CHAPTER 29

Cingulate Cortex Seizures

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Chapter contents

Epileptic seizures provide a complex contrast to lesions. Destructive lesions typically cause functional deficits. However, the activities of preserved cortical and subcortical areas, released from the influences of the destroyed or impaired tissue, can paradoxically cause focal hyperactivities. Seizures result from excessive synchronous neural discharges that can cause positive (hyperactive such as jerking) or negative (functional impairment such as weakness) changes. Lesions and seizures both provide valuable, but often not straightforward, insights into brain function. While the correlation between disease and abnormal function is often easily made, the extrapolation from disease to normal function is much more tenuous.

Hughling Jackson's localization of focal motor seizures to primary motor cortex was a remarkable leap for neurology, but his localization of déjà vu, olfactory hallucinations, and dreamy states to the mesial temporal lobe was a larger jump (Jackson, 1931). He recognized in the dreamy states the dual nature of a seizure's effects on mind. 'There is not always *loss*, but there is, I believe, always, at least *defect*, of consciousness coexisting with over-consciousness ("dreamy state")'. Just as motor seizures can be excitatory and cause clonic or tonic activity, seizures arising from limbic and associational cortices can cause positive or negative symptoms. When a seizure evokes fear, the paroxysmal occurrence of the emotion without an environmental context is readily identified by the patient. However, a transient impairment of the experience of fear would be much more difficult to detect. It would require that a fearful stimulus occur during the seizure and that the lack of responsiveness be recognized. Not surprisingly, many ictal deficits are often difficult to recognize. Motor and language deficits are most commonly detected, yet negative motor seizures may impair only complex movements, similar to effects of electrical stimulation (Luders *et al.*, 1988). Thus, if the seizure occurs while

the motor areas are not engaged, no effect may be apparent, even if a skilled clinician is observing the patient. Consider the much greater challenge in detecting seizures that produce mild alterations in motivational, social, or cognitive functions.

Our ability to precisely localize the onset of seizures that arise outside primary sensory and motor cortices remains limited. In many cases, synchronous discharges arising from small cortical areas in limbic (e.g., cingulate cortex) or association cortex do not produce subjective or objective symptoms. It is only when the discharge spreads to specific regions or a critical mass of tissue that symptoms or signs occur. Thus, the first clinical feature results from ictal propagation that is remote in time and anatomy. Spread patterns tend to be stereotypic, but can vary based on factors such as medication levels, sleep deprivation, and recurrent activation of circuitry.

Identifying robust structural–functional correlations of cingulate seizures remains very difficult. Clinical diagnosis of cingulate seizures is challenging, typically made only when a structural lesion is identified on neuroimaging or when invasive electrodes capture seizure onsets restricted to this region. The cingulate gyrus is buried deep in the intracerebral fissure, remote from scalp electrodes that can only detect seizures involving cortex well beyond the cingulate borders. Even with invasive electrode recordings, the dense venous drainage over the medial surface of the hemisphere often limits the extent of coverage. Thus, even when a mesial frontoparietal seizure focus is suspected, the cingulate gyrus is often accessed with only a few subdural, strip electrode contact points. Typically, those that are placed blindly into the interhemispheric fissure are not the most inferior points along the medial frontoparietal surface. Thus, even when extensive electrode arrays are used, often only a small percentage of the cingulate cortex and other cortical areas are covered, making determination of seizure onset and spread pattern more tentative.

Despite these limitations, studies on epilepsy patients provide invaluable insights into the human cingulate cortex. The anatomic, physiologic, imaging, pharmacologic, neurochemical, and behavioral animal studies presented in this volume provide enormous data about the cingulate cortex. Yet the extrapolation from these data sets to human behavior depends on confirmatory observations in humans. The main sources of human data are: (1) functional magnetic resonance imaging (fMRI) studies, (2) surgical or spontaneous lesions, and (3) electrical stimulation and seizure recordings in patients with epilepsy (Devinsky *et al.*, 1995). Each of these data sets has their advantages and limitations. fMRI provides the best balance between temporal and spatial imaging resolution in human cognition. However, fMRI is limited by the paradigms that can be employed, complex statistical issues in the subtraction techniques, physiological changes, and data that are often unit-less measures, limiting group comparisons. There is a rich literature on bilateral anterior cingulate cortex (ACC) and cingulum bundle neurosurgical lesions to treat psychiatric disorders, although much of this comes from before CT or magnetic resonance imaging (MRI) and correlation of lesion size and location with behavioral changes is limited (Devinsky *et al.*, 1995). Spontaneous lesions, usually from stroke or tumor, are rarely limited to cingulate cortex and correlation of the cingulate lesion and behavioral changes is difficult. Electrical stimulation studies and initial behavioral changes in cingulate epilepsy can reveal the effects of localized excitation or inhibition of cingulate cortex. These observations provide critical data points that help fill in the gaps left by animal, fMRI, and human lesion data.

Goals of This Chapter

Seizures in different parts of the cingulate cortex are expressed with unique onset symptoms and patterns of progression to adjacent areas. Electrophysiologically confirmed discharges arising in cingulate cortex are rare but provide important details of seizure etiology. Expanding on this theme in the new age of functional imaging has opened new insights into discharge origin and spread and confirms important aspects of cingulate-mediated semiology. Most importantly in this context, the imaging observations strengthen structural–functional correlations in the cingulate cortex and provide a means of accessing conscious experiences linked to complex movements, emotions, and emotional expressions such as laughter and crying. As the cingulate gyrus provides a model for the compartmentalization of emotion, we seek to accomplish the following specific goals by linking the motor elements of emotional expression to different cingulate subregions:

1 Provide an overview of the variable phenomenology of cingulate seizures including the broad clinical patterns; simple partial seizures with motor, autonomic, affective or cognitive symptoms; complex partial seizures with impaired consciousness that can be bland and brief, and 'hypermotor' and postural–tonic or atonic-seizures.

2 Assess clinical symptoms of seizure activity in each cingulate subregion:

(a) Subgenual ACC seizures modulate autonomic activity and a unique case of pilomotor epilepsy is presented.

(b) The most frequent reports of cingulate seizure activity originate in pregenual ACC as simple partial seizures with changes in motivation, thought, or feeling of control over actions, and impaired consciousness and automatisms reflect spread to other sites and spontaneous seizures giving rise to feelings such as fear.

(c) Seizures in midcingulate cortex (MCC) suggest this region provides control of emotional movements allowing for greater variation and nuancing of emotional expression.

(d) Seizures in posterior cingulate cortex (PCC) are poorly documented with available diagnostic modalities. Stimulation or inhibition of the PCC for brief periods may not produce characteristic clinical changes and may be 'silent' clinically. A study is examined using spike-triggered fMRI in patients with idiopathic generalized epilepsy and frequent spike and slow-wave discharges. Functional imaging showed reductions of PCC activity during spike and slow-wave discharges suggesting its deactivation may be related to 'absence' seizures.

3 Review the difficulties of differential diagnosis of cingulate and temporal lobe seizures with clinical symptoms and electrophysiology. As high-resolution MRI, thin slicing, and multiple spatial and weighted images show lesions associated with the epileptogenic foci, localized, gray matter structures in cingulate cortex have an excellent correlation with the seizure focus and this may be the greatest single advance in our ability to diagnose these foci.

4 Assess thoroughly studied cases of cingulate epilepsy that show evidence of mental pathology with elements of aggression, obsessive and compulsive thoughts, thought disorder, mood changes, and sociopathy. Thus, the chronic effects of electrophysiological dysfunction in cingulate cortex, often combined with structural pathology, can profoundly disrupt personality, emotional regulation, social cognition, and the cohesion of thought.

Cingulate Cortex Seizures: Clinical Phenomenology

Animal studies

A few studies explore the clinical features of cingulate seizures in animals. Wada and colleagues provided the most detailed reports of cingulate seizures kindled by repetitive electrical stimulation in baboons (*Papio papio*) and cats (Wada & Tsuchimochi, 1995; Wada & Hirayasu, 2004). In baboons, ACC kindling by daily electrical stimulation (1 sec, 60 Hz sine wave in the left hemisphere) leads to a protracted non-convulsive seizure state characterized by immobile staring with widening of eyelids and neck flexion, followed by post-ictal visual searching behavior. In contrast, PCC kindling leads to a protracted non-convulsive seizure without other features. Although the EEG discharges rapidly spread to both hemispheres, ictal, and interictal patterns remained persistently asymmetric. Evolution of the seizure to a secondary generalized tonic–clonic type was rapid once the contralateral lower facial muscles were involved and manifested twitching movements. This secondary generalization was associated with sustained head deviation to the contralateral side. Following successful kindling of the primary cingulate site, stimulation of the contralateral homotopic PCC caused afterdischarges but these remained localized and kindling did not occur. Wada and colleagues later showed that cingulate kindling can lead to a prolonged inhibition of kindling at a homotopic secondary site. Further, this is not only a primate species-specific effect, but also occurs in feline species. Further, it is not limited to a homotopic site and represents a lasting secondary antiepileptogenesis, likely from increased inhibition. These animal data provide several possible clues to human cingulate epilepsy: (1) the physiology and clinical features of ACC and PCC seizure foci may differ, and (2) cingulate seizures may suppress the development of secondary epileptogenesis and limit their spread patterns.

