Clinical commentary

Epileptic Disord 2019; 21 (5): 449-52

Electrical stimulation of the cingulate elicits involuntary singing

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Received March 07, 2019; Accepted July 09, 2019

ABSTRACT – Human neural networks important for singing have not been clearly elucidated. Here, we present a case of electrical brain stimulation of the right non-language dominant cingulate gyrus during brain surgery for epilepsy which resulted in involuntary singing of spoken language. We postulate that the current observation provides the strongest evidence as of yet that the cingulate gyrus is directly involved in voluntary motor control of singing. [*Published with video sequence*].

Key words: singing, cingulate, electrical brain stimulations

Similar to language, singing behaviour is unique to humans among primates, and people in all cultures are known to sing or make music. Like language, singing requires a finely tuned musculature and acoustic apparatus controlled by precision neural circuits and modulated via auditory and sensorimotor feedback loops (Zarate, 2013). A growing body of evidence suggests that singing is controlled by dedicated brain systems that are independent from auditory, speech, and other motor control systems. Like language, singing -and perhaps music perception and production more generally- appears to be a modular function of the brain (Peretz and Coltheart, 2003).

Human studies of neural networks important for singing have been limited. Early studies of individuals with left hemisphere damage going back as far as Paul Broca and Hewlings Jackson noted that singing ability may be spared despite dense aphasia (Lorch and Greenblatt, 2015). In addition, studies of lateralization of cerebral function during the Wada procedure have demonstrated that deficits in singing occur during sodium amytal injection into the right as opposed to left carotid artery (Gordon and Bogen, 1974). In addition, many functional MRI and PET studies of human singing suggest the existence of a dedicated singing network which is distinct from the network for spoken language (for review, see Zarate [2013]). Lastly, multiple reports of singing and humming behaviour in patients experiencing seizures have been reported and localized to the prefrontal cortex and superior temporal gyrus (Bartolomei *et al*., 2002; Guedj *et al*., 2006; Bartolomei *et al*., 2007), including seizures induced by stimulation mapping (McGonigal *et al*., 2018).

VIDEO ONLINE

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doi:10.1684/epd.2019.1096

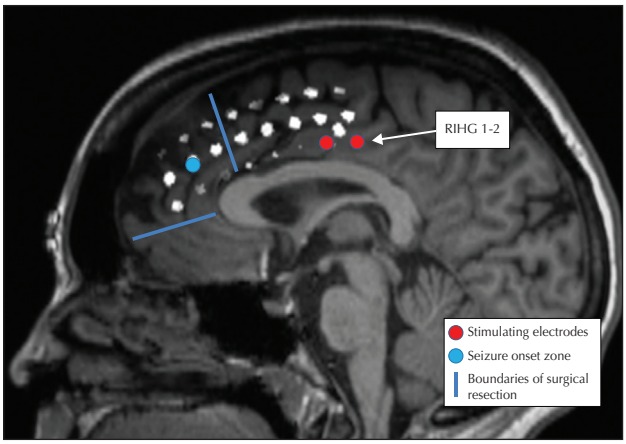

Figure 1. Location of electrodes used during EBS, region of seizure onset, and boundaries of surgical resection.

Studies of brain function using electrical brain stimulation (EBS) during surgery have provided additional evidence for the existence of a dedicated network for singing in the non-language-dominant right hemisphere. Suarez *et al*. applied EBS to the right and left posterior temporal gyrus in eight patients undergoing surgery for epilepsy and found evidence for double-dissociation of language and singing (Suarez *et al*., 2010). In that study, EBS of the left posterior temporal gyrus disrupted speech yet spared singing ability, and conversely EBS of the right posterior temporal gyrus disrupted singing yet spared speech. Furthermore, Herbet *et al*. studied a single patient with a glioma involving the right frontal, temporal, and insular lobe and found that EBS of the right inferior frontal gyrus produced spontaneous transition from speech to singing (Herbet *et al*., 2015). Lastly, Roux *et al*. used EBS to study singing ability in five patients with brain tumours and found that right inferior frontal gyrus EBS can disrupt singing but not speech (Roux *et al*., 2009). Here, we present the case of a patient who started to sing during EBS functional mapping of the mesial aspects of the right frontal lobe prior to surgical treatment for refractory epilepsy.

