Health Psychology Intervention – Identifying Early Symptoms in Neurological Disorders

Simon B. N. Thompson

Abstract**—**Cortisol is essential to the regulation of the immune system and pathological yawning is a symptom of multiple sclerosis (MS). Electromyography activity (EMG) in the jaw muscles typically rises when the muscles are moved – extended or flexed; and yawning has been shown to be highly correlated with cortisol levels in healthy people as shown in the Thompson Cortisol Hypothesis. It is likely that these elevated cortisol levels are also seen in people with MS. The possible link between EMG in the jaw muscles and rises in saliva cortisol levels during yawning were investigated in a randomized controlled trial of 60 volunteers aged 18-69 years who were exposed to conditions that were designed to elicit the yawning response. Saliva samples were collected at the start and after yawning, or at the end of the presentation of yawning-provoking stimuli, in the absence of a yawn, and EMG data was additionally collected during rest and yawning phases. Hospital Anxiety and Depression Scale, Yawning Susceptibility Scale, General Health Questionnaire, demographic, and health details were collected and the following exclusion criteria were adopted: chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, multiple sclerosis, and stroke. Significant differences were found between the saliva cortisol samples for the yawners, $t(23) = -4.263$, $p = 0.000$, as compared with the non-yawners between rest and post-stimuli, which was non-significant. There were also significant differences between yawners and non-yawners for the EMG potentials with the yawners having higher rest and post-yawning potentials. Significant evidence was found to support the Thompson Cortisol Hypothesis suggesting that rises in cortisol levels are associated with the yawning response. Further research is underway to explore the use of cortisol as a potential diagnostic tool as an assist to the early diagnosis of symptoms related to neurological disorders. Bournemouth University Research & Ethics approval granted: JC28/1/13-KA6/9/13. Professional code of conduct, confidentiality, and safety issues have been addressed and approved in the Ethics submission. Trials identification number: ISRCTN61942768. http://www.controlled-trials.com/isrctn/

Keywords**—**Cortisol, Electromyography, Neurology, Yawning.

I. Introduction

THERE is evidence for a potential relationship between yawning and cortisol in multiple sclerosis (MS). Empirical evidence for excessive yawning in MS is very limited; and more recently, the Thompson Cortisol Hypothesis [1] has proposed that the incidence of yawning is associated with rise in saliva cortisol levels. It is unclear how this mechanism may work but it is proposed that within the Hypothalamus-Pituitary-Adrenal (HPA) axis, the hypothalamus regulates temperature and, in turn, adjusts the amount of cortisol that is secreted. Regulation theory has been proposed by Gallup [2] and has arisen from animal models that are further supported by limited human case studies. Stress and fatigue are known to cause elevations in cortisol, and the incidence of yawning has been shown to be increased at times of stress and fatigue [3].

Understanding the significance of yawning has challenged philosophers and scientists for many centuries, and theories that refer to yawning as a mechanism that is essential to the maintenance of optimal oxygen levels has been contended for more than 200 years [4] with Hippocrates in 400 BC being one of the first early observers of human behavior and physiology and to report that yawning often preceded a high body temperature [5].

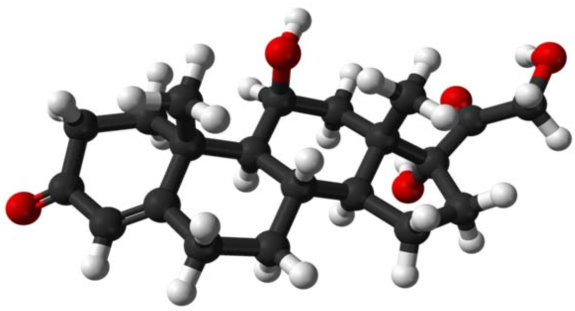

Fig. 1 Cortisol molecule

Cortisol is recognized as the stress hormone in humans (Fig. 1). Increased levels of cortisol combined with the absence of cytokines within the cerebrospinal fluid of deceased MS patients compared to healthy controls, has provided important evidence of sustained hyperactivity of the HPA axis [6]. As part of the body's defense mechanism against MS, raised cortisol levels promote recovery and prevent relapse. People with MS also appear to experience greater fluctuations in their blood plasma cortisol levels [7] with sustained hyperactivity within the HPA axis.