Human observations

The literature on cingulate epilepsy provides a remarkably coherent clinical syndrome despite the diversity of ictal phenomenology, anatomical and functional regions, and the challenges in documenting cingulate seizure foci. Most patients begin to have seizures early in life, with brief staring spells and loss of motor tone, often progressing to tonic–clonic activity. Seizures may be most frequent during sleep but diurnal events often lead to medical presentation. In later childhood, auras are often reported and seizures may develop more emotional motor expressions such as fearful facial expression or laughter, complex frenzied motor automatisms, and lateralized motor phenomena reflecting ictal spread patterns. The localization of seizure onset within the cingulate cortex provides clues to seizure onset—autonomic phenomena such as piloerection or respiratory changes with subgenual ACC (sACC) foci; fear and other emotional experiences and early impairment of consciousness with pACC foci; and emotional (e.g., laughter) or non-emotional (e.g., unilateral dystonia) motor changes with MCC seizures. PCC seizures remain obscure and may be relatively silent until the electrical discharge spreads beyond the PCC, causing symptoms such as paraesthesia.

It is difficult to document seizures arising from cingulate cortex (Devinsky *et al.*, 1995; Geier *et al.*, 1975, 1977). Before 1990 and the MRI-era, most series were retrospective studies on seizure-free patients after epilepsy surgery. Seizure freedom after a resection limited to the cingulate cortex strongly supports a cingulate focus. However, even here, there is a danger of misattribution. For example, seizures may start 'silently' in the cingulate cortex with clinical features resulting from seizure spread to adjacent regions such as the supplementary motor area (SMA). Also, the margins of the seizure focus often overlap with other frontal, or less often parietal, areas. The more recent literature, with MRI, intracranial electrodes, ictal or subtraction single-photon emission computed tomography (SPECT), and MEG (see below) provides smaller but more richly documented cases.

Four broad clinical patterns are associated with cingulate cortex seizures: (1) simple partial seizures (no impairment of consciousness) with motor, autonomic, affective, or cognitive symptoms; and complex partial seizures (impaired consciousness) that can be (2) bland and brief (i.e., 'frontal absence' or 'pseudoabsence' seizures), (3) 'hypermotor' seizures, and (4) postural (tonic or atonic) seizures. Any of these types can coexist in the same patient and all secondarily generalize. All complex partial seizure types may be associated with automatisms ranging from simple with repetitive hand motions to more complex motor acts such as laughing or screaming. Finally, like many other seizures arising outside of temporal and sensorimotor cortex, cingulate seizures often arise during sleep.

Simple and complex partial seizures

Simple partial seizures (auras) are often absent in patients with cingulate seizures, especially nocturnal events. For many, auras are non-specific (e.g., dizziness) or cause autonomic-visceral symptoms such as warmth, abdominal sensation, pallor, tachycardia, mydriasis, piloerection, fear, feeling of suffocation, urge to void, forced urination, or apnea which can be voluntarily overcome (Bancaud & Talairach, 1992; Geier *et al.*, 1975, 1977; Penfield & Jasper, 1954; Seo *et al.*, 2003; Talairach *et al.*, 1973). Other patients describe paraesthesia, probably from spread to supplementary or primary sensory areas. However, these sensory symptoms may result from direct activation of PCC, which receives robust connections with sensory cortices (see Chapter 13). These symptoms can occur in isolation or in complex, evolving combinations.

Simple partial seizures can provide excellent clinical-anatomic correlates. For example, one patient with a right cingulate focus documented by subtraction of interictal from ictal SPECT (Fig. 29.1; Seo *et al.*, 2003) and ictal EEG subdural electrode recordings (Fig. 29.2; Seo, personal observation) had isolated piloerection during seizures. Activity in the piloerector muscles is shown during the seizure in Figure 29.1B. This seizure arose from the sACC that mediates autonomic functions (Chapter 10) and had secondary sites possibly associated with skeletomotor activity in pACC and MCC.

One of our patients, a 50-year-old man with a low-grade neurocytoma in the left cingulate gyrus was diagnosed 11 years earlier. He presented with seizures characterized by a strange sensation throughout his body, but maximal in his head. This was associated with fear and within seconds, trembling movements of both right-sided extremities that could progress to involvement of all four limbs with preserved consciousness. Seizures lasted 20–30 sec and occurred mainly during sleep. Figure 29.3 shows a midsagittal section through the left hemisphere of this patient. The motor events

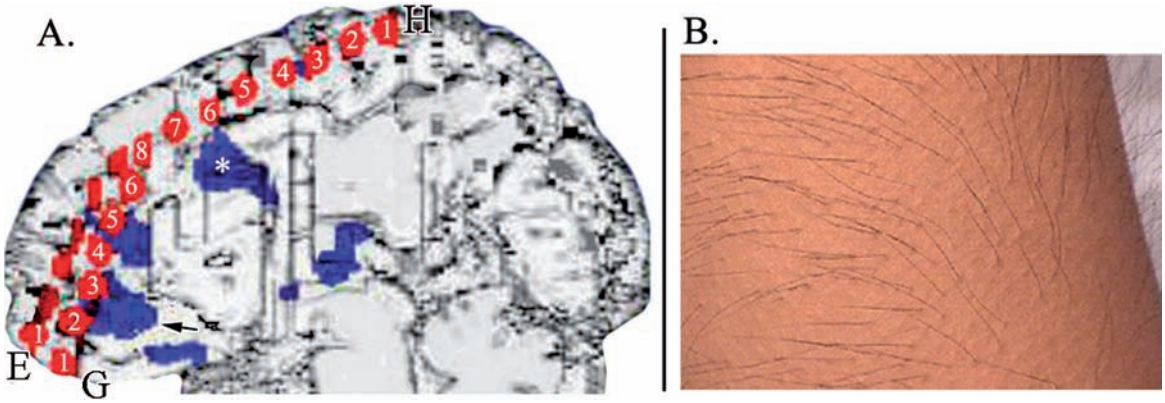

Fig. 29.1 Right cingulate focus documented by subtraction of interictal from ictal single-photon emission computed tomography with MR-CT co-registration and 3D-rendered magnetic resonance imaging. A. Image demonstrates that the hyperperfusion (coded blue) is in the medial part of the rectus gyrus, hypothalamus, and thalamus. One of the actively hyperperfused areas is in sACC (arrow) is close to electrodes G2 and G3. A second site of hyperperfusion is dorsal in pACC and a third is in midcingulate cortex (asterisk). B. Photograph of skin during a pilomotor seizure. *Used with the generous permission of D.W. Seo* (Seo *et al.*, 2003).

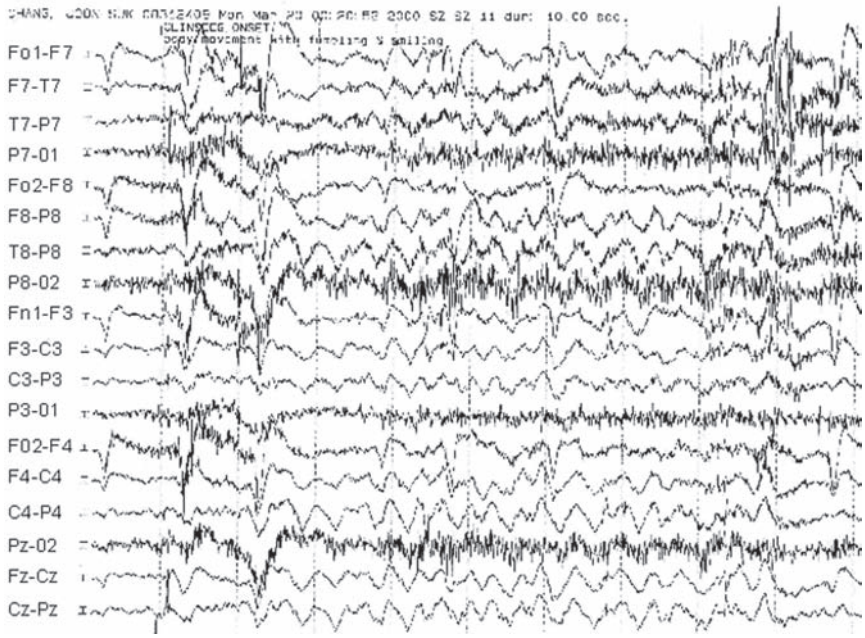

Fig. 29.2 Right cingulate focus documented by ictal electroencephalogram subdural electrode recordings. *Used with the generous permission of D.W. Seo.*

associated with this seizure activity are likely accounted for by the involvement of both cingulate motor areas. The emotional component including fear may have been due to progressive involvement of the anterior MCC that can be engaged during fear in functional imaging studies (Vogt *et al*., 2003).

Complex partial seizures of cingulate cortex origin are diverse in their clinical phenomenology, reflecting both their site of origin and spread. Consciousness is somewhat impaired, but often less then expected for the intensity of the seizure. Post-ictal states are either absent or brief (Bancaud & Talairach, 1992; Devinsky *et al*., 1995; Mazars, 1970; So, 1998). Cingulate complex partial seizures tend to be frequent, brief, stereotyped, and nocturnal. The sudden and intense motor automatisms may lead to the misdiagnosis of psychogenic non-epileptic seizures or 'hysteria' (Kanner *et al*., 1990; Williamson *et al*., 1985).

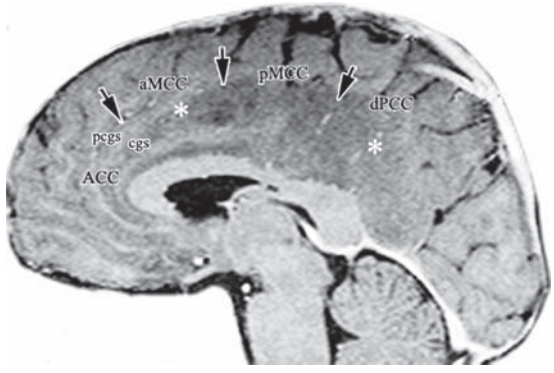

Fig. 29.3 Midsagittal section through the left hemisphere of a 50-year-old with a low-grade neurocytoma in left cingulate gyrus (between the two white asterisks). There are three arrows that show the borders of ACC/aMCC, aMCC/pMCC, and pMCC/dPCC. The cingulate motor areas (CMA) are located in aMCC (rostral CMA), and pMCC/dPCC (caudal CMA). At this level, the damage also involves the dPCC gyral surface. The caudal asterisk is over the splenial sulci and includes dPCC and RSC in the callosal sulcus. ACC, anterior cingulate cortex; MCC, midcingulate cortex; PCC, posterior cingulate cortex; cgs, cingulate sulcus; pcgs, paracingulate sulcus.

