

Case Report

Crying with depressed affect induced by electrical stimulation of the anterior insula: A stereo EEG case study



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ABSTRACT

Stereo-EEG (sEEG) is an invasive recording technique used to localize the seizure-onset zone for epilepsy surgery in people with drug-resistant focal seizures. Pathological crying reflects disordered emotional expression and the anterior insula is known to play a role in empathy and socio-emotional processing. We describe a patient where electrical stimulation mapping (ESM) of the anterior insula during sEEG generated pathological crying and profound sadness that was time-locked to the electrical stimulus.

We evaluated a 35-year-old left-handed female for repeat epilepsy surgery. The patient had drug resistant focal impaired awareness seizures despite a previous left temporal neocortical resection informed by an invasive study using subdural grid and strip electrodes seven years earlier. She was studied invasively with 10 sEEG electrodes sampling temporal, occipital, and insular targets. In the process of functional mapping, stimulation of the anterior insular cortex provoked tearful crying with sad affect, reproducible upon repeat stimulation.

Our case is unique in demonstrating transitory pathological crying with profound sadness provoked by ESM of the left anterior insula. Furthermore we demonstrate repeated time-synched crying from electrical stimulation, which supports the hypothesis that the anterior insula in the brain plays an important role in the biology of emotion, as implicated by previous studies.

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1. Introduction

Electrical stimulation mapping (ESM) is a nonphysiological and reversible “lesional” method that uses electrical stimuli to inhibit or excite functions for functional localization [1]. In addition it has also helped to identify anatomical connections projecting from these stimulation sites and has been used to investigate anatomic connectivity in the language system, motor system, parieto-frontal circuits and the visual system [1–3].

The functional anatomy of the insula is in its earliest stages of elucidation. There have been many techniques that have attempted to assess the functions of the insula including, but not restricted to ESM, functional neuroimaging, and positron emission tomography. A large meta-analysis has helped to understand the

role of the insula in viscerosensory, motor, vestibular, language, somatosensation, chemosensation, central audition, pain, self-awareness, attention, empathy, time perception, motivation and autonomic function as well as even emotions [4]. In this report, we contribute to the understanding of human insular function by presenting a unique case of ESM where stimulation of a unique electrode pair in the anterior insula resulted in reproducible mournful crying with lacrimation.

2. Case study

A 35-year-old left-handed female presented to Mayo Clinic for further evaluation and treatment of drug-resistant epilepsy. The patient had a normal birth and developmental history. She had her first seizures at 12 years of age followed by multiple recurrent seizures and was diagnosed with focal epilepsy. She was started on antiseizure medications (ASMs), which controlled her seizures until she was 19 years of age, when her seizures became

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uncontrolled despite multiple trials of ASMs. These seizures began without warning and evolved to an abrupt stare. She would repeat “I am ok” with a panicky look, then turn her head to the left with eyes open. She experienced impaired awareness lasting less than a minute, followed by a post-ictal headache. She underwent MRI of the brain with seizure protocol, which showed some areas of non-specific white matter T2 hyperintensities, but no evidence of mesial temporal sclerosis or focal cortical dysplasia. Ictal scalp video-EEG monitoring showed a poorly localized left hemispheric onset of her seizures. She previously underwent phase II evaluation with subdural grids (2 grids placed; 4 X 8 cm) which were placed in the left posteriotemporal and peri-sylvian region. Seizure onset occurred over the left temporal parietal region, and she underwent left focal temporal neocortical resection avoiding eloquent language cortex. She became seizure-free for nearly 2 years, but then started having breakthrough seizures with 30% overall reduction in the seizure frequency and reduction in the seizure intensity. Post-operative seizures manifest as “zone outs”, lip smacking, and slight stiffening of the extremities with a panicky appearance with shorter post-ictal state. She would have a second type of episode in which she would repeat “I’m okay”, would freeze, be repetitive for a few seconds, and would answer “I’m fine” and had amnesia for the event. She underwent a repeat video-EEG monitoring with multiple focal seizures recorded over the left central posterior temporal-parietal areas with left posterior temporal-central and parietal interictal discharges. She subsequently underwent placement of ten sEEG electrodes in the left temporal, parietal, occipital and insular cortices (Supplementary Fig. 1). After seizure recording, the patient’s baseline ASMs were reloaded as a prelude to ESM. The post-operative CT scan was co-registered to the pre-operative 3D T1-weighted scan and subsequently normalized to Montreal Neurological Institute (MNI) atlas space using Lead-DBS software v2.2.3 (<https://www.lead-dbs.org>). [5] The electrodes of interest and contact positions were localized manually by a board-certified neuroradiologist (E.H.M.).

