FULL-LENGTH ORIGINAL RESEARCH

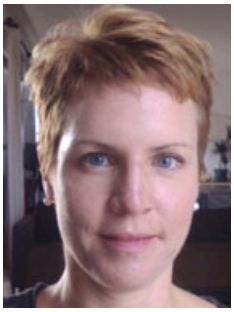
Frontal lobe seizures: From clinical semiology to localization

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Summary

Objective: **Frontal lobe seizures are difficult to characterize according to semiologic and electrical features. We wished to establish whether different semiologic subgroups can be identified and whether these relate to anatomic organization.**

Methods: **We assessed all seizures from 54 patients with frontal lobe epilepsy that were explored with stereoelectroencephalography (SEEG) during presurgical evaluation. Semiologic features and concomitant intracerebral EEG changes were documented and quantified. These variables were examined using Principal Component Analysis and Cluster Analysis, and semiologic features correlated with anatomic localization.**

Results: **Four main groups of patients were identified according to semiologic features, and correlated with specific patterns of anatomic seizure localization. Group 1 was characterized clinically by elementary motor signs and involved precentral and premotor regions. Group 2 was characterized by a combination of elementary motor signs and nonintegrated gestural motor behavior, and involved both premotor and prefrontal regions. Group 3 was characterized by integrated gestural motor behavior with distal stereotypies and involved anterior lateral and medial prefrontal regions. Group 4 was characterized by seizures with fearful behavior and involved the paralimbic system (ventromedial prefrontal cortex ± anterior temporal structures). The groups were organized along a rostrocaudal axis, representing bands within a spectrum rather than rigid categories. The more anterior the seizure organization, the more likely was the occurrence of integrated behavior during seizures. Distal stereotypies were associated with the most anterior prefrontal localizations, whereas proximal stereotypies occurred in more posterior prefrontal regions.**

Significance: **Meaningful categorization of frontal seizures in terms of semiology is possible and correlates with anatomic organization along a rostrocaudal axis, in keeping with current hypotheses of frontal lobe hierarchical organization. The proposed electroclinical categorization offers pointers as to the likely zone of organization of networks underlying semiologic production, thus aiding presurgical localization. Furthermore, analysis of ictal motor behavior in prefrontal seizures, including stereotypies, leads to deciphering the cortico-subcortical networks that produce such behaviors.**

KEY WORDS: **Frontal lobe, Epileptic seizures, Semiology, Stereoelectroencephalography, Stereotypies.**

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It is widely accepted that semiologic and electrical patterns of frontal lobe seizures are difficult to characterize, and liable to be misleading in predicting localization of seizure onset, especially those arising from anterior frontal regions (see O'Muircheartaigh & Richardson, 2012 for review). This current and widely held view reflects lack of substantial arguments to the contrary, despite a long history of investigation of frontal seizures from the end of the 19th century onward. Previous studies have compared semiologic features that could allow differentiation of frontal seizures from temporal lobe seizures (Wieser et al., 1992; Manford et al., 1996), or have looked at patterns that might point to specific frontal regions. However, the relation between semiologic patterns and sublobar localization remains more or less unclear (Laskowitz et al., 1995; So, 1998; Jobst et al., 2000; Kotagal et al., 2003; Bonelli et al., 2007; Bagla & Skidmore, 2011; Beleza & Pinho, 2011; O'Muircheartaigh & Richardson, 2012), leading some authors to comment that "relatively few seizures can be reliably localized on clinical grounds" (Manford et al., 1996). Seizures in a given patient with frontal lobe epilepsy are generally similar, with stable and reproducible electroencephalography (EEG; Schindler et al., 2007) and semiologic patterns (O'Muircheartaigh & Richardson, 2012). However, marked variation exists between patients, making categorization and classification challenging. Frontal seizures are typically brief and often manifest complex motor behavior, sometimes with emotional signs, that may be difficult to accurately observe and describe, in contrast to the relatively well-recognized patterns of temporal lobe seizures (Manford et al., 1996; O'Brien et al., 2008) in which semiologic repertoire is much more limited and seizures unfold more slowly, facilitating electroclinical interpretation. The connectivity of frontal lobe supramodal associative areas supports spread through distant cortico-cortical efferent pathways, which can be both multilobar and multidirectional, typically resulting in rapid, widespread propagation of seizure discharges originating in frontal regions, thus helping to explain both semiologic complexity and difficulties in EEG analysis. In addition, in the frontal lobe (representing 35–40% of total cortical volume in humans [Semendeferi et al., 2002]), accurate delineation of seizure onset is challenging given the large surface of buried cortex and peculiarities of craniocerebral anatomy, the ventromedial prefrontal region in particular being far from EEG electrodes placed on the scalp or on the cortical convexity. Such difficulties in electroclinical localization almost certainly contribute to poorer outcome in surgical treatment of frontal lobe epilepsy compared to other epilepsy types (Téllez-Zenteno et al., 2005).

Descriptions of "pure" samples of frontal epilepsies cured by surgical resection (Rasmussen, 1983; Chauvel et al., 1995; Kotagal et al., 2003) provide an overview of the extent and complexity of semiologic features in a large patient population. However, because ictal semiology appears to be produced via a dynamic discharge that propagates to areas both close to and remote from its origin (Chauvel et al., 1995), it is necessary to investigate the spatiotemporal evolution of this activity and its relation to clinical signs in order to better understand the relevance of different semiologic patterns. Therefore, limiting study to patients cured by surgery, in whom essentially the region of seizure onset has presumably been removed, does not allow conclusions to be drawn regarding the cerebral substrate of semiologic features, since the distributed brain networks involved in producing ictal signs will in many if not all cases involve structures distant from the zone of seizure onset. This fact can help to explain the seemingly incoherent results obtained from such "pure cultures," where semiologic patterns do not seem consistently related to seizure onset in a specific region but presumably reflect patients' individual propagation pathways. On the other hand, it seems likely that seizures with similar semiology involve neuronal activity within the same specific brain networks (O'Muircheartaigh & Richardson, 2012). Stereoelectroencephalography (SEEG), by providing a three-dimensional view of seizure dynamics, is the method of choice to study this question and appears to be equally as useful in magnetic resonance imaging (MRI)–negative cases as in those with radiologically visible lesions (McGonigal et al., 2007).

Although studies of selected populations of frontal epilepsies exist (Bleasel et al., 1996; Kriegel et al., 2012; Lee & Worrell, 2012), to date, a comprehensive overview of frontal seizures is lacking. To this aim we studied a consecutive series of patients with seizures onset in the frontal lobe as determined by SEEG. The two main questions were the following: (1) can patients with frontal lobe epilepsy actually be categorized in terms of semiologic features; and (2) are certain semiologic patterns associated with different sublobar organization of seizures? By performing cluster analysis on electroclinical SEEG data we have been able to differentiate clinical patterns according to anatomic subsystems originating in the frontal lobe.