The ictal features of cingulate seizures can evolve in complex patterns, as dynamic effects of seizure spread on level of consciousness and the clinical expression of motor phenomena. Seizures arising from the cingulate cortex often impair consciousness, probably when the ictal discharge spreads beyond the cingulate borders. Thus, even bilateral resection of cingulate cortex (cingulectomy) does not reduce level of consciousness (Whitty *et al*., 1952). In older case reports and series, some cingulate seizures were reported to resemble generalized absence or atonic seizures, with staring, behavioral arrest, or head drop (Mazars, 1970). In some cases, contraversive eye or head deviation or unilateral paraesthesia occurred, as well oral or hand automatisms. These cases with associated symptoms are easily differentiated from absence seizures. In ACC seizures with only staring, in contrast to true absence seizures, ACC 'absence' seizures usually lasted 10–30 sec and were often followed by a brief post-ictal state (Mazars, 1970; So, 1998). Like true absence seizures, these ACC seizures are usually not preceded by an aura. Notably, most reports on ACC 'absence' seizures were reported

in studies that lacked MRI, MEG, or ictal SPECT. Further, invasive EEG utilized depth electrodes that provide a much more limited coverage than subdural electrodes. Electrode localization could not be confirmed by neuroimaging.

In the largest series (Mazars, 1970), 28 of 36 patients underwent bilateral cingulectomy for seizure control, a striking contrast to the exclusively unilateral seizure onsets and resections in the recent literature. As seizures with brief impairment of consciousness as the sole manifestation are not well documented in the modern literature, their localization is considered tentative. Brief episodes of atonia with staring are documented, but rarely (Levin & Duchowny, 1991).

Skeletomotor symptoms and automatisms

Paroxysmal nocturnal, and less often, diurnal episodes of dystonia, dyskinesia, laughter, and other motor automatisms can result from MCC motor seizures (Chassagnon *et al*., 2003; Nobili *et al*., 2003; Schindler *et al*., 2001) and possibly spread to cingulate areas and other cortical motor areas. In many cases, the seizure focus likely overlapped and spread to supplementary motor cortex, with which the MCC motor area is connected (Chassagnon, 2003; Nobili *et al*., 2003; Chapter 5). Motor symptoms are more often bilateral and involve tonic extension of the extremities, but often begin on the side contralateral to the focus and are asymmetrical when bilateral movements occur. The progression from unilateral to bilateral motor signs is often rapid. In some seizures, both palpebral fissures widen and facial muscles contract on both sides, producing a wide-eyed, pained smile. The arms often elevate and abduct tonically. In one patient, seizures arising in the MCC or ACC often caused only arousal from sleep or simple motor phenomena that progressively increased in complexity with spread beyond the cingulate (Nobili *et al*., 2003).

The variable expression of symptom progression and intensity among different seizures in the same patient is well documented (Schindler *et al*., 2001; Vetrugno *et al*., 2005). For example, a 35-year-old man with a right ACC seizure focus (near the junction of sACC and pACC) (Fig. 29.4; Vetrugno *et al*., 2005) would suddenly awaken from stages 2–4 non-REM sleep with eye opening, head and trunk flexion, clearing of throat, raising the left fist to mouth, and dystonic right arm posturing. In other seizures, this pattern progressed and he would get out of bed, spit on the floor, and run around the house screaming.

A 32-year-old woman had seizures beginning in childhood characterized by 'pressure inside her head' followed by impaired consciousness, sometimes with elevation of both arms progressing to a tonic–clonic seizure. At age 27 years, her seizures became exclusively

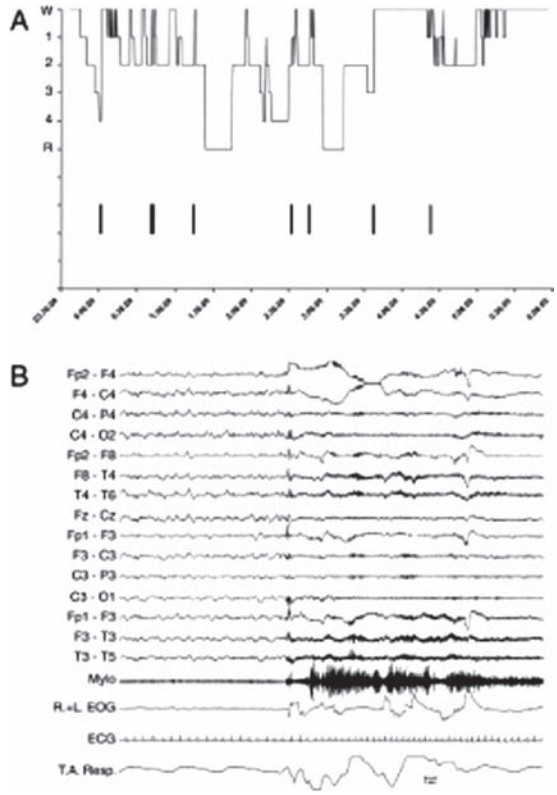

Fig. 29.4 (A) Sleep histogram showing recurrence of paroxysmal arousal (PA; vertical bars) during stages 2, 3, and 4 of non-REM sleep. (B) Polygraphic recordings showing a PA event occurring during stage 3 non-REM sleep. Fast low-voltage activity on bifrontal EEG leads is associated with EMG activity, tachycardia, and tachypnea. Mylo, mylohyoideus; EOG, electro-oculogram; T+A Resp., thoracoabdominal respirogram. *Used with generous permission from R. Vetrugno* (Vetrugno *et al*., 2005).

nocturnal, with paroxysmal arousals accompanied by right arm dystonia, elevation of the left arm and bilateral leg flexion at the hip (Fig. 29.5; Schindler *et al*., 2001). An ictal SPECT during a typical seizure showed hyperperfusion localized to the pACC (Fig. 29.6; Schindler *et al*., 2001). This patient also had attacks of nocturnal paroxysmal dystonia and epileptic nocturnal wanderings since childhood. The different manifestations of nocturnal seizures, from simple arousal to dystonia or ambulatory automatisms likely reflect different spread patterns.

Ictal automatisms elude both anatomical and physiological delineation, whether associated with seizures arising in cingulate cortex or other areas. Automatisms usually occur 5 or more seconds after the onset of a complex partial seizure. When invasive recordings are made, they are rarely associated with the initial localized ictal onset. Rather, they usually occur after the seizure has spread, often bilaterally. However, it is uncertain

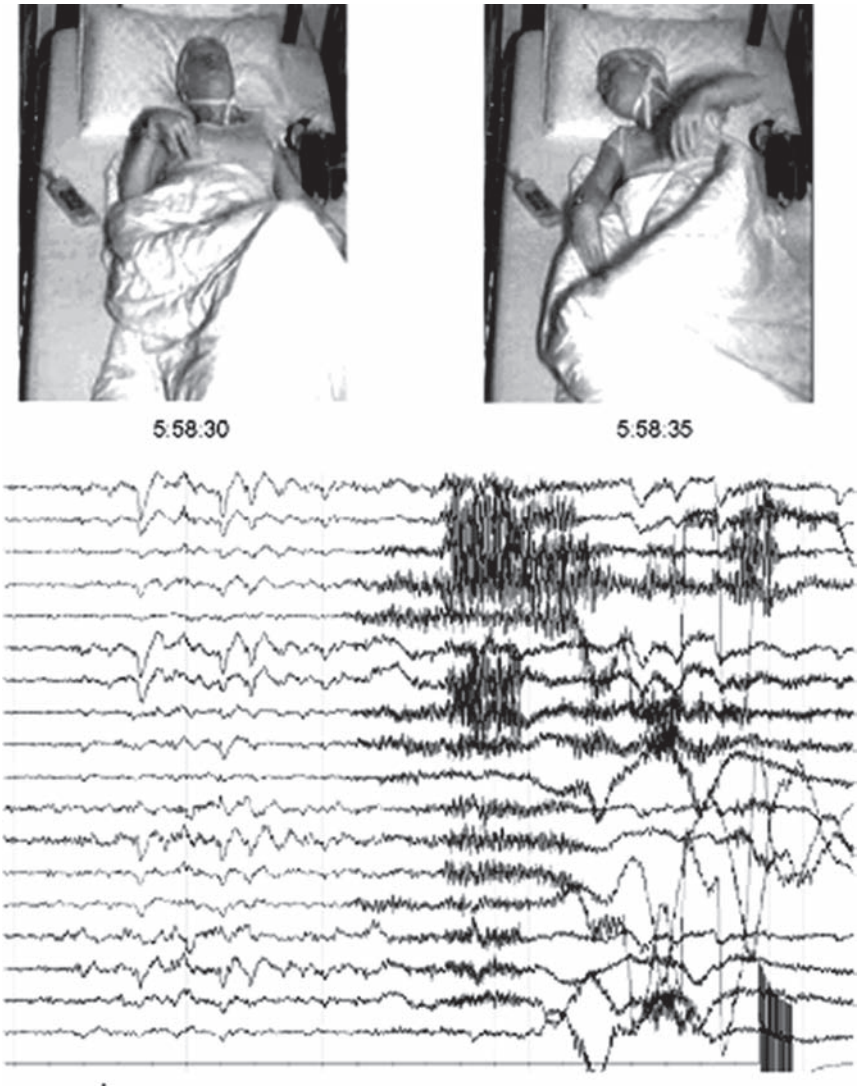

Fig. 29.5 Video-EEG monitoring of a typical seizure manifesting as paroxysmal nocturnal dystonia. The patient turns to the right while concurrently flexing her right arm at the elbow and the wrist, resulting in dystonic posturing at time 05:58:30. *Used with generous permission from K. Schindler* (Schindler *et al.*, 2001).

if automatisms result from activation, disinhibition, or both. Automatisms are well documented on invasive recordings during the post-ictal state, when the cortical EEG shows only generalized slowing (Devinsky *et al.*, 1994). They can also occur with electrical stimulation of the cingulate cortex or other regions. Cingulate stimulation can evoke restlessness and semi-elaborate movements, primarily of the contralateral leg (Escobedo *et al.*, 1973). Pedaling, face rubbing, picking, and lip movements have been documented (Bancaud *et al.*, 1976; McConachie & King, 1997). However, similar picking automatisms can occur after cingulectomy (Whitty *et al.*, 1952), paralleling post-ictal observations (Devinsky *et al.*, 1994) and suggesting that some automatisms result from loss of function causing a release of inhibition rather than the direct excitatory effect.

