

Seizure-related automatic locomotion triggered by intracerebral electrical stimulation

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Received February 6, 2008; Accepted September 1, 2008

ABSTRACT – We describe the case of an eight-year-old boy, who underwent a video-stereo EEG (SEEG) investigation for the presurgical assessment of drug-resistant epilepsy, related to a right fronto-lateral cortical dysplasia and who became seizure-free after epilepsy surgery. The unexpected finding of the investigations was that intracerebral, high frequency (50 Hz) electrical stimulation (HFS) triggered the emergence of automatic and involuntary forward-backward locomotion during a focal seizure while the boy was standing. This clinical manifestation was different from the chaotic motor activity described during epileptic wanderings. The stimulation of the same fronto-lateral region, while the patient was lying, produced only the subjective sensation that the legs were moving, although there was no physical manifestation of this. Human locomotion is an innate motor behavior that is normally due to the activation of the spinal network for locomotion (central pattern generator). The emergence of different stereotyped motor behaviors during focal epileptic seizures or sleep disorders has recently been interpreted as a release of subcortical central pattern generators (Tassinari *et al.* 2005). In view of this, we hypothesize that the involuntary and robot-like locomotion of our patient could be the ictal expression of the release of subcortical locomotor CPGs. [Published with video sequences]

Key words: locomotion, dorso-lateral frontal cortex, seizure semiology, central pattern generators, intracerebral electrical stimulation



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Semi-purposeful and prolonged ambulatory activity can occur during sleep-related, partial epileptic seizures (episodic nocturnal wanderings), as part of a complex motor manifestation (Pedley and Guillemainault 1977, Plazzi *et al.* 1995), resembling the features of sleepwalking (Gastaut and

Broughton 1965). Different types of prolonged walking or running during seizures have been grouped under the term of "epilepsia cursiva" (Strauss 1960) and "locomotor compulsion" in epileptic attacks (Wolf 1984). Recently, the emergence of stereotyped behaviors during focal epileptic

seizures and parasomnias has been interpreted as an activation of subcortical “central pattern generators” (CPGs) (Tassinari *et al.* 2003 and 2005).

Nevertheless, pure locomotor behavior has not been described in relation to epileptic seizures. Physiologically, locomotion is mediated in walking animals by the activation of CPGs, defined as neural circuits, located in the spinal cord, producing self-sustained patterns of behavior (Grillner and Zangger 1979). Spinal CPGs, subserving locomotor activity, have been extensively demonstrated in all classes of vertebrates including primates (Grillner and Zangger 1979, Kiehn *et al.* 1998, Grillner 2006). In humans, evidence of their existence is essentially indirect (Calancie *et al.* 1994, Hultborn and Nielsen 2007). In fact, in patients with complete, long-standing spinal cord injury, locomotor-like activity has been induced by electrical stimulation of the lumbar spinal cord (Dimitrijevic *et al.* 1998, Shapkova 2004), thus providing further support for the existence of a spinal locomotor network in humans too.

In this study, we report the emergence of involuntary locomotor-like activity associated with a focal seizure triggered by intracerebral electrical stimulation, performed for presurgical, invasive assessment of drug-resistant epilepsy.

Case description and methods

A right-handed, 8-year-old boy had suffered, since the age of three, from seizures characterized by a brief loss of contact, left head and eye deviation and forced laughing. From the age of six, the same ictal manifestations could be preceded by a sensation (a repetitive noise -“bum, bum”-) inside the head, followed by vegetative phenomena, tonic contraction of the four limbs and bimanual automatism. These episodes could occur several times each day, mainly during sleep-wake transitions. Interictal and ictal EEG showed epileptiform abnormalities and discharges in the right frontal regions. MRI demonstrated a dysplastic lesion in the right fronto-lateral cortex, deep within the F2-F3 sulcus.

Several antiepileptic drugs, alone or in combination, failed to control his seizures; and for this reason, a surgical approach was considered. Prolonged scalp video-EEG monitoring did not provide sufficient data to define the cerebral structures involved in seizure-onset and propagation, therefore a video-stereo-EEG (SEEG) evaluation was performed at the “C. Munari” Center of Niguarda Hospital in Milan, in accordance with the Sainte-Anne School in Paris method (Talairach *et al.* 1974). Informed consent was obtained from the patient’s parents after the type and the purposes of the procedures had been explained.

