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**Brief Communication** 

# Laughter and the mesial and lateral premotor cortex

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#### Abstract

We report the induction of laughter and smiling by cortical electrical stimulation of the frontal lobe of two patients: an 18-month-old boy with a left frontal cortical lesion extending to the vertex and the central gyrus, and a 35-year-old woman with a lesion in the right supplementary sensorimotor area (SSMA). The subjects underwent presurgical epilepsy evaluation with subdural grid electrodes to determine surgical candidacy. Stimulation of the prefrontal area reproducibly induced laughter. The adult patient reported absence of emotional content. Slowing of speech occurred under stimulation of electrodes in the upper and posterior vicinity. In this patient laughter was elicited in the anterior part of the SSMA. In the child, this response was induced by stimulation of the lateral prefrontal cortex near the midline. We conclude that the anterior portion of the SSMA/lateral premotor cortex is involved in generating the motor pattern of laughter. © 2006 Elsevier Inc. All rights reserved.

Keywords: Electrical stimulation; Laughter; Gelastic epilepsy

## 1. Introduction

Laughter and smiling have been reported as ictal symptoms in patients with epilepsy and as inappropriate signs of affect in neurological disease [1]. Cortical electric stimulation has so far demonstrated a reproducible site responsible for the generation of laughter in only a very limited number of subjects, none of whom had been suffering from lesion-associated focal epilepsy, as will be pointed out in Section 4. We report the induction of laughter and smiling by cortical electrical stimulation in the frontal lobe in two patients.

## 2. Subjects and methods

Subject 1 was an ambidextrous (as documented by self-declaration) woman, aged 35, with a lesion in the right supplementary sensorimotor area (SSMA). She experienced tonic seizures associated with preserved consciousness and complex involuntary movements of the right hand (alien hand), preceded by an ascending somatosensory aura in the left hand. Surface EEG monitoring demonstrated interictal epileptiform potentials and seizure patterns over the vertex.

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Subject 2 was an 18-month-old boy with a left frontal cortical lesion extending to the vertex and posterior to the motor area. He experienced hypomotor and tonic seizures. Surface EEG monitoring demonstrated intermittent slowing, interictal epileptiform potentials, and seizure patterns over the left frontal lobe, the last with rapid generalization.

Histology in both cases was classified as tuberal cortical dysplasia. Lesions were solitary, and there were no other signs indicating the presence of clinical tuberous sclerosis (TS). Neither patient had skin manifestations or other features of TS. The adult patient later underwent genetic testing for TSC1 and TSC2 and was reported to be negative for both. The boy had been in our care several years earlier, and nothing is known about his genetic status with respect to TS.

Both subjects remained seizure-free for at least 2 years after resection without focal neurological deficits. Neither subject ever had gelastic seizures. When they underwent presurgical epilepsy evaluation with subdural grid electrodes to determine surgical candidacy, we applied biphasic, predominantly bipolar electrical stimulation at 0.3 ms, 50 Hz, and 1- to 15-mA levels in both patients while they were undergoing subdural EEG diagnostics for identification of the epileptogenic zone and delineation of the adjacent functionally eloquent cortex.

## 3. Results

In both patients, stimulation of the premotor area induced reproducible laughter (Figs. 1 and 2, hatched electrodes). In the child, this response was induced by stimula-

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Fig. 1. Subject 1, adult. Image of SSMA lesion obtained by sagittal and axial FLAIR on stimulation of the right SSMA. Hatched circle: laughter. Grey circle: slowing of speech.



Fig. 2. Subject 2, child. Stimulation of left lateral premotor cortex. Hatched circle: laughter. Circle with black sector: motor response of right arm/hand to stimulation. Black circle: motor response of face. Black area: frontolateral cortical lesion.

tion of the lateral premotor cortex near the falx cerebri (hatched electrodes). In the adult patient laughter was elicited under an electrode in the cranial anterior part of the SSMA. She reported absence of emotional content: "That is not me!" Slowing of speech occurred during stimulation of electrodes in the upper and posterior vicinity (grey). None of the stimulation tests that caused laughter were associated with afterdischarges.

# 4. Discussion

Of 44 publications on "gelastic epilepsy" listed in Medline since 1985, 35 (including 5 reviews) concerned, predominantly or exclusively, patients with hypothalamic hamartoma. This well-established cause of gelastic epilepsy is, nevertheless, a largely unsuitable condition for studying the generation of laughter, as gelastic seizures in these patients are typically associated with heterogeneous spread of surface EEG seizure patterns [2], which does not allow demonstration of an unequivocal relationship between ictal laughter and a specific brain region. This study [2] demonstrated that temporal and generalized EEG changes were common, and the most common concomitant seizure type (11 of 17 patients) was psychomotor seizures. Noncortical brain structures are obviously involved in the generation of laughter, although for methodological reasons, it is even more difficult to define the role of certain subcortical structures in the generation of laughter. We know exactly the part of the cortex to which the electric current was applied in our cases. We cannot exclude that our paradigm activated other, possibly remote, subcortical brain structures via cortical-subcortical circuits. Tassinari et al. [3], in their review of 60 cases from the literature, concluded that the laughter of patients with hypothalamic hamartoma and frontal lobe seizures usually lacked emotional content, whereas patients with temporal lobe epilepsy usually manifested a sense of mirth. Iwasa et al. [4] described two patients with nonlesional gelastic epilepsy whose gelastic seizures were accompanied by a subjective feeling of mirth; interictal EEG dipoles were calculated in the right or left mediobasal temporal regions in these two patients, whereas in their third patient, with gelastic seizures without a sense of mirth, the dipole sources were localized in the right frontal region corresponding to the anterior cingulate.

The anterior portion of the SSMA/lateral premotor cortex is involved in generating the motor pattern of laughter. Whether other cortical areas are also involved in the generation of laughter is not certain, but there are four other cases in three published studies in the biomedical literature in which laughter could be elicited by cortical electric stimulation. Laughter response was evoked in one patient [5] by stimulation of the left posterior superior frontal gyrus, representing the anterior border of the lateral premotor cortex. In the other three patients [6,7], laughter could be elicited in the temporal lobe by electric stimulation of the left temporobasal region, and all patients experienced some disruption of speech with stimulation of adjacent electrodes. Krack et al. [8] reported the very interesting finding of mirthful laughter induced by stimulation of the subthalamic nucleus (in one patient, right-sided, and in the other, bilateral). In conclusion, laughter can be elicited in at least three areas of the brain: the frontal premotor cortex and the basal cortex of the dominant temporal lobe and the subthalamic nucleus. Of the cortical areas, the temporal site seems to be involved mostly in generating the associated emotional content. Laughter resulting from deep brain stimulation in both reported cases was associated with emotional content, which may be due to activation of corticobasal connections to the adjacent temporal lobe, whereas the motor component of laughter in our adult patient could be generated in the premotor cortex without emotional content and, therefore, probably without temporal involvement. We are aware that because only a very limited number of the patients being stimulated in these areas laugh while the remainder do not, and because the brain lesion may well have altered localization of cerebral functions, these findings must be interpreted with caution.

The striking coincidence that in both cases histology was classified as tuberal cortical dysplasia is interesting, although the significance of this finding cannot be interpreted with the data available and remains subject to further research.

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