ESM was performed with the internalized stimulation unit in the Natus system Xltek 9.1 version (Natus Medical Incorporated). Stimulation parameters included a frequency of 50 hertz at a pulse width of 500 micro-seconds. Typical trains used were up to 4 seconds. Stimulation intensity was started at 1 milliamp and augmented in 1 milliamp increments to a maximum of 5 milliamps or until after discharges were elicited. Bipolar stimulation included a unique pair in the distal anterior insula contacts (designated as LV 1–2). Lead-DBS, which has been used for localization of stereo-EEG electrodes and modeling of cortical stimulation [6,7], was used to model stimulation parameters using a finite element method solution to generate an estimated volume of tissue activated (VTA) for the cortical stimulation, as previously described [7]. Separation of gray matter and white matter compartments was performed using segmentation of the patient’s T1-weighted MRI in Statistical Parametric Mapping (SPM) software v12 (<https://www.fil.ion.ucl.ac.uk/spm>) for use in the tissue-specific conductivity model [5]. The contacts and volume of tissue activated were located in the inferior anterior insular cortex near the superior aspect of the insular pole as shown in Fig. 1.

Use of normative functional MRI (fMRI) connectomes for stimulation and lesion network mapping is a commonly utilized technique to explore connections to a specific brain region of interest [8,9]. To examine functional connectivity to the stimulated area, the VTA was used as a seed region and resting-state fMRI data from 1,000 healthy subjects in the Brain Genomics Superstruct Project [10] were used to estimate functional connectivity to the remainder of the brain, as previously described [5]. Using an atlas of normative fMRI connectomes (<https://dataverse.harvard.edu/dataverse/GSP>), the stimulated region showed widespread connectivity including anterior and posterior cingulate cortex,

amygdala, ventral tegmental area, anterior frontoinsula region, orbitofrontal cortex, peri-aqueductal gray, superior temporal sulcus, hippocampus, angular gyrus, and cerebellar Crus I (Fig. 2).

During stimulation, the patient was asked to count from 1 to 20 and was stimulated initially at 1 mA, without any change in her mental status. However when she was serially up ramped to 5 mA, and while counting out loud from 1–20, she became “emotional” and “teary eyed” and mentioned that she felt a change in her emotional status to becoming “sad” and had a “sad tear”, but was able to finish her counting and did not experience any motor deficits. She subsequently asked for a tissue and wiped her tears with it. After the stimulation was stopped, she immediately returned back to her normal state. Time locked sorrowful crying with lachrimation was again reproducible with a repeat stimulation of the same electrode pair at 5 mA. The stimulation was not repeated after, as the patient was emotionally distraught and requested the procedure to be stopped. This is shown in the video in the supplemental digital content. No reoperation was performed.

3. Discussion

This unique case report demonstrates a transitory pathological crying with profound sadness provoked by ESM of the anterior insula. The time-synched temporal effect of stimulation with reproducibility provides a strong causal pathophysiological relationship to implicate the anterior insula in the brain biology of emotion and particularly crying.

