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Case Report

Impairment of consciousness induced by bilateral electrical stimulation of the frontal convexity

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ABSTRACT

We report a case of impairment of consciousness (IOC) induced by electrical cortical stimulation (ECS) of homologous regions within the lateral frontal convexities in a patient with medically intractable epilepsy. The patient had mixed features of idiopathic generalized and focal epilepsy. On intracranial EEG recording, interictal and ictal discharges showed a high degree of synchrony across widespread bilateral fronto-parietal areas. We identified regions in the lateral frontal lobes that reliably and produced loss of consciousness by ECS. This was accompanied by evoked EEG activity of admixed frequencies over the fronto-parietal, mesial frontal and temporal regions during stimulation and was not associated with after-discharges. Symptoms were immediately reversible upon cessation of stimulation. This finding suggests that focal cortical stimulation can disrupt widespread networks that underlie consciousness. Individuals with high degrees of speculated thalamo-frontal cortical connectivity might be more susceptible to this effect, and the findings highlight the importance of standardizing the testing of level of consciousness during mapping sessions.

Although consciousness is commonly impaired in epileptic seizures, limited literature is available on loss of consciousness induced by electrical cortical stimulation (ECS) in humans undergoing intracranial EEG evaluations for localization of epileptic focus. One theory advocates the presence of consciousness 'switch' in subcortical structures. While this model is novel and simplistic, it has its inherent limitations. In this case study, we propose an alternative approach on the entity and discuss the complex circuits underlying it and correlate that with the electrophysiological findings and the pathophysiology of the phenotype of the disease and discuss potential causes for rarity of reports on the subject.

1. Introduction

This is a case of a patient with drug-resistant epilepsy with mixed features between generalized and focal epilepsy. This was supported by clinical history and suspected to have a focal seizure onset based on the results of a non-invasive pre-surgical evaluation. However there was bihemispheric widespread electrical changes at seizure onset by intracranial EEG (icEEG). During electrical cortical stimulation (ECS) for mapping function, the patient experienced reproducible impairment of consciousness (IOC) within 2 seconds of electrical stimulation over regions in the bilateral frontal convexities. There was immediate recovery of consciousness and amnesia for the events during stimulation following the end of the electrical train. The IOC correlated with emergence of evoked admixed frequencies of EEG activity over areas in the fronto-parietal cortices and in the mesial frontal and temporal regions. We discuss the pathophysiology and the pathways that possibly underlie this phenomenon and rhythms, and we discuss implications and future directions.

2. Methods

EEG was recorded using Natus Neurolink amplifiers (Natus incorporated, California, USA) with sampling frequency of 1024 Hz. The reference was an inverted strip over the right hemisphere. Visual analysis was performed per standard practice. Electrodes were implanted as discussed in a multi-disciplinary surgical conference to localize the epileptic focus. Commercially available platinum-iridium (Ad-Tech Medical, Wisconsin, USA) grids and strips were used with 10 mm inter-electrode distances, and contacts 4 mm in diameter with 2.8 mm exposed surface. On the left side, depth electrodes were targeted to the left anterior hippocampus, orbito-frontal cortex, and cingulate gyrus. Subdural strip electrodes were placed over the antero-medial temporal, orbito-frontal, inter-hemispheric (2 anterior and 2 posterior),