Emotional automatisms

In general, automatisms involving limbic areas of the frontal lobe (i.e., cingulate and orbitofrontal cortex) occur earlier in the seizure evolution and are more complex in their motor elements than during temporal lobe seizures. Common oral-alimentary (lip smacking), facial (expression of fear, facial contortion), and appendicular (touching hair or clothes, waving or hitting movements) automatisms can occur in cingulate seizures. However, other automatisms are more typical of extra-temporal foci: truncal (early occurrence of axial movements such as rocking, turning the body, assuming the fetal position) or vocal (e.g., humming, unintelligible sounds, onomatopoieas, screaming, cursing, brief phrases such as 'Oh my God,' laughing, crying, or

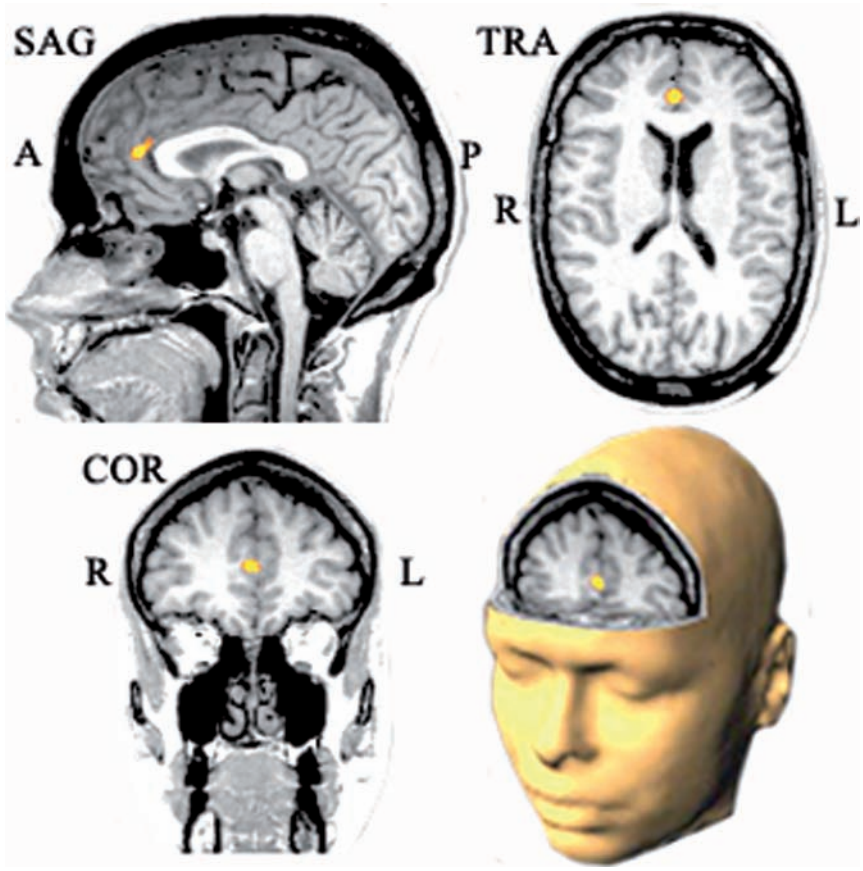

Fig. 29.6 Subtraction ictal single-photon emission computed tomography co-registered to MR (SISCOM) shows significant bilateral hyperperfusion of the pACC (Schindler *et al.,* 2001).

moaning), or tongue protrusion (Devinsky *et al*., 1995; Escobedo *et al*., 1973; Geier *et al*., 1977; Quesney *et al*., 1996; Sammaritano *et al*., 1993; Stoffels *et al*., 1980, 1981; Talairach *et al*., 1973; Vetrugno *et al*., 2005; Weiser *et al*., 1990). During some cingulate seizures, patients can voluntarily inhibit or modify the motor behavior to blend with ongoing activity (Geier *et al*., 1977; Talaraich *et al*., 1973). This may simply reflect preserved function in other areas. In some patients with cingulate seizures, ictal or possibly post-ictal automatisms with aggressive behaviors led to psychiatric hospitalization or imprisonment (Bancaud & Talairach, 1992; Devinsky *et al*., 1995).

The automatism of laughter, or rarely crying, can occur with seizures arising in or spreading to cingulate cortex, probably the MCC (Arroyo *et al*., 1993; Chassagnon *et al*., 2003; Devinsky *et al*., 1995; Iwasa *et al*., 2002; Khadalikar *et al*., 2001; McConachie & King, 1997; Sammaritano *et al*., 1993; Talairach *et al*., 1973). In contrast to other automatisms such as oral or hand movements, evidence from spontaneously recorded seizures and electrical stimulation studies strongly supports the conclusion that ictal laughter and crying phenomena result from activation of motor areas (Fried *et al*., 1998). Gelastic seizures arising from cingulate cortex are typically not associated with the experience of mirth (Arroyo *et al*., 1993; Chassagnon *et al*., 2003; Iwasa *et al*., 2002). Similarly, gelastic seizures in patients with hypothalamic hamartomas often spread to cingulate cortex, but rarely involve the emotional experience associated with laughter. Notably, seizures localized to the hamartoma can evoke laugher or crying prior to cingulate spread (Kahane *et al*., 2003). This suggests strong functional connections between a subcortical and cortical area that can both mediate the production of emotional motor acts that are dissociated from the experience of the emotion.

Where in the cingulate cortex is the site that evokes laughter? In many cases, the precise localization is uncertain. However, one patient with a circumscribed focus had a small radiosurgical lesion in the MCC and a separate one in the SMA shown in Figure 29.7 (Chassagnon *et al*., 2003) that successfully controlled gelastic seizures. In another patient with mirthless gelastic seizures, the interictal magnetic dipole was in the pACC, near the anterior border of MCC (Fig. 29.8; Iwasa *et al*., 2002).

Seizure activation of MCC can also cause facial movements that can be considered as fragments of laughter,

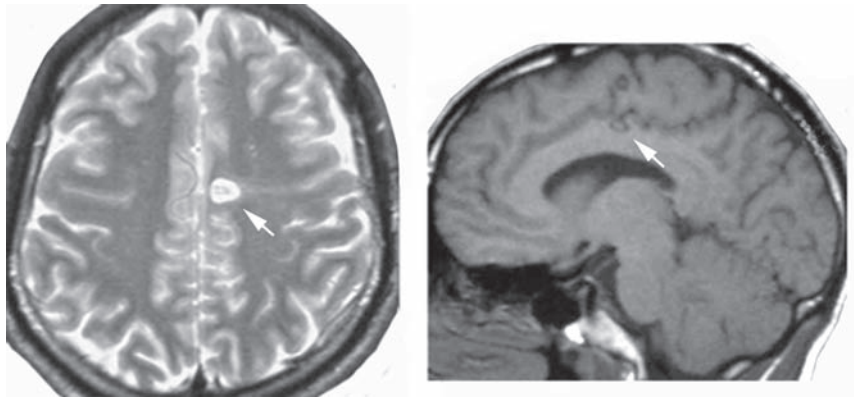

Fig. 29.7 Post-operative magnetic resonance imaging showing signal changes at the location of the stereotactic radiofrequency lesions performed 6 months before. Left: parasagittal view of the left hemisphere, T1 signal. Right: Horizontal view, T2 signal. *Used with generous permission from P. Kahane* (Chassagnon *et al.,* 2003).

