■ Clinical commentary

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Epileptic Disorders

# Visual word form area hyperexcitability associated with focal epileptiform activity in a case of reading epilepsy

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*VIDEO ONLINE*

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**ABSTRACT**

Reading epilepsy recruits critical language-related areas, with synchronization and subsequent spreading of excitation in response to the epileptogenic stimulus. The mechanism by which possible generalized discharges result in the expression of bilateral or unilateral clinical symptoms remains controversial. The cortical and subcortical areas involved may constitute part of the normal reading network, such as the visual word form area (VWFA). A right-handed, 59-year-old man was diagnosed with epilepsy at the age of 15 after tonic-clonic seizures. Later, the patient described myoclonic jerks of the masticatory and perioral muscles while reading. A multimodal approach with magnetic resonance imaging and ambulatory and video-electroencephalogram was used for seizure characterization and source analysis. A left hemisphere spontaneous occipital-temporal epileptic focus, activated by reading, was observed, spreading broadly throughout frontal and temporal language networks. There was an abnormally increased cortical response to visual word presentation in comparison to pseudowords. Spatial localization of spike sources suggested a close association between the primary epileptic focus and the VWFA. This epileptiform activity seems to be selectively triggered at an early stage of lexical processing, with a functional connection between the epileptic network and the VWFA. This multimodal and functional connectivity approach could be helpful in determining the epileptic network in reading epilepsy.

**Key words:** reading epilepsy, reflex epilepsy, visual word form area, functional connectivity, adaptative direct transfer function

Reflex seizures may occur in combination with spontaneous seizures in several epilepsy syndromes, such as Dravet syndrome and juvenile myoclonic epilepsy. Understanding how specific sensory stimuli or cognitive processes influence ictogenesis, and their connection to seizure symptomatology, might be helpful to define the tipping point - from physiology to pathology - and lead to potential therapeutic interventions for prevention of reflex seizures [1]. Notwithstanding, these seizures may occur without an epilepsy diagnosis, emphasizing the need for cautious anamnesis to recognize environmental precipitating factors.

Reading epilepsy (RE), first described by Bickford in 1956 [2], is a rare form of reflex epilepsy in which all, or virtually all seizures are triggered by language-related tasks, especially reading. Interictal EEG is often unremarkable, and the

first descriptions defined the interictal spike activity as multifocal and widespread, mostly over the left hemisphere [2]. Ictal EEG is characterized by evoked paroxysmal rhythmic theta activity or spikes over either one or both frontocentral, centroparietal or temporoparietal regions, which are more commonly bilateral with unilateral accentuation, rather than unilateral or with focal discharges [3]. Nonetheless, the underlying mechanisms are still unknown.

The functional importance of the left inferior occipital-temporal cortex in the early visual stimuli processing to orthographic categorization led Cohen [4] to propose the concept of the visual word form area (VWFA) as a cortical area in the left middle fusiform gyrus (LmFG), specialized in the automatic categorization of words. Hirshorn [5] has shown that disruption of this region leads to the loss of this ability, supporting the role of the VWFA. Activation of the LmFG by visual recognition of words can be recorded non-invasively by the N170 potential in the EEG [4].

With this RE case report, we assess the alternative possibility of focal activation with secondary spread rather than primary systemic activation.

## Methods and clinical data

A 59-year-old Caucasian male, right-handed, without a family history of epilepsy or risk factors for the disease, retired from a 30-year-long career as a salesperson, was diagnosed with epilepsy when he was 15 years old after his first unprovoked bilateral convulsive seizure while bending during daytime to grab a sweatshirt. The clinical data available at the time did not include EEG or CT results, thus no clear classification as focal or generalized epilepsy could be made. Phenytoin and phenobarbital were prescribed, and an unsuccessful self-attempt to discontinue medication at age 20, after several aborted seizures, led the patient to make the unilateral decision to reinstate therapy. The first oral myoclonic jerks induced by reading, with preserved awareness, were noticed 25 years after the diagnosis. The patient would stop reading when oral myoclonic jerks became prominent, which prevented seizures from ever progressing to bilateral tonic-clonic activity. Neurological examination was normal at the time of the assessment.

Routine and sleep-deprived EEG recordings revealed multifocal epileptiform discharges in the left hemisphere, most prominently over occipital-temporal and frontal areas, while 1.5T brain MRI, following ILAE recommendations for epilepsy, was reported to be normal.