Patients and Methods

Patients were selected to undergo SEEG exploration in the Clinical Neurophysiology Department of the Timone Hospital (Marseille, France) if clinical features suggested a possible surgical indication and if intracranial studies were necessary to localize the epileptogenic zone (EZ) and/or establish functional constraints. We included only those 54 patients in whom SEEG exploration defined the EZ as being within the frontal lobe, during the period from February 2000 until November 2010, from a total of 180 SEEG explorations during this period. We excluded patients whose eventual intracranial recording was inconclusive (n = 1) or

in whom the EZ did not predominantly involve the frontal regions. Prior to selection for SEEG (Deltamed, Natus Europe, Planegg, Germany), a phase of thorough noninvasive presurgical assessment was carried out, including detailed clinical history and surface video-electroencephalography (VEEG; Deltamed) recording, to permit analysis of habitual seizures and interictal EEG. All patients underwent MRI (1.5-Tesla Symphony, Siemens Medical Systems, Erlangen, Germany), functional imaging, and neuropsychology assessment. All patients gave informed consent prior to exploration. SEEG recordings were performed using intracerebral multiple contact electrodes (manufactured by Dixi Medical [Besançon, France] for patients explored 2000–2005; Alcis [Besançon, France] for patients explored after 2005; 10–15 contacts, length: 2 mm, diameter: 0.8, 1.5 mm apart from edge to edge) placed intracranially according to Talairach's stereotactic method (Bancaud et al., 1970; Talairach et al., 1992). Strategy of electrode positioning was established in each patient based on hypotheses about EZ localization, with the aim of defining subsequent cortectomy. Implantations were unilateral or bilateral depending on individual features of each case. Five to 15 (mean 9) electrodes were implanted per patient. Implantation accuracy was controlled perioperatively by telemetric x-ray imaging. Postoperative computerized tomography (CT) (Siemens Medical Systems) scan verified the absence of bleeding and the location of each recording lead. Following recording, intracerebral electrodes were removed and MRI performed, permitting visualization of each electrode trajectory. Finally, CT-scan/MRI data fusion was performed to locate each contact along the electrode trajectory (for illustration, see Bartolomei et al. (2004)). Patients underwent video-SEEG (128 channels Deltamed system, Natus Europe, Planegg, Germany) following complete or partial withdrawal of antiepileptic drugs during a usual period of 4–10 days (extended up to a maximum of 3 weeks if necessary) in order to record several of the patient's habitual seizures.

To investigate the relationship between semiologic features and involved brain areas, ictal clinical and electrical modifications were analyzed in each patient and a correlation test between ictal signs and brain areas was then performed for the entire series. Subsequently principal component analysis (PCA) was carried out to summarize the semiologic data in a way that would allow meaningful analysis. Based on the resulting PCA data space, a hierarchical cluster of patients was formulated, allowing identification of clinically homogeneous subgroups of patients, in which characteristic symptoms and involved regions were thus identified.

Analysis of anatomic-electroclinical features

VEEG clinical and electrical data were analyzed by three epileptologists independently (FBo, AMcG, PC), using the criteria detailed below.

For each patient, all seizures were examined and the presence or absence of 31 ictal signs noted (listed in Fig. 1). Because frontal seizures, as observed in this series, are characterized by a high reproducibility of the electroclinical pattern for a given patient's seizures, an overall semiologic score was established for each patient, based on review of all seizures, with values ranging from 0 (=absence of that sign), to a maximum of 2 for major features (=constant and early sign present in each seizure), minor features being scored as 1 (=sign not always present).

Description of semiologic features

Because observation of semiology was the essence of this study, it was crucial to choose well-defined terms to describe the different signs, in order to be able to categorize seizures. Motor semiology, characteristic of frontal lobe seizures, was the key factor allowing clinical categorization. Whereas description of elementary motor signs (such as tonic posturing) was straightforward, in order to meaningfully describe subgroups of more complex motor behaviors, it was necessary to define terms other than those proposed by existing semiologic classification (Blume et al., 2001). This issue of definition of semiologic terms has previously been highlighted (Rolnick & Parvizi, 2011).

1. Elementary motor signs. General agreement already exists concerning identification of clonic movements and tonic or dystonic contraction and/or posturing as well as head and/or eye version. Such signs were grouped together here under the generic term *elementary motor signs*.
2. Gestural motor behavior. Accurately describing the complex motor behaviors commonly observed in prefrontal seizures is challenging and many terms commonly used in the literature are less than clearly defined and subject to variable use. A notable example is "automatism," the poor definition of this term in the context of epileptology having recently been highlighted (Rolnick & Parvizi, 2011). The term "hypermotor seizure" or "hyperkinetic seizure" is also problematic, as it does not necessarily distinguish between different types of movement within the seizure or the presence or absence of emotional features. We have referred to the overall (quite heterogeneous) category of complex motor behaviors, readily distinguishable from elementary motor signs, by the term *gestural motor behavior*. This can be further categorized through identifying the presence or absence of certain features of movement within the gestural motor behavior (*stereotypies* and *hyperkinetic movements*, explained below); and overall appearance of the behavior in terms of the syntax or "naturalness" of motor sequence (*integrated* versus *nonintegrated*).
   a. Stereotypies. The stereotypies are defined, according to Ridley (Ridley, 1994), as excessive production of one type of motor act, necessarily resulting in repeti-