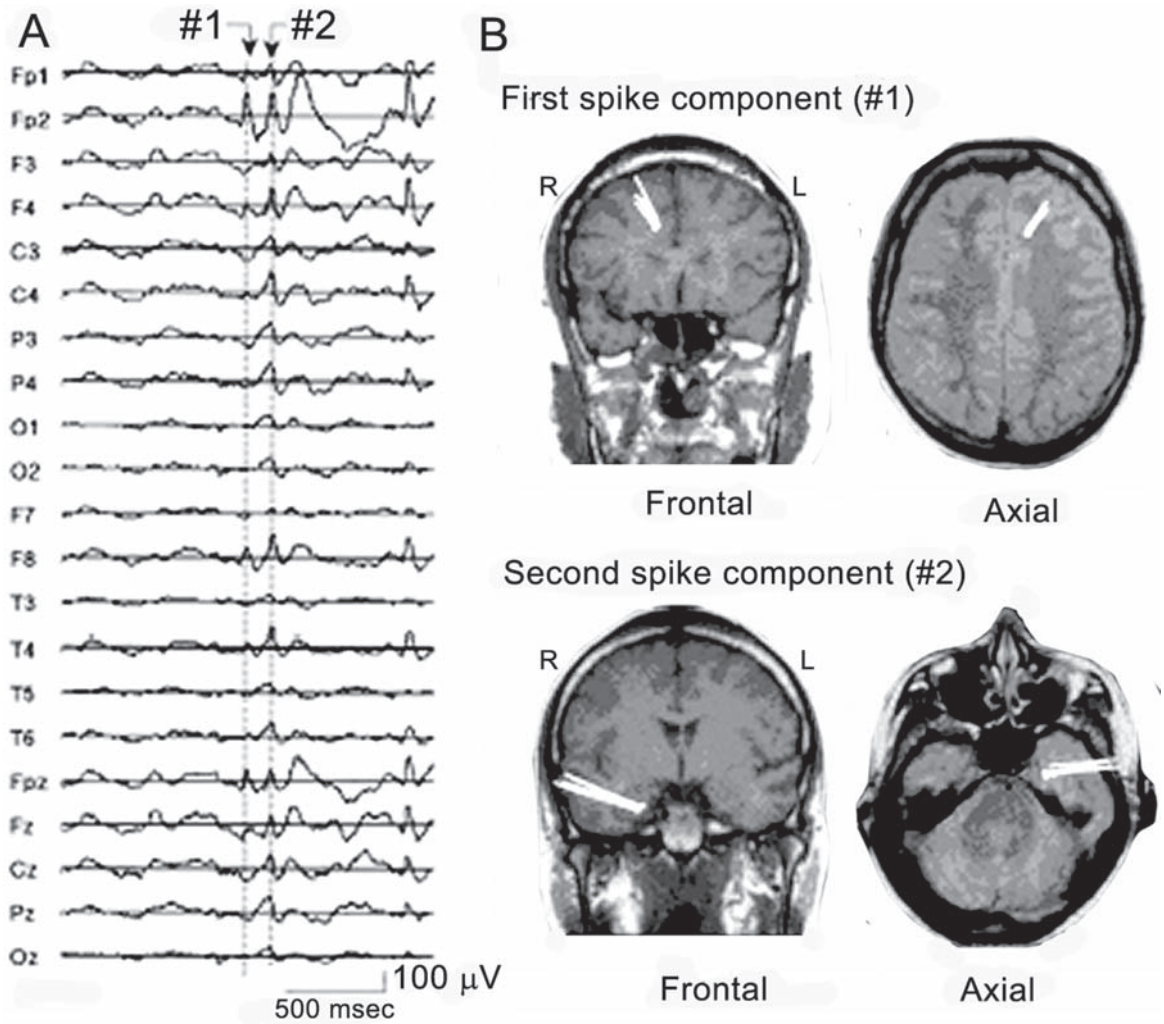

Fig. 29.8 Scalp electroencephalogram recordings that show multiple spikes and slow-wave complex in one patient (A). The dipole location and vector direction were superimposed on the magnetic resonance imaging corresponding to five antecedent spike components (No. 1) and second spike components (No. 2). *Used with generous permission from H. Iwasa* (Iwasa *et al.,* 2002).

crying, or other *motor elements of emotional expression*. In one patient, repetitive stereotypic bilateral perioral contractions resulted from activation of MCC during seizures (Fig. 29.9; Shiraishi *et al*., 2001). This patient had a lesion in the left cingulate with an interictal focus there on MEG and increased left cingulate blood flow in SPECT during a seizure. Other shards of emotional acts such as screaming, yelling, humming, facial contortion, and tongue thrusting have also been reported (Devinsky *et al*., 1995; Levin & Duchowny, 1991; Vetrugno *et al*., 2005).

The cingulate gyrus provides a model for the compartmentalization of emotion. Different aspects of emotion are encoded in different cingulate regions. In ways, the cingulate cortex can be considered a small matrix within the larger limbic matrix of emotion. The sACC modulates autonomic activity (see Chapter 10), with most other limbic areas (e.g., orbitofrontal, amygdala) also influencing autonomic output. The pACC modulates the experience of emotion, with stimulation or spontaneous seizures giving rise to feelings such as fear, which are even more commonly reported with stimulation or seizures arising in the amygdala (Halgren *et al*., 1978). These observations suggest that the ACC may be attaching emotions such as fear to environmental situations. The amygdala links emotional valence, especially negative ones such as fear to specific stimuli. The orbitofrontal area is essential in modifying (e.g., attenuating) a conditioned fear response established by the amygdala (LaBar *et al*., 1998; Morgan & LeDoux, 1995). What role does the pACC play in generating fearful responses? The pACC may be another layering in the matrix of emotional assessment. Cingulate seizures that evoke fear may simply activate this elemental emotion. However, the pACC may assess more complex emotional stimuli (e.g., a scenario and social context) than the amygdala (e.g., a snake).

The MCC provides motor output to encode stereotypic emotional displays such as laughter. Although other limbic regions in the cortex directly project to

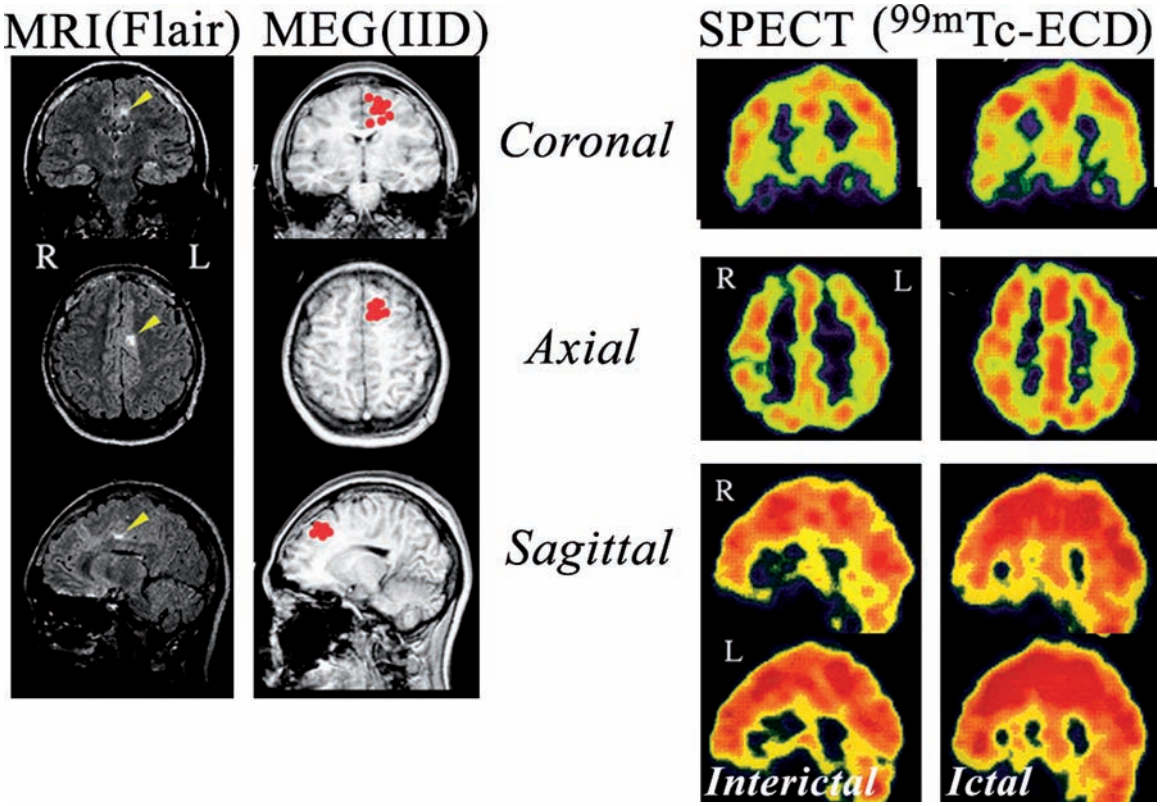

Fig. 29.9 Magnetic resonance imaging (MRI), equivalent current dipoles (ECD), and single-photon emission computed tomography (SPECT) of a patient with an activated MCC during seizures. Far left: On the MRI fluid attenuated inversion recovery (FLAIR), a high-signal, circumscribed lesion is found in the left medial frontal lobe. Left: The ECD derived from interictal magnetoencephalography (MEG) spikes (red dots) cluster in the left frontomedial lobe, possibly near the supplementary motor area. Right: Interictal SPECT shows no abnormal perfusion in the medial cortex of frontal lobe bilaterally. A greater increase on the left side can be observed during the seizure. *Used with generous permission from H. Shiraishi* (Shiraishi *et al*., 2001).

subcortical autonomic output regions, only the MCC projects to spinal motor systems. However, even stereotypic motor responses for laughter are duplicated by subcortical structures (e.g., seizures arising in hypothalamic hamartomas) (Kahane *et al.*, 2003). Seizures may therefore provide a clue to the evolutionary origin of MCC, which may exemplify two principles: reduplicated cortices that provide specialized function (Allman, 1999). and larger brains being 'better connected.' (Striedter, 2005) The MCC may provide greater cortical control of emotional movements, allowing greater variation and nuancing of emotional expression.