Glycyrrhizic acid, found in liquorice, increases the activity of cortisol on the kidney functions [8]. Inhibition of the enzyme 11-beta-hydroxysteroid dehydrogenase type 2, which normally inactivates cortisol in the kidney, results in an increase of cortisol levels and has been evidenced by the author and his research team [3].

In MS, fatigue is perhaps one of the most reported symptoms and is particularly troublesome for individuals [9], [10]. Iriarte and colleagues [11] propose that fatigue in MS falls into three categories: (i) fatigue at rest; (ii) fatigability;

S. B. N. Thompson is with the Psychology Research Centre and Dementia Institute, Bournemouth University, BH12 5BB, UK and Visiting Clinical Researcher at Université Paris Ouest Nanterre La Défense, Amiens University Hospital, and University of Picardy Jules Verne, France (phone: +44 1202 961558; e-mail: simont@bournemouth.ac.uk).

and (iii) generalized worsening of symptoms attributable to other mechanisms. It is possible that the myelin sheath might itself have a part to play in energy during wakefulness [12]. The sheath may act as a proton buffer capacitor since it is known that the constituents of myelin are excellent at retaining energy and allowing it to provide energy during waking hours.

Postert and colleagues [13] report on a patient with excessive pathological yawning, four times per minute, despite sufficient sleep, as a symptom of MS. An MRI scan showed that the patient had multiple demyelinated plaques within the brainstem. After three days of treatment with high dose steroids, yawning had completely remitted. However, demyelination of the brainstem is common in MS and so cannot be the source of pathological yawning. The authors speculate that inflammation in this area causes yawning by irritating the ascending activating reticular system.

Gallup and colleagues [14], [15] cite the thermoregulatory dysfunction characteristic of MS as evidence for the pathological occurrence in the disorder. Excessive yawning is observed in MS patients yet decreases in ambient temperature from 34 to 24 degrees do not change the frequency of yawning [16]. It is possible that pathological yawning in MS may also be the result of impaired hypothalamic function [17]; and Nahab's [18] neuroimaging research suggests that the ventromedial prefrontal cortex (vmPFC) may be involved in yawning as this area seems to be activated only by yawns. Furthermore, demyelination of the vmPFC may prevent normal functioning with the elicitation of inappropriate yawning and could be involved additionally in assisting in the release of a cortical.

The first proposed connection between yawning and cortisol in humans has been made by Thompson [1] with the Thompson Cortisol Hypothesis suggesting the incidence and frequency of yawning may be dependent upon fluctuations in cortisol levels. Animal studies are also indicative of a link between yawning and cortisol. Removal of rats' adrenal glands almost completely eliminated yawning [19] and early research with healthy humans indicates a strong correlation between cortisol levels, yawning, and increased nerve activity [20].

II. Method

A. Procedure

60 volunteers (one was subsequently eliminated for not meeting inclusion criteria) comprising 37 females and 22 males aged between 18-69 years were recruited from students and the research volunteer pool at Bournemouth University using the computerized recruitment system (SONA), and Facebook.

All participants were properly consented according to code of conduct and research guidelines, and exposed, under randomized controlled trials guidelines, to three conditions intended to provoke a yawning response – photos of people yawning; boring text about yawning; short video of person yawning. Comparisons were made with people exposed to the same conditions but who did not yawn.

Saliva samples were collected at start and again after yawning response (Fig. 2), together with electromyography data of the jaw muscles to determine rest and yawning phases of neural activity (Fig. 3).

