Original article with video sequences

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Reflex operculoinsular seizures

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ABSTRACT – Activation of specific cortical territories by certain stimuli is known to trigger focal seizures. We report three cases of well documented operculo-insular reflex seizures, triggered by somatosensory stimuli in two and loud noises in the third. Limited operculoinsular resection resulted in an excellent outcome for all. We discuss these observations in regard to the literature on reflex epilepsy and known functions of the insula. [*Published with video sequences online*]

Key words: reflex, epilepsy, insula, somatosensory, audiogenic

The insular cortex is a complex structure enclosed within the depth of the Sylvian fissure, covered by the frontal, temporal and parietal opercula (Surbeck *et al.*, 2011). Based mainly on case reports and a few small series, we know that insular seizures may feature early somatosensory symptoms (similar to parietal lobe seizures), hypermotor symptoms/complex motor behaviours (resembling frontal lobe seizures), and early visceral auditory or dysphasic symptoms (suggestive of temporal lobe seizures) (Isnard *et al.*, 2004; Nguyen *et al.*, 2009; Proserpio *et al.*, 2011; Kriegel *et al.*, 2012). We have also recently reported that insular seizures may produce gelastic seizures (Tran *et al.*, 2014), ictal orgasmic ecstasy (Surbeck *et al.*, 2013), as well as ictal bradycardia (Tayah *et al.*, 2013). Here, we describe the cases of three patients with reflex operculoinsular seizures, further broadening the clinical presentation of this focal epilepsy syndrome.

VIDEOS ONLINE

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Case studies

Patient 1

The first case (previously reported as part of a small series of patients with epilepsy treated by gamma-knife surgery) (Irislimane *et al.*, 2013) is a 40-year-old left-handed male patient who started having seizures at the age of 30, characterized by daily right hemibody somatosensory symptoms, including pain and occasionally ending with right arm elevation (*video sequence 1*). His seizures could be consistently triggered by tactile stimulation (*e.g.* by

caressing his fingers or the palm of his right hand or his groin). Recognition of an underlying epileptic condition was initially difficult, as brain magnetic resonance imaging (MRI) and positron emission tomography (PET) were normal and no epileptiform interictal discharges were detected after several scalp EEGs. Ictal recordings, however, showed late brief semi-rhythmic slowing over the left hemisphere. Ictal single-photon computed tomography (SPECT) revealed several sites of activation, including the left insula. After failing seven antiepileptic drugs, the patient underwent an invasive EEG study using: a subdural grid electrode laid over the left dorsolateral fronto-parietal region; five subdural strip electrodes to sample the interhemispheric, fronto-polar and lateral temporal regions; and two insular depth electrodes (two contacts in the anterior long insular gyrus and two in the posterior long insular gyrus) (Surbeck *et al.*, 2011). Recordings revealed active spontaneous interictal spiking in the posterior insula. Insular seizures could be triggered by rubbing his right palm (*figure 1*). Seizure freedom was eventually obtained following partial removal of the left posterior insula and complementary gamma-knife surgery (Engel class 1; follow-up of eight years).

Patient 2

This 46-year-old right-handed male patient with non-lesional refractory seizures was referred to our centre after failing 10 antiepileptic drug trials and epilepsy surgery in the left parietal operculum (guided by invasive EEG recordings but without insular coverage). The patient reported multiple diurnal seizures triggered by noise (*e.g.* phone or bell ringing, door banging, dog barking, hammering, tree sawing, grass mowing, *etc.*), with initial pain over the right side of the face, spreading to the right limbs and lasting several seconds. In addition, he presented with weekly to monthly spontaneous nocturnal hypermotor seizures. Video-EEG showed left temporal interictal spikes, rhythmic left temporal activity during noise-triggered diurnal seizures, and non-localizing artefact EEG during spontaneous nocturnal seizures. Two ictal SPECT studies were non-localizing. Magnetoencephalography (MEG) identified sources in the left superior and middle temporal gyri, and in the insula. To better localize the seizure onset zone, a second invasive EEG study was performed using a combination of depth and subdural electrodes sampling the left medial temporal structures and the perisylvian region. The operculo-insular structures were sampled using three hybrid operculo-insular electrodes, each combining two depth electrode contacts (recording the insula) and two double-sided subdural contacts (recording the hidden surface of the parietal, frontal and temporal operculum) (Bouthillier *et al.*, 2012). Post-implantation MRI confirmed the location of two depth electrode contacts in the anterior insular short gyrus (two in the posterior short insular gyrus and two in the anterior long insular gyrus). Bursts of epileptiform discharges and seizures were consistently triggered by loud noises (>80 Db; controlled by an audiometer), irrespective of sound frequency, the emotional content of auditory stimuli, or the type of ecological or musical stimuli (*video sequence 2*). Electrically, seizures originated from the left parietal operculum/posterior insula/temporal operculum area (*figure 2*). Hypermotor manifestations coincided with propagation of the ictal discharges to the anterior insula, inferior frontal gyrus and temporal pole (the orbitofrontal region was not sampled in this patient). Operculoinsular resection led to seizure freedom (Engel class 1; follow-up of 1.5 years).