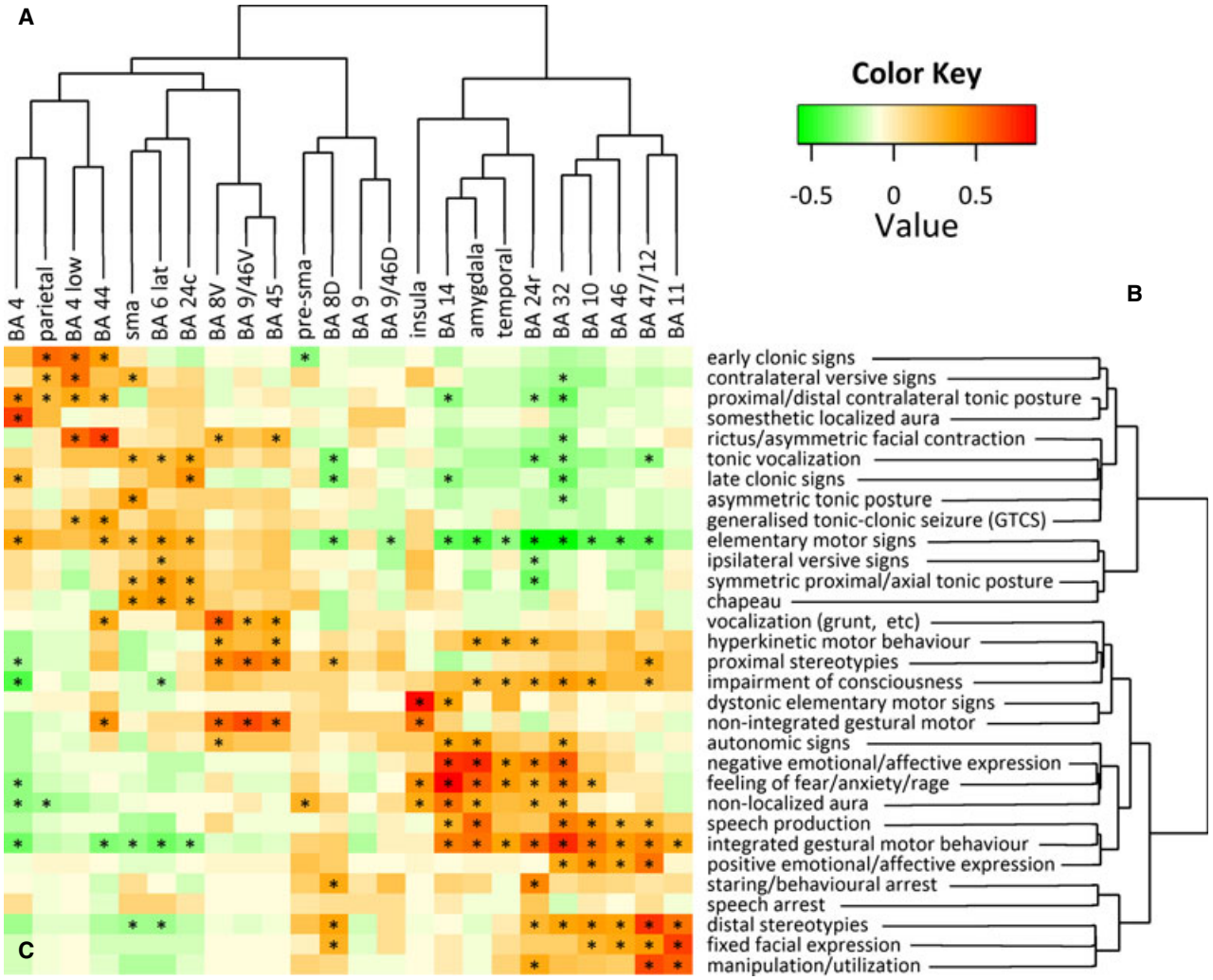


Figure 1.

Correlation matrix between cortical areas and clinical features, as ordered by hierarchical clustering basing on their reciprocal distance. (**A**) Clustering of brain regions is shown on the horizontal axis. (**B**) Clustering of clinical signs is shown on the vertical axis. In these two ordered sequences, neighboring regions as well as neighboring signs occur more frequently together than distant ones. (**C**) Correlation between areas and signs as a function of the color (red, positive correlation; green, negative correlation; starred squares, $p < 0.05$) follows a diagonal pattern of association running from more posterior (top left corner) to more anterior regions (bottom right corner). This pattern, which is conserved for significant correlation ($p < 0.05$ starred squares), indicates the emergence of clinical spectrum developing along a caudorostral axis from primary motor cortex to the frontal pole (BA, Brodmann area; SMA, supplementary motor area; pre-SMA, presupplementary motor area). Architectonic subdivision of lateral and medial prefrontal Brodmann areas according to (Petrides & Pandya, 1994).

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tion. We thus included in this category rhythmic repetitive movements of trunk and limbs (*proximal stereotypies*), or of hands/feet (*distal stereotypies*; Chauvel et al., 1995). These could have a nonpurposeful appearance (e.g., whole body rocking) or a semi-purposeful one (e.g., manipulating an object).

b. Hyperkinetic movements. The term *hyperkinetic* was used here not to describe the whole seizure but rather in a quantitative sense to describe excessive amount of movement (hyperactivity) and/or excessive amplitude, speed, and acceleration. This allowed distinction of the character of movement from other clinical features occurring within the same seizure (such as vocalization, autonomic signs, emotional expression, and so on). Motor components of gestural motor behavior could thus be hyperkinetic, or stereotyped; both stereotyped and hyperkinetic; or neither of the two.

c. Integrated and nonintegrated gestural motor behavior. The overall appearance of the sequential pattern of motor action, whether or not including stereotyped and/or hyperkinetic elements, could also be classified

as *integrated* or *nonintegrated*. These terms were chosen to convey the notion of whether or not the sequence of movements appeared to follow a recognizable and somewhat "naturalistic" pattern, even though the overall behavior might appear greatly exaggerated or incongruent in the social context. *Integrated* gestural motor behavior included recognizable, ordered sequences of movement within the seizure such as reaching, grasping, pedalling, kicking, tapping, rocking, or hitting. In addition for integrated behavior, facial appearance was within a "normal range" of human facial expression (Ekman, 1993), whether showing emotion or not, and tended to be congruent with other ictal behavioral features (for example happy facial expression with singing, laughing, and rhythmic tapping). In contrast the motor sequences of *nonintegrated* gestural motor behavior had a disjointed or even anarchic appearance including facial expression.

Definition of early spread network

Concerning analysis of ictal intracerebral EEG, cortical regions involved by ictal discharge were similarly scored according to degree of participation in ictal discharge, by reviewing all seizures from each patient. From an anatomic standpoint, electrode sampling allowed study of 20 cortical