The insula is one of the least understood regions of the brain and not much is known about its role in emotional processing. This is mainly due to its location in the depths of Sylvian fissure which makes it difficult to access, and to the very low prevalence of isolated insular lesions [11]. Based on the functional neuroimaging studies, a large meta-analysis by Kurth et al based on functional neuroimaging experiments suggested the existence of four functionally distinct regions in the human insula (1) sensorimotor region in the mid-posterior insula (2) a central –olfactory-gustatory region (3) a socioemotional region in the anterior-ventral insula and (4) cognitive anterior-dorsal region [4]. Stimulation of the insular cortex has been shown to provoke a wide variety of experiences. Mazzola *et al* conducted a large study in which 669 insular stimulations were performed in 222 patients (50 Hz, trains of 5 seconds, pulses of 0.5 ms, intensity of 0.2–3.5 mA) [12]. Stimulations commonly provoked somatosensory responses (61% of evoked sensations), pain and visceral sensations (14.9%), auditory sensation (8%), vestibular illusions (7.5%), speech impairment (5%), gustatory (2.7%) and olfactory (1%). Very few electrodes were placed in the anterior insula and upon stimulation of these sites no affective change such as crying was noted in their series. The neural circuits involved in the different components of emotional crying (i.e. facial muscular activity, vocalization, tear production, emotional experience) involve the central autonomic network and include 1) the insular and medial prefrontal cortex (2) central nucleus of amygdala (3) hypothalamus (4) periaqueductal gray matter (5) parabrachial region of pons (6) nucleus of the solitary tract (7) ventrolateral medulla [13]. Hence our case report provides a novel finding of reproducible emotional crying involving all components of neural circuits upon stimulating the anterior insula. There have been some reports in literature of pathological crying, particularly in the setting of deep brain stimulation with subthalamic nuclei or cerebellar activation [14,15]. However, pathological crying is different from emotional crying as it involves inappropriate crying without characteristic feelings imparted. Cytoarchitecturally the insular cortex is roughly divided into an anterior agranular por-