Fig. 2 Saliva cortisol test kit

Fig. 3 Electromyograph with surface-placed electrodes

If there was no yawning response, then a second saliva sample was taken at the end of the experimental paradigm. A yawning susceptibility scale, designed in a previous study [3], Hospital Anxiety and Depression Scale (HADS) [21], [22], General Health Questionnaire GHQ28 [23]-[26], and demographic and health details were also collected from each participant.

Exclusion criteria were**:** chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, multiples sclerosis, and stroke. Between- and within-subjects comparisons were made using t-tests and correlations using the SPSS package [version 19]. This enabled a comparison to be made between yawner and non-yawner participants as well as between rest status and yawning episodes.

B. Ethics

Bournemouth University Research & Ethics approval granted: JC28/1/13-KA6/9/13. Professional code of conduct, confidentiality, and safety issues have been addressed and approved in the Ethics submission. Data collected was made anonymous, coded, securely stored and destroyed after completion of the study analysis. Protective measures were put in place for collection and analysis of saliva samples and the right of participants to withdraw from the study was made clear to all participants. Trials ID: ISRCTN61942768. http://www.controlled-trials.com/isrctn/

C. Funding

This research received funding of £8000 from the host institution, Bournemouth University, United Kingdom, to support the purchase of essential equipment and materials.

D. Competing Interests

None.

III. Results

There were no significant differences between groups in terms of age, HADS anxiety and depression scores, and GHQ28 scores. Established normative data for saliva cortisol lies within the collection ranges: (i) Morning 3.7×10^{-9}– 9.5×10^{-9} per ml; (ii) Noon 1.2×10^{-9} – 3.0×10^{-9} per ml; (iii) Evening 0.6×10^{-9}– 1.9×10^{-9} per ml, of saliva.

In saliva cortisol sample 1, the means for non-yawners was 1.9886 (SD = 1.33147) as compared with that of the yawners which was 2.3667 (SD = 1.65310). In sample 2, the means were 2.4914 (SD = 2.15002) for non-yawners, and 3.0208 (SD = 2.00975) for the yawners. Therefore, the yawners had higher levels of resting and post-experiment saliva cortisol levels than the non-yawners.

Using repeated-measures t-test, there was a significant difference between saliva cortisol sample 1 and sample 2 amongst the yawners: $t (23) = -4.263$, $p = .000$, but not for the non-yawners: $t (34) = -2.404$, $p = .022$. Additionally, there was high significance for the two groups overall but non-significant interaction, $F (1, 58) = .286$, $p = .595$ Table I).

For the electrical nerve activity data, there was a significant correlation between cortisol change between the first and second samples and the EMG score: rho (59) = .276, $p = .017$ Table II).

At rest, for the yawners, the EMG range was -90 to 200 millionth of a volt with a mean of 50.4 as compared with -250 to 400 and a mean of 138.3 after yawning. For non-yawners, the range was -40 to 79 with a mean of 15.7, and -30 to 81 with a mean of 15.9 after the stimuli presentation. The yawners showed a larger electrical spike with the onset of a yawn compared to the non-yawners post-presentation EMG activity.

There was a difference between the yawners and non-yawners in EMG, using t-test: $t (57) = -3.986$, $p = .000$. Using analysis of variance (ANOVA), there was a difference between EMG measures at rest ($p = .000$) and after yawn (or after presentation) ($p < .000$).

