Neural network underlying ictal pouting (“chapeau de gendarme”) in frontal lobe epilepsy

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ARTICLE INFO

Article history:
Received 17 May 2014
Revised 5 July 2014
Accepted 7 July 2014
Available online 9 August 2014

Keywords:
Frontal lobe epilepsy
Anterior cingulate cortex
Focal cortical dysplasias
Intracranial recordings
Ictal semiology

ABSTRACT

In order to determine the anatomical neural network underlying ictal pouting (IP), with the mouth turned down like a “chapeau de gendarme”, in frontal lobe epilepsy (FLE), we reviewed the video-EEG recordings of 36 patients with FLE who became seizure-free after surgery. We selected the cases presenting IP, defined as a symmetrical and sustained (>5 s) lowering of labial commissures with contraction of chin, mimicking an expression of fear, disgust, or menace. Ictal pouting was identified in 11 patients (8 males; 16–48 years old). We analyzed the clinical semiology, imaging, and electrophysiological data associated with IP, including FDG-PET in 10 and SEEG in 9 cases. In 37 analyzed seizures (2–7/patient), IP was an early symptom, occurring during the first 10 s in 9 cases. The main associated features consisted of fear, anguish, vegetative disturbances, behavioral disorders (sudden agitation, insults, and fighting), tonic posturing, and complex motor activities. The epileptogenic zone assessed by SEEG involved the mesial frontal areas, especially the anterior cingulate cortex (ACC) in 8 patients, whereas lateral frontal onset with an early spread to the ACC was seen in the other patient. Ictal pouting associated with emotional changes and hypermotor behavior had high localizing value for rostroventral “affectve” ACC, whereas less intense facial expressions were related to the dorsal “cognitive” ACC. Fluorodeoxyglucose positron emission tomography demonstrated the involvement of both the ACC and lateral cortex including the anterior insula in all cases. We propose that IP is sustained by reciprocal mesial and lateral frontal interactions involved in emotional and cognitive processes, in which the ACC plays a pivotal role.

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1. Introduction

Changes in facial expression have been reported in frontal lobe epilepsy (FLE) but have not been related to a specific region [1–6]. The facial manifestations are often embedded in a set of noisier events, such as complex and bizarre behavior or sudden agitation, and are rarely described separately. Among them, we identified a particular facial feature characterized by the turned-down mouth, traditionally described in French as the “chapeau de gendarme”, referring to the shape of the gendarme’s hat at the time of Napoleon 1st. This ictal pouting (IP), mimicking an expression of fear, displeasure, or disgust, appears frequently enough during partial seizures to draw attention. Consisting of an inverted smile with puckering of the mouth, it seems rather to correspond to a behavioral manifestation than to a motor symptom and belongs to the FLE spectrum since it is not, to our knowledge, observed in other localizations. The aims of our study were to understand the significance of this sign, to identify the neural network underlying the so-called “chapeau de gendarme” in FLE, and to assess its potential value as a means of localizing seizures in the frontal lobe. We postulated that IP could be related to the involvement of mesial frontal areas, especially the anterior cingulate cortex (ACC).

2. Patients and methods (flow chart: Fig. 1, Table 1)

We included all patients who 1) were operated on in our institution for drug-resistant partial epilepsy between 1992 and 2011 (n = 598); 2) underwent surgical resection in the frontal lobe, excluding the central area (n = 79); 3) were seizure-free after surgery during a minimum follow-up of 2 years (n = 55); 4) had at least one usual seizure analyzable using surface or depth EEG recordings without early secondary generalization (n = 45); and 5) presented facial changes clearly analyzable on video recordings (n = 36). All video recordings of these 36 patients were reviewed in detail. One of the authors (ZS) performed a first independent clinical analysis, followed by confirmation by two others (EL and FC) and reconsideration by consensus in case of discrepancy. To reduce individual clinical variability, seizures were considered representative when corresponding to the most usual seizure type for each patient. Ictal pouting was defined as a turned-down mouth with symmetrical sustained (>5 s) lowering of the labial commissures and commonly accompanied by contraction of the chin. Grinning with
horizontally stretched mouth and asymmetric attraction of the lips were ruled out. Eleven patients fulfilled all these criteria and constituted the studied population.

