■ Clinical commentary

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Epileptic Disorders

The ventral precuneal-posterior cingulate region as a site of epileptogenicity

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ABSTRACT

The ventral precuneal and posterior cingulate area (VP-PC) represents a distinct but topographically variable mesial parietal site of epileptogenicity that may manifest as a common temporal lobe-mediated ictal expression. In a review of records of 62 presumptive epilepsy surgery cases, two cases of primary epileptogenicity expressed within the VP-PC were identified and are detailed to bring attention to this electroencephalographically-hidden area of ictal expression. Details of their investigation and surgical treatment illustrate distinctly different approaches addressing the problem and bringing about a seizure-free outcome.

Key words: precuneus, posterior cingulate, default mode network, temporal lobe epilepsy, responsive neurostimulation, laser interstitial thermal therapy

The precuneus is well-defined topographically, both anteriorly and posteriorly, by the marginal branch of the cingulate sulcus and the parieto-occipital sulcus, respectively. A subparietal branch of the cingulate sulcus in many cases provides a partial ventral boundary with a great deal of variability otherwise present [1]. A complete subparietal sulcus extending from the marginal sulcus to the parieto-occipital sulcus was present in only 8.9% of 56 cadaveric cerebral hemispheres with, otherwise, an assortment of varied sulcal branches extending into the posterior cingulate area [1]. The local topography of this region is a confluence of the ventral precuneus and the subjacent posterior cingulate area. Cytoarchitectonically, Brodmann areas 23, 30, and 31 dominate the ventral precuneal-posterior cingulate area (VP-PC) [2]. Speculation has arisen regarding the VP-PC as constituting the actual hub of the default mode network (DMN) in this location rather than the entire precuneal and subjacent surface [3, 4]. To this end, task-related suppression of gamma band activity in the DMN, recorded by stereoencephalography (SEEG), correlates with blood oxygenation level-dependent (BOLD) imaging signal, specifically, the area of the PC [3].

The manifestations of an epilepsy arising in the VP-PC are varied and represent not only activation of functions ascribed to the immediate area but those ostensibly belonging to a network with which it is connected [4-8]. The VP-PC represents a prominent hub within the DMN through which other sites may be activated, adding to the semiology [9, 10]. Dorsal and ventral streams connect the VP-PC with the ventromedial prefrontal cortex and the parahippocampal gyrus, respectively [4]; they serve as a potential conduit for spread of ictal activity to remote destinations. This complicates the search for the actual site of epileptogenicity. The manner of establishing the

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site of ictal origin within the VP-PC therefore remains a considerable challenge.

Prior experience with both posterior cingulate [6] and precuneal [7] ictal onset emphasized the difficulty in establishing the origin either by semiology or with other non-invasive methods in non-lesional situations. The ventral precuneus has connections with both the posterior cingulate gyrus and the mesial temporal area [4]. Similarly, reciprocal connections exist between the mesial temporal area and both the retrosplenial and ventral PC [11]. The critical nature of these connections emphasizes the importance of thoughtful interpretation of electrographic and neuroimaging findings on preoperative assessment. The two surgically resolved cases offered here identify the nature of the presenting problem, its investigation, and final resolution by which correct conclusions may be drawn.

