Can stroke localisation be used to map out the neural network for yawning behaviour?

Olivier Walusinski

What are the neuroanatomical structures involved in repetitive yawning during stroke?

Since the 19th century, cases of pathological yawning have occasionally been published in medical journals. In this issue of *J Neurol Neurosurg Psychiatry*, Singer *et al*[1] present the first study to focus specifically on yawning during acute stroke affecting the middle cerebral artery territory ***(see page 1253)***.

None of seven patients suffering from abnormal repetitive yawning had diencephalic lesions. Classically, yawning is thought to originate in archaic brain structures common to all vertebrates. It appears to be a powerful muscular stretch which recruits specific control systems, particularly the paraventricular nucleus of the hypothalamus, locus coeruleus and reticular activating system; these structures explain its ability to increase arousal. A persistent vestige of the past, yawning has survived evolution with little variation.[2] Singer *et al*[1] suggest that neocortical brain areas have an inhibitory effect on the paraventricular nucleus of the hypothalamus, and that in certain middle cerebral artery strokes this region is liberated, provoking repetitive yawning. This hypothesis merits discussion.

According to Lapresle,[3] palatal myoclonus is the human homologue of a primitive respiratory reflex in gill breathing vertebrates, submerged but not lost, reappearing when the inhibitory system is damaged by lesions to the dentato-olivary pathway.

We coined the term "parakinesia brachialis oscitans"[4] to describe cases of hemiplegia where the onset of yawning coincides with involuntary raising of the paralysed arm. We argued that a lesion in the internal capsule affecting an inhibitory pathway liberates certain subcortical structures that coordinate the massive inspiration of yawning and the motor control associated with quadrupedal locomotion.

In these examples, loss of cortical inhibition following stroke releases a hidden function, phylogenetically more primitive. Singer *et al*[1] do not provide evidence of such an event.

Face scratching, nose–face rubbing, yawning and sighs are automatisms frequently reported after epileptic seizures. These behaviours are also considered a characteristic pattern in healthy subjects on waking. Movement speed and repetition are the factors that vary, based on whether the context is physiological (sleep, arousal) or pathological (epileptic seizure, stroke). These behaviours are related to the brainstem and diencephalic activation that occurs when the cortex is disconnected from these areas (where the "central pattern generators" are located) by an epileptic discharge or a stroke.[5]

Adaptive behaviours depend on interactions between neural networks at various levels, requiring continuous mutual feedback. Yawning is an exterior manifestation of the tonic stimulation of the cortex by subcortical structures, particularly when the brainstem does not receive appropriate feedback from the cortex.

I agree with the conclusion reached by Singer *et al*[1]: further studies are necessary to determine the exact neuroanatomical structures involved in repetitive yawning during stroke and the pathophysiological role of this behaviour.

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Correspondence to: Dr Olivier Walusinski, 20 rue de Chartres, Brou 28160, France; walusinski@baillement.com

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SHORT REPORT

Yawning in acute anterior circulation stroke

Oliver C Singer, Marek C Humpich, Heiner Lanfermann, Tobias Neumann-Haefelin

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Pathological yawning can be a clinical sign in disorders affecting the brainstem. Here we describe seven patients with pathological yawning caused by acute middle cerebral artery stroke, indicating that pathological yawning also occurs in supratentorial stroke. We hypothesise that excessive yawning is a consequence of lesions in cortical or subcortical areas, which physiologically control diencephalic yawning centres.

Pathological yawning has been described in various neurological disorders, including migraine, epilepsy, basal ganglia disorders, multiple sclerosis and brain tumours.[1] In patients with focal brain lesions, infratentorial lesions dominated and pathological yawning was linked to a disturbance of the ascendant activatory reticular system. While various neurotransmitters (dopamine, acetylcholine, serotonin, gamma-aminobutyric acid) or hormones (oxytocin, adrenocorticotrophic hormone) as well as nitric oxide have proved to modulate yawning, the exact anatomical structures involved in yawning are still not well characterised. However, there is experimental evidence that the hypothalamus (especially the paraventricular nucleus (PVN)) plays a pivotal role in the elicitation of yawning. A current hypothesis claims that activation of oxytocinergic neurons of the PVN projecting to extrahypothalamic regions, including the hippocampus, pons and the medulla oblongata, elicits yawning.[2 3] Recently, the involvement of anatomical structures of the lower brainstem in human yawning has been highlighted by a case report of two patients presenting with pathological yawning caused by acute brainstem ischaemia.[4] The authors speculated that the brain lesions, located at the pontomesencephalic junction, liberated the control of a putative yawning centre caudal to the described lesions. However, little is known about the involvement of cortical–subcortical brain areas in the control of yawning. We hypothesised that if neocortical structures are involved in the control of spontaneous yawning, it is likely that pathological yawning also occurs in acute supratentorial stroke.