TABLE I
Overall Effect for Within-Subjects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Sample:					
Sphericity Assumed (SA)	9.530	1	9.530	16.696	.000
Greenhouse-Geisser (GG)	9.530	1	9.530	16.696	.000
Huynh-Feldt (HF)	9.530	1	9.530	16.696	.000
Lower-bound (LB)	9.530	1	9.530	16.696	.000
Sample * Yawn:					
SA	.163	1	.163	.286	.595
GG	.163	1	.163	.286	.595
HF	.163	1	.163	.286	.595
LB	.163	1	.163	.286	.595
Error (Sample):					
SA	32.535	57	.571		
GG	32.535	57	.571		
HF	32.535	57	.571		
LB	32.535	57	.571		

TABLE II
Correlation between Cortisol Change and EMG

			Change	EMG Hi
Spearman's rho	Change	Correlation Coefficient	1.000	0.276*
		Sig. (1-tailed)	-	0.017
		N	59.000	59.000
Spearman's rho	EMG Hi	Correlation Coefficient	0.276*	1.000
		Sig. (1-tailed)	0.017	-
		N	59.000	59.000

* Correlation is significant at the 0.05 level (1-tailed).

Differences between cortisol absolute values for yawners and non-yawners (saliva cortisol sample 1) were found ($p = .000$), and when analyzing saliva cortisol sample 2: $p = .000$.

Power and effect sizes were computed based on repeated measures t-tests for both the yawning and non-yawning group.

IV. Discussion

Significant differences were found in saliva cortisol levels between the first and second samples for those who yawned. This is consistent with the Thompson Cortisol Hypothesis. EMG activity also increased with elevated cortisol levels and also when yawning.

A yawn reflex may give rise to an increase in cortisol levels in order to afford relief in symptoms of stress. However, there is an alternative proposal that elevated cortisol levels may be produced by the yawn reflex to provide symptom relief.

Gallup [15] reports how MS patients report symptom relief following yawns; therefore, it is possible that the temperature regulatory function of the hypothalamus is also governed by the levels of cortisol to maintain homeostasis of both temperature and for fatigue regulation.

Cortisol involved in the HPA may play an important role via yawning in the regulation of body temperature and fatigue. It is highly possible that there is a complex interaction of neurotransmitters involved, such as that suggested by Walusinski [27]. He proposes that changes in cerebrospinal fluid may elicit yawning because the default-mode network is switched to the attentional system with the increase in circulation of cerebrospinal fluid.

Complex interactions of neurotransmitters have also been found in other neurological disorders such as Parkinson's disease [28]. It is also possible that there are other psychological factors that influence the yawning reflex, as is the case with processing information, especially traumatizing information [29].

Since yawning is fundamental and not exclusive to particular disorders, complexity may surround the conundrum that is the yawning reflex.

V. CONCLUSIONS

The release of cortisol into our circulation system appears to have many roles, including protection and regulation of other neurochemicals. Yawning and cortisol is of particular interest and whilst still presenting a scientific conundrum in terms of its origin and mechanism, research has indicated that it features in a number of neurological disorders as well as in healthy individuals.

With the move towards health education and ill-health prevention, it is essential to understand mechanisms within the healthy functioning human body in order to extrapolate implications for impaired mechanisms and structures. Collaborative research is underway at Bournemouth University, UK, Amiens University Hospital, France, and the University of Picardy Jules Verne, France.

It is hoped that a clearer understanding of the yawning reflex and its intimate relationship with cortisol will provide a potential diagnostic tool for identifying early signs of neurological disorder, such as MS, in the future.

