behaviour, and Immunity, 20, 27-36.
82. MUCHNIK, S., FINKIELMAN, S., SEMENIUK, G., & de AGUIRRE, M. I., 2003. Yawning and temporal lobe epilepsy. Medicina (B Aires), 63, 137-139.
83. MULLEY, G., 1982. Associated reactions in the hemiplegic arm. Scandinavian Journal of Rehabilitation Medicine, 14, 117-120.
84. NATER, U. M., MALONEY, E., BONEYA, R. S., GURBAXANI, B. M., LIN, J.M., JONES, J. F., REEVES, W. C., & HEIM, C., 2008. Attenuated morning salivary cortisol concentrations in a population-based study of persons with chronic fatigue syndrome and well controls. Journal of Clinical Endocrinology and Metabolism, 93, 703-709.
85. OLSSON, T., 1990. Urinary free cortisol excretion shortly after ischemic stroke. Journal Internal Medicine, 20, 1685-1690.
86. O'NEILL, P. A., DAVIES, I., FULLERTON, K. J., & BENNETT, D., 1991. Stress hormone and blood glucose response following acute stroke in the elderly. Stroke, 22, 842-847.
87. PENDE, A., MUSSO, N.R., VERGASSOLA, C., PUPPO, F., IOVERNO, A., CRISCULOLO, D., IDIVERI, F., & LOTTI, G., 1990. Neuroendocrine effects of interferon alpha 2-a in healthy human subjects. Journal of Biological Regulators and Homeostatic Agents, 4, 67-72.
88. PLATEK, S. M., CRITTON, S. R., MYERS, T. E., & GALLUP, G. G., 2003. Contagious yawning: the role of self-awareness and mental state attribution. Cognitive Brain Research, 17(2), 223-227.
89. PLATEK, S. M., MOHAMED, F. B., & GALLUP, G. G. Jr., 2005. Contagious yawning and the brain. Brain Research Cognitive Brain Research, 23, 448-452.
90. PLONK, J. W., BIVENS, C. H., & FELDMAN, J. M., 1974. Inhibition of hypoglycaemia-induced cortisol secretion by the serotin antagonist cyproheptadine. Journal of Clinical Endocrinology & Metabolism, 38, 836-840.
91. POSTERT, T., POHLAU, D., MEVES, S., NASTOS, I., & PRZUNTEK, H., 1996. Pathological yawning as a symptom of multiple sclerosis. Journal of Neurology, 243, 300-301.
92. PRASAD, H., 2008. Yawning and why yawns are contagious: A theory on evolution and atavism. Medical Hypotheses, 71, 307-325.
93. PROVINE, R., 2005. Yawning. American Scientist, 93, 532-539.
94. PROVINE, R., 1986. Yawning as a stereotyped action pattern and releasing stimulus. Ethology, 72, 109-122.
95. PROVINE, R., HAMERNICK, H. B., & CURCHACK, B. B., 1987. Yawning: relation to sleeping and stretching in humans. Ethology, 76, 152-60.
96. RAPHAEL, K. G., JANAL, M. N., & NAYAK, S., 2004. Comorbidity of fibromyalgia and posttraumatic stress disorder symptoms in a community sample of women. Pain Medicine, 5, 33-41.
97. REDER, A., & LOWY, T. M., 1992. Interferon-B treatment does not elevate cortisol in multiple sclerosis. Journal of Interferon Research, 12, 195-198.
98. REDFORD, E. J., KAPOOR, R., & SMITH, K. J., 1997. Nitric oxide reversibly block axonal conduction: demyelinated axons are especially susceptible. Brain, 120, 2149-2157.
99. RUBIN, G. J., HOTOPF, M., PAPADOPOULOS, A., & CLEARE, A., 2005. Salivary cortisol as a predictor of postoperative fatigue. Psychosomatice Medicine, 67, 441-447.
100. SANDYK, R., 1998. Yawning and stretching. A

behavioural syndrome associated with transcranial application of electromagnetic fields in multiple sclerosis. International Journal of Neuroscience, 95, 107-113.

101. SCHUDER, S. E., 2005. Stress-induced hypocortisolemia diagnosed as psychiatric disorder responsive to hydrocortisone replacement. Annuals of the New York Academy of Sciences, 1057, 466-478.

102. SCHURMANN, M., HESSE, M. D., STEPHAN, K. E., SAARELA, M., ZILLES, K., HARI, R., & FINK, G. R., 2005. Yearning to yawn: the neural basis of contagious yawning. NeuroImage, 24, 1260-1264.

103. SEEMAN, T. E., SINGER, B. H., RYFF, C. D., DIENBERG LOVE, G., & LEVYSTORMS, L., 2002. Social relationships, gender and allostatic load across two age cohorts. Psychosomatic. Medicine, 64, 395-406.

104. SEPHTON, S., KRAEMER, H. C., & SPIEGEL, D., 2000. Diurnal cortisol rhythm as a predictor of breast cancer survival. Journal of the National Cancer Institute, 92, 994-1000.