Patient 3

This 32-year-old right-handed woman with a history of febrile seizures developed drug-refractory epilepsy at the age of 14. She had daily seizures characterized by a pulsating sensation over the left hand and lips, followed by minimal motor movements, asymmetric tonic posturing, or complex motor behaviour. Seizures could be triggered by various stimuli, such as washing her hands with soap, rubbing her left-hand fingers together or on her lips, feeling the vibration of an underground train when holding a handrail, or feeling the contact of water on her lips when showering (*video sequence 3*). During video-EEG monitoring, frequent right temporo-parietal spikes and occasional left temporal spikes were noted interictally, while seizures were associated with diffuse EEG changes. MEG source localization identified a cluster over the left anterior temporal region and another at the junction of the right parietal operculum/frontal operculum/superior posterior insula. A biased review of the MRI, guided by MEG results, identified a subtle cortical dysplasia in the right parietal operculum. A subsequent intracranial EEG study was performed using: a subdural grid electrode over the right dorsolateral fronto-parieto-temporal region, two hybrid operculo-insular electrodes (two depth electrodes ending up in the right posterior short insular gyrus and two in the right anterior long insular gyrus), as well as depth electrodes sampling mesiotemporal lobe structures, bilaterally. Thirty-two stereotypical seizures (as described above) were found to start from the right parietal/frontal opercula and posterior insula, in

