# Yawning and cortisol levels in multiple sclerosis: potential new diagnostic tool

Yawning and cortisol diagnostic

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# Abstract

Yawning is a significant behavioural response and, together with cortisol, is potentially a new diagnostic marker of neurological diseases. Evidence of an association between yawning and cortisol was found which supports the Thompson Cortisol Hypothesis and thermoregulation hypotheses, indication that brain cooling occurs when yawning. 117 volunteers aged 18-69 years were randomly allocated to experimentally controlled conditions to provoke yawning. Thirty-three had been diagnosed with multiple sclerosis. Saliva cortisol samples were collected before and after yawning or after stimuli presentation in the absence of yawning. Hospital Anxiety and Depression Scale, General Health Questionnaire, demographic and health details were collected. Comparisons were made of yawners and non-yawners, healthy volunteers and MS participants. Exclusion criteria: chronic fatigue, diabetes, fibromyalgia, heart condition, high blood pressure, hormone replacement therapy, stroke. Yawners had significant differences between saliva cortisol sample 1 and 2 among healthy participants ($p<.007$) and MS participants ($p<.003$). There was significant difference between the healthy versus MS non-yawners ($P<.042$) but not between yawners ($p<.862$). These results support the Thompson Cortisol Hypothesis suggesting that cortisol levels are elevated during yawning. Furthermore, this evidence suggests cortisol levels in the MS participants (non-yawners) are significantly different to those of healthy participants. Changes in cortisol levels may be similar in healthy and MS participants but when associated with observations of excessive yawning may become a new diagnostic tool in the early diagnosis of neurological symptoms.


# Introduction

The first evidence-based report of cortisol level rises in multiple sclerosis (MS) together with observed yawning is presented as a potential new diagnostic indicator of signs associated with the onset of MS.

MS is a chronic debilitating condition that is progressive and affects the fatty tissue sheath surrounding nerves. Incomplete innervation due to loss of the myelin sheath is considered to be responsible for uncoordinated movements (1). Brain temperature fluctuations are seen in people with MS together with symptoms of fatigue and especially when carrying out mentally or physically demanding tasks.

These are also associated with excessive yawning (2-3). Yet the cause of fatigue in MS is not fully understood.

Attempts to clarify brain recruitment during fatigue in MS has revealed involvement of the dorsolateral prefrontal cortex, , inferior parietal cortex, anterior cingulate cortex and the thalamus (4).

Fatigue in MS has been investigated using variations in inducing fatigue together with MRI scans to determine functional areas of brain activation. For example, Thompson *et al.* (5) discovered that cortisol levels were found to be higher during mental versus motor (physical) tasks. Recruitment of brainstem and hypothalamus regions, important in cortisol activity, was affected differently (Fig 1).

**Fig 1. Brain scans of hypothalamus and brainstem activity averaged across participants (5)**

Hypothalamus Brainstem

At low cortisol levels, mental task participants had less activity in the hypothalamus than their physical task counterparts (Fig 2). When cortisol levels were higher, wider spread recruitment of both the hypothalamus and brainstem was observed in the mental task participants, and for the physical task participants, the spread was at comparative low levels of cortisol.

**Fig 2. Brain scans of hypothalamus activity in "Mental" *versus* and "Physical" task participant at lowest level of cortisol (5)**

Mental Physical

The authors concluded that cortisol is implicated in these brain regions and that brain region recruitment is likely to be dependent upon factors such as perception of stress in the task. It is likely that the mental tasks were perceived more stressful than the physical tasks and therefore required higher cortisol levels to promote wider spread brain region activity.

The hormone cortisol has been associated with yawning and fatigue and described in the Thompson Cortisol Hypothesis (6). Threshold level rises of cortisol appear to trigger the yawn which is proposed to be part of a complex mechanism for lowering brain temperature (7). Brain temperature rises dramatically in people with MS (8) and it has been proposed that cortisol is able to regulate brain temperature because of its role within the hypothalamus-pituitary-adrenal (HPA-axis) (9), even in the foetus and in young babies (10).

