

Crying with sorrow evoked by electrocortical stimulation

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ABSTRACT – Dacrystic seizures are rare and have been reported in patients with hypothalamic hamartoma as well as fronto-temporal epilepsy, involving the non-dominant hemisphere. We describe the first reported case of cortical stimulation of the left posterior orbito-frontal gyrus, generating consistent and reproducible crying with affective content in a 41-year-old woman with medically intractable left temporal lobe epilepsy, who underwent extraoperative intracranial video-EEG monitoring for resective non-lesional epilepsy surgery.

Key words: dacrystic seizures, extraoperative intracranial video-EEG, subdural electrode implantation, cortical stimulation

Little is known about the pathways involved in laughter and crying, or the associated emotional substrates. Ictal laughter and, much less commonly, ictal crying (dacrystic episodes), with or without a corresponding affective component, can rarely manifest during epileptic seizures. The most common case is that of hypothalamic hamartoma (Blumberg *et al.*, 2012), classically giving rise to emotionless laughter, but also reported to produce ictal crying. The mechanism is secondary to intrinsic epileptogenicity of the hamartoma although the relationship with cortical pathways is unclear (Kahane *et al.*, 2003; Mittal *et al.*, 2008). Epileptic seizures which manifest as weeping and crying have also been seen in patients with a posterior quadrant seizure focus (Offen *et al.*, 1976) and with a fronto-temporal focus (Luciano *et al.*, 1993; Wang *et al.*, 1995), predominantly in the non-dominant

cerebral hemisphere. Ictal crying has also been reported in a patient with left mesial temporal lobe epilepsy and reproduced during left hemispheric injection on Wada testing (Tatum and Loddenkemper, 2010).

There are scant reports of weeping and/or crying with or without emotional substrate evoked by direct electrocortical stimulation; a widely accepted method for localising symptomatogenic zones and cortical functions. Nevertheless, a specific putative crying centre has yet to be discovered.

We report a case in which direct electrical stimulation of subdural electrodes overlying the left posterior orbito-frontal gyrus (Brodmann area 11) induced crying with an affective component, as part of the standard evaluation of a patient undergoing two-stage cortical resection for pharmacoresistant epilepsy.

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Case study

A 41-year-old, right-handed woman presented with non-lesional, medically-refractory, left temporal lobe epilepsy. She had automotor seizures with derangement of consciousness and occasional secondary generalisation since the age of 30. Infrequently, mild right-sided hemiparesis was noted, postictally. Seizure frequency and severity remained unchanged despite increasing doses of phenytoin and gabapentin, and addition of levetiracetam. She had episodes of depression, crying, and tearfulness, triggered by thoughts about death of a loved one, which were believed to be worse following bouts of seizures. General and neurological examination was normal.

Scalp video-EEG monitoring revealed her typical seizures with electrographic onset in the left temporal region with maximum discharge at electrodes T3, Sp1, and F7. High-resolution MRI with epilepsy protocol was normal and FDG-PET showed hypometabolism of the left anterior temporal, bilateral superior temporal, and right parietal cortices. Intracarotid amobarbi-

tal (Wada) testing demonstrated bilateral language representation and normal memory scores. Left hemispheric epilepsy was suspected and the patient underwent further evaluation with the placement of the following subdural grids and strips with numbered platinum contacts with 10-mm, inter-contact spacing (Ad-Tech Medical Instrument Corporation, Racine, WI): anterior subtemporal 2×8 grid (AT 1-16), posterior subtemporal 2×8 grid (PT 1-16), fronto-parietal 4×8 grid (FP 1-64), subfrontal 1×6 strip (SF 1-6), and temporo-occipital 2×8 grid (TO 1-16). In addition, two 6-contact platinum depth electrodes (5-mm, contact spacing) were stereotactically implanted in the left anterior (AD 1-6) and posterior (PD 1-6) hippocampus and one 6-contact depth electrode was laid flat in the insular cortex after microsurgical opening of the left Sylvian fissure (IS 1-6). *Figure 1* outlines the intracranial electrodes. Three-dimensional reconstructed brain surface was created by coregistration of the preoperative volumetric MRI with the post-implantation CT scan using the MPI-tool software (Advanced Tomo Vision, Erfstadt, Germany), 3D-tool surface rendering