To avoid uncontrolled language-related stimuli during wakefulness, resting-state spikes were obtained on a 24-hour ambulatory EEG (aEEG) recording during the nocturnal sleep period, using the 10-20 international system of electrode placement (10-20 IS) with four additional electrodes (TP9/10 and P9/10) and an EKG channel. A Micromed® LTM device was used.

The reading test was performed with the patient seated in a video-EEG epilepsy monitoring unit, with the aim of characterizing the semiology of the events using the 10-20 IS with additional electrodes, C1/2 and C5/6, and bilateral facial EMG (*figure 1A, right panel, video 1*). Synchronized video-EEG (Micromed® SystemPlus™) was acquired during 20 minutes of a reading task, which was interrupted when perioral myoclonus became prominent.

Event-related potentials (ERP) to visually presented orthographic (five- to seven-letter words and pronounceable pseudowords) and non-orthographic (faces) stimuli were obtained using a high-resolution EEG set of 124 AgCl electrodes (EASYCAP GmbH® cap) (*figure 2C*). Stimuli were presented with the Stim2 software, and the EEG recorded with a SynAmps2 Amplifier system (Compumedics® Neuroscan™).

Spike activity on the aEEG recording was detected using automatic software (Persyst®14) followed by manual validation by a trained clinical neurophysiologist (AL). Source analysis was performed with CURRY software, version 6.0 (Compumedics® Neuroscan™) using anatomical information from brain MRI and the sLORETA algorithm applied on the averaged spikes exported from Persyst®14 (*figure 1B*). Only spikes detected during sleep were processed.

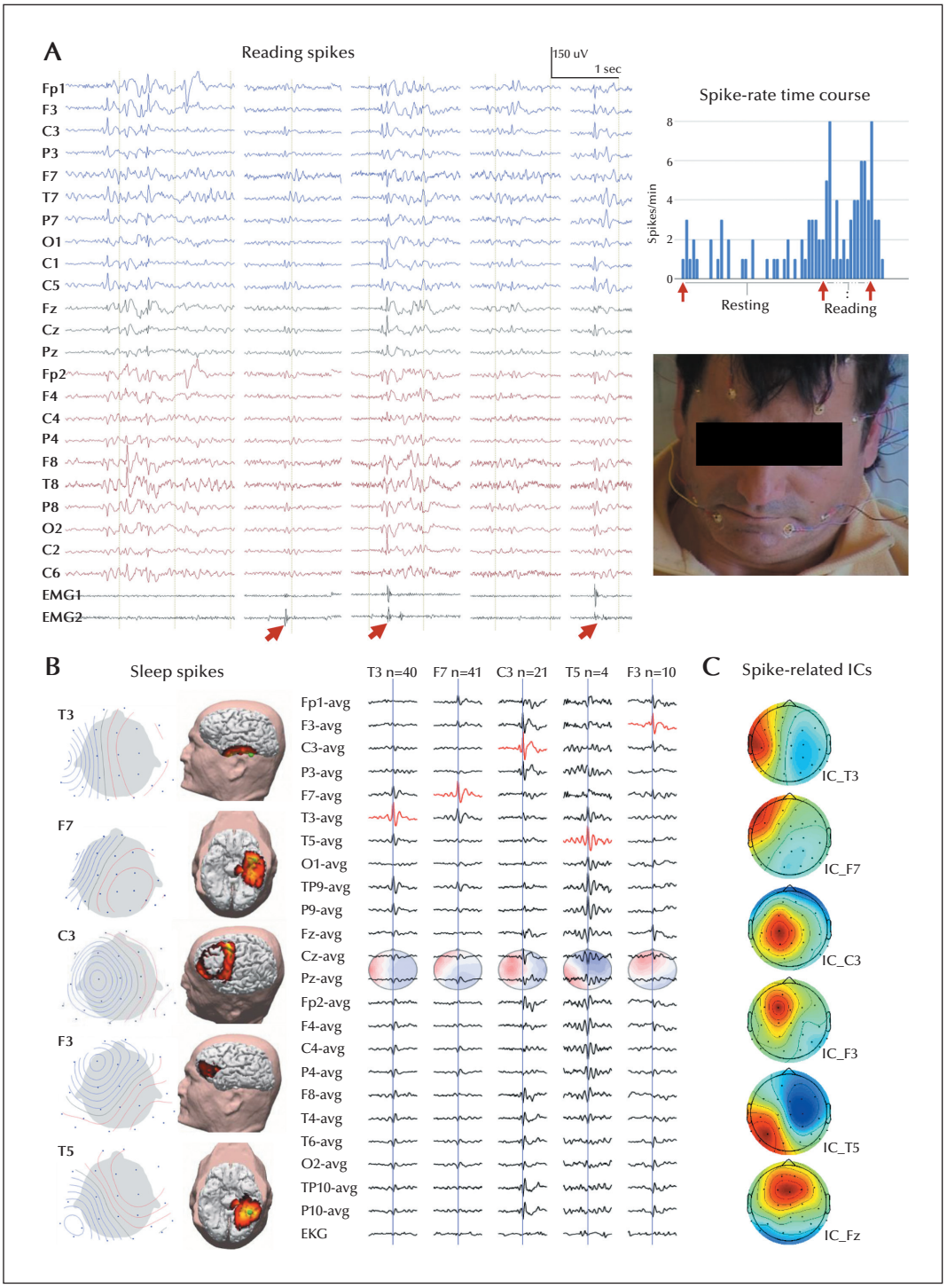
Reading video-EEG was reviewed by AL, with all spikes marked and tagged to the respective electrodes, allowing a detailed quantification of spike frequency throughout the duration of the test (*figure 1A, right panel*).