Materials and methods

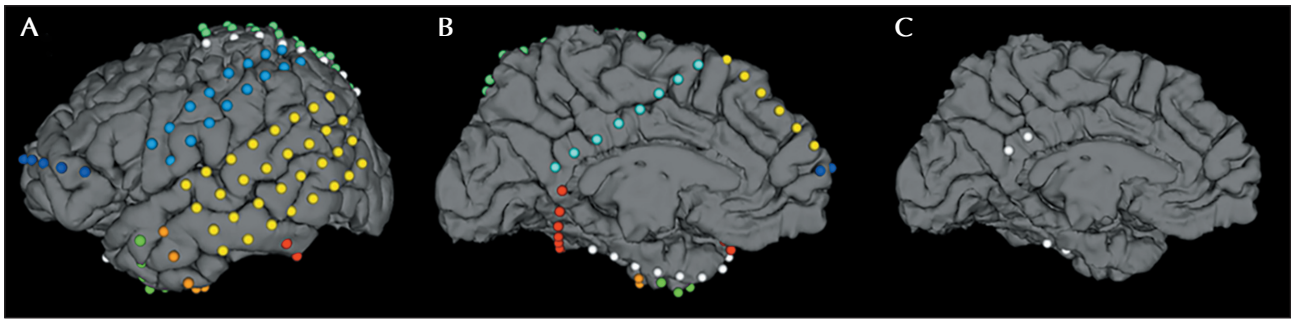
A standard investigation was undertaken for all patients identified by history and prior scalp electroencephalography (EEG) with a suspected focal-onset epilepsy and presenting for surgical consideration. Inpatient video-EEG monitoring over a minimum five-day period (Phase I) was performed along with magnetic resonance imaging (MRI) using our standard epilepsy protocol, positron emission tomography (PET), single photon emission computed tomography (SPECT), sodium amobarbital study, neuropsychological profile and, in several cases, magnetoencephalography (MEG). In those cases where discordant features arose, particularly dealing with laterality and epileptogenic origin, a Phase II study (*i.e.*, intracranial electrocorticography) was performed. The latter was undertaken with surface electrode arrays and/or multicontact depth electrodes targeting areas of concern in one or both cerebral hemispheres.

Results

A review of charts of patients presenting with a presumptive temporal lobe epilepsy (TLE) identified cases harboring an extratemporal ictogenic site that manifested in a manner to suggest a temporal origin. Of 62 cases accrued over three years and identified as manifesting as what appeared to be a TLE, four were found to possess distinct extratemporal ictal origins. Apart from two cases of mesial parietal epileptogenicity reported here, the remaining two each presented with either a mesial frontobasal angioma or a parietal ventricular nodular heterotopia. The VP-PC drew particular attention because of its deeply situated location within the interhemispheric fissure and its propensity to spread into the mesial temporal area to manifest electrographically as remote epileptogenicity. In the absence of overt initial neuroimaging features in the form of a structural anomaly or signal change and poor localization by scalp EEG, clinical localization presented a considerable challenge.