Magnetic resonance imaging was available for all patients and interictal 18F-FDG-PET scan for 10 of them, the latter all being performed after 2000. Nine patients underwent stereoelectroencephalography (SEEG). Engel’s class I outcome [7] was obtained in all patients (2–to 20-year follow-up, mean: 8). A total of 37 seizures were analyzed (2–7/patient, mean: 3.36). Clinical features were classed as preceding, simultaneous with, or following IP. Seizure duration was calculated from the first change of activity on EEG preceding the clinical manifestations. Ictal pouting chronology (occurrence and duration) was calculated using the same criteria and was classified as early (occurring during the first 10 s after the discharge onset) or late (>10 s after the discharge onset). In patients who underwent SEEG, ictal electrical onset was defined as a low-voltage fast discharge preceded by a burst of high amplitude spikes. Seizures elicited by electrical stimulations were compared with spontaneous seizures. Precise correlations distinguishing onset seizure zone and ictal discharge spread [8] allowed us to identify accurately the neural network underlying IP. Fluorodeoxyglucose positron emission tomography examination was done using either a head-dedicated PET camera with 5.8-mm in-plane and 5-mm axial resolution (ECAT 953/31B Siemens: 3 patients) or a 3D camera allowing axial sampling of 2.46 mm (HR + CTI Exact Siemens, Knoxville, TN, USA: 7 patients). Fluorodeoxyglucose was injected intravenously at a mean dose of 220 MBq/70 kg body weight. Reconstructed images were corrected for attenuation using transmission scans obtained from a germanium source. Positron emission tomography findings were visually analyzed after superimposition on MRI. In addition, statistical analysis was performed using statistical parametric mapping (SPM5, Wellcome Department of Cognitive Neurology, London, UK), as previously described [9]. Briefly, normalization and smoothing of 18F-FDG-PET images were performed using a homemade adult template. The parametric image of each patient was compared with that of a group of 30 healthy subjects using a t-test analysis. The p-value was fixed at 0.005 and a 20-voxel correction was applied.

All patients gave informed written consent for photographs of their face during seizures to be published, and the study was approved by the local ethics committee.

3. Results (Table 1)

3.1. Clinical data

In the 11 selected patients (8 males; mean age: 28 years, range: 16–48), IP was found as an early symptom occurring during the first 10 s of the seizure in 9 patients and during the first half of the seizure in the 2 others (mean onset time: 9 s, range: 5–33; mean seizure duration: 38 s, range: 20–96 [the longest seizure was in a patient with secondary temporal involvement]). According to our definition, IP was easily identified and highly reproducible in each seizure for a given patient (mean duration: 14 s, range: 7–20). Subjective manifestations were reported in 10 patients, mainly consisting of a psychic aura with fear or anguish. A frightened or disgusted expression was observed in 4 patients, whereas a menacing face was seen in 3 others. A less intense emotional face was seen in the remaining patients, with an appearance of suffering, grimacing, or discontent (Fig. 2). Seven patients had their eyes open (with staring in 4 patients), whereas the others had mainly closed eyes during the initial part of the seizure. Hypermotor seizures with sudden agitation and complex motor behaviors (turning, pedaling, waddling, grasping, and fighting) occurred in 7 patients, head turning and/or tonic posturing in 7, and postictal disinhibition with inappropriate laughter in 6. Seven patients had a loss of contact, but consciousness was preserved in the remaining 4 patients. Vegetative symptoms (changes in cardiac or respiratory rhythm, including bradycardia in 1 and apnea in 2, rubefaction, and/or pallor) were observed in 10 cases. All patients had a high seizure frequency (up to 300 seizures/month) with childhood epilepsy onset. Sleep-related epilepsy was found in 6 patients. Neurologic examination was normal in all patients, and no mental retardation was found, but 4 patients had low IQ (<80). Behavioral or psychotic disorders were noted in 3 patients, associated with frontal lobe disturbances in 2 of them whereas the latter were isolated in another patient.