The functional connectivity at the peak of spike-related independent components was calculated using the Adaptative Direct Transfer Function [6], as implemented in the toolbox E-Connectome 2.0 [7] running in MATLAB R2010a (MathWorks®).

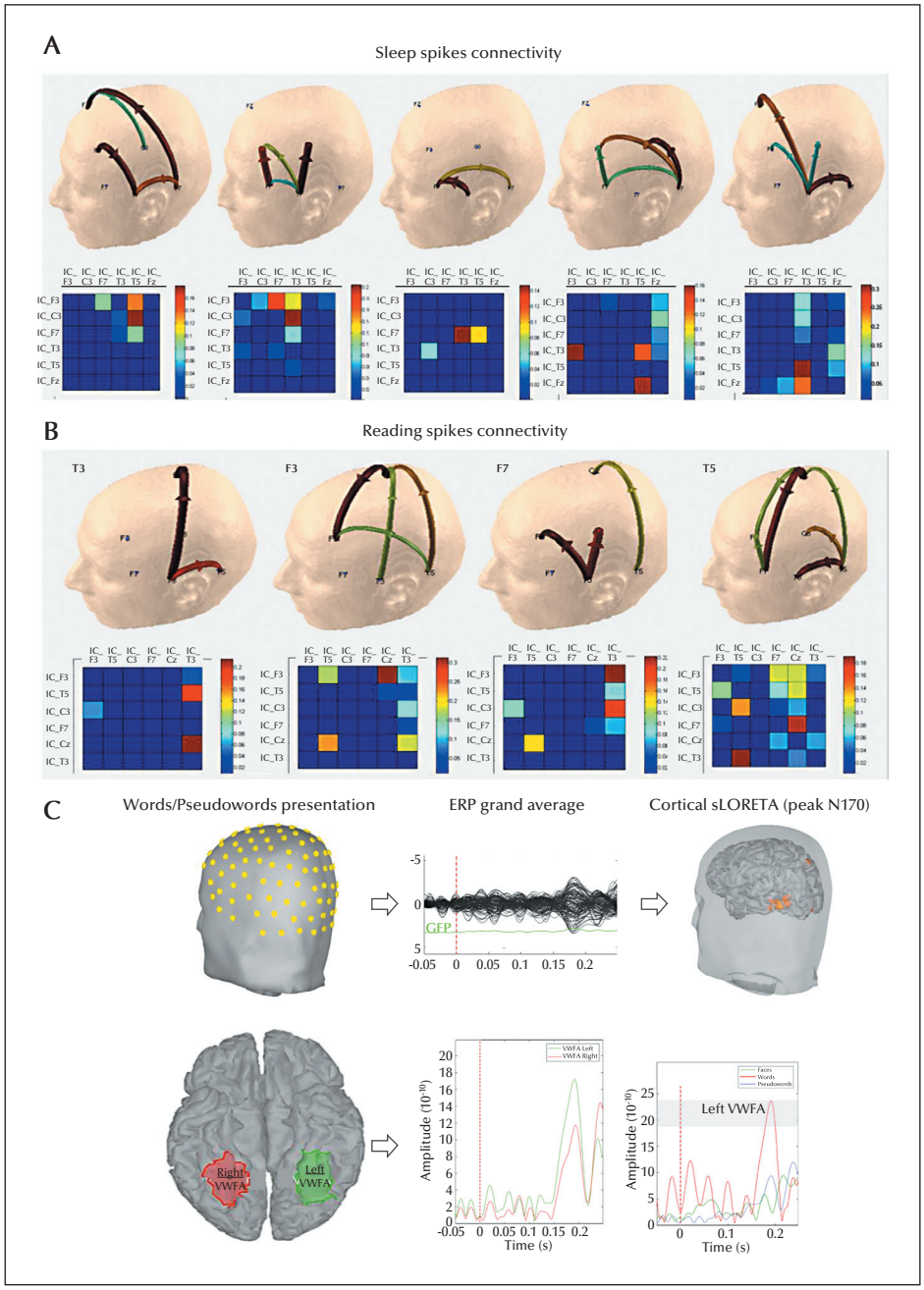
ERP were pre-processed with the Scan 4.5 software (Compumedics® Neuroscan™), including filtering (1-30 Hz), segmentation in epochs, manual exclusion of epochs with artifacts and averaging. The average ERP for the stimulus categories (words, pseudowords and faces) were imported into the BrainStorm software [8] using MATLAB R2020b (MathWorks®), where source analysis was performed.