METHODS

During an observation period of 6 months, patients referred to our neurological department with a clinical suspicion of acute middle cerebral artery (MCA) stroke (symptom onset <12 h) were observed immediately after arrival (ie, when taking the patient's history or shortly thereafter) for abnormal yawning frequency. This was arbitrarily defined as more than 3 yawns in 15 min. Healthy individuals yawn about 20 times per day, although the frequency differs substantially according to age, circadian rhythms and between individuals (range 0–28 per day).[5 6] However, more than 3 yawns per 15 min appears to be a reasonable cut-off between "physiological" and "excessive" yawning. Restriction to patients with a defined symptom onset shorter than 12 h prior to admission was chosen to minimise secondary reasons for an increased yawning frequency, such as tiredness associated with the sudden disturbance of the daily routine or space occupying cerebral oedema compromising blood flow in vascular territories other than the primarily affected. Basic clinical data, the time point of examination, as well as the National Institutes of Health Stroke Scale (NIHSS) scores at admission and modified Rankin Scale scores at discharge were assessed. All patients underwent CT immediately after arrival. Values are given as mean (SD) unless otherwise stated.

RESULTS

During the observation period, we registered seven acute stroke patients (three males, mean age 73 (12) years, time interval between symptom onset and examination 5 (3.6) h) with an abnormal high yawning frequency (mean 7.3 (5.3) in 15 min) (table 1). Five patients arrived at the hospital during the day (between 9.40am and 5.00pm), while two patients were examined in the evening (7.00pm to 9.20pm). Six patients experienced ischaemic and one patient a haemorrhagic stroke (table 1). Five patients had left hemispheric and two patients right hemispheric strokes. Mean NIHSS score at admission was 17 (SD 4). Four patients had a mild disturbance of consciousness on arrival (patients not being alert but arousable by minimal stimulation, scored 1 on the "LOC" item of the NIHSS). There was no association between the level of consciousness and yawning frequency. All patients presented with signs of cortical dysfunction (aphasia n = 5, neglect n = 3, gaze palsy n = 6). Outcome at hospital discharge was unfavourable in 6 of 7 patients (modified Rankin Scale 5 or 6).

Computed tomography revealed signs of cerebral infarction of more than one-third of the MCA territory in five of six patients. No patient had CT signs of additional infarctions in areas other than the MCA territory. Only one patient (No 2) had CT morphological evidence of relevant space occupying cerebral oedema at presentation.

DISCUSSION

The observation of pathological yawning in seven patients with acute anterior circulation stroke provides strong evidence that excessive yawning can be a sign of supratentorial lesions affecting the MCA territory.

The interpretation of this finding in the light of the known neuroanatomy of yawning is not straightforward. Both the hypothalamus and the brainstem, which include regions critical for yawning, are not supplied by the MCA. Currently, the PVN in particular is believed to be the dominant diencephalic relay station, which sends oxytocinergic neurons to brainstem structures involved in yawning. One possible explanation for our finding of pathological yawning in supratentorial stroke could be that the lesions release the PVN from (presumably existing) neocortical control mechanisms, leading to an increase in the activity of the PVN. Whether this phenomenon is caused by a sudden reduction in an inhibitory input from cortical structures resulting in disinhibition of the PVN or by an increase in excitatory input (ie, via anoxic depolarisation of penumbral tissue) remains speculative.