3.2. MRI and histologic findings

In 5 patients, MRI showed typical features of focal cortical dysplasia (FCD) located in the mesial part of the frontal lobe in all cases. Magnetic resonance imaging was negative or doubtful in the 6 others. Focal
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender/age (years)/epilepsy onset/HD/seizure frequency</th>
<th>Neuropsychologic/psychiatric examination</th>
<th>Imaging localization (MRI/PET)</th>
<th>No. of analyzed seizures</th>
<th>SEEG/no. of electrodes</th>
<th>Ictal semiology</th>
<th>IP onset (mean, s)</th>
<th>IP duration (mean, s)</th>
<th>Seizure duration (mean, s)</th>
<th>EZ location ictal onset/spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/18/3/RH 45/month SRE</td>
<td>FLD IQ 73 psychic</td>
<td>Negative MRI, R orbitofrontal (area 11)/ACC/GF/temporal hypometabolism</td>
<td>4</td>
<td>10</td>
<td>Fear, frightened, staring, IP, vocalization, HL head deviation, NV, LC, CL tonic posturing, confusion, laughter, disinhibition</td>
<td>12</td>
<td>10</td>
<td>30</td>
<td>R orbitofrontal cortex-ACC/inferior frontal gyrus</td>
</tr>
<tr>
<td>2</td>
<td>M/20/5/RH 45/month SRE</td>
<td>IQ 76 psychotic</td>
<td>Negative MRI, R inferior frontal (area 24)/insula/ACC temporal hypometabolism</td>
<td>3</td>
<td>10</td>
<td>Anguish, disgusted, NV, LC, IP, vocalization, HL head and eye deviation, CL posturing, confusion, laughter</td>
<td>8</td>
<td>11</td>
<td>20</td>
<td>R inferior frontal gyrus/ACC-insula</td>
</tr>
<tr>
<td>3</td>
<td>M/39/12/RH 10/month SRE</td>
<td>IQ 88 normal</td>
<td>Negative MRI R ACC/insula/temporal hypometabolism</td>
<td>2</td>
<td>9</td>
<td>Abdominal aura, anguish, menacing, staring, agitation, NV, LC, IP, gestural automatism, confusion, inhibition</td>
<td>33</td>
<td>16</td>
<td>96</td>
<td>R ACC-orbitofrontal cortex/insula-temporal lobe</td>
</tr>
<tr>
<td>4</td>
<td>M/48/7/RH 100/month SRE</td>
<td>IQ 108 normal</td>
<td>R ACC FCD, focal hypometabolism (bottom of sulcus)</td>
<td>2</td>
<td>_</td>
<td>Staring, menacing, growling, IP, insulting, agitation, turning</td>
<td>6</td>
<td>14</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>M/16/12/LH 150/month SRE</td>
<td>FLD IQ 98 normal abnormal social behavior</td>
<td>Negative MRI, R ACC/insular hypometabolism</td>
<td>7</td>
<td>11</td>
<td>Fear, frightened, staring, IP, NV, LC, vocalization, turning, waddling, pedaling, grasping, laughter, disinhibition</td>
<td>5</td>
<td>11</td>
<td>33</td>
<td>R ACC/LACC-R insula</td>
</tr>
<tr>
<td>6</td>
<td>M/42/7/RH 300/month SRE</td>
<td>FLD IQ 75</td>
<td>Negative MRI no PET</td>
<td>3</td>
<td>9</td>
<td>IP, menacing, NV, LC, vocalization, CL, head deviation, eyes half-closed, agitation, grasping, sit up straight, fighting</td>
<td>10</td>
<td>19</td>
<td>40</td>
<td>L ACC/orbitofrontal cortex-inferior frontal gyrus</td>
</tr>
<tr>
<td>7</td>
<td>F/16/8/LH 125/month SRE</td>
<td>IQ 105 normal</td>
<td>Negative MRI, L inferior frontal (area 44)/insula/ACC hypometabolism</td>
<td>2</td>
<td>_</td>
<td>Sensation in the CL arm, NV, IP, seems disgusting, HL head and eye deviation</td>
<td>5</td>
<td>15</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>F/18/3/RH 30/month SRE</td>
<td>IQ 89 normal</td>
<td>L mesial prefrontal (area 9) FCD/concordant hypometabolism</td>
<td>2</td>
<td>7</td>
<td>Psychic aura, grimacing, IP, closed eyes, vocalization, NV, LC, CL, head deviation, face and arm cramps, pedaling, disinhibition, confusion, laughter</td>
<td>5</td>
<td>20</td>
<td>48</td>
<td>L mesial prefrontal cortex-ACC</td>
</tr>
<tr>
<td>9</td>
<td>M/29/7/RH 150/month SRE</td>
<td>IQ 100 normal</td>
<td>L mesial prefrontal (area 9) FCD/concordant hypometabolism</td>
<td>2</td>
<td>9</td>
<td>Anguish, suffering, IP, vocalization, closed eyes, NV, LC, sudden agitation, pedaling, waddling, turning, confusion</td>
<td>9</td>
<td>15</td>
<td>40</td>
<td>L mesial prefrontal cortex-ACC</td>
</tr>
<tr>
<td>10</td>
<td>M/40/7/RH 120/month SRE</td>
<td>IQ 123 normal</td>
<td>L mesial premotor (area 8) FCD, concordant hypometabolism</td>
<td>6</td>
<td>8</td>
<td>Psychic aura, grimacing, IP, HL head deviation, blinking, NV, agitation, laughter</td>
<td>6</td>
<td>7</td>
<td>20</td>
<td>L mesial premotor cortex-ACC</td>
</tr>
<tr>
<td>11</td>
<td>M/42/17/RH 120/month SRE</td>
<td>IQ 68 normal</td>
<td>L pre-SMA FCD SMA/ACC/insular hypometabolism</td>
<td>4</td>
<td>7</td>
<td>Cephalic aura, seems worried, IP, closed eyes, NV, CL, posturing, R finger movements</td>
<td>5</td>
<td>17</td>
<td>30</td>
<td>L pre-SMA-ACC</td>
</tr>
</tbody>
</table>