Based on the clinico-EEG features of the seizures previously recorded on scalp video-EEG, 13 SEEG electrodes were implanted (*figure 1A*) to explore the lateral (orbital region, F2 and F3 and operculum) and mesial (superior

fronto-mesial cortex, supplementary motor area genu and fronto-central part of the gyrus cinguli) portions of the right frontal lobe and the right superior temporal gyrus.

To determine the exact sites of the recording/stimulating SEEG-electrodes, as well as the locations of the discharges, the cerebral structures explored by each electrode were identified in the three-dimension proportional grid system devised by Talairach and Tournoux (1988). The trajectories of each electrode on the post-implantation MRI images were reconstructed (*figure 1*).

SEEG recordings were performed with a bipolar montage from pairs of nearby contacts. Electrophysiological signals were acquired with a 128-channel, computerized video-EEG system for long-term monitoring (Telefactor Corp, West Conshohocken, PA, USA), with a sampling frequency of 400 Hz. Bipolar, high frequency electrical stimulation (HFS) was carried out by delivering 50 Hz trains of rectangular electrical stimuli of alternating polarity (IRES 600 CH electrical stimulator, Micromed, Italy) with a pulse width of 1 millisecond through pairs of nearby contacts to reproduce ictal phenomena and to assess the participation of the stimulated brain structures in seizure semiology. Throughout the electrical stimulation procedures, stereo-EEG was continuously monitored to detect any afterdischarge or seizure activity. The stimulation procedures were performed under video monitoring, with the patient either lying in bed or standing; during stimulation, the patient was also asked to count aloud, to detect any modification of speech or of consciousness.

In this patient, the analysis of 12 spontaneous seizures and of three seizures induced by HFS indicated that the epileptogenic zone included the intermediate portion of the F2-F3 gyri, with inconsistent spreading to the fronto-mesial regions. On the basis of these data, a right, fronto-lateral lesionectomy and cortectomy, including F2 and F3 circumvolutions, was performed. The histological diagnosis of the lesion was Taylor-type II cortical dysplasia. Since surgery, the patient has been seizure-free (follow-up: four years).

Results

The unexpected finding that we report here was obtained with HFS (intensity 3 mA; duration 2.5 s) of the right frontal dorso-lateral cortex (electrode G, contacts 6-7; Brodmann area: 46), while the patient was standing. With these stimulation parameters, HFS induced the initial part of a typical seizure (head sensation, cessation of counting, right version of head and eyes, right mouth corner deviation), then diffuse tremor-like movements, followed by involuntary automatic locomotor activity. It resembled stereotypic, forward and backward walking movements (somewhat similar to that of a robot) for few steps (*see video sequence*). During this episode, consciousness was probably retained: in fact, he could recall what was going

