

Stimulation-induced ictal vocalisation of left frontal lobe origin

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ABSTRACT – Pure ictal non-speech vocalisation occurs in frontal and temporal lobe epilepsies. Electrical stimulation of supplementary motor areas is reported to evoke vocalisation in selected patients. Here, we report a patient with focal epilepsy of the left anterior insula who had isolated monotonous vocalisation elicited by electrical stimulation of the left superior frontal gyrus. Quantitative analysis of audio signals was performed and compared with a former patient with left frontal lobe epilepsy who had pure ictal vocalisation. Both patients showed a comparable reduction in frequency variation indicating a monotonous voice. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: frontal lobe epilepsy, vocalisation, SEEG, epilepsy surgery, cortical stimulation

Pure ictal non-speech vocalisations have been observed in selected patients with frontal and temporal lobe epilepsies (Janszky *et al.*, 2000; Rego *et al.*, 2006; Bonelli *et al.*, 2007; Horvath *et al.*, 2009). Previously, we reported pure ictal vocalisation in a patient with left frontal lobe epilepsy (FLE) (Rego *et al.*, 2006). In this report, we present another patient with FLE in whom we consistently elicited monotonous vocalisation by electrical stimulation of the white matter of the left superior frontal gyrus.

Case study

A 31-year-old, right-handed female with medically refractory focal

epilepsy of the left anterior insula since the age of 12 was admitted for invasive EEG monitoring with depth electrodes (Patient 1). Despite antiepileptic drug treatment, she continued to have motor seizures mainly during sleep with an average frequency of 2-3 per week. Her past medical history was unremarkable. Family history revealed a brother with pharmacoresistant focal epilepsy who was seizure-free after resective epilepsy surgery. Her neurological examination was normal. Cranial MRI did not reveal any lesions. She underwent non-invasive continuous EEG monitoring to evaluate the option of epilepsy surgery which showed either frontal non-lateralized or left frontal



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seizure onset. Interictal non-invasive EEG revealed no interictal epileptiform discharges. Interictal 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed hypometabolic areas in the left insula as well as in bilateral parietal, temporal, and central regions. Ictal single-photon emission computerized tomography (SPECT) (neulolite 99mTc) showed hyperperfusion in the left inferior temporal and left orbito frontal regions. Diffusion tensor imaging (DTI) demonstrated U-fibre density reduction in the left frontal area (*figure 1A*). Invasive EEG evaluation with stereotactically implanted depth electrodes was performed to localise the seizure onset zone and to outline the eloquent cortex (*figure 1B*). The exact localisation of intracranial electrodes was defined by fusion of 3-dimensional reconstruction post-implantation

computed tomography (CT) scans and preoperative MR images. The invasive evaluation localised the seizure onset in 31 seizures to the left anterior insula (H 2-6) which propagated into the left frontal lobe (D 5-8, F 5-7) within a few seconds. Maximum interictal epileptiform discharges were located mainly in the left anterior insula (H 1-4) and, to a lesser extent, in the left superior (A, C, D) and middle frontal gyrus (F) (*figure 1C*). Extraoperative electrical stimulation mapping (monopolar stimulation was performed with a distant reference electrode overlying non-eloquent cortex). C6-C8: continuous prolongation of a monotonous vowel lasting for the duration of stimulation; D1-D7, C2-C10: tonic reaction of the right arm and shoulder and right foot; G6-G8: speech arrest during a naming task; and H2-H4, F1, C1: cessation of bilateral voluntary movements without loss of awareness (negative motor area).