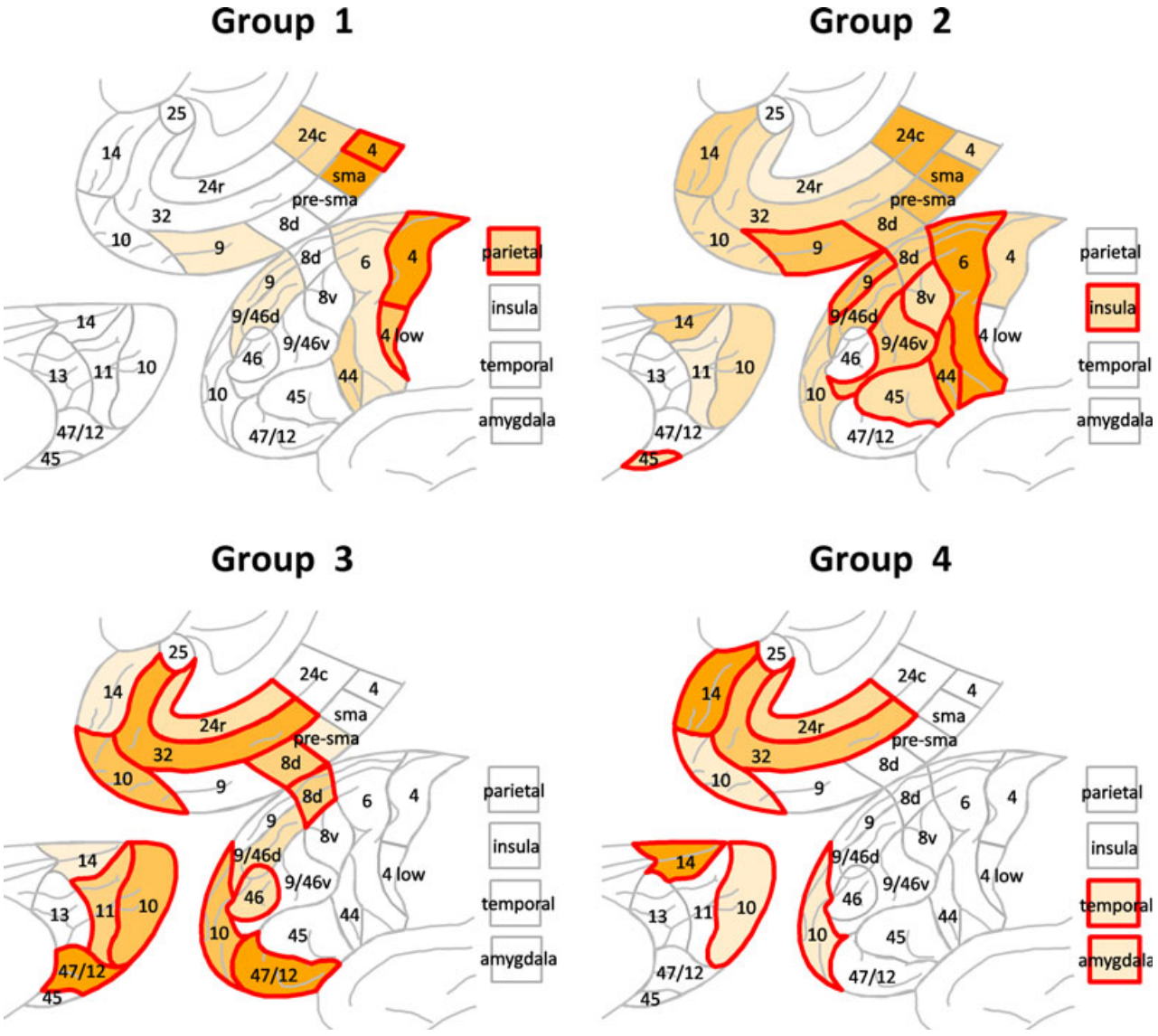


Figure 2.

Cortical regions that characterize the four groups of patients. Brain areas forming part of the early spread network (scored as 2 basing on ictal SEEG) are colored with darker shading, based on the proportion of patients in the group with implication of that area. Brain areas significantly more often involved in one group than the others (value-test > 2) are red bordered. Architectonic subdivision of lateral and medial prefrontal Brodmann areas according to (Petrides & Pandya, 1994).

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regions within the frontal lobe, mostly corresponding to Brodmann's areas (BA; Fig. 2). We analyzed the time-window from electrical onset to full emergence of all semiologic elements (that is until clinical semiology is completed), in order to identify the subset of anatomic structures underlying the period of production of ictal signs. We termed these regions the "early spread network" to distinguish this from the epileptogenic zone (defined as the region of primary organization of ictal discharge; Bancaud et al. (1965)), since in the present study we were interested not only in zone of seizure onset but also early propagation of ictal discharge within the cortical network during appearance of clinical signs.

We thus estimated the level of participation of each region by taking into account the earliness of appearance of ictal activity in that structure as well as degree of change (in frequency, amplitude, or rhythmicity) compared to preictal activity in the same structure. A structure not involved by seizure activity, namely without any EEG modification, was scored as 0, while a structure immediately involved at electrical onset by a low voltage rapid discharge (LVRD) was scored as 2. The intermediate score 1 was used when ictal activity was seen later (after initial electrical onset but within time window of appearance of all clinical features) or when this consisted of lower frequency rhythmic activity, for instance theta or alpha discharge. In the rare case of seizure discharge characterized by slower rhythmic activity (for example spike wave) rather than the usual pattern of LVRD, regions immediately showing EEG change were scored as 2, whereas regions with delayed changes were scored as 1.

In this way two matrices, respectively, encompassing 31 (clinical signs) and 24 (brain areas) variables, scored 0–1–2 for each of the 54 patients, were obtained.

Statistical analysis

Based on these two matrices (signs × patients and areas × patients) two dissimilarity matrices were computed, which were used to perform automatic hierarchical cluster analysis (R software version 2.13.1; R Core Development Team, 2013). Cluster analysis allows ordering of variables such that the proximity of variables within the dendrogram represents their degree of similarity. In other words, signs more commonly occurring together during seizures, or areas more commonly involved together by ictal discharge, appear close to each other. An ordered sequence of ictal signs and another of brain areas were thus obtained, each arranged according to the frequency of their co-occurrence. A correlation matrix between these sequences of signs and areas was then computed in order to demonstrate the relationship between ictal symptoms and involved areas, and to measure the strength of this association. The Kendall correlation test was finally used to assess the significance at $p < 0.05$ for each correlation.

In a second step, given the large number of examined clinical features, principal component analysis (PCA) was performed in order to convert all possibly correlated variables (signs) into a smaller number of linearly uncorrelated variables (principal components). These components account for the largest possible variance, in decreasing order from the first to the last component. As a result the size of the transformed data is reduced and the first components are able to best explain the variance in the data. Because the scores used to represent the degree of presence of signs (0, 1, or 2) are ordinal data, we performed PCA on score ranks in order to better represent the scores and their intrinsic ordinal information.

Lastly, patient position within the new lower-dimensional space supplied by PCA was computed, as defined by ictal signs used as coordinates. Using these new coordinates, hierarchical clustering was performed, aiming to distinguish clinically homogeneous groups of patients.

Semiologic features and involved cortical regions were analyzed with respect to the resulting clusters of patients. For each variable and in each group, the difference was calculated between the mean for patients belonging to that group, and the mean for patients belonging to the other groups. This was expressed in units of standard deviation from the mean (value-test ≥ 2). This enabled identification of the most characteristic clinical features and the most typically involved brain areas.

Results

General characteristics, semiologic features, and SEEG findings

Twenty-two of the 54 patients were male and 32 were female. Mean age at recording was 24.9 ± 9.5 years; mean epilepsy duration was 16.9 ± 8 years. Half of the series (27/54) had normal MRI. Following SEEG exploration, 35 patients (65%) underwent surgical resection. In some patients, due to location of seizure organization (e.g., involving Broca's area or motor cortex), surgery with curative intent was not possible, since resection had to be limited according to functional data; if performed surgical procedures (e.g., gamma knife radiosurgery or callosotomy) were thus not expected to result in seizure freedom but rather in a palliative effect. One patient is awaiting surgery, delayed because of other health problems. Seven had gamma knife radiosurgery. Surgery was contraindicated on the basis of SEEG findings in 8 of 54 patients. Three patients who were considered operable eventually declined surgery, one because of improvement in seizures and two because of other health problems. Of the patients having undergone resection with at least 24 months follow-up (n = 32), 19 are in International League Against Epilepsy (ILAE) class 1 (59%), one in class 2, 2 in class 3, 5 in class 4, and 5 in class 5 (Wieser et al., 2001). In terms of histopathology (n = 33), 19 (58%) had focal dysplasia or dysembryoblastic neuroe-

pithelial tumor and 14 (42%) had gliosis, ectopic neurons, or other nonspecific change. Of those who became seizure free (ILAE class I), two thirds (12/19) had focal cortical dysplasia, whether visible (3/12) or not (9/12) on MRI.

A total of 374 seizures were recorded with SEEG and analyzed. Two to 60 (mean 11, median 7) seizures were recorded per patient, with seizure duration from 2 s to a maximum of 2.5 min (median 29 s) in 52/54 patients. In two patients seizures were longer and lasted a maximum of 10 min.