M = male, F = female, HD = handedness, RH = right-handed, LH = left-handed, R = right, L = left, SRE = sleep-related epilepsy, FLD = frontal lobe disturbances, IQ = intellectual quotient, FCD = focal cortical dysplasia, CL = contralateral, HL = homolateral, NV = neurovegetative, IP = ictal pouting, EZ = epileptogenic zone, N = number, LC = loss of contact, ACC = anterior cingulate cortex, SMA = supplemental motor area.
cortical dysplasia type 2 was identified by histology in all cases. It was located within the ACC in 4 patients and in its vicinity in 4 others. In the remaining cases, FCD involved the orbitofrontal region (area 11) in 1 patient and the anterior part of the inferior frontal gyrus (areas 44 and 45) in the 2 others. The surgical resection was performed in the right hemisphere in 5 patients and in the left in 6. Postoperative MRI images showing the extent of the cortical resection are provided in Fig. 3.
3.3. Epileptogenic zone (EZ) organization

In the 9 patients investigated by SEEG, the typical pattern characterizing electrically FCD type 2 [9] was identified. The low-voltage fast discharge corresponding to the seizure-onset zone (Fig. 4) involved the ACC primarily (8 cases) or secondarily (1 case); interestingly, in the latter case, the clinical features including IP only appeared when the ACC was affected by the discharge. Thus, the ACC was included in the EZ or symptomatic zone in all patients (Fig. 5). In addition, when the patients had their eyes wide open or staring with an expression of intense emotion, the rostroventral part of the ACC (affective division) was involved, whereas when the patients had their eyes closed and/or a more neutral expression, the dorsal part (cognitive division) was involved. The neural network including the early spread zones involved the mesial frontal areas adjacent to the ACC (orbitofrontal region and prefrontal and premotor areas), with an early contralateral propagation when bilateral electrodes were implanted (3 patients, Fig. 6). Insular involvement was demonstrated when sampled by depth electrodes (in 3 patients). Noteworthy, the motor cortex and the precentral operculum were never seen to be affected by the rapid discharge, despite the electrodes being placed in these areas in 7 cases. Electrical stimulations allowed us to elicit seizures reproducing the electroclinical spontaneous seizures in all patients either by low frequency (1 Hz, 3 ms, 3 mA) in 2 cases or high frequency (50 Hz, 1 ms) but low intensity (1 to 2 mA) in the other cases. The site of these stimulations was the ACC in 2 cases or the immediately adjacent areas in 4 others, whereas in the 3 remaining patients, it was in the same region but not adjacent to the ACC. In 8 out of 9 cases, IP occurred during the first 5 s of the elicited discharge.