Diagnosis of Cingulate Cortex Epilepsy

The diagnosis of cingulate cortex epilepsy is very difficult if the MRI does not point to a structural lesion. There is no clinical feature of the history, neurologic or psychiatric examination, or seizure semiology that is pathognomonic. Temporal lobe and cingulate cortex seizures occasionally have overlapping features (e.g., staring, visceral aura, emotional expression of laughter or fear, oral or hand automatisms), although the EEG signature of a temporal lobe seizure is usually (but not always!) distinct from those arising in cingulate cortex. For seizures arising in the frontal lobe, outside of primary motor cortex, clinical features do not permit reliable guides to the localization of the seizure focus (Jobst *et al.*, 2000). Thus, frenetic nocturnal automatisms can occur with seizures arising in numerous parts of the prefrontal or cingulate cortex (Jobst *et al.*, 2000). The segmental neurological examination is usually normal in patients with cingulate epilepsy. When abnormal, it is typically not from dysfunction of cingulate cortex, but nearby frontal and parietal cortex or white matter. For example, mildly increased contralateral reflexes, slight contralateral grasp reflex, depressed contralateral nasolabial fold, or asymmetric emotional smile or laugh do not localize pathology to the cingulate cortex, but may be observed in patients with cingulate cortex seizure foci. Seizures with autonomic, affective, or motor symptoms commonly arise from temporal or other frontal regions. Ictal laughter or crying can also result from temporal or hypothalamic seizure foci. Nocturnal occurrence of arousal with complex motor automatisms can also occur with many other extratemporal localizations of the seizure focus.

Laboratory studies and etiologies

The most important non-invasive tools in localizing cingulate cortex seizure focus are the MRI, ictal or subtraction SPECT, and MEG. Although the scalp-recorded EEG can be helpful, findings are often non-specific and may be misleading. Based on non-invasive data, the diagnosis of cingulate epilepsy is likely if the MRI reveals a single lesion in the cingulate cortex (e.g., cavernous angioma, low grade tumor) and the seizure semiology is consistent with a cingulate focus (e.g., nocturnal, brief, gelastic with dystonic posturing contralateral to the lesion). This caveat becomes less secure in patients with pathological processes that affect the brain diffusely (e.g., head trauma) or in multiple discrete areas (e.g., herpes encephalitis). Other non-invasive tools such as ictal or subtraction SPECT and MEG can support the diagnosis, but do not provide confirmation. Invasive EEG recordings with subdural or depth electrodes can help confirm or establish a cingulate cortex focus and allow correlation of clinical features with anatomic spread of the seizure.

Electroencephalographic recordings

Scalp EEG is notoriously ambiguous and often non-lateralizing or falsely lateralizing when seizures arise in medial frontal areas (So, 1998). Interictal discharges generated by the cingulate cortex may be seen over one or both temporal lobes on scalp EEG (Munari & Bancaud, 1992; Williamson *et al.*, 1985). On occasion, the interictal scalp EEG reveals intermittent lateralized slow waves and consistent asymmetries in epileptiform discharges that are lateralized or predominant (amplitudes or onset) over the ipsilateral frontal or parietal cortex. Scalp EEG recorded seizures provide limited data. The ictal discharge often spreads to the contralateral hemisphere (secondary bilateral synchrony) and lateral frontal regions rapidly and the temporal course and spatial distribution of this spread produces a wide field on scalp-recorded EEG. In other cases, the ictal discharge produces low voltage fast activity and attenuation of the background rhythms limited to regions that are remote from the scalp electrode, which only records muscle and movement artifact.

The best way to correlate symptomatology with EEG onset is with intracranial subdural and depth electrode recordings. Unfortunately, intracranial studies can be difficult to lateralize due to secondary bilateral synchrony (Ralston, 1961), which may be more common and rapid after anti-epileptic drugs are reduced or discontinued in an attempt to provoke seizures. This effect is compounded by the issue of limited cingulate sampling with invasive electrodes. Subdural grids are difficult to place over the lateral aspect of the cingulate gyrus in an anterior–posterior orientation. Thus, even with several strips along the medial surface of the brain, there will often be only three contact points over the entire extent of cingulate cortex; <5% of the surface area of the cingulate cortex will be covered and depth electrodes are even more limiting. Post-implantation MRI is important to confirm electrode position. Perhaps the greatest value of intracranial electrodes is

the ability to correlate the evolution of specific symptoms with ictal spread patterns. Bilateral subdural strips or depth electrodes are often used to lateralize the seizure focus when neuroimaging and other non-invasive testing (e.g., scalp EEG, SPECT, MEG) are equivocal or contradictory about lateralization. Unfortunately, when bilateral strips and/or depths are utilized, in some, electrographic discharges appear bilateral synchronously, especially in patients with frontal absence seizures (Mazars, 1970). This first invasive monitoring study may be followed by a second procedure, typically months later, in which more extensive coverage is focused on the region(s) identified as the seizure focus based on the initial invasive survey.

In one study, a patient with frontal lobe epilepsy with sleep–wake seizures had both scalp and subdural EEG recordings. Figure 29.10 (Nobili; personal observation) demonstrates the patient's interictal epileptic activity during wakefulness, NREM, and REM sleep (Nobili; personal observation). During wakefulness it is evident that there is a continuous epileptic activity recorded from the frontal cingulate gyrus while scalp EEG is negative. Only during NREM sleep, epileptic activity diffused over other frontal regions thus allowing the transmission of epileptic activity on scalp EEG. The REM sleep pattern is similar to wakefulness.

Neuroimaging: MRI

Recent advances in neuroimaging have revolutionized the diagnosis and surgical treatment of epilepsy. High-resolution MRI, thin slicing, and multiple different spatial and weighted images, lesions associated with the epileptogenic focus that were pathological diagnoses only 20 years ago are now seen routinely on MRI. For example, small tumors, vascular lesions, and areas of cortical dysgenesis or encephalomalacia are identified on MRI. Single localized lesions encompassing gray matter structures such as cingulate cortex have an

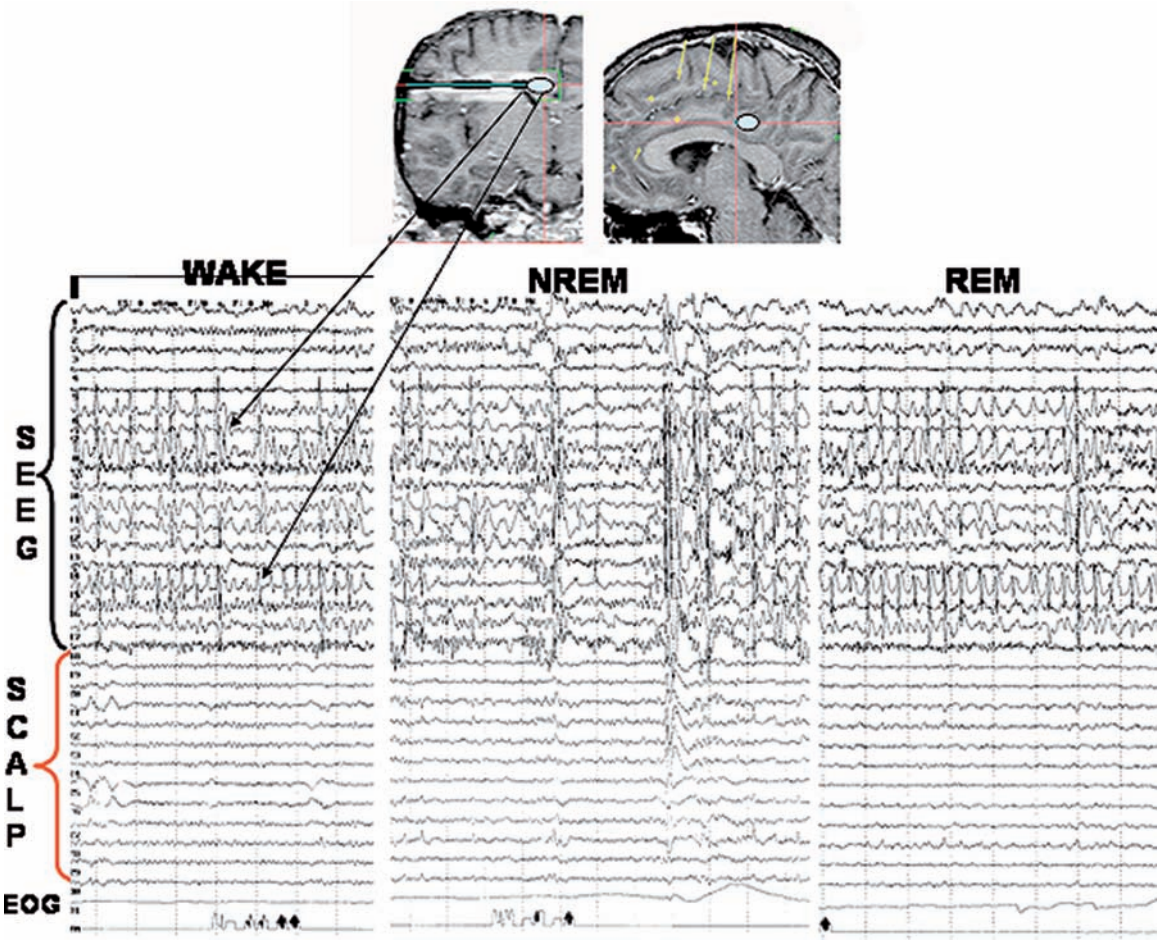

Fig. 29.10 Scalp and subdural interictal electroencephalogram recordings during wakefulness, NREM, and REM in a patient with frontal lobe epilepsy with sleep–wake seizures. *Used with generous permission from L. Nobili.*

excellent correlation with the seizure focus (whether confirmed by intracranial recordings or seizure-freedom after surgery). This visualization of cingulate lesions with MRI may be the greatest single advance in our ability to diagnose cingulate cortex foci.