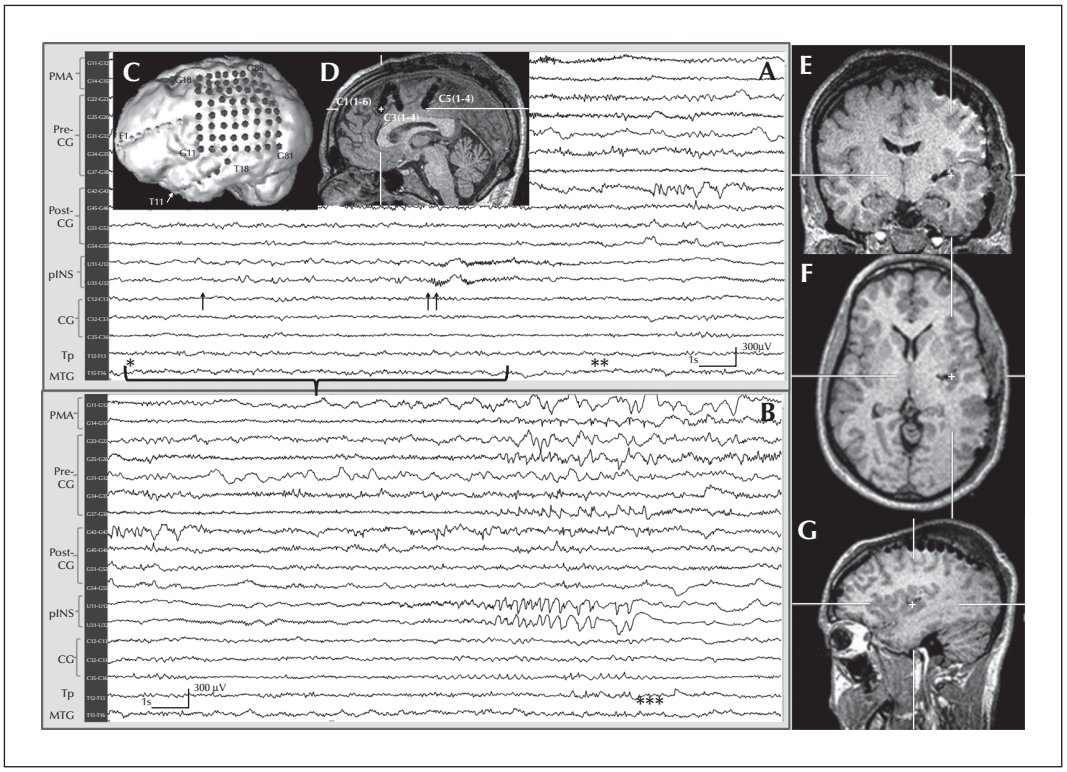

Figure 1. Invasive EEG recording of somatosensory evoked seizure in Patient 1. The recording sites are shown on a 3-D representation of the patient's brain in insets (C) and (D). In the upper EEG recording, rubbing the patient's right hand (*indicates onset of stimulus; horizontal bracket shows the duration of stimulation) triggers low-amplitude preictal spikes (↑) in the left posterior long insular gyrus (triangulated in the insets: [E] coronal view, [F] axial view, and [G] sagittal view) and frontal operculum, transitioning into a low-voltage fast activity ictal pattern (↑↑). Clinically, the patient feels right hemibody pain and lifts his right arm (**) until the end of the ictal discharge (***lower EEG recording). The latency between the trigger and the first epileptiform discharge was 2.850 seconds. PMA: premotor area; Pre-CG: precentral gyrus; Post-CG: postcentral gyrus; pINS: posterior insula; CG: cingulate gyrus; Tp: temporal pole; MTG: middle temporal gyrus.

addition to a single dyscognitive seizure without aura from the left hippocampus. Resection of the right parietal/frontal opercula and posterior insula has so far led to seizure freedom (Engel class 1a; follow-up of 1.3 years).

Pathological evaluation of resected tissue was unfortunately not possible for these patients because of the technique of sub-pial aspiration of the cortex used to perform the surgeries in this delicate area.

Discussion

In this report, we describe three extensively investigated patients presenting with reflex operculoinsular seizures. The nature of the triggering stimulus varied between patients, from a simple somatosensory stimulus (usually prolonged cutaneous stimulation) for Patients 1 and 3, to a loud audiogenic stimulus for Patient 2. In addition to our cases, we have found in the literature another case of reflex insular seizures, this time induced by eating (Blauwblomme *et al*., 2011). Indeed, this patient's seizures could be specifically triggered by the consumption of strawberry syrup. Resection of the right middle short insular gyrus led to seizure freedom as well.

Reflex seizures are generally considered to be caused by pre-existing cortical hyperexcitability (acquired or innate), which on sensory stimulation produces paroxysmal (localized or generalized) EEG discharges, accompanied or not by clinical manifestations (Binnie, 2004). For example, in touch-induced and movement-induced seizures, certain clues (such as sensorimotor symptoms, Jacksonian propagation, and localization of EEG anomalies) converge to implicate primary sensorimotor cortex or closely related regions (Yacubian *et al*., 2004). In reflex eating epilepsy, the perisylvian region appears to be an important zone overlapping with central neuronal networks processing food stimuli, *i.e*. the orbitofrontal and temporo-insulo-opercular cortices (Patel *et al*., 2013). In audiogenic epilepsy, trigger of seizures is attributed to direct projection of sensory