Abbreviations: BA, Brodman area; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PVN, paraventricular nucleus

Table 1 Patient characteristics and outcome

Patient No	Age (y)/ Sex	Hemisphere	Ischaemic/ haemorrhagic	Initial NIHSS	mRS at discharge	Cortical signs	CT findings
1	68/M	Left	Ischaemic	18	6	Forced gaze palsy, severe aphasia	1–2/3 MCA, frontal, insular central
2	69/F	Left	Ischaemic	20	5	Forced gaze palsy, severe aphasia	1–2/3 MCA, frontal, insular
3	83/F	Right	Haemorrhagic	19	6	Forced gaze palsy, multimodal neglect	1/3 MCA, frontal, precentral
4	69/M	Right	Ischaemic	8	5	Mild gaze palsy, unimodal neglect	1–2/3 MCA, frontal, temporal, parietal
5	82/M	Left	Ischaemic	16	2	Severe aphasia	1/3 MCA, frontal
6	51/F	Left	Ischaemic	22	5	Mild gaze palsy, severe aphasia, unimodal neglect	>2/3 MCA, frontal, temporal, parietal
7	86/F	Left	Ischaemic	18	6	Forced gaze palsy, severe aphasia	>2/3 MCA, frontal, temporal, parietal

MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Because of the small sample size and often large lesions of our patients, we did not attempt an exact topographic lesion analysis. However, there is little doubt that circumscribed neocortical dysfunction can lead to excessive yawning, as several case reports on yawning after epileptic seizures (predominantly temporal lobe seizures) confirm.[7 8] Of further interest is a case report of a woman experiencing excessive (spontaneous) yawning months prior to the development of a bulbar/pseudobulbar palsy due to amyotrophic lateral sclerosis.[9] The author speculated that her pathological yawning was caused by dysfunction of the upper motor neurons loosing their inhibitory influence on the brainstem and lower motor neurons.

There is evidence from functional MRI studies that neocortical areas are involved in the well known phenomenon of contagious (visually mediated) yawning: Platek *et al*[10] describe substantial activations in the posterior cingulate cortex (Brodman area (BA) 31) and precuneus (BA 23) bilaterally as well as in the thalamus and parahippocampal gyrus (BA 30) of both hemispheres. In addition, Schürmann *et al*[11] found significant bilateral activation of the anterior part of the superior temporal sulcus and in the posterior part of the right superior temporal sulcus, being involved in the visual processing of observed yawning. More importantly, they found a negative association between the subjective yawning susceptibility and the BOLD response in the left periamygdalar region, an area mostly supplied from the anterior choroidal artery.[12] Given the known tight hippocampal–hypothalamic neuroanatomical connections, the fact that five of our patients had left hemispheric strokes, partially involving temporal structures, and case reports on yawning after temporal lobe seizures, it is tempting to speculate that dysfunction of the hippocampal/periamygdalar structures may be linked to excessive yawning. However, functional MRI data refer to the specific phenomenon of visually mediated contagious yawning; thus their relevance for spontaneous yawning remains speculative.

Our pilot study has several shortcomings: firstly, the cut-off for excessive yawning (≥3/15 min) was somewhat arbitrary as healthy individuals may also yawn in clusters of similar frequency. However, we believe that frequent yawning in the setting of hospital admission and physical examination is inappropriate, especially as the majority of patients arrived during the day. Secondly, we did not keep a screening log, making estimates on the incidence of excessive yawning in acute stroke impossible. Finally, we did not attempt a qualitative or phenomenological description of the yawns (ie, if appearing solitary or in sequences).

We conclude that pathological yawning can occur in supratentorial stroke. Our observations suggest that neocortical brain areas have a regulatory effect on diencephalic and brainstem yawning centres. Further imaging studies will need to clarify the exact neuroanatomical structures involved in the higher control of (excessive) spontaneous yawning.

Authors' affiliations

Oliver C Singer, Marek C Humpich, Tobias Neumann-Haefelin, Department of Neurology, JW Goethe-University Frankfurt am Main, Frankfurt, Germany
Heiner Lanfermann, Institute for Neuroradiology, JW Goethe-University Frankfurt am Main, Frankfurt, Germany

Competing interests: None.

Correspondence to: Dr Oliver Singer, Department of Neurology, JW Goethe-University Frankfurt am Main, Schleusenweg 2-16, D-60528 Frankfurt/Main, Germany; o.singer@em.uni-frankfurt.de

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