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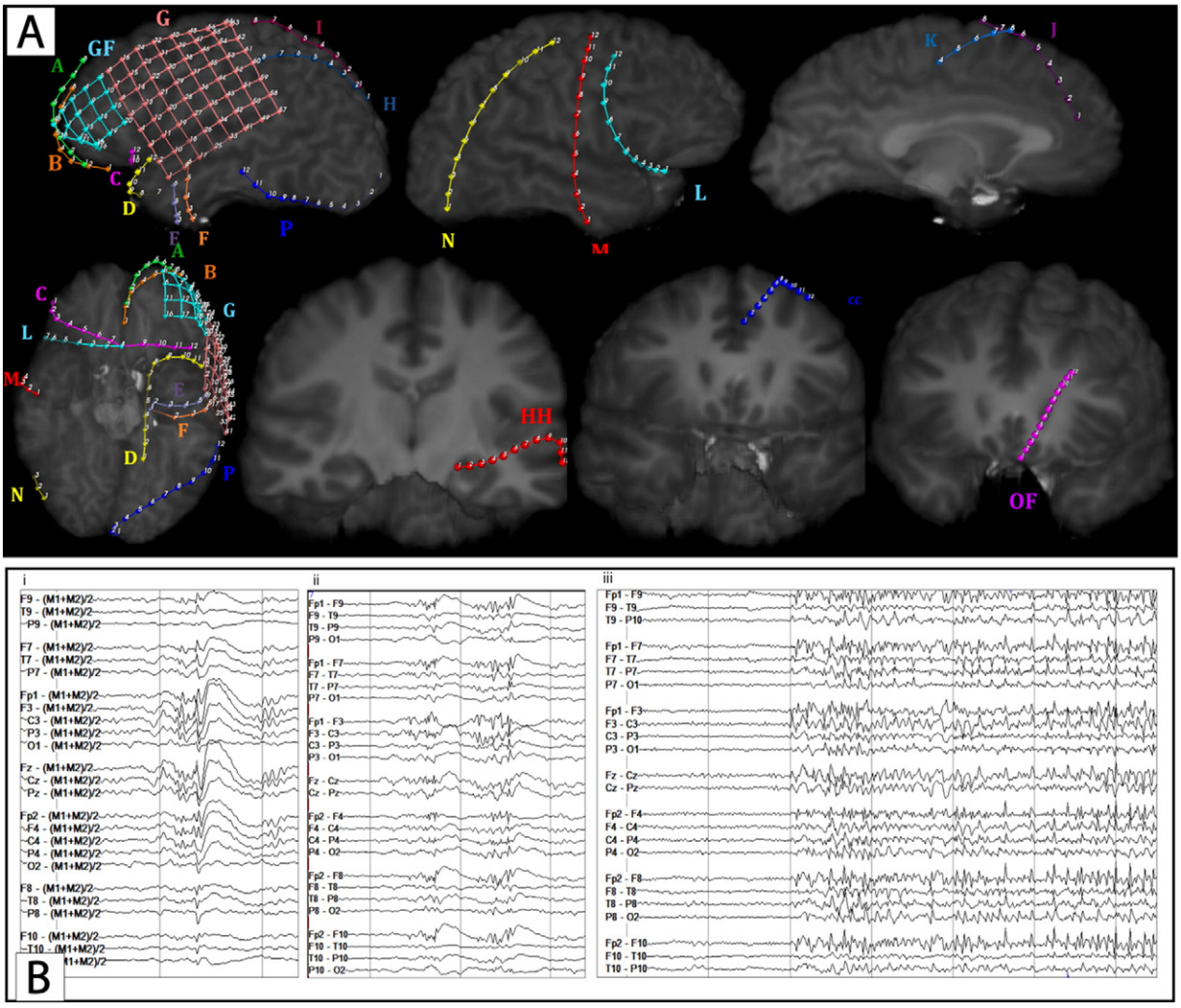

Fig. 1. A. Electrode placement as seen on reconstructed images of MRI of the brain. B. i. Generalized interictal epileptiform discharge on mastoid average reference montage. The activity is maximum in amplitude over the left fronto-central region. ii. Generalized interictal polyspike-and-wave discharges maximum in bilateral frontal regions, viewed on an anterior–posterior bipolar montage. iii. Scalp EEG recording of a habitual seizure. Clinical onset consisted of right non-versive head turn followed in less than a second by bilateral arm tonic then generalized clonic jerking. Electrographic onset consisted of evolving generalized polyspike activity maximum in the left frontal region. All traces shown use low frequency and high frequency filter settings of 1 and 70 Hz, respectively.