105. SINGER, O.C., HUMPICH, M.C., LANFERMANN, H., & NEUMANN-HAEFELIN, T., 2007. Yawning in acute anterior circulation stroke. Journal of Neurology, Neurosurgery & Psychiatry, 78, 1253-1254.

106. SMITH, K. J., & McDONALD, W. I., 1999. The pathopohysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. Philosophical Transactions of the Royal Society B: Biological Sciences, 354, 1649-1673.

107. SOMMET, A., DESPLAS, M., LAPEYRE-MESTRE, M., & MONTASTRUC, J. L., 2007. Drug-induced yawning: a review of the French pharmacovigilance database. Drug Safety, 30, 327-331.

108. SOUKUP, J., ZAUNER, A., DOPPENBERG, E. M. R., MENZEL, M., GILMAN, C., YOUNG, H. F., & BULLOCK, R., 2002. The importance of brain temperature in patients after severe head injury: relationship to intracranial pressure, cerebral perfusion pressure, cerebral blood flow and outcome. Journal of Neurotrauma, 19, 559-571.

109. SUNG, C. Y., LEE, T. H., & CHU, N. S., 2009. Central hyperthermia in acute stroke. European Neurology, 62, 86-92.

110. TARULLA, A. R., & GUNNER, M., 2006. Child maltreatment and the developing HPA axis. Hormones and Behaviour, 50, 632-639.

111. TER WOLBEEK, M., VAN DOORNEN, L. J., COFFENG, L. E., KAVELAARS, A., & HEIJNEN, C. J., 2007. Cortisol and severe fatigue: a longitudinal study in adolescent girls. Psychoneuroendocrinology, 32, 171-182.

112. THOMPSON, S. B. N., 2006. Dementia and memory: a handbook for professionals and students. Aldershot: Ashgate.

113. THOMPSON, S. B. N., 2010. The Dawn of the yawn: is yawning a warning Linking neurological disorders. Medical Hypotheses, 75, 630-633.

114. THOMPSON, S. B. N., 2011. Born to yawn Cortisol linked to yawning: a new hypothesis. Medical Hypotheses, In Press. doi: 10.1016/j.mehy.2011.07.056.

115. TOPPER, R., MULL, M., & NACIMIENTO, W., 2003. Involuntary stretching during yawning in patients with pyramidal tract lesions: further evidence for the existence of an independent emotional motor system. European Journal Neurology, 10, 495-499.

116. TOPS, M., VAN PEER, J. M., WIJERS, A. A., & KORF, J., 2006. Acute cortisol administration reduces subjective fatigue in healthy women. Psychophysiology, 43, 653-656.

117. TUCKER, P., RUWE, W. D., MASTERS, B., PARKER, D. E., HOSSAIN, A., TRAUTMAN, R. P., & WYATT, D. B., 2004. Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder. Biological Psychiatry, 56, 121-128.

118. VAN DEN EEDE, F., MOORKENS, G., VAN HOUDENHOVE, B., COSYNS, P., & CLAES, S. J., 2007. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. Neuropsychobiology, 55, 112-120.

119. VAN HOOF, E., CLUYDTS, R., & DE MEIRLEIR, K., 2003. Atypical depression as a secondary symptom in chronic fatigue syndrome. Medical Hypotheses 61, 52-55.120. WALUSINSKI, O., 2007. Can stroke localisation be used to map out the neural network for yawning behaviour Journal of Neurology, Neurosurgery & Psychiatry, 78, 1166.

121. WALUSINSKI, O., 2009. Yawning in Diseases, European Neurology, 62, 180-187.

122. WALUSINSKI, O., NEAU, J. P., & BOGOUSSLAVSKY, J., 2010. Hand up! Yawn and raise your arm. International Journal of Stroke, 5, 21-27.

123. WEI, T., & LIGHTMAN, S. L., 1997. The neuroendocrine axis in patients with multiple sclerosis. Brain, 120, 1067-1076.

124. WERBEL, S. S., & OBER, K. P., 1993. Acute adrenal insufficiency. Endocrinology and metabolism clinics of North America, 22, 303-328.

125. WERNER, R., & VENS-CAPPELL, F., 1985. Changes in plasma cortisol during acute cold exposure in enthermic European hedgehogs: thermoregulatory role of the hypothalamo-pituitary-adrenal axis. Journal of

Comparative Physiology B: Biochemical, Systemic and Environmental Physiology, 155(2), 219-226.
126. WILLIAMS, D. R., 2000. The yawning reflex: an upper motor neuron sign in amyotrophic lateral sclerosis. Neurology, 55, 1592-1593.
127. YANKOVSKY, A. E., ANDERMANN, F., & DUBEAU, F., 2006. Post-ictal forceful yawning in a patient with nondominant hemisphere epilepsy. Epileptic Disorders, 8, 65-69.
128. ZILLI, I., GIGANTI, F., & UGA, V., 2008. Yawning and subjective sleepiness in the elderly. Journal of Sleep Research, 17, 303-308.

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