In all recorded seizures, clinical signs began after appearance of SEEG ictal discharge. Time from electrical onset to completion of clinical semiology was generally short, ranging from 1 to 12 s (median 4 s); shorter values usually occurred with predominantly motor/premotor cortex onset and longer values with prefrontal onset. The interval between electrical and clinical onset varied from 0.5 to 10 s (median 3 s). However, in five patients this delay was particularly long, due either to subtle, gradual onset of clinical symptomatology or to a slow "buildup" of ictal discharge.

We observed as a global tendency in all patients' seizures that ictal discharge with onset in prefrontal or premotor regions, when it did not remain local, propagated toward more caudal regions (respectively, premotor and precentral). Conversely, propagation in the opposite direction, that is from caudal to rostral frontal areas, was not observed in this series.

The occurrence of each ictal sign, and anatomic structures involved in the early spread network, were noted for each patient. For the whole group, elementary motor signs occurred in 72.2% of patients; gestural motor behavior in 46.3%; any form of facial change in 63%. Facial change included the "chapeau de gendarme," a characteristic downturned appearance of the mouth produced by bilateral lip and chin contraction; other facial change included emotional facial expression or fixed neutral facial expression. Impairment of consciousness occurred in 74.1% of cases; autonomic signs (altered cardiac rate/rhythm, pallor, facial flushing, sweating, nausea/vomiting, piloerection, or micturition) in 51.9%; any kind of aura in 39%; and secondary generalization in 16.7%.

Cluster analysis and anatomic-electroclinical correlations

Clinical features and brain areas belonging to the early spread network as classified with hierarchical cluster analysis are shown in Figure 1. Semiologic features are subdivided into two main groups, one comprising exclusively almost all elementary motor signs and the other one including the remaining signs, namely emotional features (objective or subjective), gestural motor behavior, stereotypies, and autonomic changes (Fig. 1B). Smaller clusters at a lower level indicate ictal signs, which are most frequently present together during seizures, such for instance somesthetic localized aura, contralateral versive signs, contralateral tonic posture, and early clonic signs. Cluster analysis of brain regions allows grouping together of motor, premotor and caudal prefrontal regions, separated from rostral prefrontal regions. In addition smaller groups of brain structures grouped together at lower cluster levels also show strong associations; for example SMA, lateral BA6 and caudal cingulate cortex (BA24c); rostral cingulate cortex (BA32), frontal pole (BA10) and other rostrolateral prefrontal regions (Fig. 1A).

Matrix correlation between ictal signs and involved cortical areas, ordered as a function of their reciprocal distance obtained with clustering, shows a diagonal pattern of correlation (Fig. 1C), which follows the posterior-anterior axis of the ordered brain areas. Red-orange squares indicate positive correlation (sign always seen in association with a given brain area) and green squares indicate negative correlation (sign never seen in association with a given brain area). This indicates that certain clinical features occurring together (e.g., early clonic signs, contralateral versive signs, contralateral tonic posture, and somesthetic localized aura) are correlated with certain cortical areas involved together and located in the more caudal regions (namely, primary motor cortex, rolandic operculum). At the opposite corner, other groups of clinical features (e.g., staring, speech arrest, manipulation behavior, and fixed facial expression) are correlated with the more rostral and frontopolar region, thus forming an anatomic rostrocaudal gradient according to the occurrence of ictal clinical signs. Such a diagonal structure is conserved for significant correlation ($p < 0.05$; Fig. 1C, starred squares).

Matrix correlation also shows that certain signs, or groups of signs according to cluster analysis, are associated with different brain regions with varying degrees of specificity: for example, early clonic signs are correlated only with the more posterior regions and manipulation behavior only with the more anterior prefrontal regions. On the other hand, some features, such as hyperkinetic movements or impairment of consciousness, present a weaker association with multiple areas, being correlated with both caudal and rostral prefrontal regions. Therefore, certain semiologic features or patterns seem to be specific to certain systems, whereas others are more "distributed" and thus less valuable indicators of localization along this rostrocaudal axis.

PCA yielded three principal components accounting for 42.36% of variance, thus resuming 31 clinical signs in three groups of signs (which are shown in Table S1). Hierarchical classification of patients according to occurrence of clinical signs, based on the new coordinates obtained by PCA, results in clusters of clinically homogeneous patients (Figs. S1 and S2). The cluster arborization can be cut at progressively lower levels producing ever-smaller subgroups of patients, each sharing specific semiologic features. A cut was chosen that resulted in four main groups, allowing distinction of clusters with sufficient size and clinical homogeneity (Fig. S2). Each group of patients is characterized by a number of

Table 1. Semiologic features for the four groups of patients obtained with hierarchical clustering performed on new PCA coordinates

Group 1		Group 2		Group 3		Group 4	
v-Test	Sign	v-Test	Sign	v-Test	Sign	v-Test	Sign
4.59	Early clonic signs*	4.38	Symmetric proximal/axial tonic posture*	7.16	Distal stereotypies*	5.77	Negative emotional/affective expression*
3.76	Elementary motor signs*	3.76	Nonintegrated gestural motor *	5.33	Fixed facial expression*	4.58	Feeling of fear/anxiety/rage*
3.61	Proximal/distal contralateral tonic posture*	3.75	Chapeau*	4.97	Integrated gestural motor behavior*	4.21	Speech production*
3.56	Somesthetic localized aura*	2.43	Nonlocalized aura*	4.86	Manipulation/utilization*	3.94	Integrated gestural motor behavior*
3.45	Contralateral versive signs*	2.24	Elementary motor signs	3.00	Positive emotional/affective expression*	3.04	Autonomic signs*
3.33	Asymmetric tonic posture*	2.12	Vocalization (grunt, etc.)	2.90	Proximal stereotypies*	2.49	Nonlocalized aura*
3.16	Tonic vocalization*	−2.00	Manipulation/utilization	2.66	Impairment of consciousness*	2.47	Hyperkinetic motor behavior*
2.04	Generalized tonic–clonic seizure (GTCS)	−2.17	Speech production	2.07	Speech production	2.09	Impairment of consciousness
2.01	Rictus/asymmetric facial contraction	−2.19	Fixed facial expression	−2.07	Ipsilateral versive signs	−3.39	Elementary motor signs*
−2.08	Speech production	−2.57	Early clonic signs*	−2.09	Proximal/distal contralateral tonic posture		
−2.09	Negative emotional/affective expression	−2.94	Distal stereotypies*	−2.15	Late clonic signs		
−2.09	Chapeau	−3.34	Integrated gestural motor behavior*	−2.40	Symmetric proximal/axial tonic posture*		
−2.10	Nonintegrated gestural motor			−2.51	Tonic vocalization*		
−2.11	Autonomic signs			−4.73	Elementary motor signs*		
−2.19	Hyperkinetic motor behavior						
−2.21	Distal stereotypies						
−2.36	Proximal stereotypies*						
−2.59	Feeling of fear/anxiety/rage*						
−3.12	Integrated gestural motor behavior*						
−3.78	Impairment of consciousness*						
−3.83	Nonlocalized aura*						

Ictal signs typically present in a group are identified by positive value-test (>2, green colored), whereas typically absent ictal signs are identified by negative value-test (<2, red colored).*p-value < 0.01; p-value < 0.05.

positive and negative signs, a positive sign being a distinctive clinical feature of that group and a negative sign being a clinical feature typically absent (Table 1). Similarly, involved brain areas were analyzed as a function of the resulting homogeneous groups of patients and the characteristics of the early spread networks obtained for each group (Fig. 2).