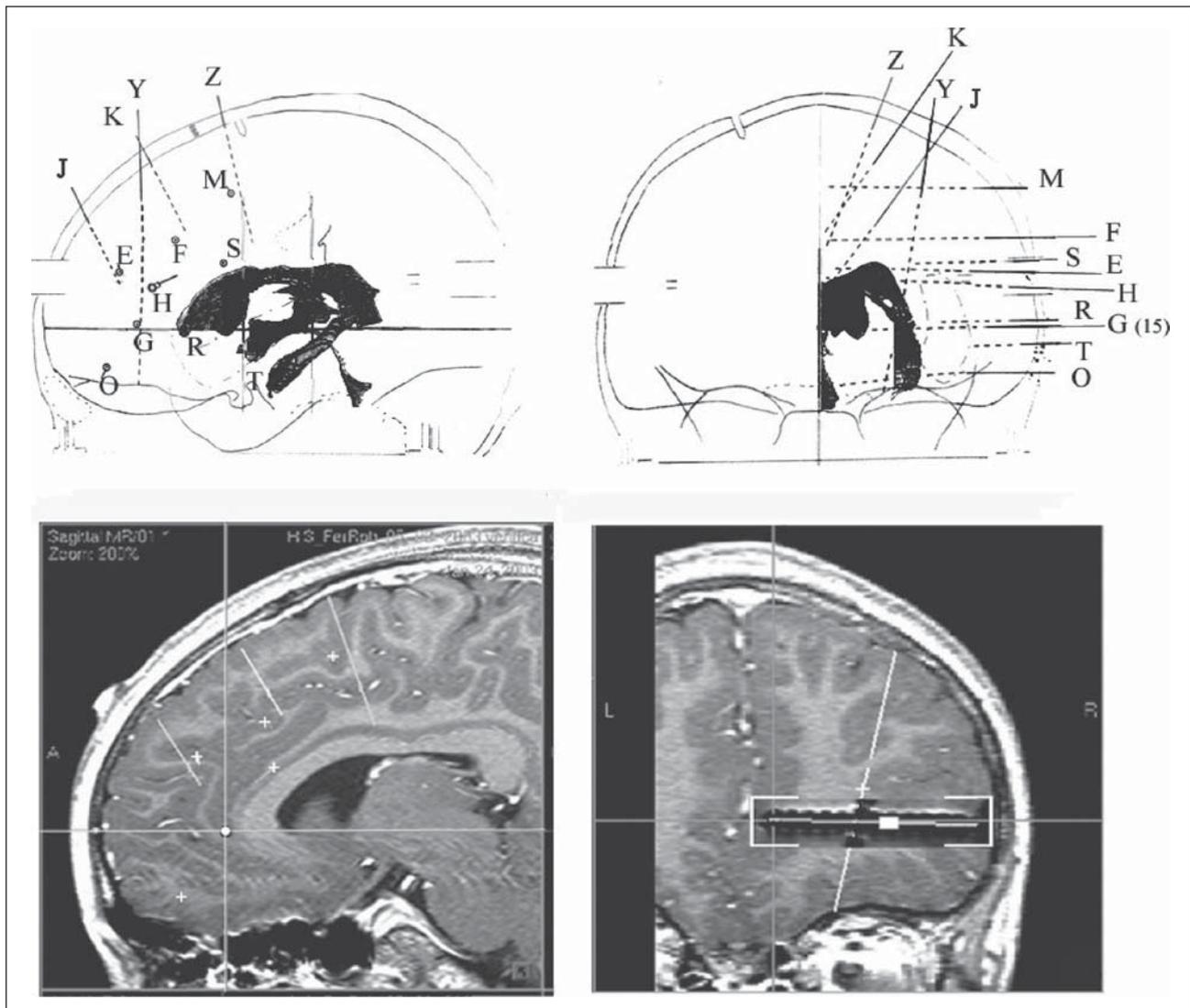


Figure 1. Stereotaxic schemes of SEEG exploration (upper panels; right lateral and frontal views of the skull) and MRI images illustrating the trajectories of depth cerebral electrodes. For each electrode, the lowest numbers indicate the inner contacts, whereas the highest indicates the outer contacts. Left MRI sagittal slice: the trajectory of electrodes J, K, Z (lines) and the antero-posterior location of electrodes G (point), O, E, H, F and M (crosses) are shown. Right MRI coronal slice: the trajectory of electrodes G (featuring 15 contacts) and Y (18 contacts) are illustrated; contacts G 6–7 (white square) and Y 7–8 (white cross) take place in the depth of the F2-F3 sulcus (Brodmann area 46).

on, and when asked about his brief walk, he replied that “the legs made him move”. He did not refer to any sensation that could justify his behavior, such as an “urge to move”. The SEEG tracing showed that the HFS initially produced a rapid, recruiting, low voltage discharge of the lesional part of the F2-F3 gyri, spreading widely to the fronto-lateral and fronto-mesial cortices, in particular to the frontal portion of the gyrus cinguli and the orbital gyrus (corresponding to involuntary forward locomotion). This was followed by a slower, sinusoidal activity with the same topography (figure 2). Since the main goal of HFS is to reproduce habitual seizures, and this locomotor behavior not being part of the usual ictal manifestations of the

patient at the time of the investigation, the stimulation was not replicated.