## Results

Sleep aEEG showed spontaneous multifocal spike activity over the left hemisphere, with rare paroxysms located over the frontal and temporal lobes




■ **Figure 1.** Spike quantification and source analysis. (A) Dataset of reading spikes obtained in the reading task, using 10-20 IS with C1/2 and C5/6 with average reference and bilateral facial EMG, revealed bursts of dissimilar spikes, more prominent over the left frontal and central areas, with occasionally contralateral involvement and bilateral or lateralized perioral myoclonic jerks (arrows). A comparison of spikes between resting state and reading is presented in the histogram (upper right panel). (B) Spike types identified during sleep (center), with the corresponding average topography and source (left). (C) Topographies of the spike-related independent components. EMG: electromyogram; IS: international system.




■ **Figure 2.** Spike connectivity analysis. ADTF information flow at the peak of spike-related ICs while sleeping (A) and during the reading task (B). The flow of information reads from column to row in the connectivity matrix (below) and along arrows in the head model. The T3 and T5 spike-related ICs consistently act as outflow sources. C) ERP protocol to assess cortical excitability to orthographic and non-orthographic stimuli, using HR-EEG (124ch) and the sLORETA source localization method (upper panel). Visual presentation of words and pseudowords induced N170 activation in the occipital-temporal areas (right upper panel), which were of higher amplitude for orthographic than for non-orthographic visual stimuli in the left hemisphere (lower center panel). Activation of the left VWFA to words (red) was greater than for pseudowords (blue) (right lower panel). ADTF: adaptative directed transfer function; ERP: event-related potentials; HR-EEG: high-resolution electroencephalography; ICs: independent components; VWFA: visual word form area.

(*figure 1B*). A total of 116 spikes identified in the 345 calculated minutes of night sleep resulted in a rate of 0.34 spikes/minute.
The reading task doubled the baseline spike frequency (*figure 1A*) and presented as brief bursts of spikes with similar morphology, more prominent over the left hemisphere, particularly over the central and frontal areas. These bursts were sporadically associated with secondary propagation to the contralateral hemisphere and bilateral or lateralized perioral myoclonic jerks (*video 1*).
Source analysis of the interictal spikes showed activity in multiple cortical areas over the left hemisphere frontal (inferior and superior dorsolateral) and temporal (inferior) lobes, (*figure 1B, left panel*).
Connectivity analysis showed that the middle and posterior temporal regions of the epileptic network consistently acted as outflow sources, both during sleep (*figure 2A*) and reading (*figure 2B*), suggesting that the epileptiform activity began in the left middle-posterior temporal lobe and secondarily propagated to other areas. As for the apparently independent frontal spikes, these always appeared as sinks in the connectivity analysis, both during sleep and reading, supporting the interpretation that information was provided by other nodes of the epileptic network, rather than being the source of such information.
Visual presentation of words and pseudowords induced N170 potentials in the occipital-temporal area (*figure 2C, upper panel*). N170-ERP on the left inferior temporal lobe showed a higher amplitude for orthographic than for non-orthographic visual stimuli (*figure 2C, lower middle panel*), consistent with the VWFA concept.
VWFA reactivity to orthographic stimuli demonstrated higher-amplitude N170 over the left temporal lobe compared with the homologous right hemisphere areas. Also, VWFA activation to words was increased compared to pseudowords (*figure 2C, lower right panel*), suggesting unexpected differential excitability of the cortical area to the two orthographic subcategories.