Newer MRI techniques appear promising for diagnosing cingulate epilepsy, as well as other non-lesion, extratemporal foci. Preliminary studies suggest that fMRI with temporal clustering analysis can help localize the area of seizure onset without EEG (Morgan *et al.*, 2004). This technique will be most helpful for extratemporal epilepsies, including those arising from cingulate cortex. Diffusion tensor imaging-derived tractography provides quantitative data on the microstructural integrity of white matter fibers. In patients with unilateral temporal lobe epilepsy, bilateral abnormalities in the fornix and cingulum are present (Concha *et al.*, 2005). Application of this technique in the cingulate epilepsies may provide information on spread patterns and fibers involved in the epileptic network.

Proton magnetic resonance spectroscopy (MRS) is a technique that allows for quantitative measurement of several brain metabolites. It has been used primarily as a research tool in temporal lobe epilepsy (Kuzniecky, 2004) where MRS demonstrates an absolute and relative reduction in N-acetylaspartate (NAA). In one patient with a cingulate seizure focus, MRS revealed a significant decrease in the NAA/phosphocreatine-creatine and the NAA/choline compounds and phosphocreatine-creatine (Guye *et al.*, 2005) in both the primary and secondary epileptogenic areas as confirmed by invasive recordings.

Neuroimaging: SPECT

SPECT scanning can be particularly helpful in mesial frontal epilepsies, with their predilection for non-lateralizing interictal and ictal scalp EEG recordings. Several case reports document the value of SPECT for identifying cingulate cortex seizure foci (Khadalikar *et al.*, 2001; Seo *et al.*, 2003; Fig. 29.11).

The most valuable data are obtained by performing both an ictal and interictal SPECT scan. In an ictal SPECT, isotope is introduced intravenously as near the beginning of the seizure as possible. The isotope is taken up more intensely in the region of the onset focus, and the films reveal a bright spot in that region. This technique can be difficult in patients with cingulate seizures as they are often brief (and ictal SPECT recordings are more valuable with seizures lasting longer than 20–30 sec) and often nocturnal (isotope is difficult to obtain after 5 PM at most medical centers). An interictal SPECT can be injected when the patient has been seizure-free for some period and may reveal a region of decreased perfusion in the epileptogenic region, correlating with dysfunctional brain tissue. A comparison is then made between the ictal and interictal SPECT scans, which can be made visually or with computerized assistance to subtract the two images (Knowlton *et al.*, 2004). Although SPECT does not have the spatial resolution of MRI, the comparison of ictal and interictal scans may be the most revealing diagnostic study in cingulate and other prefrontal epilepsy sources (Schauble & Cascino, 2003).

A case of pilomotor seizures illustrates the critical role of SPECT imaging in providing the critical data to identify cingulate focus and target the placement of intracranial electrodes. A 27-year-old man began to develop seizures that were unresponsive to medications at age 7 years. He reported 'goose bumps' in his right leg that ascended to the right arm. MRI and interictal positron emission tomography (PET) were normal. Ictal SPECT, interictal SPECT, and subtraction of these images localized the seizure focus to the ACC. Subsequently, intracranial electrodes localized the seizure focus to the sACC (Fig. 29.12) and resection of this region and neighboring areas (Fig. 29.12; Seo; personal observation) led to cessation of seizures.

Positron-emission tomography

PET has limited value in the diagnosis of cingulate epilepsy in patients without structural pathology, but PET provides insights into the physiology of cingulate function. PET has greater resolution than SPECT but can only be obtained during the interictal period in most patients, limiting its value as cingulate foci usually do not show interictal abnormalities if MRI is normal. Flumazamil-PET, which images most GABA-A receptors, reveals reductions in the middle cingulate gyrus in patients with occipital lobe epilepsy.

Magnetoencephalography

Magnetoencephalography (MEG) detects magnetic fields and sources that are produced by the same electrical current movement that produces EEG potentials. The advantage of MEG over EEG is that it utilizes many more recording sensors and can identify deeper sources as there is no significant impedance to the magnetic field signal. These dipole sources can subsequently be mapped onto an MRI of the patient's brain with some fidelity as the head contour is taken at the beginning of the MEG session, highlighting certain landmarks that make co-registration possible. Thus, MEG can provide a detailed three-dimensional map of the dipole source whereas EEG provides only a rough two-dimensional map. MEG has already proven valuable in mapping both interictal and ictal seizure foci in patients with mesial frontal epilepsies (Shiraishi *et al.*, 2001).

It can help solve the problem of secondary bilateral synchrony (i.e., seizure foci which arise from restricted areas but rapidly spread to involve both

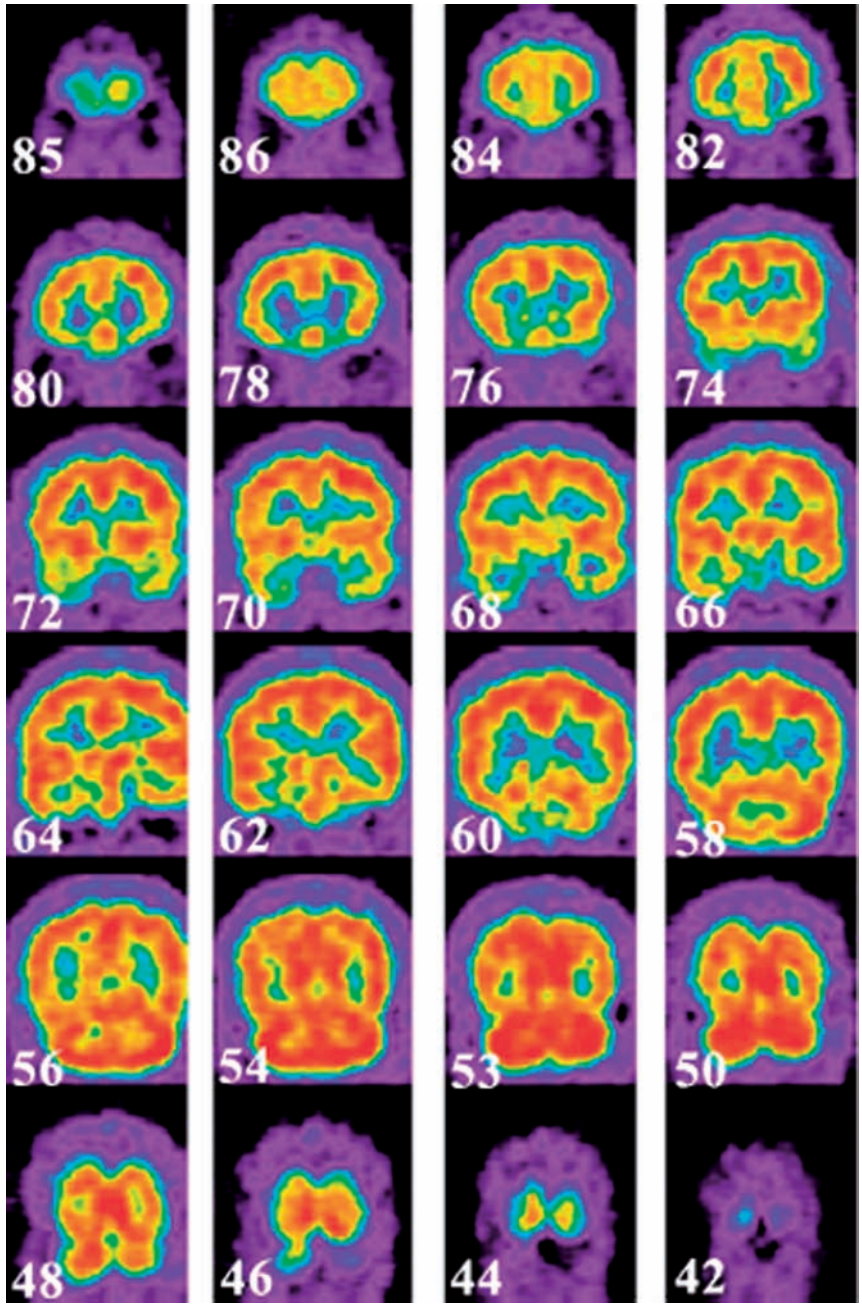

Fig. 29.11 Single-photon emission computed tomography demonstrates increased right cingulate blood flow. See Figures 29.1 and 29.2. *Used with generous permission from D.W. Seo* (Seo; personal observation).

hemispheres; Tanaka *et al*., 2005) with a higher time resolution and an ability to visualize evolving dipoles over time. Secondary bilateral synchrony is a common issue for seizures arising in medial frontal regions, including the cingulate cortex.