Secretion of cortisol is controlled by three inter-communicating regions of the brain: hypothalamus, pituitary and adrenal glands. During low levels of cortisol in the blood, the hypothalamus releases corticotrophin-releasing hormone causing the pituitary gland to secrete adrenocorticotropic hormone into the bloodstream. High levels of adrenocorticotropic hormone are detected in the adrenal glands which stimulate the secretion of cortisol, causing blood levels of cortisol to rise. As the cortisol levels rise, they start to block the release of corticotrophin-releasing hormone from the hypothalamus and adrenocorticotropic hormone from the pituitary (7). As a result, the adrenocorticotropic hormone levels start to fall resulting in a fall in cortisol levels. This mechanism is known as a negative feedback loop.

Cortisol has been noted during exposure to stressful events and may even be modulated by contagious yawning (11). Yawning has also been observed to reduce facial temperature in rats (12) but substantive evidence of brain cooling in humans has been elusive to date.

Thompson (13-14) presented the Thompson Cortisol Hypothesis which is the first evidence-based report linking cortisol with yawning in healthy participants and demonstrates that cortisol rises when we yawn. Other researchers have postulated that yawning may promote increased clearing of central nervous system-derived fluid into the central venous structures (15-16).

Produced by the zona fasciculate of the adrenal cortex within the adrenal gland (17), it is suggested that the rise in cortisol level triggers the yawning response in healthy people. When we become fatigued either mentally or physically, and in particular in MS, yawning becomes important for regulating cortisol. We believe that cortisol also affects the hypothalamus temperature regulation within the HPA-axis and may signal brain cooling particularly when elevation in brain temperature is common such as in MS.

In addition to the hypothalamus, evidence of the effects of cortisol has been found in the brainstem and motor cortex (18). Hasan *et al.* (19) found sophisticated motor receptors in mice. The efficiency of cortisol-specific receptors and the communication between sensory and primary motor neurons is enhanced during motor learning.

It is postulated that the link between the established sites within the HPA-axis and those of the motor cortex and brainstem may be less intimately linked by neural networks but instead by hormone system. This would help in our understanding of why brainstem lesion stroke patients may raise their affected arm during yawning where the yawning response is possibly triggered by threshold levels of cortisol. Cortisol-specific receptors on the motor end plates would give rise to muscle movements in the arm.

In stroke patients, cortisol levels may be inadequately detected and due to incomplete innervation, the brainstem may fail to act on changes in cortisol levels to prevent arm movement resulting in the observed *parakinesia brachialis oscitans* seen in brainstem ischaemic patients (20-21). Whilst it is accepted that hormones work within a system that comprises other hormones and complex neural circuitry, it is often through direct observation that pathways can be understood. It is hoped that such observation of people with MS (and yawning and cortisol) might provide us with an increased understanding of why brain temperature fluctuates with fatigue. This might have greater implications for people with a wide range of neurological disorders and cortisol-insufficiency syndromes such as Cushing's disease (22). It may also be a potential diagnostic tool for detecting the signs of MS in the future.

# Materials and methods

## Participants

One-hundred-and-seventeen volunteers were recruited to the study. Eighty-four healthy volunteers (30 male, 54 female) aged between 18-69 years recruited from students and the research volunteer pool at Bournemouth University using the computerised recruitment system (SONA), and Facebook. Two of these participants were subsequently excluded from data analyses due to the analytical laboratory receiving two sets of dry saliva samples.

A further 33 volunteers (12 male, 21 female) who had a diagnosis of multiple sclerosis were recruited from attendees of the Multiple Sclerosis Society

Bournemouth Branch and were aged between 34-70 years). All participants were properly consented according to code of conduct and research guidelines. Exclusion criteria was: chronic fatigue, congestive heart disorder, diabetes, fibromyalgia, heart condition, high blood pressure, history of stress, psychiatric disorder, hormone replacement therapy, renal problems, respiratory disorder, stroke, and multiple sclerosis (except for the multiple sclerosis participants).

## Stimuli and procedure

As described in detail previously (23), all participants were exposed to three conditions intended to provoke a yawning response – photos of people yawning; short video of person yawning; and reading to self a 'boring' lengthy text about yawning. Comparisons were made with those exposed to the same conditions but who did not yawn.

Saliva samples were collected before and again after the yawning response. If there was no yawning response, then a second saliva sample was taken after the last stimulus was presented. Cortisol levels are easily detected in saliva and are a less intrusive collection method than intravenous cortisol collection. Presence of cortisol in saliva is highly correlated with blood assay (24-26) and it is also much cheaper to analyse in the laboratory.