Stimulations of nearby contacts of the same electrode produced no visible phenomena, whereas the stimulation of an adjacent portion of the same cortical area (Brodmann area 46; electrode H, contacts 8–9), at the same intensity and for a longer duration (3 mA; 5 s), with the patient lying in bed, evoked a typical seizure, followed by mild trunk swinging and pelvic thrusting and the sensation that legs were involuntarily pulled back (no visible phenomena were detected). The corresponding SEEG tracing showed that the morphology and the spreading of the ictal discharge evoked from HFS were similar of those

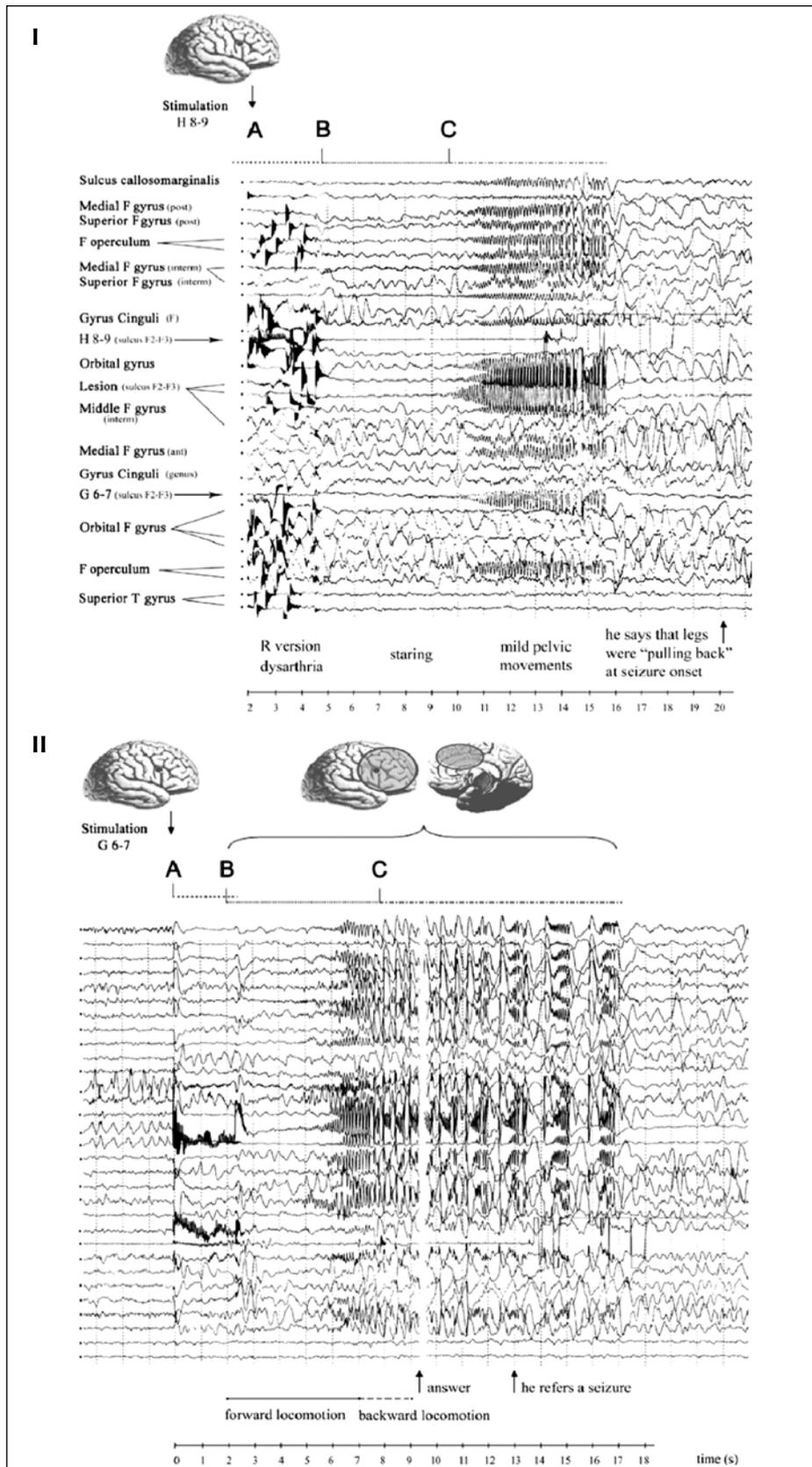


Figure 2. SEEG recordings of the intracranial activity after electrical stimulation (HFS) of the depths of the F2-F3 sulcus. **I**) HFS of electrode H, contact 8-9 (3 mA / 5 s). (A) During the stimulation, the SEEG activity in most part of the derivations is covered from an artefact. (B) Follows a rapid, low voltage discharge (for 5 seconds) mainly involving the F2-F3 sulcus and the intermediate part of the medial frontal gyrus, the gyrus cinguli (genus and frontal part) and the orbital gyrus; among external derivations, the orbito-frontal gyrus and the frontal operculum. (C) Spike and wave (SW) sinusoidal discharge (8-9 Hz), diffuses to the former regions (more widely involving, the F2-F3 sulcus) and spreading also to the posterior part of the medial and superior frontal gyri. This activity abruptly stops after six seconds and is followed by an electrical depression or by rhythmic delta activity. **II**) HFS of electrode G, contact 6-7 (3 mA / 2.5 s). (A) A tonic flattening of the lesional portion of the F2-F3 sulcus and of the adjacent fronto-dorsal regions, also involving the anterior fronto-mesial derivations, appears at the beginning of the HFS. (B) About two seconds after the beginning of HFS, a rapid and recruiting, low-voltage discharge appears, widely involving the dorso-frontal structures (F2 and F3 gyri, frontal operculum and orbital gyrus), the medial portion of middle frontal gyrus and the frontal part of the gyrus cinguli (BA 24) (tonic discharge). (C) About five seconds later, this tonic rhythm is fragmented by a delta activity, producing a SW sinusoidal discharge, which stops abruptly after 11 seconds. The