Value-test > 2 for variables not used to build clustering indicates that the occurrence of variable(s), namely of involved brain area(s), in one group is significantly different to its occurrence in the whole population. For active variables, that is, for ictal signs used to construct the hierarchical cluster, the value-test represents a measure of similarity between specific ictal sign(s) and groups.

Group 1, composed of 16 patients, is characterized by the presence of one or more of the following elementary motor signs: clonic signs, contralateral tonic posture, contralateral versive signs, asymmetric tonic posture, secondary generalization, or asymmetric facial contraction. Somesthetic localized aura and tonic vocalization could also typically occur in these patients. Moreover, this group is characterized by the absence of gestural motor behavior and of emotional features (Table 1, group 1). Significant involvement (value-test > 2) of rolandic cortex (BA 4) and rolandic operculum (low BA4; red bordered in Fig. 2), as well as parietal cortex occurred in this group; involvement of other caudal regions could also be present, particularly lateral and medial premotor cortices (Fig. 2). Ictal discharge could involve both medial and lateral premotor regions at onset, or propagate from lateral to medial aspect, or more rarely in a mesiolateral direction.

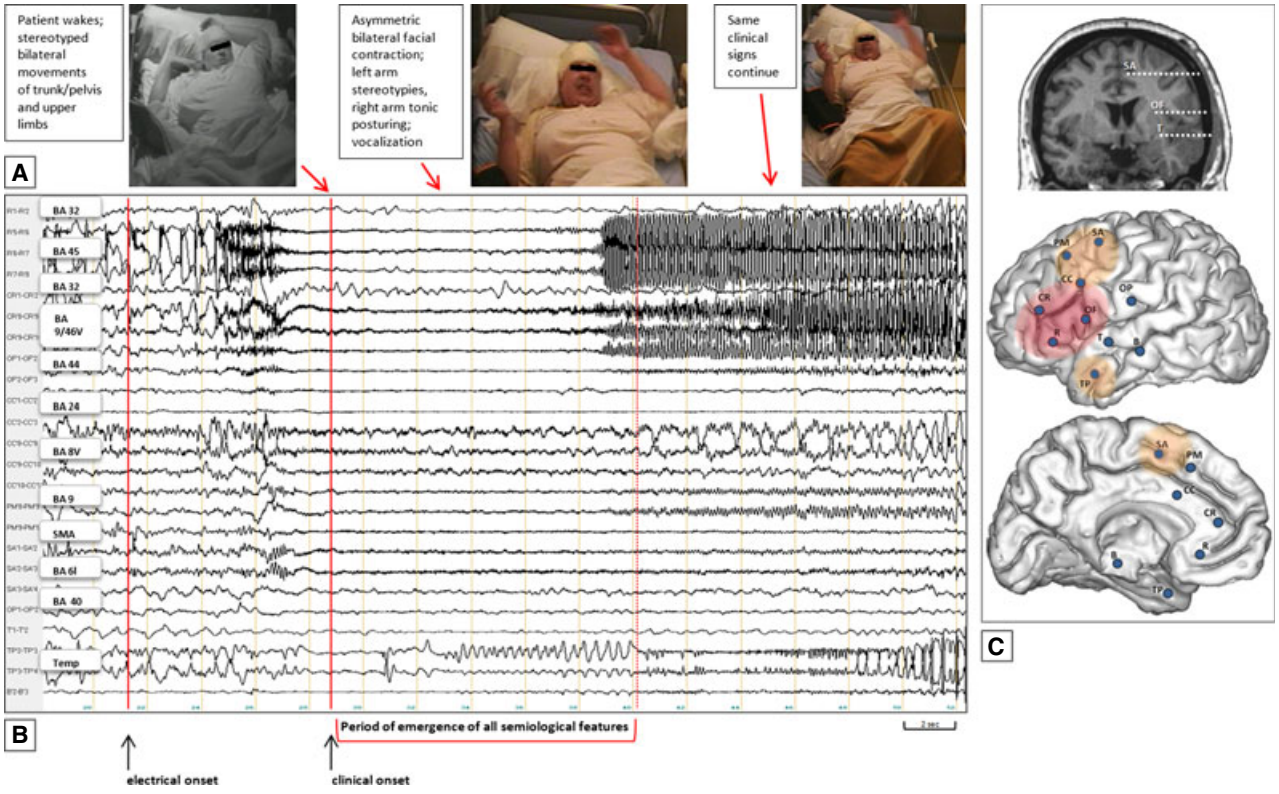


Figure 3.

Anatomic-electroclinical features of a patient from group 2. (**A**) Semiology is characterized by nonintegrated gestural motor behavior with proximal stereotypies of pelvis, trunk, and left upper limb; elementary motor signs (asymmetric bilateral facial contraction, tonic/dystonic posture of right upper limb); and vocalization. (**B**) Ictal SEEG shows increasing synchrony, rhythm, and amplitude of interictal spikes and superposition of a low voltage rapid discharge at electrical onset in the ventrolateral prefrontal cortex (BA 45, BA 9/46V, BA 44; red-colored in box C), followed at clinical onset by a less tonic low voltage fast activity involving premotor and posterior lateral prefrontal areas (BA 8V, BA 9, SMA and lateral BA 6; orange-colored in box C) and by a rhythmic slower activity in the temporopolar region (orange-colored in box C). (**C**) Coronal view of patient's T_1 MRI with three implanted electrodes and lateral and medial view of all implanted depth electrodes on a three-dimensional (3D) reconstruction of the neocortical surface of the brain. Regions showing major involvement in the generation of the ictal discharge are colored in red and regions showing minor involvement in orange. BA, Brodmann area. Electrodes labels: B = Hippocampus; CC = BA 8V (external contacts), BA 24 (internal contacts); CR = BA 9/46V (external contacts), BA 32 (internal contacts); OF = BA 44; OP = BA 40; PM = BA 9 (external contacts), pre-SMA (internal contacts); R = BA 32 (external contacts), BA 45 (internal contacts); SA = lateral BA 6 (external contacts), SMA (internal contacts); TP = temporal pole; T = superior temporal gyrus.