3.4. PET findings

Fluorodeoxyglucose positron emission tomography demonstrated a focal hypometabolism in all cases, encompassing the MRI lesion when visible and the surrounding areas. Focal or regional hypometabolism was identified after coregistration of PET on MRI in the negative or doubtful MRI cases. Hypometabolic areas involved the ACC in 9 out of 10 cases, as well as mesial prefrontal–premotor areas (4 cases), lateral frontal areas and insula (5 cases), and the temporal lobe (3 cases). Statistical parametric mapping analysis was totally or partially concordant with visual analysis in all cases. The main difference consisted of an ACC hypometabolism that was visually detected but was not found by SPM.

Fig. 4. SEEG recording, spontaneous seizures in patient 5. The ictal discharge (low-voltage fast activity preceded by a burst of rapid rhythms) started in the ACC (area 24, depth part of the electrode F and middle part of X, black arrow) and spread to adjacent areas, especially the infragenual ACC (areas 25–33, electrode G), the insula (electrode I), and the contralateral ACC (F'). IP occurred 5 s after the onset of the discharge (red arrow). Note the absence of involvement of the precentral operculum (electrode R). Coregistration of PET on MRI demonstrated a focal hypometabolism in the right ACC, corresponding to the seizure–onset zone. SPM analysis confirmed the presence of a strong hypometabolism in the ACC, bilateral but predominating on the right side.
Fig. 5. Overview of the seizure-onset zone in the 9 patients who underwent an SEEG. The ACC was primarily involved in 8 cases, with a maximal location in the affective division, whereas the cognitive division was involved in 2 cases, and an intermediate location was found in 2 others. Lateral seizure onset (area 45) was observed in only one patient (patient 2), with a secondary spread to the ACC. Affective division (in blue) includes the ventral Brodmann areas (BA) 25 and 33 and the rostral part of BA 24 and 32; cognitive division (in red) includes the dorsal part of BA 24 and 32.

From Bush et al. [27].

Fig. 6. Depth electrode location in the 9 patients investigated by SEEG (the contralateral electrodes are marked in black).
in two patients, whereas in one of them, a temporal hypometabolism appeared predominant (patient 3). Group analysis, separating the patients according to the EZ and FCD location (mesial versus lateral), demonstrated the involvement of both the ACC and the insula, the latter being bilaterally involved in the two groups (Fig. 7).

4. Discussion

In these selected patients with FLE who were thoroughly investigated and seizure-free after surgery, IP was an early symptom, conferring on it a high localization value regarding the EZ. Despite the retrospective nature of the study and the limited sampling of SEEG, we have described a focal and reproducible network that enabled us to establish anatomical and electrical correlations during IP. This discrete sign may go unnoticed among other, noisier manifestations characteristic of hypermotor seizures. It can also be easily missed during nocturnal seizures, while the patient is lying prone, with his or her head on a pillow. However, if detected, IP will be found to be highly reproducible and easily recognizable, and it may help to determine more precisely the region involved by the ictal discharge. Based on a combination of neurophysiologic and metabolic findings, our results provide evidence of the involvement of mesial frontal structures and the crucial role of the ACC in IP generation.