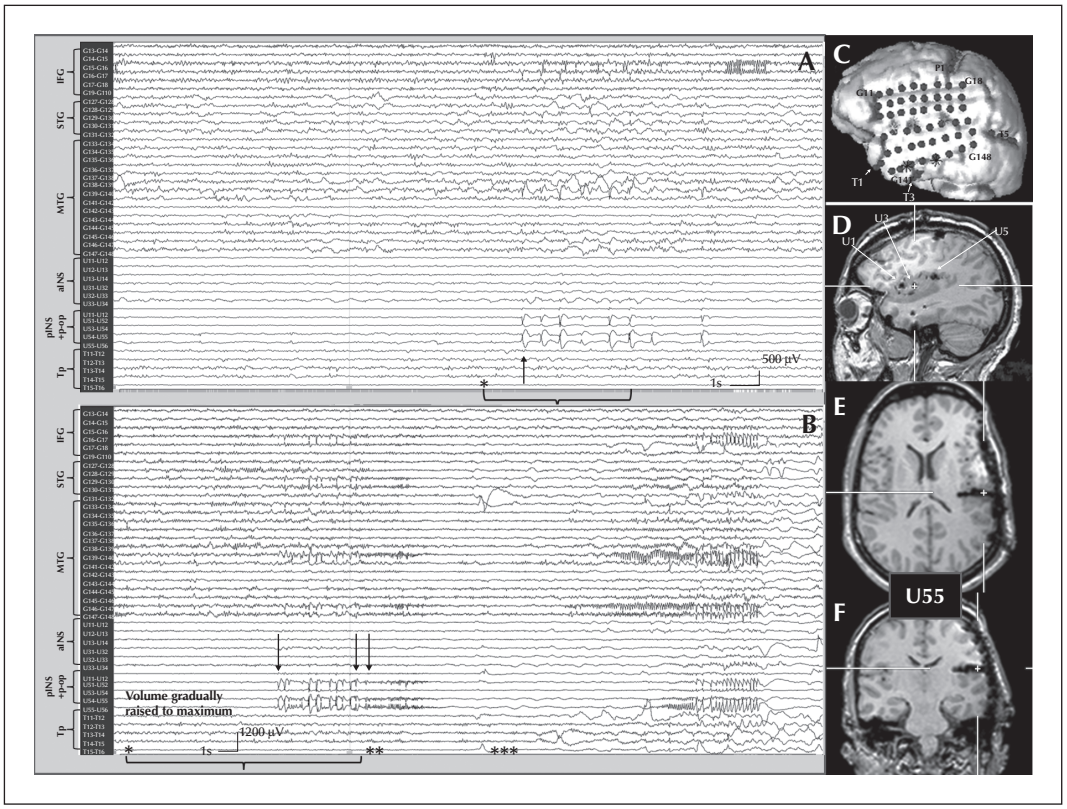

Figure 2. Invasive EEG recording of reflex audiogenic operculoinsular spikes (A) and seizure (B) in Patient 2. The recording sites are shown on a 3-D representation of the patient's brain in inset (C). In the upper EEG recording (A), an auditory stimulus to the left ear (2000 Hz, 85 dB) (*indicates onset of auditory stimulation; horizontal bracket indicates duration of stimulus) triggers, within a second, asymptomatic rhythmic spike-and-wave discharges (↑), maximum over the left posterior insula (as triangulated in the insets: [D] sagittal view, [E] axial view, and [F] coronal view) and parietal more than temporal opercula. High-pass filter: 0; low-pass filter: 35 Hz. In the lower EEG recording (B), listening to a piece of classical music gradually raised to maximum volume (*indicates onset; horizontal bracket shows stimulus duration) triggers a similar burst of spikes (↑) transiting into a seizure (↑↑) with the appearance of a high-frequency discharge in the posterior insula, parietal and temporal opercula. Clinically, the patient suddenly feels his aura, quickly removes his headphones (**), but is unable to abort subsequent evolution into complex motor behaviours (***). High-pass filter: 0 and low-pass filter: 20. IFG: inferior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; aINS: anterior insula; pINS: posterior insula; P-op: parietal operculum; Tp: temporal pole.

afferents (*e.g.* the primary auditory cortex) to motor areas (Martinez-Manas *et al.*, 2004). In praxis induction reflex epilepsy, actual or contemplated movements gain access and activate sensorimotor areas that are preferentially hyperexcitable and perhaps abnormally linked to other areas, to constitute the critical mass needed for seizure induction (Inoue and Zifkin, 2004). Hence, it should come as no surprise that the operculoinsular area may be implicated in some forms of focal reflex epilepsies.