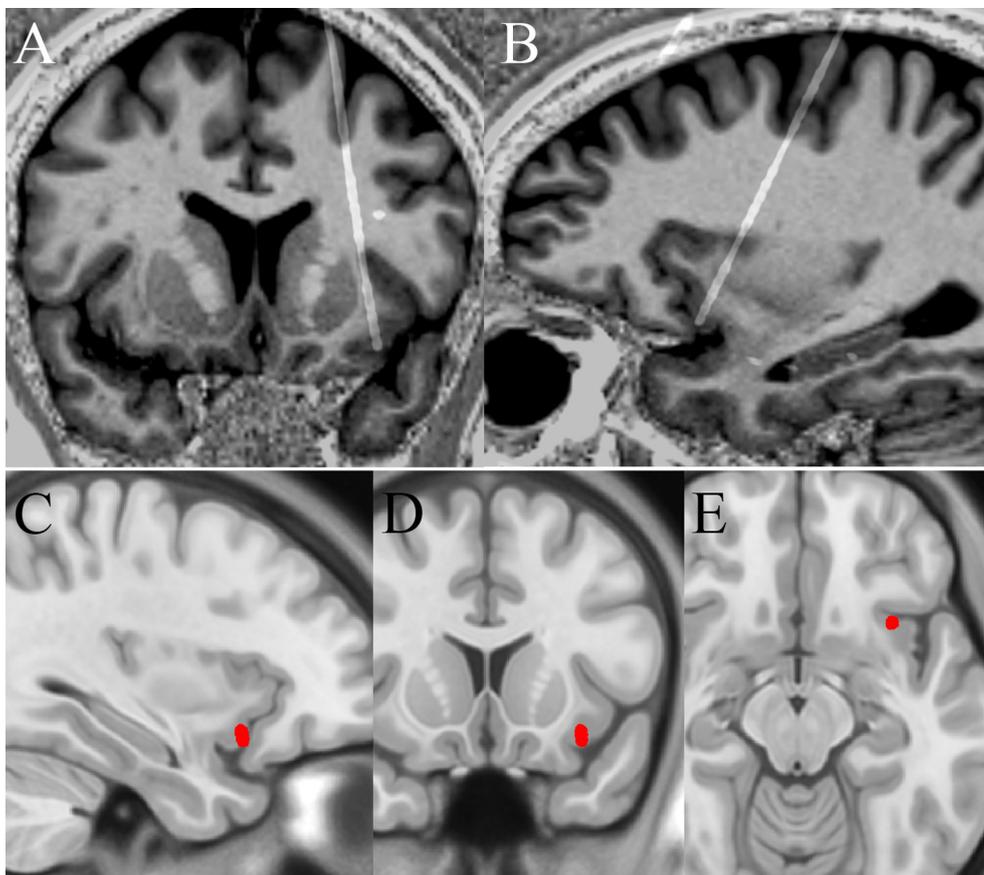


Fig. 1. Coronal (top) view of the sEEG electrode location and estimated volume of tissue activated (red). Sagittal (bottom left), coronal (bottom center), and axial (bottom right) views in Montreal Neurological Institute (MNI) template space showing the estimated volume of tissue activated (red).

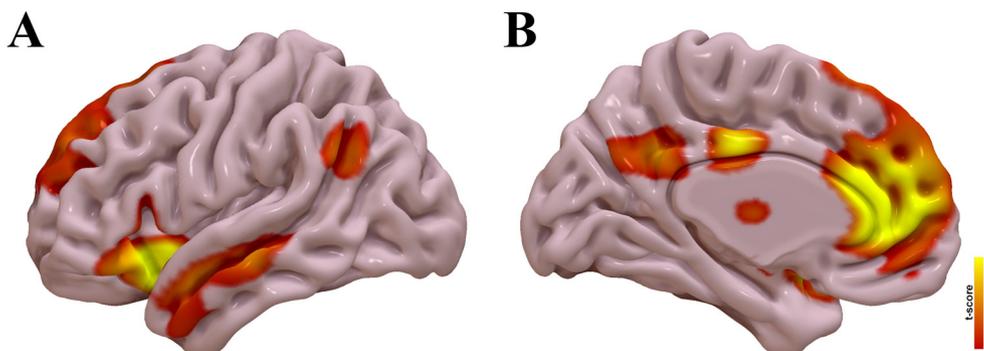


Fig. 2. Estimated Functional Connectivity: The volume of tissue activated was used as a seed region with resting state fMRI data from 1000 healthy subjects in the BRAIN GENOMICS SUPERSTRUCT PROJECT (<https://dataverse.harvard.edu/dataverse/GSP>). Regions of connectivity represented as color coded t score values.

tion (anterior insula), a middle dysgranular portion and a posterior granular portion with each subdivision has its own unique connectivity and functional features [16]. Furthermore the anterior insula is among the most differentially expanded neocortical regions in the humans and it also contains a special group of large, bipolar, spindle shaped neurons known as Von Economo neurons, which are most abundant in humans and are found in the layer Vb in the anterior cingulate cortex and the frontoinsula cortex [17]. These are thought to be involved in empathy, social awareness and self-control [18]. We hypothesize that stimulation of the anterior insula in our patient activated a complex neural network that probably includes its established rich connectivity with anterior cingulate cortex.

As this is a unique case, one cannot extrapolate too much from functional findings from one pair of electrodes. This is the first instance, to our knowledge, demonstrating reproducible episodes of emotional crying upon anterior insular stimulation. Our simple observation clearly requires validation, which may be facilitated by the recent popularity of sampling insular anatomy utilizing sEEG electrodes in invasive epilepsy presurgical evaluations. This curious case study contributes to further our awareness of the insula and its complex functionality involving emotion.

Ethical statement

The patient involved in the study gave us her written permission to use her image and video for the study and for research pur-

poses. The study was approved by the Mayo Clinic institutional review board.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebr.2020.100421>.