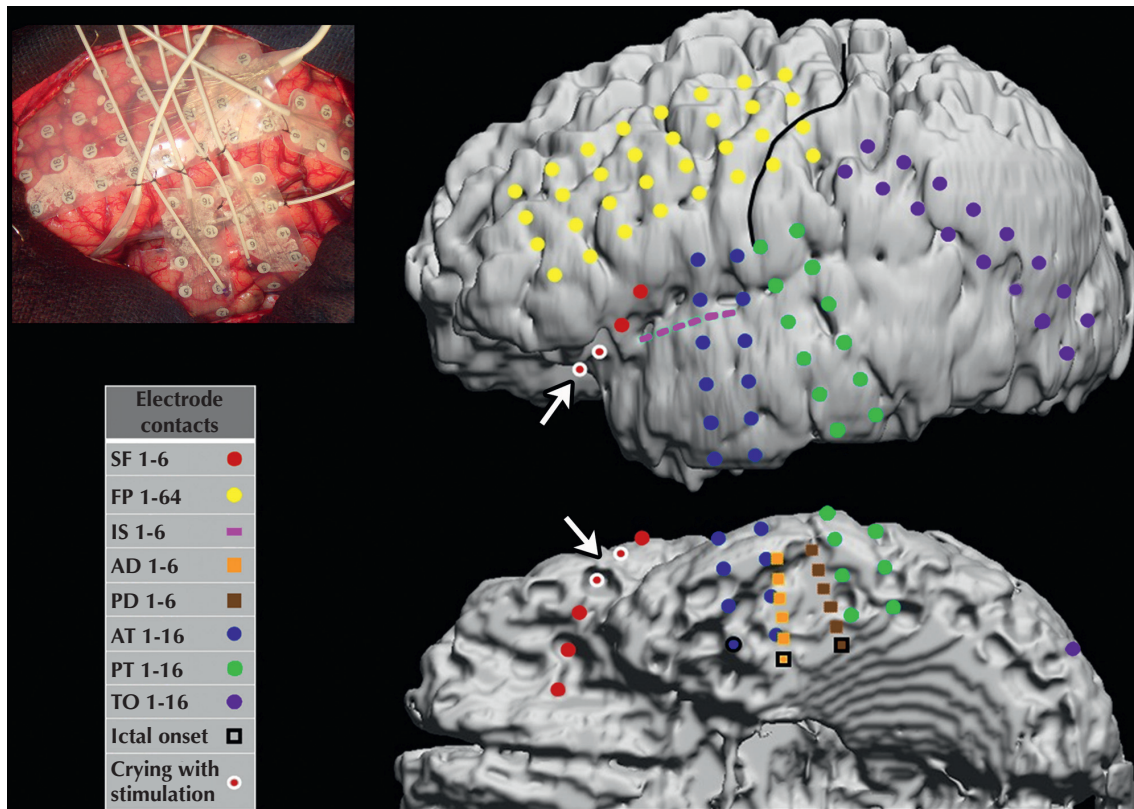


Figure 1. Three-dimensional reconstructed brain surface created by coregistration of preoperative MRI and post-implantation CT showing placement of intracranial subdural and depth electrodes over the left hemisphere.

By convention, electrode 1 is most medial. AT: anterior subtemporal; PT: posterior subtemporal; FP: fronto-parietal; SF: subfrontal; TO: temporo-occipital; AD: anterior hippocampal depth; PD: posterior hippocampal depth; IS: insular. Electrodes AT1, AD1, and PD1 showed ictal onset. Electrodes SF3 and SF4 along the posterior orbito-frontal gyrus resulted in crying upon electrical stimulation (arrows). Intraoperative photograph of electrode placement is shown in the top left corner.

software (Max-Planck Institute, Cologne, Germany), as well as in-house developed software (ET/MR Imaging Laboratory, Detroit, MI). Extraoperative monitoring demonstrated her typical seizures with left hippocampal ictal onset at AT1, AD1, and PD1 electrodes with subsequent spread to SF3 and SF4 electrodes, overlying the posterior orbito-frontal gyrus within 20 to 25 seconds. She then underwent MRI-guided volumetric resection of anterior and medial temporal lobe structures. She had an uneventful recovery and has remained seizure-free for over 24 months.

Prior to resective surgery, direct cortical stimulation for mapping of eloquent cortex was performed extraoperatively using a Grass S12 cortical stimulator (Astro-Med Inc., West Warwick, RI). Stimulation trains lasted for 3 to 10 seconds, utilising 300- μ s pulses at 50 Hz. Intensity varied from 1.5 to 9.5 mA in increments of 1 mA. Activation of the subfrontal electrodes SF3 and SF4 (overlying the left posterior orbito-frontal gyrus; *figure 1*) consistently produced emotional crying at 4.5-7.5 mA with no afterdischarges noted. The crying was associated with a sorrowful facial expression, sobbing body movements, and a voice inflected with sadness. These physical manifestations ended with the termination of stimulation and the patient described feeling sad, but could not express the trigger for the sadness or crying. Results were consistent and reproducible.