Cumulative work over many years has shown that the insula plays many roles (Boucher, 2014, Augustine, 1996). It is a multimodal area involved in the processing of various sensory stimuli, from viscerosensory/somatosensory stimuli (Penfield and Faulk, 1955) to special senses such as hearing (Bamiou *et al.*, 2003), taste (Small, 2010) and smell (Frasnelli *et al.*, 2007). The insula is also part of the language, pain, vestibular, autonomic and limbic networks (Singer *et al.*, 2004; Kurth *et al.*, 2010; Baldo *et al.*, 2011), and has been associated with several other cognitive processes, such as attention, social cognition and higher-order executive functions (Boucher *et al.*, 2014). A widespread network of connections (to the frontal, temporal and parietal lobes, in addition to the thalamus and basal ganglia) subserve these functions, as demonstrated by tracing studies in macaques (Mesulam and Mufson, 1982b, Mesulam and Mufson, 1982a) and more recently tractography studies in humans (Ghaziri *et al.*, 2015) The diverse stimulations eliciting seizures in the cases of reflex operculoinsular epilepsy described above thus seem to correspond to the various functions and networks in which the insula is thought to be involved and are also consistent with the functional segmentation of the insular cortex documented with neuroimaging and cortical stimulation techniques. Indeed, our patients

with seizures triggered by simple somatosensory or auditory stimuli were found to have an epileptogenic zone in the posterior part of the insula, which is thought to be more specifically involved in somatosensory and auditory processing (Isnard *et al*., 2004; Nguyen *et al*., 2009; Kurth *et al*., 2010). For the case reported by Blauwblomme *et al*. (2011), who exhibited reflex insular seizures triggered ~30 seconds after strawberry syrup intake, the epileptogenic zone was found to be located in the anterior part of the insula, which is known to be one of the key structures forming the gustatory network. The variability in latency between the stimulus and the occurrence of spikes or seizures among patients could be due to the degree of complexity of the stimulus, the multisynaptic connections according to the associative function of the insular cortex, or the incomplete spatial sampling of the insular cortex which could delay the recording of first discharges.

The main limitation of our study is the relatively low number of cases. Potential explanations for the small number of well documented cases of reflex (operculo) insular seizures at our centre and in the literature in general include the rarity of such reflex seizures, dismissal of observations made by patients for particular triggers, and/or failure to sample the insula during intracranial EEG studies of refractory reflex epilepsies. We hope that this report will motivate others to report similar anecdotal operculoinsular reflex cases in order to better refine the clinical presentation of operculoinsular epilepsy.

Conclusion

Operculoinsular seizures may manifest as eating, audiogenic and somatosensory-evoked reflex epilepsy. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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Legends for video sequences

Video sequence 1

Seizure triggered by the physician rubbing Patient 1's right hand.
00:01 → Start of stimulus
00:08 → Onset of seizure
00:30 → End of seizure

Keywords for the video research on www.epilepticdisorders.com

Syndrome: focal epilepsy
Aetiology: unknown
Phenomenology: reflex painful seizures
Localization: right posterior insula

Video sequence 2

Seizure triggered by listening to loud classical music in Patient 2.
00:01 → Start of stimulus (Volume raised to the maximum at 00:06)
00:12 → Onset of seizure
00:35 → End of seizure

Keywords for the video research on www.epilepticdisorders.com

Syndrome: focal epilepsy
Aetiology: unknown
Phenomenology: reflex audiogenic seizures
Localization: left parietal operculum; posterior insula

Video sequence 3

Seizure triggered in Patient 3 by rubbing and playing with her fingers.
Two minutes prior to the video, the patient rubbed and played with her fingers, on and off.
00:12 → Onset of seizure
01:09 → End of seizure

Keywords for the video research on www.epilepticdisorders.com

Syndrome: focal epilepsy
Aetiology: focal cortical dysplasia
Phenomenology: reflex somatosensory seizures
Localization: right parietal operculum; posterior insula

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TEST YOURSELF

(1) What are reflex seizures?

(2) Name some of the triggered factors in reflex seizures.

(3) What type of reflex seizures may be encountered in operculo-insular epilepsy?

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