

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

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3 Yawning and cortisol diagnostic

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29 **Abstract**

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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.

55 **Introduction**

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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.

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

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

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

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

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79 Hypothalamus Brainstem

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

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

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88 Mental Physical

89 The authors concluded that cortisol is implicated in these brain regions and
 90 that brain region recruitment is likely to be dependent upon factors such as
 91 perception of stress in the task. It is likely that the mental tasks were perceived more

92 stressful than the physical tasks and therefore required higher cortisol levels to
93 promote wider spread brain region activity.

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

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

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

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

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

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

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

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

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152 **Materials and methods**

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154 **Participants**

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

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

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

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171 **Stimuli and procedure**

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

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

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

187 Between- and within-participants comparisons were made using t-tests in the
188 SPSS package version 23. This enabled a comparison to be made between rest

189 status and yawning episodes (where yawning occurred); yawning and non-yawning
190 participants; and healthy and multiple sclerosis participants.

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192 **Ethics**

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

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203 **Results**

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

212 For the healthy participants, there was no significant difference ($p < .106$)
 213 between cortisol sample 1 and 2 for the non-yawners. For the participants with MS,
 214 there was also no significant difference ($p < .183$) for the non-yawners (Tables 1 and
 215 2).

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

			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

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

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

225 **Table 3. (Descriptive data) MS Yawners: Cortisol Sample 1 vs Cortisol Sample**
 226 **2**
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			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

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

			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

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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.

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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						
		F	Sig.	T	df	Sig. (2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the 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

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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						
		F	Sig.	T	df	Sig. (2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the 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

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255 Discussion

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257 There are several interesting findings of this study. Of those participants who
258 did not yawn, the cortisol samples at rest and then at the end of stimuli presentations
259 was not significantly different within each group of participants. This is perhaps not

260 surprising since it is known that cortisol levels rise during episodes of stress,
261 whether perceived to be mentally fatiguing or if they are physically demanding. It
262 may be that for those who did not yawn, the tasks were not demanding in mental or
263 physical terms.

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

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

278 It is proposed that people with threshold levels of cortisol yawn, whether they
279 have MS or not; however, changes in cortisol levels after yawning were not
280 significantly different between the healthy and MS participants although there was a
281 significant difference between the groups in their second saliva sample for the non-
282 yawners. This is interesting because significant difference in levels between healthy
283 participants and those with MS might suggest that cortisol levels are important in
284 MS; and when associated with excessive yawning, these levels may signal MS

285 symptoms. It will be interesting to see if the effects of these cortisol levels are
286 directly correlated to lowering brain temperature since yawning seems to lower
287 temperature.

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

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

302

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309

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