superior occipital, and inferior occipital regions. An 8 by 8 grid was placed over the left fronto-parietal-temporal surface along with a smaller grid over the anterior lateral frontal cortex extending to the frontal pole. On the right side, three strips were placed over the fronto-parietal and fronto-temporal (one anterior and one middle) regions. See (Fig. 1-A) for reconstruction of the electrodes and co-registration with MRI of the brain using co-registration tools available in bioimage suite (www.bioimagesuite.org). Visual analysis of interictal and ictal EEG was performed implementing a high pass digital filter at 3 Hz, and low pass digital filter at 500 Hz which is conventional for intracranial EEG. Figure 3 is shown with other filter settings for display purposes. Electrical cortical stimulation (ECS) was carried out using a current-controlled Nicolet cortical stimulator. The testing was performed through sequential 3–5 seconds of 50 Hz, bipolar, biphasic, rectangular waveforms, of 300 micro-seconds pulse width [1]. The current intensity was increased by 0.5–1 mA until change in function or after-discharges were seen up to 12 mA (15 mA if monopolar). Monopolar stimulation employing an uninvolved reference was used in case of overlap of function between two adjacent electrodes [2]. The intracranial and scalp EEG were monitored for after-discharges or electrographic seizures [3–5], and the patient was asked about perceptual changes. We employed Yale language testing paradigm which is evidence-based. A language site was marked as positive if reproducible language deficits observed in >50% of trials. At any site, where there was a complete arrest of verbal output, testing for negative motor areas ensued [6]. For consciousness examination, we evaluated the alertness, attention, and awareness by asking the patient to remember a phrase and objects presented during stimulation, and asked them to perform tasks before and during stimulation. Behaviors were observed based on video review [7]. IOC defined as failure to respond to alertness, attention, and awareness questions correctly on three consecutive trials in a time-locked fashion to stimulation [8]. ECS mapping was performed in several sessions over two-day period. Equivocal results were confirmed in separate sessions.

3. Clinical history

This is a 34-year-old right handed man with longstanding history of seizure disorder. Seizures began at 12-years old and were well-controlled on valproate from the teenage years until mid-20s when they increased to every 2–4 weeks despite the use or addition of several antiseizure medications. At the time of surgery, he experienced a seizure every 1 to 2 months on lamotrigine, clobazam, and oxcarbazepine [9]. The seizures were always diurnal, and were characterized and described as generalized convulsions. There was no known history of

daytime staring spells or myoclonic jerks. Prior trials of levetiracetam, topiramate, and clonazepam had no noticeable effect on his seizures. There was no history of developmental abnormalities, febrile seizures, or family history of epilepsy.

All recorded habitual seizures on scalp video-EEG were similar and characterized by a non-versive right head turn, followed by asymmetric bilateral arm extension with the right arm more extended, then arms crossing followed by generalized clonic activity. Scalp electrographic ictal onset was characterized by evolving, non-localizable spike or polyspike and wave discharges, slightly and consistently higher in amplitude over the left fronto-central region (F3). Interictally, there were generalized and left frontal maximal spike-and-wave discharges with associated wide-spread involvement (Fig. 1-B). MRI revealed left hippocampal malrotation and a left periventricular focus of T2 hyperintensity. The left hippocampus was 20% smaller than the right by quantitative volumetry. FDG-PET showed mild, broad subtle right temporal hypometabolism on visual analysis without any clear abnormalities by quantitative measures. Neuropsychological testing revealed attentional fluctuation that influenced performance in other domains. Verbal and non-verbal memory were fundamentally strong but were at times influenced by variable attention.

3.1. Electrocorticography (ECoG)

Given the subtle asymmetries noted in regard to semiology, neuroimaging findings, and EEG and the probable slight improvement with the sodium-channel blocker oxcarbazepine suggesting focal onset, he underwent icEEG evaluation for delineating a possible left fronto-temporal epileptic focus for surgical treatment. See (Fig. 1-A) for a reconstruction of implanted electrodes into the suspected regions of interest based on the non-invasive presurgical evaluation. On intracranial EEG recordings, there were widespread interictal discharges observed maximum in amplitude and occasionally with a subtle lead over the left fronto-central contacts. Two habitual seizures were recorded over an 18-day monitoring period. Clinically, they consisted of right head turn, asymmetric bilateral upper extremities extension more noticeable on the right, arms crossing, and then generalized clonic activity. Electrographically, both seizures began with wide-spread polyspikes in both hemispheres but higher in amplitude over the superior lateral frontal cortex in grid locations G21-G22-G29-G30-G39-40. Post-ictally, the patient experienced marked decreased responsiveness for seven to 10 minutes. On EEG, there was generalized post-ictal attenuation followed by generalized delta slowing.