References

- [1] Ritaccio AL, Brunner P, Schalk G. Electrical Stimulation Mapping of the Brain: Basic Principles and Emerging Alternatives. *J Clin Neurophysiol* 2018;35(2):86–97. <https://doi.org/10.1097/WNP.0000000000000440>.
- [2] Matsumoto R, Nair DR, LaPresto E, Bingaman W, Shibasaki H, Luders HO. Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. *Brain* 2007;130:181–97.
- [3] Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain* 2004;127:2316–30.
- [4] Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct* 2010;214(5–6):519–34. <https://doi.org/10.1007/s00429-010-0255-z>.
- [5] Horn A, Li N, Dembek TA, Kappel A, Boulay C, Ewert S, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. *NeuroImage* 2019;184:293–316. <https://doi.org/10.1016/j.neuroimage.2018.08.068>.
- [6] Chaitanya G, Romeo AK, Ilyas A, Irannejad A, Toth E, Elsayed G, et al. Robot-assisted stereoelectroencephalography exploration of the limbic thalamus in human focal epilepsy: implantation technique and complications in the first 24 patients. *Neurosurg Focus* 2020;48:E2.
- [7] Sabsevitz DS, Middlebrooks EH, Tatum W, Grewal SS, Wharen R, Ritaccio AL. Examining the function of the visual word form area with stereo EEG electrical stimulation: A case report of pure alexia. *Cortex* 2020;129:112–8. <https://doi.org/10.1016/j.cortex.2020.04.012>.
- [8] Wong JK, Middlebrooks EH, Grewal SS, Almeida L, Hess CW, Okun MS. A Comprehensive Review of Brain Connectomics and Imaging to Improve Deep Brain Stimulation Outcomes. *Mov Disord* 2020;35(5):741–51. <https://doi.org/10.1002/mds.28045>.
- [9] Boes AD, Prasad S, Liu H, Liu Qi, Pascual-Leone A, Caviness Jr VS, Fox MD. Network localization of neurological symptoms from focal brain lesions. *Brain* 2015;138(10):3061–75. <https://doi.org/10.1093/brain/awv228>.
- [10] Buckner RL, Roffman JL, Smoller JW. *Brain Genomics Superstruct Project (GSP)*. V10 ed.; Harvard Dataverse; 2014.
- [11] Cereda C, Ghika J, Maeder P, Bogousslavsky J. Strokes restricted to the insular cortex. *Neurology* 2002;59(12):1950–5. <https://doi.org/10.1212/01.WNL.0000038905.75660.BD>.
- [12] Mazzola L, Manguière F, Isnard J. Functional mapping of the human insula: Data from electrical stimulations. *Revue Neurologique* 2019;175(3):150–6. <https://doi.org/10.1016/j.neurol.2018.12.003>.
- [13] Bylsma LM, Gračanin A, Vingerhoets AJJM. The neurobiology of human crying. *Clin Auton Res* 2019;29(1):63–73. <https://doi.org/10.1007/s10286-018-0526-y>.
- [14] Low HL, Sayer FT, Honey CR. Pathological Crying Caused by High-Frequency Stimulation in the Region of the Caudal Internal Capsule. *Arch Neurol* 2008;65(2). <https://doi.org/10.1001/archneurol.2007.53>.
- [15] Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying: a link to the cerebellum. *Brain* 2001;124:1708–19.
- [16] Gu X, Hof PR, Friston KJ, Fan J. Anterior insular cortex and emotional awareness: Anterior Insular Cortex and Emotional Awareness. *J. Comp. Neurol.* 2013;521(15):3371–88. <https://doi.org/10.1002/cne.23368>.
- [17] Bauernfeind AL, de Sousa AA, Avasthi T, Dobson SD, Raghanti MA, Lewandowski AH, Zilles K, et al. A volumetric comparison of the insular cortex and its subregions in primates. *J Hum Evol* 2013;64(4):263–79. <https://doi.org/10.1016/j.jhevol.2012.12.003>.
- [18] J.M. Allman N.A. Tetreault A.Y. Hakeem K.F. Manaye K. Semendeferi J.M. Erwin S. Park V. Goubert P.R. Hof The von Economo neurons in the fronto-insular and anterior cingulate cortex: Allman et al. 1225 1 2011 59 71 10.1111/j.1749-6632.2011.06011.x