REFERENCES

[1] S. B. N. Thompson, "Born to yawn? Cortisol linked to yawning: a new hypothesis," Medical Hypotheses, vol. 77, pp. 861-862, 2011.
[2] A. C. Gallup, and G. G. Jr. Gallup, "Yawning as a brain cooling mechanism: nasal breathing and forehead cooling diminish the incidence of contagious yawning," Evolutionary Psychology, Vol. 5, no. 1, pp. 92-101, 2007.
[3] S. B. N. Thompson, and P. Bishop, "Born to yawn? Understanding yawning as a warning of the rise in cortisol levels: randomized trial," Interactive J Medical Research, vol. 1, no. 5, pp. 1-9, 2012, doi: 10.2196/ijmr.2241.
[4] O. Walusinski, "Historical perspectives," in The mystery of yawning in physiology and disease, J. Bogousslavsky, Eds. Basel: Karger, 2010, pp. 1-21.
[5] M. J. Vigier (translated by), "Les aphorismes d'Hippocrate," J-A. Lyon: Huguetan, 1620.
[6] Z. A. Erkut, E. Endert, I. Huitinga, and D.F. Swaab, "Cortisol is increased in post-mortem cerebrospinal fluid of multiple sclerosis patients: relationship with cytokines and sepsis," Multiple Sclerosis, 2002, vol. 8, pp. 229-236.
[7] F. M. Butterworth, G. E. Ristow, and E. Collarini, "Fluctuation of plasma cortisol levels in multiple sclerosis," Le Journal Canadien des Sciences Neurologiques, 1979, vol. 6, no. 1, pp. 59-63.
[8] G. Flesner, A. Ek, and O. Soderhamn, "Lived experience of MS-related fatigue – a phenomenological interview study," International J Nursing Studies, 2003, vol. 40, pp. 707-717.
[9] B. Périn, O. Gogefroy, S. Fall, and G. de Marco, "Alertness in young healthy subjects: an fMRI study of brain region interactivity enhanced by a warning signal," Brain and Cognition, 2010, vol. 72, pp. 271-281.
[10] R. J. Mills, and C. A. Young, "A medical definition of fatigue in multiple sclerosis," Quarterly J Medicine, 2008, vol. 101, pp. 49-60.
[11] J. Iriarte, M. L. Subira, and P. De Castro, "Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors," Multiple Sclerosis, 2000, vol. 6, pp. 124-130.
[12] A. Morelli, S. Ravera, and I. Panfoli, "Myelin sheath: a new possible role in sleep mechanism," Sleep Medicine, 2011, vol. 12, pp. 198-199.
[13] T. Postert, D. Pöhlau, S. Meves, I. Nastos, and H. Przuntek, "Pathological yawning as a symptom of multiple sclerosis," J Neurology, 1996, vol. 243, no. 3, pp. 300-301.
[14] A. C. Gallup, and G. G. Jr. Gallup, "Yawning and thermoregulation," Physiology and Behavior, 2008, vol. 95, pp. 10-16.
[15] A. C. Gallup, G. G. Jr. Gallup, and C. Feo, "Yawning, sleep, and symptom relief in patients with multiple sclerosis," Sleep Medicine, 2010, vol. 11, pp. 329-330.
[16] A. C. Gallup, M. L. Miller, and A. B. Clark, "The direction and range of ambient temperature influences yawning in budgerigars (Melopsittacus undulates)," J Comparative Psychology, 2010, vol. 124, pp. 133-138.
[17] F. Zellini, G. Niepel, and C. R. Tench, "Constantinescu CS. Hypothalamic involvement assessed by T1 relaxation time in patients with relapsing-remitting multiple sclerosis," Multiple Sclerosis, 2009, vol. 15, no. 12, pp. 1442-1449.
[18] F. Nahab, "Exploring yawning with neuroimaging," in The mystery of yawning in physiology and disease, J. Bogousslavsky, Eds. Basel: Karger, 2010, pp. 128-133.
[19] J. Anias-Calderon, L. Verdugo-Diaz, and R. Drucker-Colin, "Adrenalectomy and dexamethasone replacement on yawning behavior," Behavior Brain Res, 2004, vol. 154, pp. 255-259.
[20] H. Krestel, C. Weisstanner, C. Hess, C. Bassetti, A. Nirkko, and R. Wiest, "Insular and caudate lesions release abnormal yawning in stroke patients," Brain Struct Funct, 2013, doi 10.1007/s00429-013-0684-6.
[21] R. P. Snaith RP, and A. S. Zigmond, "Hospital Anxiety and Depression Scale," Acta Psych Scand, 1994, vol. 67, pp. 361-370.
[22] O. A. Abiodun, "A validity study of the Hospital Anxiety and Depression Scale in general hospital units and a community sample in Nigeria," Br J Psychiatry, 1994, vol. 165, pp. 169-172.
[23] D. Goldberg, "Use of the General Health Questionnaire in clinical work," Br Med J, 1986, vol. 293, pp. 1188-1189.
[24] M. H.Banks, "Validation of the General Health Questionnaire in a young community sample," Psychological Medicine, 1983, vol.13, pp. 349-353.
[25] A. Lobo, M. J. Pérez-Echeverría, and J. Artal, "Validation of the scaled version of the General Health Questionnaire (GHQ28) in a Spanish population," Psychological Medicine, 1986, vol. 16, pp. 135-140.
[26] K. W. Bridges, and D. Goldberg, "The validation of the GHQ28 and the use of the MMSE in neurological in-patients," Br J Psychiatry, 1986, vol. 148, pp. 548-553.
[27] O. Walusinski, "How yawning switches the default-mode network to the attentional network by activating the cerebrospinal fluid flow," Clinical Anatomy, 2014, vol. 27, pp. 201-209.
[28] S. B. N. Thompson, "Dementia and memory. A handbook for students and professionals," Aldershot: Ashgate, 2006, pp. 117-118.
[29] G. Abbey, S. B. N. Thompson, T. Hickish, and D. Heathcote, "A meta-analysis of prevalence rates and moderating factors for cancer-related post-traumatic stress disorder," Psycho-Oncology, 2014, vol. 23, pp. 1-12, doi: 10.1002/pon.3654.