## Discussion

In this right-handed patient, we documented the existence of a left hemispheric spontaneous occipital-temporal epileptogenic focus, activated by reading, spreading throughout frontal and temporal language networks. We found an increased reactivity to words in the same cortical area supporting a relationship between the hemispheric localization of the VWFA and the lateralization of language in healthy subjects [9], suggesting that the late specialization of the VWFA at the time of reading acquisition occurs in close connection with the development of language networks in the same hemisphere.
We found increased cortical response to visual word presentation (N170) in comparison to pseudowords in our patient, an unexpected finding in contrast to the similar response to the two orthographic categories previously described [10].
A functional connection of the epileptic network in our patient with the output stages of the VWFA could explain both the susceptibility to words typical of RE and the fast spike propagation throughout the language networks. A subgroup of RE patients presented with ictal visual manifestations, supporting the association with visual and language networks [11]. Source analysis studies demonstrated an origin of epileptiform activity in the left inferior occipital-temporal cortex [12, 13]. Previous authors have described RE cases both with selective susceptibility to words [14] and to non-lexical stimuli [15], which led Pegna [14] to propose a lexical and a sub-lexical subtype. Despite not formally testing the capability of stimuli to induce spike activity, the observed differential cortical excitability in response to words and pseudowords supported a lexical type of RE.
The connectivity analysis of the spikes showed a flow of information from the left occipital-temporal area towards the frontal region, supportive of temporal dynamics, similar to that of a rare type of RE with onset in the left occipital areas [11], which was also found in other RE cases by means of spike source analysis [12, 13]. These methods provide a more powerful insight into epileptic network dynamics than the traditional visual methodology [16].
Spatial and temporal dynamics of spikes were similar during reading and sleep, while reading increased the spike rate. Interestingly, the spike rate was higher during wakefulness (*figure 1A, right panel*) than during sleep (0.34 spikes/min), suggesting that the latter is more representative of the unstimulated resting state. Several authors have reported reading-induced spikes in cortical areas with no previous epileptiform activity [15]. In contrast, our results in the resting state show that reading potentiates spike activity in the left hemisphere only in areas that were already affected in the resting state.
Our clinical case presented with atypical features, late onset, and an initial seizure event unrelated to reading, which may preclude it from being considered as a true RE case. Because the initial seizure presented with generalization, clear characterization of the previous environmental context from the patient was not possible, and, for a long time, the effectiveness of the antiepileptic drugs prescribed prevented the occurrence of new events. Moreover, as the patient was continuously medicated for 25 years, it was difficult to ascertain the true onset of the

condition and to establish the exact time when the interictal propagation pattern we detected was established. Despite these limitations in information, we believe that the reading-related seizures, the typical oral myoclonus, the multifocal EEG spikes over the brain language networks, and the absence of neurological or MRI abnormalities make the condition fundamentally similar to the most common type of RE [11]. No clinical or EEG data was identified supporting a primarily generalized epilepsy and no other type of seizures were reported. As for the possibility of whether our case was an idiopathic or symptomatic type of RE, we could find no evidence of the latter, as the neurological and cognitive examination, as well as brain MRI, were found to be normal, and neither a history of head trauma nor slow focal activity on the EEG were detected.

In summary, the dynamic analysis of spike activity in our patient favors the hypothesis of focal onset near the VWFA, with secondary propagation to language networks. This connection is further supported by the increased cortical excitability in response to words. This case report emphasizes the importance of a multimodal approach for this type of epilepsy. ■

**Supplementary material.**
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors have no conflicts of interest to declare.

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## Legend for video sequence

The patient is seated in a video-EEG epilepsy monitoring unit, using the 10-20 international system of electrode placement with additional channels: C1/2 and C5/6 and furthermore bilateral facial EMG derivations. The corresponding synchronized video-EEG trace demonstrates epileptiform activity – spikes – more prominent over the left frontal and central areas, with occasionally contralateral involvement associated with lateralized oral myoclonic jerks, with apparent retained awareness, since the patient recollected fittingly the text read during the task.

**Key words for video research on www.epilepticdisorders.com**
*Phenomenology*: reflex seizures; myoclonic (perioral); reading
*Localization*: temporal lobe (left)
*Syndrome*: reflex epilepsy
*Aetiology*: unknown

## TEST YOURSELF

**(1) The Visual Word Form Area (VWFA) is a cortical area located in:**
A. Left middle fusiform gyrus
B. Supramarginal gyrus
C. Angular gyrus
D. Opercular part of the inferior frontal gyrus

**(2) Which of the following may be used to study the relationship between different cortical epileptiform generators?**
A. Positron emission tomography (PET)
B. Functional magnetic resonance imaging (fMRI)
C. Invasive recording in the context of epilepsy surgery
D. Functional connectivity studies

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.*