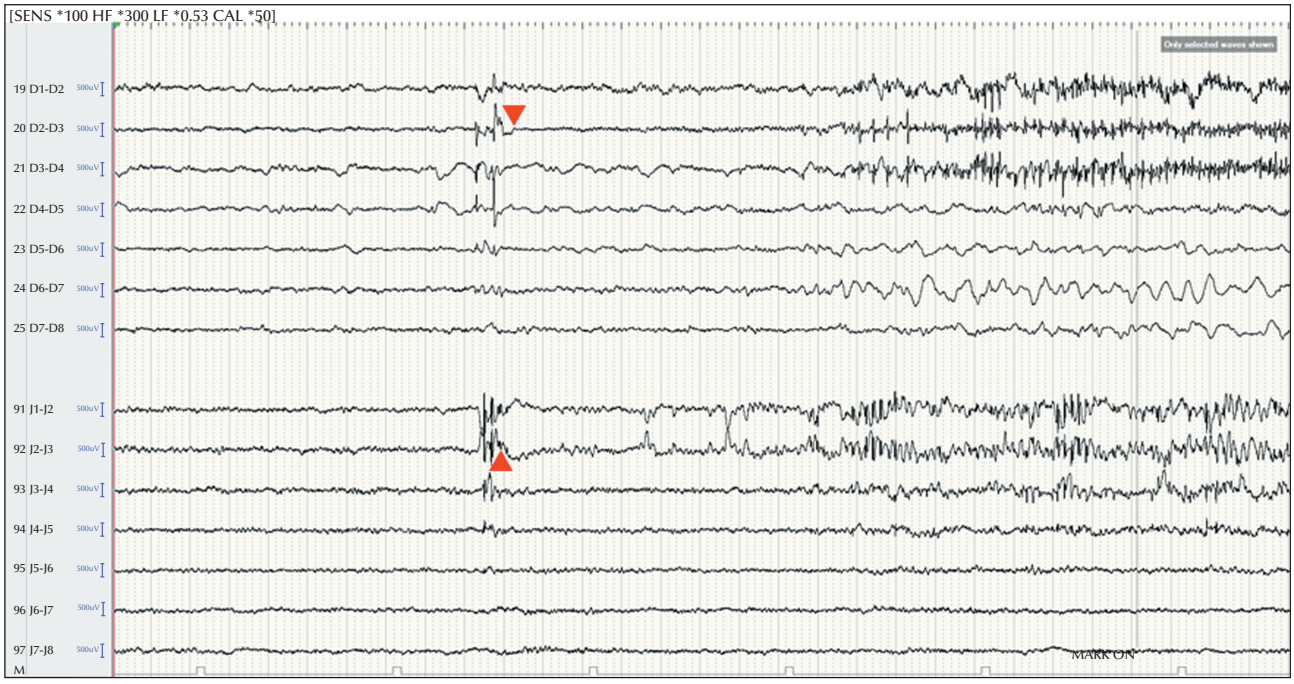
Case 1

A 14-year-old male presented with epilepsy since the age of six months without evident risk factors. He would commonly feel an epigastric discomfort without a rising sensation or experiential sensations. Behavioral arrest with staring progressed to a rightward versive motion of the eyes and a tendency to walk intentionally in a particular direction. On some occasions, the semiology manifested as a tonically flexed posture at the waist and extension of the right arm backward with the palm up-facing, suggesting spread in the mesial frontal direction. Any vocalization was inarticulate or nonsensical. The two semiologies suggested possible independent ictal origins in both temporal and mesiofrontal sites or, likewise, a central site with spread to both locations. At times, particularly with events clustered, he would remain disabled for a time with poor word finding capability and fatigue. Medical management at the time of initial surgical assessment consisted of lamotrigine, carbamazepine, topiramate, perampanel, and clonazepam. Scalp EEG identified left parasagittal interictal centroparietal activity. MRI showed no overt pathology and PET was unremarkable. Magnetoencephalography (MEG) was also unremarkable with minimal dipoles in a right central location. Neuropsychological testing identified left hemispheric relative dysfunction with gradual cognitive decline from ages 10 through to 14 years with Full Scale IQ (FSIQ) diminishing from 105 to 86, the Verbal Comprehension Index (VCI) from 95 to 86, and the Perceptual Reasoning Index (PRI) (*i.e.*, fluid reasoning, spatial processing and visual-motor integration) from 106 to 94. Functional MRI demonstrated left hemispheric speech dominance. Electrodes were implanted targeting the left parietal and temporal lobes primarily. A surface contact coverage was undertaken to provide greater regional electrode density in those areas considered suspect as epileptogenic sites to ensure adequate surveillance given the level of uncertainty raised with preliminary studies. All electrographic ictal discharges consistently manifested initially in the VP-PC with a short lead-in before activity appeared in the posterior parahippocampal region (*figures 1, 2*). A higher discharge tonicity was also evident in the former location suggesting a greater epileptogenicity index [12]. Clinical onset followed 45 seconds after