Simon B. N. Thompson BA (Honours) Psychology, University of Portsmouth, UK, 1982; PGD Information Systems, University of Portsmouth, UK, 1984; PhD Stroke Prognosis, University of Portsmouth, UK, 1988; MPhil clinical psychology, University of Edinburgh, Scotland, 1991; PGC Learning & Teaching in Higher Education, University of Portsmouth, UK, 2006; PhD Dementia Diagnosis, Bournemouth University, UK, 2010; PGC Research Degree Supervision, Bournemouth University, UK, 2010.

He is Associate Professor of Clinical Psychology & Neuropsychology and Clinical Lead, Bournemouth University, UK. He is also Visiting Clinical Researcher, Université Paris Ouest Nanterre La Défense, Amiens University Hospital, and University of Picardy Jules Verne, France. He has been Consultant Clinical Neuropsychologist at several National Health Service provisions and has published extensively:

- S. B. N. Thompson, "Yawning, fatigue and cortisol: expanding the Thompson Cortisol Hypothesis," *Medical Hypotheses,* 2014, doi:10.1016/j.mehy.2014.08.009.
- S. B. N. Thompson, and P. Bishop, "Born to yawn? Understanding yawning as a warning of the rise in cortisol levels: randomized trial,"

Interactive J Medical Research, vol. 1, no. 5, pp. 1-9, 2012, doi: 10.2196/ijmr.2241.

- S. B. N. Thompson, "Born to yawn? Cortisol linked to yawning: a new hypothesis," *Medical Hypotheses,* vol. 77, pp. 861-862, 2011.
- S. B. N. Thompson, "*Psychology of trauma: clinical reviews, case histories, research,"* Portsmouth, Hampshire, UK: Blackwell-Harvard-Academic, 2013.
- S. B. N. Thompson, "*Dementia and memory: a handbook for students and professionals,"* Aldershot, Hampshire, UK: Ashgate, 2006.
- S. B. N. Thompson, "*Neuroanatomy - a beginner's guide. For medical, clinical and health professional students,"* Saarbrüken, Saarland, Germany, Lambert Academic, 2012.

Associate Professor Dr Thompson is a Member of the UK Register of Expert Witnesses for the Royal Courts of Justice, London, UK; Practitioner Full Member of the British Neuropsychological Society; Member of L'Association pour la Recherche sur les Bâillement; Member of the New York Academy of Sciences; Fellow of the Royal Society for the encouragement of Arts, Manufactures & Commerce.