4.1. Ictal semiology in ACC seizures

Whether ictal semiology is reliable for assessing the seizure-onset zone in FLE remains debated [4–6]. Hyperkinetic frenetic behavior has been related to FLE, especially the mesial aspect of the frontal lobe [10]. However, such striking behavior is not considered to be associated with any specific region within the frontal lobe [3,11] and can also originate from the insula [12]. Although a few studies have provided a detailed description of seizures that originated from the ACC, most reported sudden behavioral changes, with intense fright and a facial expression of fear; aggressive verbalizations or acts; complex motor activities including thrashing and kicking, grasping, running, hand shaking, and clapping; oral sphere activities such as spitting, lip smacking, mouth puckering, kissing, or sucking; dyskinetic movements; and inappropriate laughter [1,2,13–16]. Importantly, these motor behaviors can contain very complex and strange gesticulations but often remain in interaction with the environment. Electrical stimulation of the ACC (area 24) elicited behavioral responses, including arousal, motor and oral activities, and intense mood changes [17,18], whereas stimulation of anterior cingulate motor areas elicited reaching/grasping movements [19]. Finally, epileptic discharges involving the ACC induce behavioral changes and complex motor activities that can be modulated by external stimuli. Interictal behavioral problems and personality changes have also been reported in cingulate epilepsies [14,20,21].
4.2. IP as a negative emotional expression

We found that clinical manifestations associated with IP belong to the FLE spectrum and clearly point to the ACC. We have described here a particular facial expression indicating a range of negative emotions that can be grouped under the heading “7D feelings”: disgust, distress (from discomfort to anxiety and fear), displeasure (from discontent to irritation or anger), disappointment, disaggreement, and doubt. In this view, IP belongs to a behavioral rather than a motor manifestation. We suggest that it reflects a defensive or negative mimicry and postulate that it represents an embodied response to internal or external stimuli with an affective or a cognitive component. Ictal pouting could also correspond to the resurgence of an archaic reflex similar to grasping [22]. Pouting with the mouth turned down is rarely seen in neurologic diseases, except as a dysmorphic feature such as the Smith–Magenis syndrome, a rare genetic developmental disorder including intellectual disability, distinctive facial features, sleep disturbances, and behavioral problems [23]. However, outside the field of pathology, it gives the face a characteristic appearance, immediately identified by others as a warning, and can be considered as an inverted smile. This facial expression plays a role in communication between individuals and, therefore, represents a tool of social interaction. It is worth noting that neural networks sustaining smiling include, but extend beyond, the face motor area, recruiting brain regions known to be involved in social cognition, including the posterior cingulate cortex [24,25].

4.3. Neural network underlying IP

Based on our data combining SEEG and metabolic information, we propose that IP occurrence can be related to the simultaneous involvement of a network including at least the ACC and the anterior part of the insula, most likely bilaterally. We suggest that a common mechanism would sustain this sign, regardless of the entry point in the network. We, thus, interpret the significance of IP according to the following scenario: when the ictal discharge starts in the rostroventral part of the ACC (affective division, including ventral Brodmann areas (BA) 25, 33, rostral part of BA 24 and 32, Fig. 5), or in its vicinity, the clinical picture is characterized by an intense emotional pattern (fear or aggressive behavior) associated with an arousal reaction, vegetative symptoms, staring, or open eyes and followed by a hyperkinetic behavior suggesting a flee or fight reaction. In these cases, IP expresses fear or menace. When seizure onset occurs more posteriorly within the ACC (cognitive division, dorsal part of BA 24 and 32), the affective component may be less intense with an attenuated emotional expression and often closed eyes. Ictal pouting then translates to a more “cognitive” facial expression such as discontent, disappointment, disagreement, or doubt, without necessarily being accompanied by the emergence of the hypermotor component. This interpretation may be confronted with the theory of “negative surprise”, corresponding to the reaction elicited by the nonoccurrence of an expected event, which has been linked to the dorsal ACC function [26]. Notably, we did not find hemispheric asymmetry regarding ictal symptomology that was similarly observed in both hemispheres. An emotional component appeared to be more frequent on the right side; however, right lateralization of the EZ was mostly associated with rostroventral ACC involvement, whereas left lateralization was found in more posterior locations. In addition, early contralateral involvement was demonstrated either by SEEG or by PET. Therefore, IP can be helpful for localizing the EZ but has no lateralizing value. On the other hand, when seizure onset primarily involves the lateral aspect of the frontal lobe (inferior frontal gyrus) with spread to the ACC and insula, patients tend rather towards mimicry of disgust, without hypermotor features. In this situation, the following symptoms consist of head deviation, vocalization, and tonic posturing, reflecting the predominant involvement of the dorsolateral premotor cortex. Another interpretation could be a triggered reflex to a sensorial stimulus (analyzed in the insula) and considered as potentially dangerous (in the ACC). Ictal pouting could, thus, be considered to result from a distasteful perception causing mimicry of disgust and inducing spitting. In this view, the mechanism could be related to a cortico-subcortical network, and the involvement of the motor operculum does not seem necessary. As observed in our study, this area was never found to be involved by the rapid discharge despite sampling by depth electrodes in most cases. By contrast, as demonstrated by SEEG and/or individual PET, the insula was involved in half of the cases, supporting a role of this area in IP generation. In addition, both the ACC and the insula were found to be involved when analyzed with SPM, regardless of the seizure-onset zone (mesial versus lateral frontal onset), suggesting a reciprocal connectivity between the two areas.