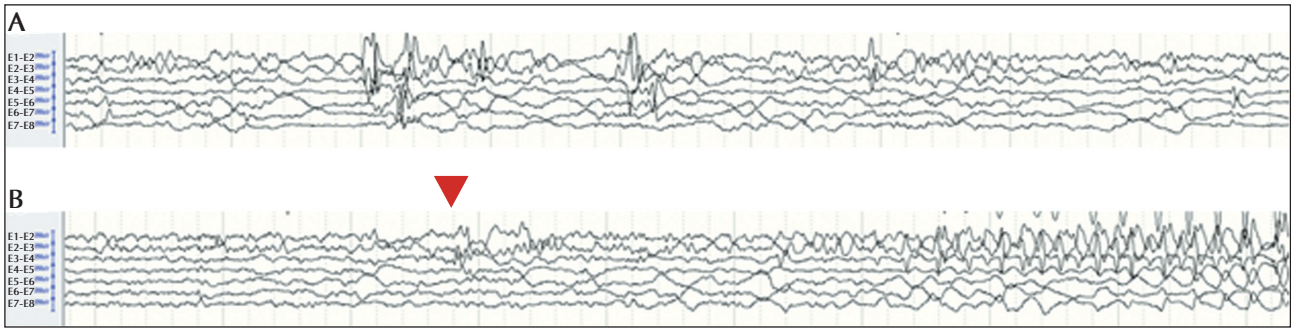


■ **Figure 1.** Case 1. Convexity (A) and mesial hemispheric (B) surface representations showing the distribution of surface electrodes used during Phase 2 evaluation. The final therapeutic intervention (C) is accomplished by the implantation of local surface electrodes targeting the VP-PC, in particular, and the parahippocampal gyrus with responsive neurostimulation (RNS) to bring about a seizure-free status. The two salient electrode contacts in each array are identified.

electrographic onset. Stimulation applied at the site of excitability within the posterior parahippocampal gyrus elicited the familiar epigastric discomfort without an afterdischarge. In the case of the VP-PC, stimulation again elicited epigastric discomfort with and without an afterdischarge on separate occasions. With antiseizure medications fully resumed, stimulation of the VP-PC caused a prolonged afterdischarge but again without progression to an ictal episode. Both the VP-PC and posterior parahippocampal areas were subsequently targeted using surface electrodes coupled with a Responsive Neurostimulation (RNS;



■ **Figure 2.** Case 1. Phase II electrocorticography showing ictal onset in the VP-PC (upper arrowhead) with a 100-ms lead-in, followed by onset of activity in the posterior parahippocampal area (lower arrowhead). Both a higher discharge tonicity and earlier lead-in suggests a greater epileptogenicity index for the former site. Clinical onset occurred 45 seconds following electrographic onset.



■ **Figure 3.** Case 2. Phase II electrocorticography by strip electrode array situated anteroposteriorly along the parahippocampal gyrus showing interictal background and epileptiform discharge (A) and ictal onset activity manifesting in the right mesial temporal area (B). Electrode contact E1 was situated most posteriorly along the gyrus. The arrowhead identifies the apparent clinical ictal onset with a behavioral pause, a throat clearing sound, followed by rapid flexion-extension motion of the fingers of the right hand.