Neurosurgical therapy

Neurosurgical therapy for cingulate epilepsy is usually safe although efficacy varies based on the confidence of a single discrete seizure focus. If a single lesion is present, the surgery has a higher success rate (~65–70%) than in cases with normal or multifocal MRI scans (≤50%; Jobst *et al*., 2000; Rasmussen, 1991; Tassi *et al*., 2001). Surgical success correlates with the type of, and concordance of data to support a single, well-defined focus. MRI is the most important localizing non-invasive test. Intracranial recordings are extremely helpful in confirming the lateralization and localization of the

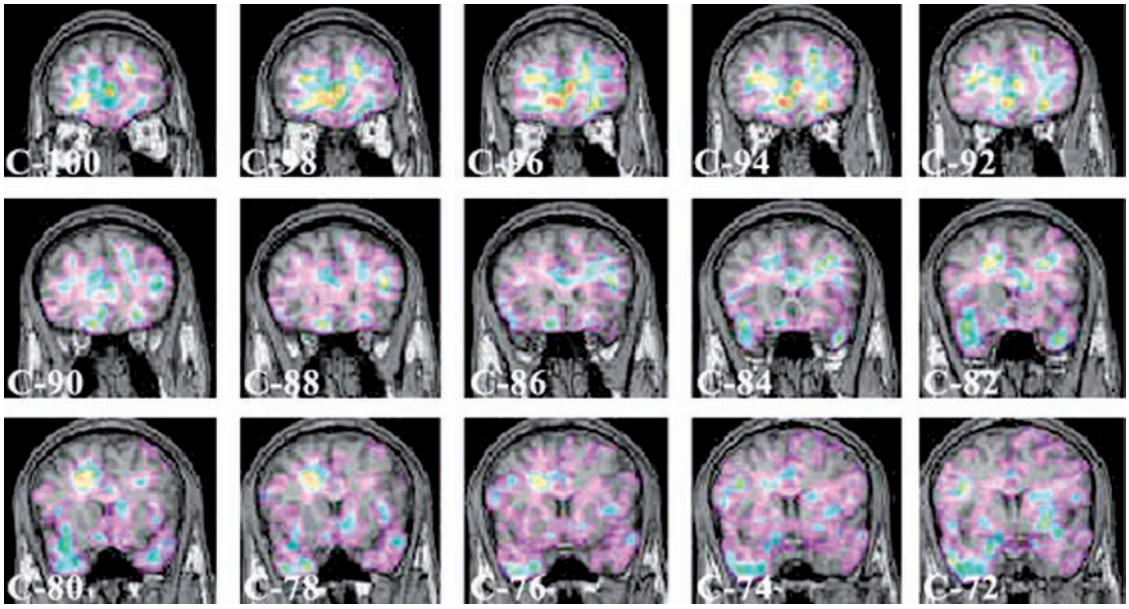

Fig. 29.12 Ictal single-photon emission computed tomography (SPECT), interictal SPECT, and subtraction of these images localized the seizure focus mainly to the ACC in one patient and to a lesser extent the caudal cingulum bundle. *Used with generous permission from D.W. Seo* (Seo; personal observation).

seizure focus, and defining the extent of the area of seizure origin. The value of SPECT and MEG in predicting surgical success is less certain. Several cases document successful surgery after localizing SPECT data (Seo *et al*., 2003) and MRS data (Guye *et al*., 2005).

The effects of limited cingulate resection are small. Large experiences in which bilateral cingulotomy or cingulectomy were performed to improve psychiatric disorders show few cognitive or behavioral problems after these extensive procedures. However, a likely reason is that we do not have sensitive neuropsychological tests to assess many cingulate cortex functions. Indeed, many patients showed improvement in behavioral function while cognitive changes were mild and sometimes were characterized by changes in motivational status or personality preferences (Tow & Whitty, 1953; Wilson & Chang, 1974). In contrast, reports from much more restricted unilateral cingulate resections for epilepsy surgery tend to show stable or improved mood and personality after surgery.

In some cases, if risks of or harm in developing a disconnection syndrome are low, a partial or complete corpus callosotomy may be carried out to reduce generalization of the seizures and the risks associated with atonic or tonic–clonic seizures. Also, additional recordings may help lateralize the focus of seizures for which secondary bilateral synchrony obscured initial onsets.

Pathogenesis and Neuropsychiatrical Comorbidity

The pathogenesis of cingulate epilepsies is similar to other partial epilepsies. Patients fall into two broad groups: (1) those with structural lesions identified on MRI (e.g., tumors, vascular lesions, gliosis, malformations of cortical development); and (2) those whose MRIs that are normal or reveal only non-specific findings (Devinsky *et al*., 1994; Seo *et al*., 2003). The cingulate cortex appears to be neither predisposed nor immune to any specific pathological processes that affect the cerebral cortex. However, it is a less common site for gliosis after head injury than orbitofrontal, frontopolar, or the polar or basal regions of the temporal lobe (Adams *et al*., 1980). Clinical, EEG, and functional imaging suggest that autosomal dominant frontal lobe epilepsy (ADFLE) may have a mesial frontal origin (So, 1998), but as this disorder is usually controlled with low doses of medication, neither intracranial nor pathological data are available. ADFLE results from abnormalities in the nicotinic receptor subunits and has clinical (brief, stereotyped, and sudden arousals to more complex dystonic–dyskinetic seizures) and neurophsyiological features that overlap with more common, sporadic forms of frontal lobe epilepsy (Combi *et al*., 2004).

Neuropsychiatrical comorbidity is frequently reported in patients with cingulate epilepsy, although detailed

neuropsychiatrical data are reported for only case reports, small series, or older series. The use of cingulotomy and cingulectomy to treat psychopathology in the 1950s may have contributed to a view that cingulate hyperfunction could cause psychopathology, similar to the view of temporal lobe psychomotor epilepsy during this era (Gastaut *et al.*, 1955; Pond & Bidwell, 1959/1960). As cingulectomy and cingulotomy were considered effective for a variety of mental disorders, their value in patients with cingulate and mental pathology would be expected (Mazars, 1970).

In the earliest and still the largest series of epilepsy surgeries for cingulate cortex foci (Mazars, 1970), reported that the majority of the 36 patients suffered from fixed or intermittent psychoses or episodic outbursts. The psychoses differed from those seen in patients with temporal lobe epilepsy as the cingulate patients lacked the hypomania and logorrhea but had more paroxysmal aggressive outbursts and more antisocial behavior. These problems were often improved after bilateral cingulectomy. Ledesma and Paniagua (1969) also observed similar aggressive behaviors in epilepsy patients and improved aggression and epilepsy after bilateral cingulectomy.

More recent cases documented with MRI and/or intracranial electrodes support that even restricted cingulate resections can improve behavior in patients with cingulate epilepsy and psychopathology. An 11-year-old girl had medically refractory seizures since age 2.5 years initially had atonic but later complex partial seizures. At age 3, she developed obsessions and by age eight she had severe obsessive and compulsive symptoms. She was preoccupied with Satan and feared punishment for imagined and real behaviors, and she spent long periods cleansing her body. MRI was normal; scalp video-EEG showed partial seizures arising from the right frontal region. Depth electrode recordings documented seizure onset from the right cingulate cortex with secondary generalization. Surgical destruction of 4 cm of the right MCC eliminated seizures and markedly reduced obsessive–compulsive behaviors during the first 15 post-operative months (Levin & Duchowny, 1991). Other patients with severe sociopathic behaviors have similarly been dramatically improved after removal of their cingulate seizure focus (Devinsky *et al.*, 1995).

The frequency of psychopathology with cingulate epilepsy is difficult to determine. However, many of the well-studied patients show evidence of mental pathology with elements of aggression, obsessive and compulsive thoughts, thought disorder, mood changes, and sociopathy. None of these findings are specific for cingulate epilepsy, but with a larger patient series, a range of characteristic behavioral changes may be discerned. Regardless, behavioral changes in patients with cingulate epilepsies will likely vary based on the genetic soil, the environmental milieu, and biological factors related to the underlying pathology and epilepsy. In some patients, onset of cingulate epilepsy in early childhood was associated with profound mental retardation while others suffered only mild cognitive problems (Shiraishi *et al.*, 2001) and in others, who developed the cingulate epilepsy, especially in adulthood, enjoy normal cognitive and behavioral function.

Overview of Structure–Function Correlations for Seizures in Cingulate Cortex

Seizures arising from the cingulate cortex often present with specific semiologic, neurophysiologic, and neuroimaging characteristics. In general, the precise correlation of symptoms during or between seizures and seizure focus localization is very difficult in the extratemporal epilepsies (Jobst *et al.*, 2000). For example, brief nocturnal seizures with intense axial motor automatisms can result from seizure foci in other orbital, lateral, polar regions of the frontal lobe, as well as the cingulate cortex or medial parietal regions. Despite these limitations, seizures arising in the cingulate cortex can be correlated, if not confidently localized, to specific subregions (see Chapter 1). Thus, seizures arising in sACC, with its autonomic functions, can modify a range of autonomic functions as evidenced in the case of pilomotor epilepsy (Seo *et al.*, 2003). Seizures arising in pACC, probably the majority of those reported in the literature, may have simple partial seizures in which there is a change in their motivation, thought, or feeling of control over their actions, as well as more typical evolution with impaired consciousness and automatisms that reflect spread pattern more than site of origin.

Seizures arising in or spreading to the MCC can cause shards of stereotyped emotional expression such as bilateral perioral contractions to more fully expressed, but mirthless expressions of laughter and occasionally crying. Spread of seizures from the MCC to adjacent supplementary motor or premotor areas can cause more typical dystonic and tonic seizure symptoms.

Finally, seizures arising in the PCC are the least well documented in the medical literature. PCC seizures are rare and difficult to document with available diagnostic modalities. Stimulation or inhibition of the PCC for brief periods may not produce characteristic clinical changes that remain unknown, or may be 'silent' clinically. Of interest, a recent study examined spike-triggered fMRI in patients with idiopathic generalized epilepsy and frequent spike and slow-wave discharges. Blood oxygen level-dependent activity showed significant reductions of the PCC during spike and slow-wave discharges, suggesting that PCC deactivation may be

related to 'absence' (Archer *et al*., 2003). We await better description of PCC seizures, but the involvement of PCC may contribute to the clinical phenomenology of a common epilepsy syndrome.

Psychopathologic disorders can complicate the interictal state in patients with cingulate epilepsy. These problems include emotional lability, psychosis, aggression, obsessive–compulsive behaviors, and sociopathy. In the cingulate cortex, the chronic effects of electrophysiological dysfunction, often combined with structural pathology, can profoundly disrupt personality, emotional regulation, social cognition, and the cohesion of thought. These interictal behavioral changes provide another window into the long-term ('area under the curve') effects of both excitation and inhibition of cingulate cortex. Jackson's postulate regarding the dual effects of seizures may provide even more insight into their interictal effects, where the negative and positive symptoms become more complex and more disabling.

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