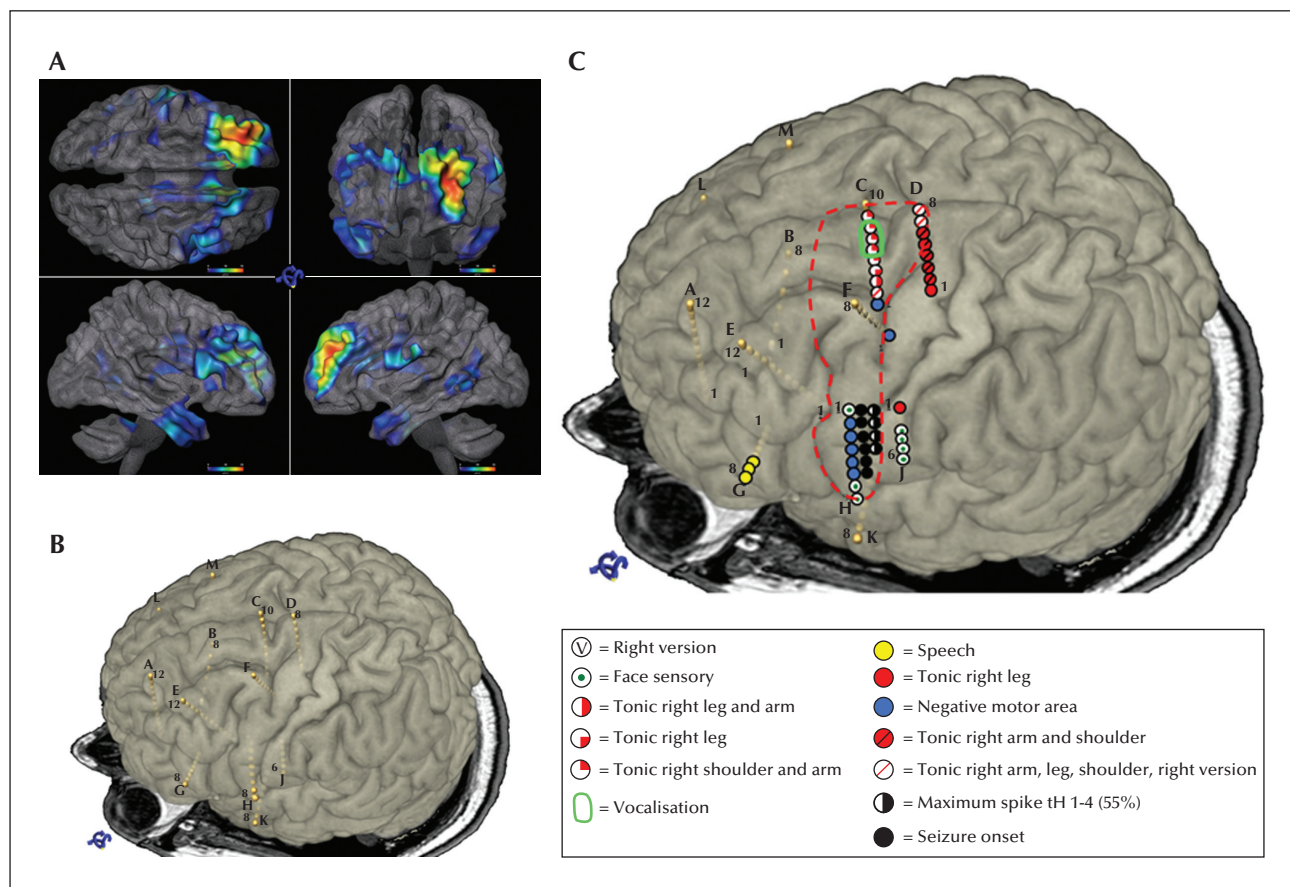


Figure 1. (A) Diffusion tensor imaging (DTI) demonstrates a clear U-fibre density reduction in the left frontal area, illustrated by high signal in the colour scale. (B) Three-dimensional reconstructed brain surface created by coregistration of preoperative MRI and post-implantation CT shows placement of intracranial depth electrodes on the left hemisphere. Electrode 1 represents the innermost contact; A1-A12: left superior frontal gyrus (frontobasal, anterior); B1-B8: left superior frontal gyrus (frontobasal); C1-C10: left superior frontal gyrus (medial); D1-D8: left superior frontal gyrus (posterior); E1-E12: left middle frontal gyrus (anterior); F1-F8: left middle frontal gyrus (posterior); G1-G8: left inferior frontal gyrus; H1-H8: left anterior insula; J1-J6: left posterior insula; K1-K8: left anterior temporal lobe; L1-L11: right superior frontal gyrus (frontobasal); and M1-M12: right middle frontal gyrus. (C) Results of extraoperative electrical stimulation mapping (monopolar stimulation was performed with a distant reference electrode overlying non-eloquent cortex). C6-C8: continuous prolongation of a monotonous vowel extended for the duration of stimulation; D1-D7, C2-C10: tonic reaction of the right arm and shoulder and right foot; G6-G8: speech arrest during a naming task; and H2-H4, F1, C1: cessation of bilateral voluntary movements without loss of awareness (negative motor area).