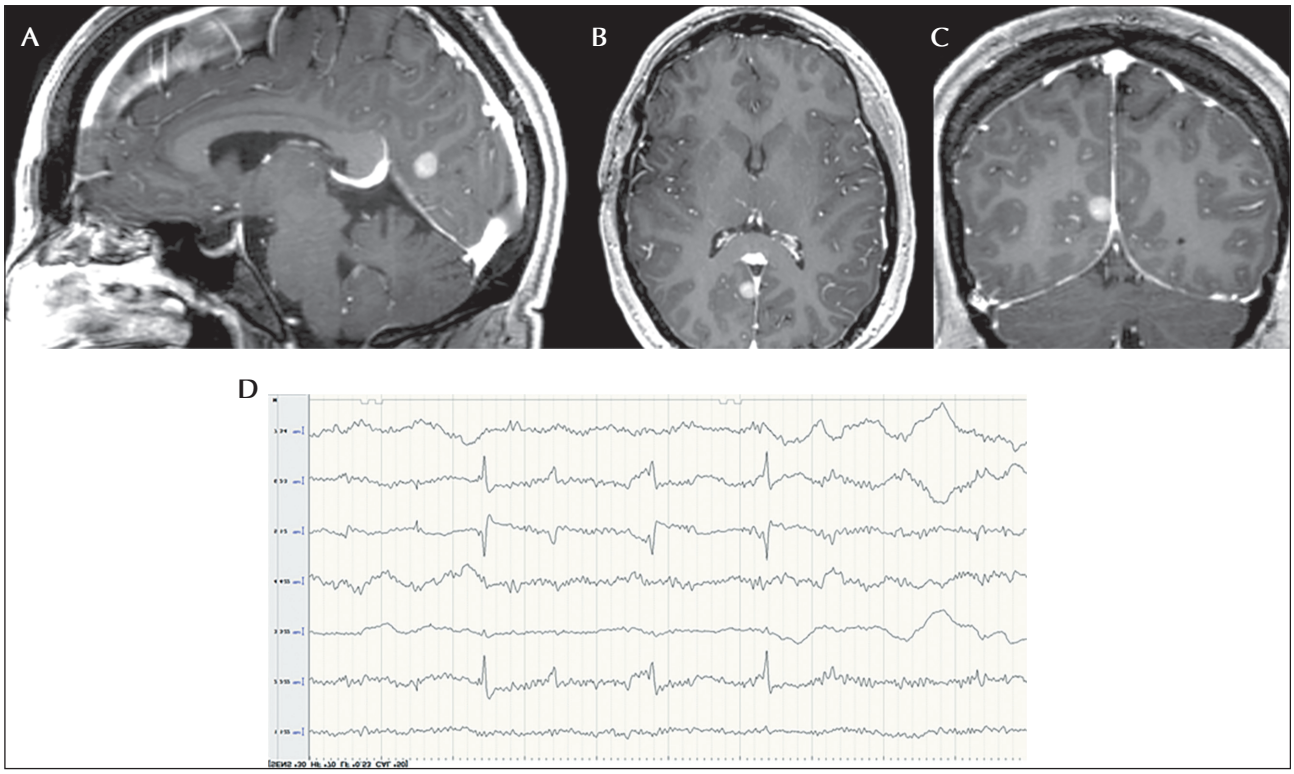
NeuroPace, Mountain View, CA) unit to ensure adequate control of epileptic expression (*figure 1C*). The antiepileptic regimen at the time of discharge included lamotrigine, carbamazepine, topiramate and levetiracetam. Medication taper has continued with the most recent regimen now consisting of lamotrigine and brivaracetam. The patient has remained without clinically expressed seizure activity for six years while RNS recordings continue to show predominant VP-PC interictal spike activity. After three years, FSIQ increased to 92, VCI remained unchanged while the Visual Spatial Index increased from 94 to 114 and the Working Memory Index improved from 97 to 100. He is gainfully employed as a mechanic.

Case 2

A 21-year-old female presented with a one-year history of focal unaware seizures with an aura of nausea and malaise followed by a tendency to abruptly wander off, mumble incomprehensively, spit, and rub or pinch her nose with her right hand. Postictal fatigue commonly manifested. Scalp EEG showed right anterior temporal interictal sharp waves and anterior-midtemporal ictal onset. Medical management at the time of initial surgical assessment consisted of lamotrigine, oxcarbazepine, levetiracetam and clonazepam. Neuropsychological assessment showed both verbal and non-verbal memory within normal range and no significant discrepancy between VCI and PRI abilities with generally average scores. PET and MRI at the outset showed no lateralizing or localizing features. This case was included in a prior quantitative neuroimaging study of a large cohort of putative temporal lobe epilepsy cases (P22) [13]. Phase II intracranial electrocorticography with frontoparietotemporal convexity and mesiobasal temporal coverage appeared to confirm a right mesial temporal epilepsy by interictal and ictal recording leading to resection (*figure 3*). The right mesial frontoparietal cerebral surface was not sampled in the recording. After seven months, the patient experienced three generalized seizures followed by a return of her habitual seizure pattern, although with decreased intensity. Follow-up MRI showed a slowly evolving enhancing lesion situated in the right VP-PC, posteriorly (*figure 4A-C*). Intraoperative stereotactic depth electrocorticography showed a very active interictal discharge (*figure 4D*) and pathology revealed a pilocytic astrocytoma with adjacent features of a focal dysplasia. Laser interstitial thermal therapy (LITT) ablated the lesion, resulting in a seizure-free outcome over the past four years. MRI confirmation of centrality of the fiberoptic cable within the lesion confirmed the earlier placement of the recording electrode within the lesion using the same trajectory. The patient is nearing completion of a taper of her antiepileptic medication with the current regimen consisting of clobazam. She is part-time employed. A tractographic analysis was performed to identify the proximity of fibers projecting from the lesion and its immediate lateral perimeter to the site within the temporal lobe, initially determined to harbor the primary epileptogenicity. This identified the projection directly into the resection cavity left behind where local electrocorticography had identified epileptogenicity (*figure 5*).