Discussion

The process of weeping and crying normally consists of negative emotional substrate associated with vocalisation, changes in facial appearance and expressions, increased lacrimation, and autonomic variations. Several neuroanatomical correlates are likely to be involved in the process of crying (Parvizi, *et al.*, 2001; Wild *et al.*, 2003; Arias, 2011). Given that humans are unique to this clinical presentation, an experimental model is lacking and much of the information about the localisation of weeping and crying is based on clues from pathological conditions which include observations related to dacrystic seizures and limited cortical stimulation studies. Involvement of the posterior orbito-frontal region or Brodmann area 11 in crying has not been previously reported.

Dacrystic epilepsy was first named by Offen and colleagues in 1976 (Offen *et al.*, 1976). The authors described a patient with neurosyphilis and right hemispheric focal findings who presented with episodes of paroxysmal crying, devoid of affective content, associated with right posterior quadrant, low-voltage, 2-Hz, delta rhythms on surface EEG. Although there had been several prior cases reporting paroxysmal crying episodes which were thought to be seizures, this was the first to be corroborated by simultaneous EEG.

Crying as a manifestation of epileptic seizures has been considered to be rare and rather a prominent feature of paroxysmal non-epileptic spells (Bergen and Ristanovic, 1993). However, several reports have demonstrated a higher incidence of epileptic crying than expected. Luciano *et al.* reported seven patients who presented with crying episodes with ictal activity and reviewed 11 other previously published cases (Luciano *et al.*, 1993). Crying was described in the ictal or immediate postictal state, with or without coexisting negative emotions, with or without preservation of consciousness, fronto-temporal in localisation, right-sided in origin, and presumably non-dominant in lateralisation (Luciano *et al.*, 1993). The non-dominant lateralisation of negative emotional states is supported by observations that lesions and strokes yield pathological crying when the left hemisphere is affected and laughter when the right hemisphere is affected, via loss of function (Sackeim *et al.*, 1982; Starkstein *et al.*, 1987). Episodic crying behaviour has also been described in a patient with left temporal complex partial seizures and reproduced during left intracarotid sodium amobarbital testing (Tatum and Loddenkemper, 2010). A recent review of nine patients with dacrystic seizures described the underlying aetiology to be hypothalamic hamartoma in five cases, left mesial temporal sclerosis in four, and a left frontal glioblastoma in one patient (Blumberg *et al.*, 2012).

In human stimulation studies, there are several cases of pathological crying, based on therapeutic neurostimulation of subcortical structures such as the thalamus, limbic structures, pons, and/or cerebellum (Okun *et al.*, 2004; Wojtecki *et al.*, 2007). The latter structure has been implicated in motoric crying displays, including associated facial expression and lacrimation (Parvizi *et al.*, 2001). Stimulation of the right superior temporal gyrus at the margin of the Sylvian fissure, inferior to the precentral gyrus, resulted in fear, distress, and weeping in a patient with a right temporal glioma (Penfield and Jasper, 1954).

Crying and weeping, with and without emotional substrate, may be similar to laughter which can occur with and without mirth due to, presumably, distinct pathways for emotional qualia and the motoric expression of such (Arroyo *et al.*, 1993). In addition, stimulation studies suggest that laughter without mirth is likely to be localised to the anterior cingulate and superior frontal gyrus of both hemispheres, and the sensation of mirth may be represented in the temporal and frontal lobes of the dominant hemisphere close to language and negative motor areas (Fernandez-Baca Vaca *et al.*, 2011). Remarkably, direct stimulation of hypothalamic hamartomas can reproduce both laughing and crying spells in the same patient (Kahane *et al.*, 1997; Kahane *et al.*, 2003). It has been hypothesized that pathological crying and laughter may be due to

disruption of the inhibitory cortical pathways to the hypothalamus and brainstem (Wild *et al.*, 2003; Wortzel *et al.*, 2008).

Moreover, functional studies of emotion, particularly in patients suffering from treatment-resistant depression, can help elucidate the pathways implicated in crying. The subcallosal (subgenual) cingulate gyrus (Brodmann area 25) appears to play a critical role in major depression and has been the target for deep brain stimulation in order to treat treatment-resistant depression (Phan *et al.*, 2002; Lozano *et al.*, 2012). Interestingly, the proximity and possible interplay between the orbito-frontal gyrus and subcallosal cingulate gyrus may provide additional insight into the neuroanatomical substrate for emotional processing. In our case, we used direct cortical stimulation to identify the posterior orbito-frontal gyrus as a key component of the pathways producing sorrowful crying. Previous assignment of crying and negative emotions to the non-dominant hemisphere is challenged by lateralisation of our case to the left, however, dominance could not be clearly established in our patient since there was a presence of bilateral language function, as evidenced by intracarotid sodium amytal testing and functional MRI. Furthermore, ictal discharge reached this region within 20-25 seconds and may have been contributory to the overall depressed mood of this patient and her worsening of depression postictally. □

Disclosures.

None of the authors have any conflict of interest to disclose.

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