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Group 2 (23 patients) was characterized by the co-occurrence of elementary motor signs (typically symmetric axial tonic posture and facial contraction such as "chapeau de gendarme") and nonintegrated gestural motor behavior. In this more heterogeneous group, nonlocalized aura and more complex nonverbal vocalization were also frequently present, whereas integrated gestural motor behavior, distal stereotypies, early clonic signs, and fixed facial expression never occurred (Table 1). Nonintegrated gestural motor behavior could include proximal stereotypies and could have a hyperkinetic character or not (example illustrated in Fig. 3). Frequent co-involvement of both pre-motor and lateral prefrontal regions occurred. Ictal discharge could involve both medial and lateral aspect at onset. The more frequent propagation pattern was from lateral to medial regions. However, ictal discharge originating in medial premotor areas (SMA and pre-SMA) could propagate to lateral premotor regions (Fig. 2).

Typical semiologic features of group 3 (10 patients) were the following: integrated gestural motor behavior with distal stereotypies, fixed facial expression or, alternatively, positive emotional expression, proximal stereotypies, and speech production. On the other hand, the absence of any elementary motor sign was a significant characteristic of these patients (Table 1). Early spread network underlying these clinical manifestations involved rostral prefrontal ventrolateral regions (BA 47/12, BA 10, BA 11, BA 46) and the rostral cingulate gyrus (BA 32 and rostral BA 24; Fig. 2). A peculiarity of this group was systematic co-involvement of ventrolateral prefrontal cortex and anterior cingulate area, either simultaneously at seizure onset or by propagation in a lateromedial direction.

Group 4 was composed of five patients presenting with integrated gestural behavior of fear, sometimes hyperkinetic, with attempt to fight or to escape, frightened facial expression, sometimes screaming or swearing, and autonomic signs. Elementary motor signs never occurred and underlying involved regions corresponded to the orbital and medial-prefrontal network (BA 14, BA 32 and 24r, BA 10) with propagation to amygdala and anterior temporal regions (Fig. 2), but not propagation to lateral frontal cortex.

The distinctive early spread networks of each semiologically distinct group of patients are shown in Figure 2, with partial overlap between groups of areas as defined by hierarchical clustering (Fig. 1).

Discussion

In this study we report electroclinical characteristics of 54 patients with frontal lobe seizures, looking for characteristic semiologic traits that localize the likely zone of seizure organization. Despite the complex systems involved, and the large number of semiologic variables studied, our results do allow identification of electroclinical patterns, providing a comprehensive overview of this population. Notably two main results were evidenced: the separation of patients into groups according to similarity of semiologic pattern, which correlated with topography of the brain regions involved; and the demonstration that these groups should not be seen as rigid categories but rather bands within a spectrum organized along a rostrocaudal axis. This was possible due to the chosen methodology, in which a large number of consecutive frontal patients were explored using SEEG, with categorization of their semiologic traits, and analysis of not only initial seizure discharge but also propagation pathways during the period of production of ictal signs. Evaluation of this early spread network was indeed crucial in perceiving the relevance of different semiologic patterns to seizure localization, and perhaps helps to explain why certain previous works have not demonstrated a clear relationship between semiologic picture and anatomic substrate across different frontal seizure types (Manford et al., 1996; So, 1998; Rheims et al., 2008).

Categorization of frontal seizures: subgroups or spectrum?

Electroclinical subgroups

Cluster analysis was chosen as the method ideally suited to identify similarities in this a priori heterogeneous population characterized by complex data. Moving anteriorly from the central sulcus results can be summarized as follows: in group 1, seizures were organized within precentral and/or premotor regions, characterized by elementary motor signs with no gestural motor behavior. Within this group distinction can be made between predominantly precentral and premotor patterns. However, "pure" premotor seizures proved to be rare (Ajmone-Marsan & Goldhammer, 1973; Chauvel et al., 1992). The next group moving anteriorly (group 2) is an intermediate one, characterized by nonintegrated gestural motor behavior associated with proximal tonic posturing and facial contraction; the presence of tonic signs that hindered movement magnified the disjointed appearance of motor behavior. Seizures arising from this zone overlapping premotor and posterior prefrontal regions, including the dorsolateral prefrontal convexity, have traditionally remained the most difficult to define (Bancaud & Talairach, 1992). The two anterior prefrontal groups (groups 3 and 4) both manifested integrated gestural motor behavior but no elementary motor signs. As in group 2, both hyperkinetic and normokinetic gestural motor behavior could be observed, not only within the same group of patients, but also in the same patient from one seizure to another, rending this feature per se not a useful indicator of seizure localization. Group 3 seizures primarily involved lateral prefrontal cortex and/or frontal pole, with projection of seizure activity toward anterior cingulate cortex, characterized by gestural motor behavior incorporating distal stereotypies. Grasping or clutching as a semiologic feature occurs more frequently in seizures arising from frontal than

extrafrontal regions (Gardella et al., 2006; Leiguarda et al., 2008), evoking similar phenomena observed outside the context of seizures such as utilization behavior. A previous stimulation study of anterior cingulate gyrus provoked grasping and hand-to-mouth movements (Talairach et al., 1973). In Group 3 behavior, was either apparently devoid of emotional content, or conversely manifested positive emotional expression (joviality, with singing or humming), in which the stereotypies formed part of an overall behavior appropriate to the emotional expression (e.g., rocking and tapping in time to music). In contrast in group 4, seizures arising from ventromedial prefrontal cortex were typified by fearful emotional expression associated with (nonrepetitive, and therefore nonstereotyped) gestural motor behavior evoking a defensive or attacking reaction. The clinical aspect is in keeping with previous descriptions including the original observation of "orbitofrontal seizures" (Tharp, 1972; Ludwig et al., 1975; Williamson et al., 1985). The electroclinical pattern also resembles "type 1 hypermotor seizures (HMS1)" (Rheims et al., 2008), with the important exception that movements were not invariably hyperkinetic in the present study. That the "fearful" seizure pattern was so reproducible between patients likely relates in part to the fact that the paralimbic temporopolar-insular-orbitofrontal network forms a clearly defined and relatively isolated anatomic system (Mesulam & Mufson, 1985), with subcortical outputs but limited connections to other cortical structures (Damasio, 1998; Ghashghaei et al., 2007); its role in seizures involving fearful behavior has been discussed previously (Devinsky et al., 1995; Biraben et al., 2001; Bartolomei et al., 2005; Nobili et al., 2007).

Electroclinical spectrum following a rostrocaudal gradient

Although the present results can therefore readily be expressed as clusters, these should not, however, be regarded as rigidly separated compartments. There is in fact a gradual transition both in terms of ictal semiology and underlying early spread networks, between the four clinical subgroups described, forming a continuum along a rostrocaudal axis. This is illustrated by the matrix correlation between ictal signs and involved brain regions, clearly demonstrating the clinical spectrum developing from rolandic cortex to frontal pole. The most highly integrated behavior was produced by seizure activity arising from rostral prefrontal regions, becoming progressively less integrated in posterior prefrontal regions; in even more posterior motor regions, exclusively elementary motor signs (with no gestural component) occurred. A transition within groups as well as between groups was thus seen. Indeed the most anterior prefrontal seizures, characterized by the most integrated behavior, were immediately striking, since because of their resemblance to normal behavior patterns, for the observer analyzing the semiology, the globally naturalistic appearance of ictal behavior dominated its individual elements, hence our use of the term "integrated." This was quite different from the most posterior prefrontal seizures in which disparate semiologic elements, while complex in their composition, did not allow for instinctive recognition of any fragments of "normal" seeming behavior. However, the most anterior seizure localizations of the intermediate group 2, at the border zone between the premotor-prefrontal and purely prefrontal seizures, could show rhythmic coordinated movement (body rocking) that started to approach the more clearly integrated behaviors of groups 3 and 4. In addition, for group 2 seizures, semiologic differences reflected relative contribution of prefrontal and premotor structures, since seizures arising more anteriorly showed evident (non-integrated) gestural motor behavior relatively unrestricted by tonic posturing, whereas more posterior seizure organization produced prominent tonic posturing that seemed to hinder expression of gestural behavior.