Discussion

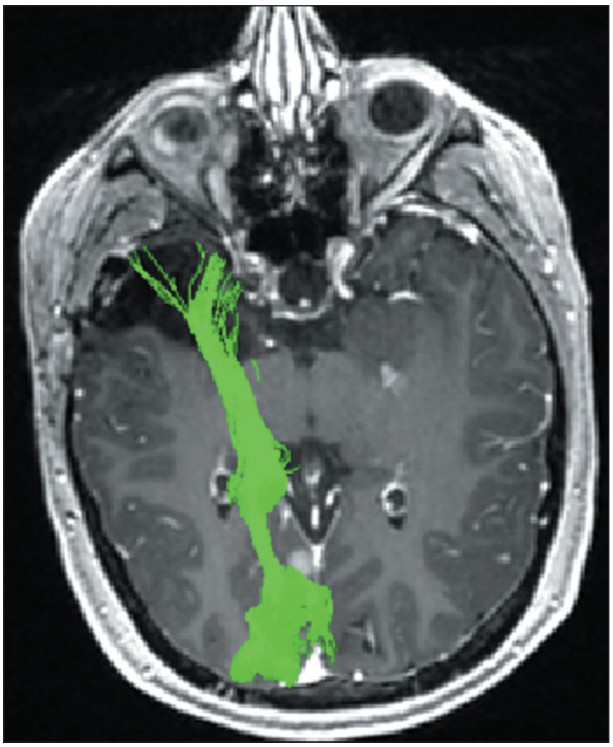
In the two patients presented here, a mesial parietal ictal origin was identified that manifested clinically with semiological features of a mesial TLE. The



■ **Figure 4.** Case 2. Sagittal (A), axial (B) and coronal (C) MR images identifying a VP-PC contrast-enhancing lesion. This was later identified as a pilocytic astrocytoma associated with a cortical dysplasia and representing a discrete area of epileptogenicity. (D) Intraoperative four-contact depth electrocorticography reveals prominent interictal discharge activity from within the targeted lesion.

findings of each assessment are notable for their very similar epileptogenic locations within the VP-PC, as verified by electrographic recording and by their response to treatment. A notable semiological feature in both cases was the tendency for intentional and self-directed, although seemingly purposeless, ambulation. Although various hypermotoric or complex motor behavioral ictal features have been described in cases of precuneal epilepsy [7], there is no reference to locomotor or ambulatory activity as seen with our two cases. Whether the self-referential features of the DMN underlie such spontaneous activity is a matter for further discussion. There is, however, considerable variability in ictal behavior resulting from regional expression within the VP-PC in addition to abundant network-related connectivity with cortical and subcortical structures [4, 5, 7]. Electrical stimulation of the ventral anterior midcingulate area has been shown to lead to "whole-body movements toward extrapersonal space (*e.g.*, the impulse to get up)", to indicate a putative emotionally-prompted motoric behavior, such that ictal spread from the VP-PC to this site could have instigated the action [14].