upper figures provide a schematization of the sites of HFS and of the topography of EEG spreading. At the bottom are summarized the concomitant clinical manifestations; in particular, it is noteworthy that forward locomotion coincides with the widespread, frontal recruiting discharge, and stops with its fragmentation into an SW rhythm. F: frontal; post: posterior; interm: intermediate; ant: anterior.

described in the seizure with involuntary locomotion (figure 2).

Conversely, the stimulation of a nearby couple of derivations (electrode Y, contacts 7-8; Brodmann area: 46) at lower intensities (1 mA; 4 s), with the patient lying in bed, only evoked the manifestations of a typical seizure followed by diffuse tremor. In this case, the spreading of the ictal discharge involved only a circumscribed cortical area across the depth of the F2-F3 sulcus and the orbital-opercular region, while only the subsequent slow rhythmic activity spread to fronto-mesial derivations. This last episode exactly reproduced the clinical and SEEG features of the boy's spontaneous seizures.

Discussion

Experimental evidence in animals has shown that electrical stimulation of spinal and supraspinal structures, such as the brainstem (the so-called "mesencephalic locomotor region") (Shik *et al.* 1966, Jordan 1991, Grillner *et al.* 1997) and cerebellum (Mori *et al.* 1998), can initiate locomotion. Even though the brainstem and cerebellar structures participate in the initiation of the locomotor program, basal ganglia are responsible of the selection of the appropriate locomotory CPGs, through the inhibitory action of striatal neurons on the pallidum, which exerts a tonic, inhibitory drive on CPG networks. Striatal neurons can, in turn, be activated by the neocortex (Grillner 2006). In man, certain data have demonstrated that electrical stimuli delivered to the spinal cord at a lumbar level, might evoke locomotor-like activity in paraplegic patients (Dimitrijevic *et al.* 1998, Shapkova 2004). Moreover, capacity to generate rhythmic, muscular activity in the lower limbs of a spinal cord-lesioned patient has been reported (Calancie *et al.* 1994). Thus, based on this evidence, it is assumed that in man too, locomotory CPGs do exist in the spinal cord (Grillner 2006, Hultborn and Nielsen 2007).