4.4. Relationship with emotional and cognitive processes

We propose that IP is sustained by mesial and lateral frontal cortex interactions including the insula, in which the ACC plays a pivotal role. This hypothesis is supported by the connections and functions of the different parts of ACC. The affective division of the ACC belongs to a network including the anterior insula, the amygdala, the ventral striatum, and the prefrontal and multimodal sensory regions, involved in emotional and motivational information and the regulation of emotional responses [27,28]. Fear as a main ictal symptom in patients with epilepsy has been linked to the involvement of orbitofrontal, ACC, and temporolimbic areas [29]. It has also been demonstrated that functional connections between the ACC and the amygdala play an essential role in fear learning and emotional processes [30]. Overall, interactions between the amygdala and the associative cortex have been described in all basic emotions, including fear and disgust [31]. Moreover, functional neuroimaging and neurophysiologic studies support the experiential role of the anterior insula, showing that feelings such as anger, fear, and disgust may recruit the same neural network including the ACC, the orbitofrontal cortex, and the insula [32–37]. Regarding the cognitive division of the ACC, strong connections with the lateral prefrontal cortex, the parietal cortex, and the premotor and supplemental motor areas have been described [27,38]. Neuropsychologic studies have demonstrated that the dorsal ACC is implicated in prediction of errors, in inhibition of responses associated with undesirable outcome, and, finally, in the learning rate adjustment [26]. Interestingly, patients with attention disorders, who do not activate the cognitive division of the ACC during cognitive tasks, show strong bilateral activations of the anterior insula, these findings being considered as a compensatory mechanism for a dysfunctional cingulo-frontal network [27].

Neuropsychologic and functional neuroimaging studies provide evidence that mesial and lateral frontal interactions including the anterior insula are then integrated in most emotional and cognitive processes. We report the first study in humans with epilepsy, to our knowledge, that demonstrates the involvement of these mesial–lateral neural networks including the ACC and insula during frontal lobe seizures. In addition, we show how the study of ictal symptomology allowed us to distinguish between the symptomatology generated by the affective division of the ACC and that generated by its cognitive division. We emphasize that ictal discharges follow a spread pathway corresponding to physiologic circuits. Conversely, we pointed out that type 2 FCDs, which are characterized by a focal EZ, represent a suitable model for analyzing the interconnections within a functional network. These findings allow the location of the EZ and the underlying epileptogenic lesion to be accurately established, even though imaging is negative [8,9,39]. In line with these results, most patients with a favorable outcome after ACC resections had dysplastic lesions [16,21,40], as was the case with the patients in the present study.

Finally, we have demonstrated that IP may be a reliable sign in FLE, since it has a high localizing value when associated with intense emotional changes and hypermotor behavior. These data may be helpful in determining the seizure-onset zone in patients with FLE.
Acknowledgments

The authors thank Mrs. D. Toussaint, Mr. P. Bodilis, and Dr. B. Turak for patient care and for their contribution to this study.

Disclosure

All authors report no disclosures.

References