Materials and methods

The patient was a 42-year-old, right-handed woman with a diagnosis of medically refractory epilepsy who underwent intracranial EEG for localization of seizure onset prior to epilepsy surgery. The patient underwent uncomplicated implantation of grid and strip electrodes covering the right frontal lobe. The electrode array included an interhemispheric grid which covered the cingulate gyrus and the interhemispheric portion of the superior frontal gyrus of the right hemisphere (*figure 1*). Standard procedure for coregistration of post-surgical CT scan with electrode locations and patient's presurgical MRI were utilized. Seizure onset was localized to the anterior portion of the grid (*figure 1*). The patient underwent standard functional mapping using a Grass 12X stimulator using the following settings: pulse frequency of 50 Hz, pulse width of 300 microseconds, pulse duration of two seconds, and pulse intensity of 0.5 to 10 mA.

Results

During the course of functional mapping, we incidentally observed that EBS of electrodes RIHG 1-2 at 5-mA intensity induced the patient to sing normal spoken speech (*figure 1, 2 and video sequence 1*). Patient responded in a melodic singing voice which included appropriate body language to questions asked. Singing persisted following cessation of EBS until the patient finished the phrase or utterance that she had started to say (*figure 2, video sequence 1*). EBS of other regions in the grid did not produce any disruption to singing. Following EBS mapping, resection of the seizure onset zone involved areas anterior to the electrodes RIHG 1-2 (*figure 1*). On examination following resection, the patient did not suffer any loss or inability to sing and has been seizure-free since surgery.

Discussion

The current observation of clear involuntary singing of spoken speech during EBS of the right cingulate gyrus provides the strongest evidence so far that this brain region is involved in neural representation of signing. Outside of EBS, multiple other lines of evidence support the involvement of the cingulate gyrus in singing. First, animal studies have shown that EBS or pharmacological stimulation of cingulate causes vocalizations (Dujardin and Jurgens, 2005). Second, human studies have demonstrated deficits with voluntary initiation and emotional control of voice in patient with lesions of the cingulate gyrus (Jurgens, 2009; Simonyan and Horwitz, 2011; Zarate, 2013). Third, human functional imaging studies of singing reveal activation in cingulate regions with singing as opposed to speaking (Zarate, 2013).
Evidence from prior EBS studies (Hébert *et al*., 2003; Roux *et al*., 2009; Suarez *et al*., 2010) and evidence from the current EBS study support the existence of a distinct network important for singing localized to the right (non-language-dominant) hemisphere which includes the right posterior superior temporal gyrus, right posterior inferior frontal gyrus, and right cingulate gyrus. These cortical regions involved in singing, as identified using EBS, are consistent with the model of singing based on functional MRI imaging proposed by Berkowska and Dalla Bella (2009) and

Figure 2. Written transcript of the video depicting EBS mapping. The patient's utterance is shown above with items in standard case depicting speaking and items in bold depicting singing. The approximate timing of EBS is shown below. Dashed line represents no EBS, X represents EBS.

further revised by Zatare (2013) (*figure 3*). Similar to EBS observations, this model assigns importance to the cingulate gyrus, inferior frontal gyrus, and the superior temporal gyrus in singing. The revised model places the cingulate gyrus along with supplementary motor area in regions important for voluntary motor initiation and control of singing.

The physiological mechanism for elicitation of involuntary singing in this patient is uncertain. EBS can either activate a brain region (*e.g.* causing hand movements during EBS of the motor cortex), inhibit a brain region (*e.g.* causing language arrest during EBS of Broca's area), or activate/disinhibit a distant neural network to the site of EBS (David *et al*., 2010; Mandonnet *et al*., 2010). The involuntary signing experienced by our patient may be the result of activation of the singing network itself, may result from activation of a distant brain region via neural connections from the cingulate cortex, or conversely may result from disinhibition of a distant brain region.