Our report shows that electrical stimulation of the right dorso-lateral frontal cortex triggering an "atypical" seizure, with epileptic activity spreading to fronto-mesial regions, could induce an involuntary locomotor behavior, suggesting a possible releasing role of the cerebral cortex on spinal locomotory CPGs, in agreement with the experimental data that support a role for the neocortex, via basal ganglia, in CPG activation. Indeed, we have recorded three electroclinical episodes evoked by electrical stimulation of different portions of the same cortical area; when the HFS induced a self-sustaining tonic discharge relatively confined to the fronto-lateral dysplastic region, the patient only presented the clinical features of his habitual seizures. Otherwise, when tonic afterdischarge spread rapidly to a wide frontal area, broadly including the fronto-mesial regions, the patient presented involuntary locomotion, when standing, and only a subjective sensation of this when lying down. Considering that the appear-

ance and the maintenance of locomotion was strictly associated with an afterdischarge involving a wide fronto-mesial and lateral region, we postulate that the relationships between dorso-frontal HFS and the emergence of locomotor behavior has to be mediated by a relatively widespread, cortical dysfunction involving fronto-mesial regions.

We propose that a cortical frontal perturbation might induce a consequent activation of the basal ganglia projecting to locomotor neuronal networks, ultimately disinhibiting the brainstem command centers activating the spinal CPGs; this hypothesis is supported by the widely acknowledged existence of different frontal-subcortical circuits reciprocally connecting frontal lobe, striatum, globus pallidus/substantia nigra, and thalamus in humans (Alexander *et al.* 1986, Groenewegen *et al.* 1990, 2001, Leh *et al.* 2007). In addition, a role of the motor cortex in walking, through direct cortico-spinal fibers, has been demonstrated in humans by means of transcranial magnetic stimulation (Schubert *et al.* 1997, Capaday *et al.* 1999).

A further interesting aspect of our observation was that involuntary locomotion was observed only when the patient was standing; conversely, stimulating the same cortical area with quite similar parameters when he was supine, produced no overt motor activity, despite the spreading of the following discharge. An effect of posture on locomotion initiation might depend on the activation of specific neural structures located in the brainstem. Indeed, the stimulation of the diencephalic locomotor region (lateral hypothalamic area), the mesencephalic locomotor region (posterior midbrain) of the dorsal and ventral tegmental fields (along the midline of the caudal pons), has been demonstrated to induce site-specific changes in posture and locomotor synergies in the cat (Mori *et al.* 1998). In addition, a role of proprioceptive inputs related to the standing position may be hypothesized. Indeed, evidence showing that sensory feedback participates directly in the drive to the spinal motoneurons (Yang *et al.* 1991) suggests a facilitatory influence of afferent signals from peripheral receptors in the activation of spinal locomotory CPGs (Pearson 1995).

Another feature of the involuntary locomotion induced by intracranial stimulation in our patient was the robot-like movement. CPGs provide the basis for generation of rigidly fixed action patterns in the absence of sensory afferences (therefore, locomotion depending solely on CPG activation should look like an automaton); peripheral inputs are essential for modulating CPG activity, rendering the motor activity more flexible and adapted to the environment (Grillner 2006). Ictal locomotor activity in this boy appeared devoid of the harmonic features of normal walking, as well as of the refinement provided by peripheral sensory inputs on CPGs.

In conclusion, our observations are quite different from the chaotic motor activity characterizing epileptic wanderings or "epilepsia cursiva", and may be interpreted as an

expression of the release of subcortical locomotor CPGs, due to a transitory loss of upper inhibitory influences, caused by the epileptic activity. □

Legend for video sequence

The patient is standing, with arms outstretched; he had been asked to count loudly. The duration of the electrical stimulation is indicated by the yellow square in the upper right corner. When the stimulation begins, he stops counting, becomes red in the face and begins forward, robot-like walking; after the end of the seizure, he mentioned that his "legs were walking him". It remains unclear whether the backward part of this walking (not requested by the examiner) was voluntary or not.

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