The Hospital Anxiety and Depression Scale (HADS) (27), General Health Questionnaire (GHQ28) (28-29) and demographic and health details were collected from all participants.

Between- and within-participants comparisons were made using t-tests in the SPSS package version 23. This enabled a comparison to be made between rest status and yawning episodes (where yawning occurred); yawning and non-yawning participants; and healthy and multiple sclerosis participants.

## Ethics

Bournemouth University Research & Ethics approval granted: DEC/PS03.10.11; 05.10.11; 01.03.12; 18.10.12; DEC/JC28.01.13; FST/KA06.09.13; FST/SB26.09.16; Multiple Sclerosis Society: MSSBB/RS11.01.17. Protective measures were put in place for collection and analysis of saliva samples; for example, disposable gloves were worn during collection and analysis. All data was coded for anonymity, confidentiality and privacy held in a secure location. The right of participants to withdraw from the study at any time without consequences was upheld and all saliva cortisol samples were destroyed following analysis.

# Results

The mean age of the healthy participants was 28 years compared with 57 years for the MS participants. There were no significant differences between groups in terms of HADS anxiety and depression scores and GHQ28 scores. Normative data for saliva cortisol is known, and lies within the following ranges: (i) Morning collection is 3.7 – 9.5 nanograms (one billionth of a gram or $10^{-9}$) per millilitre of saliva; (ii) Noon collection is 1.2 – 3.0 nanograms per millilitre; (iii) Evening collection is 0.6 – 1.9 nanograms per millilitre.

For the healthy participants, there was no significant difference (p<.106) between cortisol sample 1 and 2 for the non-yawners. For the participants with MS, there was also no significant difference (p<.183) for the non-yawners (Tables 1 and 2).

**Table 1. (Descriptive data) Healthy Group Non-Yawners: Cortisol Sample 1 vs Cortisol Sample 2**

**Paired Samples Statistics**

| | | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|---|
| Control | Pair 1 | Saliva sample 1 | 2.1814 | 43 | 1.67264 | .25508 |
| | | Saliva sample 2 | 2.4930 | 43 | 2.08423 | .31784 |
| MS | Pair 1 | Saliva sample 1 | 10.3500 | 18 | 23.84287 | 5.61982 |
| | | Saliva sample 2 | 7.0000 | 18 | 13.62580 | 3.21163 |

**Table 2. (Test data) Healthy Group Non-Yawners: Cortisol Sample 1 vs Cortisol Sample 2**

**Paired Samples Test**

| | | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference Lower | Upper | | | |
| Control | Pair 1 | Saliva sample 1 - Saliva sample 2 | -.31163 | 1.23755 | .18872 | -.69249 | .06923 | -1.651 | 42 | .106 |
| MS | Pair 1 | Saliva sample 1 - Saliva sample 2 | 3.35000 | 10.25006 | 2.41596 | -1.74724 | 8.44724 | 1.387 | 17 | .183 |

However, significant difference (p<.007) was found between cortisol sample 1 and 2 in the healthy participants; and in the MS participants, there was a greater significant difference of p<.003 (Tables 3 and 4).

**Table 3. (Descriptive data) MS Yawners: Cortisol Sample 1 vs Cortisol Sample 2**

**Paired Samples Statistics**

| | | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|---|
| Control | Pair 1 | Saliva sample 1 | 2.6341 | 41 | 1.99231 | .31115 |
| | | Saliva sample 2 | 3.1268 | 41 | 2.26550 | .35381 |
| MS | Pair 1 | Saliva sample 1 | 2.5867 | 15 | 1.11859 | .28882 |
| | | Saliva sample 2 | 3.1000 | 15 | 1.03026 | .26601 |

**Table 4. (Test data) MS Yawners: Cortisol Sample 1 vs Cortisol Sample 2**

**Paired Samples Test**

| | | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | | Lower | Upper | | | |
| Control | Pair 1 | Saliva sample 1 - Saliva sample 2 | -.49268 | 1.10914 | .17322 | -.84277 | -.14259 | -2.844 | 40 | .007 |
| MS | Pair 1 | Saliva sample 1 - Saliva sample 2 | -.51333 | .56299 | .14536 | -.82510 | -.20156 | -3.531 | 14 | .003 |

Comparison between healthy participants and MS participants revealed significant difference ($p<.042$) between their second cortisol sample (Table 5) suggesting that the level of cortisol in those with MS is significantly different. However, in the yawners, there was no significant difference ($p<.862$) between the two groups (Table 6). This may indicate that changes in cortisol levels are similar in both groups but actual levels of cortisol are significantly different and therefore worthy of further investigation.