One of our patients (Case 1) also showed evidence of a bilateral asymmetric tonic postural ictus on occasion, revealing a propensity to manifest different semiologies, attributable to the spread of activity, in this case, to the supplementary motor area. The clinical presentation prompted a rather wide coverage of the left hemisphere, including its mesial surface, to identify ictal onset and its manner of spread. The site of ictal origin was ultimately surmised to be the VP-PC with spread either toward the latter mesial frontal site or the parahippocampal site, to manifest with features more aligned with temporal lobe involvement. RNS implantation was felt suitable in the absence of a targetable lesion and uncertainty regarding actual volume of epileptogenic cortex. Moreover, the brief latency in activation of the parahippocampal site prompted placement of one of the two RNS electrode arrays here in order to optimize control of this activity for a better outcome. Adjustment of stimulation parameters and possibly electrode configuration would then be implemented to exert control. Neither patient exhibited auras of visual distortion, vestibular experiences, sensations of falling, or self-dissociation



■ **Figure 5.** Case 2. Reformatted in-plane post-contrast T1 MRI showing the VP-PC lesion, the prior temporal resection site, and an overlay of fibers found between both as the likely substrate underlying ictal spread from the VP-PC. Both the lesion center and its immediate lateral perimeter were seeded for this purpose. The tract has multiple fibers projecting into the site of resection within the mesial temporal area where distinct epileptogenicity was identified.

[8, 15]. Memory appeared unaffected in our patients despite evidence that disturbance of the posterior cingulate area impairs episodic memory [16].

Distinct mesial temporal semiological attributes were otherwise noted with manifestations of epigastric distress and nausea, behavioral arrest, staring, mumbling, nose-rubbing, and a postictal fatigue [5, 8]. Scalp EEG typically is of limited use and reliance is placed upon invasive recording. Even so, sampling bias in Phase II may have proven to be at fault in Case 2 with the absence of coverage of the VP-PC during the initial studies when a lesional presence in the area was not yet identifiable by neuroimaging.

Medical intractability was quite evident in our two patients and coincides with similar experience elsewhere [4, 7]. There is insufficient evidence in the literature to judge how universal the problem of controlling seizures may be in an area which may itself be semiologically silent [6] but have a great propensity to spread [10]. Otherwise, intrinsic cortical excitability, mounting over time, will add to the difficulty in seizure control [17]. Surgical management does appear to be effective and safe, as judged by our own experience and others, particularly, with the advent of minimally invasive approaches with LITT and the introduction of RNS technology [8]. Open procedures also appear to have similar results, although with increased risks [7].

Conclusions

The VP-PC appears to be a unique site, given its prominence as a discrete hub within the DMN and its functional connectivity with widespread areas of the brain. Adding to its particularly strategic location for ictal spread is the considerable variability in local clinical expression including distinctly silent sites. A confounding element in the investigation, particularly in the absence of any structural or signal anomaly on MRI or nuclear medicine imaging, is its deep interhemispheric location, hiding it from detection by EEG or MEG. Hence, clinical acumen coupled with the application of appropriate and detailed neuroimaging factor heavily in providing insight into a possible ictal origin in the VP-PC. ■

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

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TEST YOURSELF

(1) The ventral precuneal-posterior cingulate (VP-PC) region:
A. is a topographically poorly demarcated region of the medial parietal surface
B. manifests task-related gamma band suppression
C. is definable by blood oxygenation level-dependent (BOLD) MRI signal
D. A and C
E. A, B, and C

(2) Preliminary surface EEG and MEG for seizures suspected of arising in the VP-PC:
A. provide adequate appreciation of epileptogenicity within the VP-PC
B. may identify distinct epileptogenic activity remote from the VP-PC
C. are aided by a distinct semiology, exclusively manifested by an epileptogenic VP-PC
D. can be aided by a number of neuroimaging applications
E. B and D

(3) A surgical solution for medically-refractory VP-PC epileptogenicity:
A. is possible only in the presence of an imaging-defined lesion in the VP-PC
B. can be accomplished with an open procedure in most circumstances and with negligible risk
C. is amenable to a neuromodulatory approach with a closed-loop responsive neurostimulation unit
D. should not be attempted

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