Two distinct phenomena have been described in the literature with regards to singing and EBS. First are the observations that EBS of certain cortical regions impair singing but leave language intact. This observation was described by Suarez *et al*. (2010) and Roux *et al*. (2009). A distinct phenomenon in which EBS caused a person to involuntarily sing while they were trying to speak was described by Herbet *et al*. (2015) and is further described in this study. The exact reasons for these distinct observations are uncertain. We speculate that in our patient EBS depolarized the cingulate (*i.e.* thus inactivating it) which in turn disinhibited downstream cerebral networks, resulting in involuntary singing of spoken speech. This idea may be consistent with the model of singing proposed by Zatare (2013) which assigned voluntary control of signing to the cingulate gyrus. We have no direct evidence that this mechanism played a role.

The most important limitation to this observation is knowing exactly how EBS produced this behaviour. As discussed above, we are uncertain whether EBS caused activation of a neural network for signing or disinhibited a region which in turn activated a distant network. Likewise, it is difficult to assess from EBS experiments the extent of the brain volume which is influenced by EBS. For instance, perhaps EBS in this patient activated or inhibited a distant cortical region and not the cingulate. Some of these uncertainties have been addressed by reports of good motor outcomes in surgical resections, up to 1 cm of cortical distance from eloquent regions mapped by EBS (Gregorie and Goldring, 1984). In addition, during EBS, it is often noted that adjacent electrode sites are not affected by the EBS. This occurred in our patient as we did not detect any effect on singing with EBS of other electrode sites in the grid pictured in *figure 1*. □

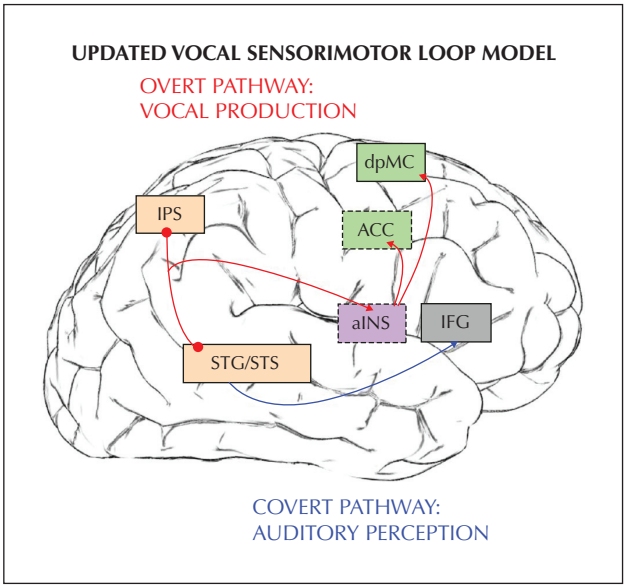

Figure 3. Cerebral network model of singing as proposed by Berkowska and Dalla Bella (2009) and revised by Zatare (2013). The overt pathway for vocal production (red arrow) includes the anterior cingulate cortex (ACC), superior temporal gyrus and sulcus (STG/STS), intra parietal sulcus (IPS), anterior insula (aINS), and dorsal premotor cortex (dPMC). Light orange indicates auditory processing, green for vocal motor control, and purple for multimodal processing (this figure is adapted from Zatare [2013]).

Legend for video sequence

During normal conversation, the patient sings normal speech upon electrical brain stimulation at electrodes RIHG 1-2 (at 5-mA intensity). The patient responds to questions in a melodic singing voice with appropriate body language. Following cessation of the stimulation, the singing persists until the patient finishes the phrase or utterance that she had started.

Key words for video research on www.epilepticdisorders.com

Phenomenology: singing
Localisation: cingulate gyrus
Syndrome: not applicable
Aetiology: not applicable

Disclosures.
None of the authors have any conflict of interest to declare.

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