Integrated behavior and the rostrocaudal axis

The concept of integrated behavior is thus fundamental to appreciating this spectrum of frontal seizure patterns. Integrated behavior describes an overall comportment encompassing complex sequences of movement organized in a congruous manner, appropriate to the current state of the organism, its environment, and goals. Observation, description and categorization of such behaviors are clearly difficult (Barlow, 1996). The notion of "syntactic sequence" has previously been used to help characterize motor behavior in neuroethologic and neurobiologic studies (Lashley, 1951; Berridge et al., 2005). Understanding the role of prefrontal cortex in producing integrated behavior remains a great challenge (Goldman-Rakic, 1988).

Our observations regarding the rostrocaudal pattern of semiologic expression in frontal seizures echo current thinking on the rostrocaudal hierarchy of frontal lobe function (Koechlin et al., 2003; Badre & D'Esposito, 2009). Integrated appearance of ictal behavior seems likely related to pathologic activation of established prefrontal circuits that would normally be brought into play in production of specific goal-directed behaviors (Pickenhain, 1988), or in emotional responses such as fear (Damasio, 1998). Although some motor acts are common to many species and programmed such that they may be performed in a largely unconscious manner (for example, the movements of locomotion), more complex behavior necessarily involves more flexibility and variability, being more directly influenced by emotional state or environmental cues as well as by individual experience. It therefore seems logical that prefrontal seizures should involve such diverse and variable ictal manifestations, in contrast to the much narrower repertoire of premotor seizures, for example.

Is medial versus lateral distinction a reliable indicator for localization?

Although the anteroposterior axis thus clearly emerged both in terms of preferential direction of propagation of

individual seizures and discrimination of different anatomic-electroclinical subgroups of semiologic patterns, a similar organization was not observed for the mesiolateral axis. During the time lapse of the early spread, as defined above, characteristics of a semiologic trait could not be attributed only to the lateral or medial origin of the discharge, but also to the medial or lateral pattern of its propagation. For instance, there was a clear tendency for ictal discharge beginning in lateral prefrontal cortex to propagate to medial structures, notably the anterior cingulate region and the pre-SMA, or for ictal discharge beginning in the SMA and pre-SMA to propagate to lateral areas 6 and 8. Primate frontal lobes are characterized by strong cortico-cortical connections from lateral prefrontal cortex to pre-SMA, SMA, and anterior cingulate cortex (Barbas & Pandya, 1989; Bates & Goldman-Rakic, 1993; Devinsky et al., 1995; Morecraft & Tanji, 2009). It seems likely that, even in dorsolateral or ventrolateral prefrontal seizures, projection to medial structures plays an important role in producing the observed motor semiology. Indeed the medial premotor and cingulate regions could be seen as a "final common pathway" for anterior frontal lobe seizure organization.

Stereotypies in frontal seizures

Stereotypy within overall gestural behavior, in its different distal and proximal forms, proved to be an important semiologic category, which allowed distinction between anterior and posterior prefrontal involvement. In addition, stereotypies were predominantly associated with seizures in which lateral prefrontal cortex was involved at onset, projecting to anterior cingulate cortex and/or pre-SMA (Fig 2). The definition of stereotypy has been recently revisited (Edwards et al., 2012). Animal and human models of reduced movement repertoire with abnormal perseveration of one movement pattern have led to identification of physiologic and pathophysiologic roles of specific basal ganglia circuits in producing such movements (see Graybiel, 2008 for review). The developmental role of stereotypies in motor learning has been proposed (Graybiel, 2008; Edwards et al., 2012). In human seizure semiology it has been suggested that "fixed action patterns" such as locomotion are produced via a release mechanism, that is, impairment of higher cortical control over subcortical structures (Tassinari et al., 2005); a possible direct effect of cortical activity on subcortical circuits has also been evoked (Gardella et al., 2008). The findings of the present study, with striking reproducibility of seizure patterns in individual patients, indeed argue in favor of a structured basis of even the most complex ictal behaviors. Considering the pathophysiologic basis of prefrontal seizures within a connectionist context (Fuster, 2001), the recurrence of characteristic ictal motor sequences could indicate a process of "learning" due to seizure activity repeatedly occurring within the cortical compartment of the same cortico-subcortical circuit, becoming progressively more fixed with repetition. Known anatomofunctional separation of specific frontostriatal connections (Alexander & Crutcher, 1990) would seem highly relevant to this hypothesis. Better understanding of the role of subcortical structures in defining seizure networks and their semiologic expression thus offers an intriguing direction for future research.

The clinical utility of such correlations between semiology and anatomy is twofold. In epilepsy surgery, successful operation results from accuracy of presurgical electrode implantation anatomic planning. As this planning cannot exhaustively sample the brain, its strategy hinges upon the localization, beyond a putative lesion, of an epileptogenic network expressing clinical semiology. Because the epileptogenic zone and early spread network are intimately connected, localizing the latter through analysis of its semiologic expression provides access to the region of seizure onset. Furthermore, even in "lesional" cases where surgery can be achieved without invasive presurgical assessment, preoperative surgical planning takes account of anatomic-electroclinical correlations to encompass the same network, in order to augment the chances of postoperative seizure freedom. Because the proposed electroclinical categorization offers pointers as to the likely zone of seizure organization, the present results concern a much wider group of epilepsy patients. The data described here are of interest with regard to guiding imaging postprocessing, particularly where initial MRI appears normal, since localizing a region of interest through electroclinical data facilitates subsequent identification of subtle but detectable lesions. Indeed in one study of surgical outcome of MRI-negative epilepsies, eight of nine patients with initially negative MRI were subsequently found to have visible lesions once the zone involved was known and the MRI restudied (Bien et al., 2009). In the light of the present data, prevailing pessimism regarding the localizing value of semiologic patterns in frontal seizures thus appears to be unjustified; with the caveat that, particularly for seizures not confined to primary areas, clinical expression should be viewed as arising from excessive activation of brain networks at the macroscale level, rather than being symptomatic of outward spread of focal discharges to neighboring normal, passively driven, cerebral cortex.

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Disclosure

None of the author has any conflict of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. First three components issued from PCA performed on score ranks accounting for 44.36% of variance.

Figure S1. Patients' position in PCA space colored as a function of resulting clusters: the first two components are represented in Figure 1A and the first three components are represented in Figure 1B.

Figure S2. Hierarchical classification of patients based on PCA-resulting space distinguishes four homogeneous groups.