**Table 5. Cortisol Sample 2 Non-Yawners: Healthy Group vs MS**

**Independent Samples Test**

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 95% Confidence Interval of the Difference | |
| | | F | Sig. | T | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | Lower | Upper |
| Saliva_2 | Equal variances assumed | 7.273 | .009 | -2.083 | 58 | .042 | -4.44762 | 2.13538 | -8.72205 | -.17319 |
| | Equal variances not assumed | | | -1.378 | 17.338 | .186 | -4.44762 | 3.22751 | -11.24697 | 2.35174 |

**Table 6. Cortisol Sample 2 Yawners: Healthy Group vs MS**

**Independent Samples Test**

| | | Levene's Test for Equality of Variances | | t-test for Equality of Means | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | 95% Confidence Interval of the Difference | |
| | | F | Sig. | T | df | Sig. (2-tailed) | Mean Difference | Std. Error Difference | Lower | Upper |
| Saliva_2 | Equal variances assumed | 4.979 | .030 | .174 | 53 | .862 | .10500 | .60287 | -1.10420 | 1.31420 |
| | Equal variances not assumed | | | .237 | 50.553 | .813 | .10500 | .44265 | -.78385 | .99385 |

# Discussion

There are several interesting findings of this study. Of those participants who did not yawn, the cortisol samples at rest and then at the end of stimuli presentations was not significantly different within each group of participants. This is perhaps not surprising since it is known that cortisol levels rise during episodes of stress, whether perceived to be mentally fatiguing or if they are physically demanding. It may be that for those who did not yawn, the tasks were not demanding in mental or physical terms.

It is interesting that those participants with MS who did not yawn also had no significant difference in their cortisol levels which tends to suggest that, in the absence of yawning, cortisol levels in these participants did not significantly change by the end of the testing session.

Perhaps of more scientific interest is the finding that participants who yawned had elevated cortisol levels. Previous studies by the research team have found that in healthy participants who yawn their cortisol levels rise significantly (10,23). People who have MS often become fatigued and yawning are often observed as a common symptom of MS (8). Therefore, it is of note that in those MS participants who did yawn during the stimuli presentations, their cortisol levels significantly raised in levels greater than their resting levels. It is also of note that not all of the participants yawned; this may be because their symptoms of MS were not identical to those who did yawn. Alternatively, it may be due to threshold levels of cortisol not being reached, as compared with healthy participants who did not yawn.

It is proposed that people with threshold levels of cortisol yawn, whether they have MS or not; however, changes in cortisol levels after yawning were not significantly different between the healthy and MS participants although there was a significant difference between the groups in their second saliva sample for the non-yawners. This is interesting because significant difference in levels between healthy participants and those with MS might suggest that cortisol levels are important in MS; and when associated with excessive yawning, these levels may signal MS symptoms. It will be interesting to see if the effects of these cortisol levels are directly correlated to lowering brain temperature since yawning seems to lower temperature.

These findings tend to support the Thompson Cortisol Hypothesis (1,6) that proposes yawning occurs when threshold levels of cortisol are reached in order to reduce brain temperature. This is shown in both the healthy and MS participants. Communication with the motor cortex via cortisol-specific receptors may also explain how involuntary movement of the arm in brainstem ischaemic patients can occur partly due to incomplete innervation and irregulation of cortisol within the HPA-axis which has been extensively discussed elsewhere (1,20,21,30).

The picture in neurological and biological diseases is complex because they present with a range of symptoms and severity. However, cortisol features in many disorders as well as the body’s natural stress hormone. Hence it is suggested that it may provide an important key to our understanding of the way many neurological disorders are linked. It may also provide scientists and practitioners in the near future with a potential identifier or even diagnostic indicator of underlying and untoward neurological disease systems including MS.

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