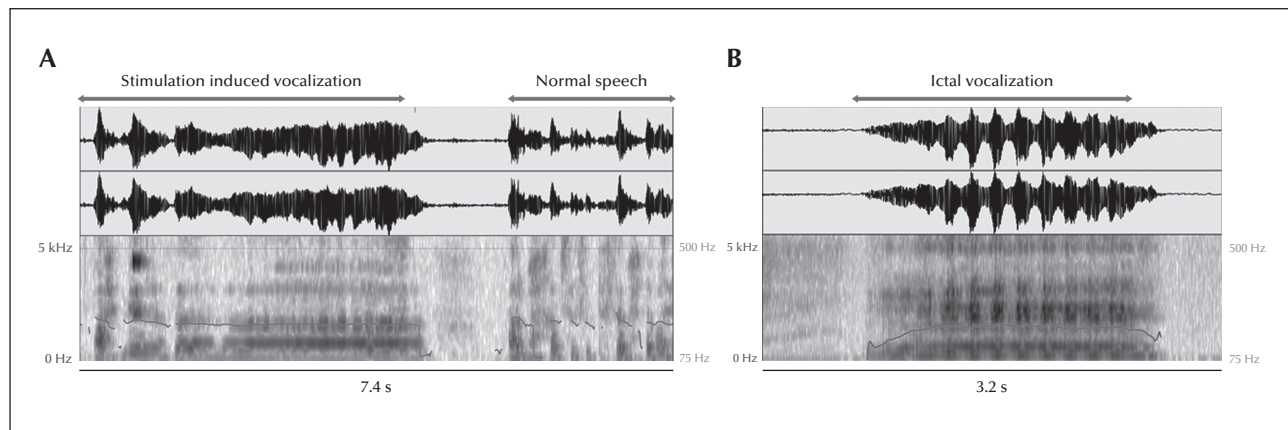


Figure 2. (A) Spectrogram of Patient 1 showing the electrical stimulation-induced vocalisation of the left superior frontal gyrus. The course of formant f_0 (blue line) shows a reduction in frequency variation during stimulation compared to her voice without stimulation. Likewise, the spectrogram of Patient 2 (B) shows a reduced formant f_0 variation of ictal voice. Dark: high energy; light: low energy.

of the head followed the vocalisation. The results of electrical stimulation at all electrodes are illustrated in *figure 1C*. Neurosurgical resection of the left anterior insula and the superior and medial frontal gyrus was planned.

We were puzzled by the similarity of the vocalisation elicited by electrical stimulation between this patient and a former patient who had left FLE with pure ictal monotonous vocalisations reported several years ago (Rego *et al.*, 2006) (Patient 2) (*video sequence 2*). The stimulation-induced vocalisation was not part of the habitual seizures of Patient 1. Quantitative analysis of audio signals was performed in both patients. Quantitative analysis leads to a description of the frequency of peaks of a sound, which are called formants. Audio signals were recorded with Shure MX202 microphones (Shure, Niles, IL, USA), using the uncompressed pulse code modulation format and a bitrate of 64 kbit/s, and saved as waveform files. Quantification of the pitch (f_0), i.e. the fundamental vocalisation frequency in Hertz, was obtained by using the pitch listing tool of the audio-analysis software, Praat (Version 6.0.05, freeware, www.fon.hum.uva.nl/praat/; ©1992-2015 by Paul Boersma and David Weenink, University of Amsterdam, Netherlands [Boersma and Weenink, 2015]). Regarding the audio analysis of Patient 1, the mean fundamental frequency (f_0) of the vowel was higher and showed considerably less frequency variations (expressed as standard deviation of frequency) for the stimulation-elicited voice compared to her voice without stimulation (mean pitch frequency: $213.5 \text{ Hz} \pm 5.3$ vs $207 \text{ Hz} \pm 27.3$, respectively) (*figure 2A*). Regarding the audio analysis of Patient 2, the mean fundamental frequency (f_0) of the vowel, which was produced ictally, was higher and the frequency variation was lower compared to the interictal state (mean pitch frequency: $184.6 \text{ Hz} \pm 19.2$ vs $172.1 \text{ Hz} \pm 62.1$, respectively) correspondingly (*figure 2B*).

Discussion

In this report, we show that pure ictal vocalisation in a patient with FLE, which we published 12 years ago (Rego *et al.*, 2006), sounded very similar to electrically evoked non-speech monotonous vocalisation in another patient. Pure ictal vocalisations, defined as an audible non-speech sound, not accompanied by apnoea or generalized tonic-clonic or clonic seizures (including groaning, grumbling, shouting, and weeping sounds), have been reported in patients with FLE with conflicting results on lateralization (Janszky *et al.*, 2000; Bonelli *et al.*, 2007). However, ictal vocalisations corresponding to any sounds without speech quality, as part of any seizure type, have also been observed in dominant temporal lobe epilepsy (Gabr *et al.*, 1989; Horvath *et al.*, 2009). Spread of the ictal activity from the temporal to the frontal lobe has been speculated in these patients to be responsible for ictal vocalisation (Gabr *et al.*, 1989; Horvath *et al.*, 2009).

The electrodes from which stimulation elicited the similar sound to the ictal vocalisation of our former patient were located in the superior frontal gyrus (Rego *et al.*, 2006). This observation is, therefore, suggestive of a symptomatogenic zone of vocalisation in the left superior frontal gyrus. Our results are in concordance with previous reports that non-speech vocalisation is evoked by electrical stimulation of predominantly the left superior frontal gyrus (supplementary motor area [SMA]); a sound described that was similar to those in our patients (Penfield and Welch, 1951; Fried *et al.*, 1991; Lim *et al.*, 1994). Former studies have identified representation of the human laryngeal motor cortex in the primary motor cortex (area 4) (Penfield and Boldrey, 1937). However, functional imaging studies showed a widely distributed network including the medial SMA, anterior cingulate cortex, and motor and premotor regions in the left hemisphere producing

vowels and syllables (Loucks *et al.*, 2007; Simonyan *et al.*, 2009).

Our approach is new in the sense that we analysed the audio signal quantitatively, showing similarity between the vocalisations. Quantitative analysis of the evoked vocalisation (by electrical stimulation of the left superior frontal gyrus) of the first patient demonstrated a higher mean fundamental frequency (f_0) of the vowel and a decreased alteration of the variation of the pitch compared to spontaneous voice, which is similar to the ictal vocalisations of the second patient with left FLE (Rego *et al.*, 2006). In a recent study, more prominent increases in ictal f_0 were identified during seizures arising from the frontal lobe compared to those from the temporal lobe, suggesting frontal lobe involvement in laryngeal control and speech production (Speck *et al.*, 2018). In addition, ictal alteration of vocal prosody, as shown by change in the frequency of formant f_0 and a reduction in frequency variation during speech, was found mostly in seizures arising from the non-dominant temporal lobe (Peters *et al.*, 2011). Quantitative voice analysis contributes to objective evaluation of ictal and postictal vocalisations in epilepsy patients (Peters *et al.*, 2011).

Since the symptomatogenic zone of ictal vocalisation is overlapping with some negative motor areas with subsequent arrest of motion arising from prolonged electrical stimulation of the left mesial frontal area (SMA) (Ikeda *et al.*, 2009), we also elicited negative motor responses in the regions adjacent to those where electrical stimulation caused pure vocalisation in the left superior frontal gyrus (C1). The role of other regions adjacent to stimulated cortex cannot be excluded due to limitation of sampling with depth electrodes in our patient.

Conclusion

We conclude that continuous monotonous prolongation of a vowel as the sole manifestation of an epileptic seizure can originate from the left superior frontal gyrus. This phenomenon should be further evaluated with quantitative audio analyses as this may be potentially useful for presurgical evaluation of epilepsy patients. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

Legend for video sequences

Video sequence 1

The video shows extraoperative electrical stimulation of the left superior frontal gyrus (electrodes C6-C8) of Patient 1. Sequences of stimulations consistently elicited a monotonous vowel lasting for the duration of stimulation.

Video sequence 2

The video shows two of four similar recorded seizures of Patient 2. Sequences show arousal, monotonous vocalization, full responsiveness upon testing, and a preceding non-specific aura ("tingling" of the whole body) (Rego *et al.*, 2006).

Key words for video research on
www.epilepticdisorders.com

Phenomenology: stimulation-induced vocalisation (video 1), isolated monotonous vocalisation (video 2)

Localization: left superior frontal gyrus (video 1), left frontal lobe (video 2)

Syndrome: insular lobe epilepsy (video 1), frontal lobe epilepsy (video 2)

Aetiology: unknown

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TEST YOURSELF



(1) Where are the symptomatogenic zones of vocalisation in the brain?

(2) What does quantitative audio analysis contribute to the evaluation of seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".