3.2. Functional mapping

Language and motor mapping results are summarized in (Fig. 2). Explicit and exclusive semantic and paraphasic deficits were identified in the anterior-inferior lateral frontal lobe. The patient was frequently asked following the end of stimulation trains over language sites to describe the experience, which he characterized as having difficulty finding the correct word. Motor function of the hand, face, and tongue were localized to the expected regions of the precentral gyrus. We identified a region of a few centimeters square over the caudal superior and middle left frontal gyri as well as the caudal right middle frontal gyrus, in which transient IOC could be induced consistently by ECS at current intensities of 4–5 mA (Fig. 2). The patient had a dazed, fixed look without blinking during IOC. He was amnestic for the period of stimulation and had no recall of being asked to perform tasks and he did not remember the phrase and objects presented during stimulation. The region in which IOC could be provoked was anterior to, and overlapped with the area identified by the clinical team as exhibiting the maximal hyperexcitability due to

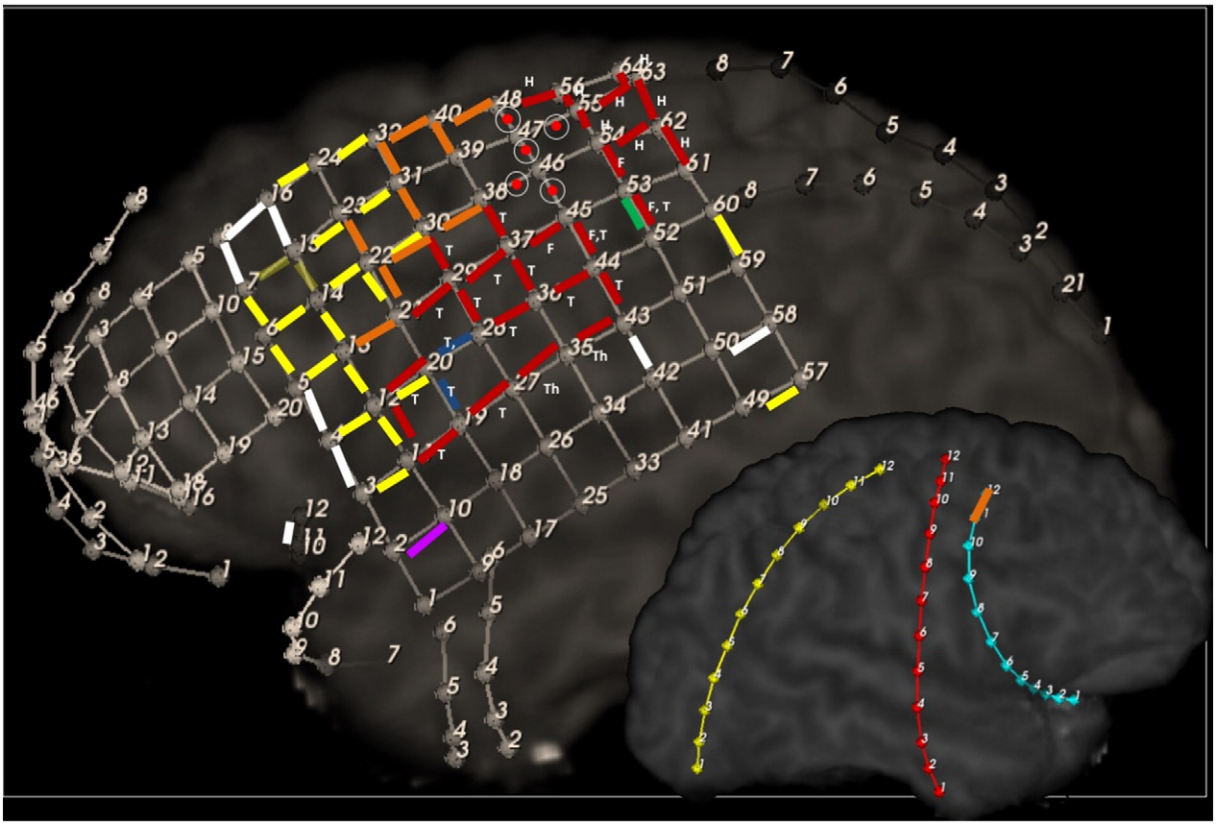

Fig. 2. Functional map from cortical stimulation. Red: positive motor; Green: sensory; Yellow: Language. Orange: Stimulations that triggered consistent impairment of consciousness with trains greater than 2 seconds; Circle with central red dot: Frontal eye field; Blue: negative tongue motor; Purple: Non-epileptic experiential auditory déjà vu; White: Tested up to 12 mA with no observable function identified. T = tongue, Th = throat, F = face, H = hand.

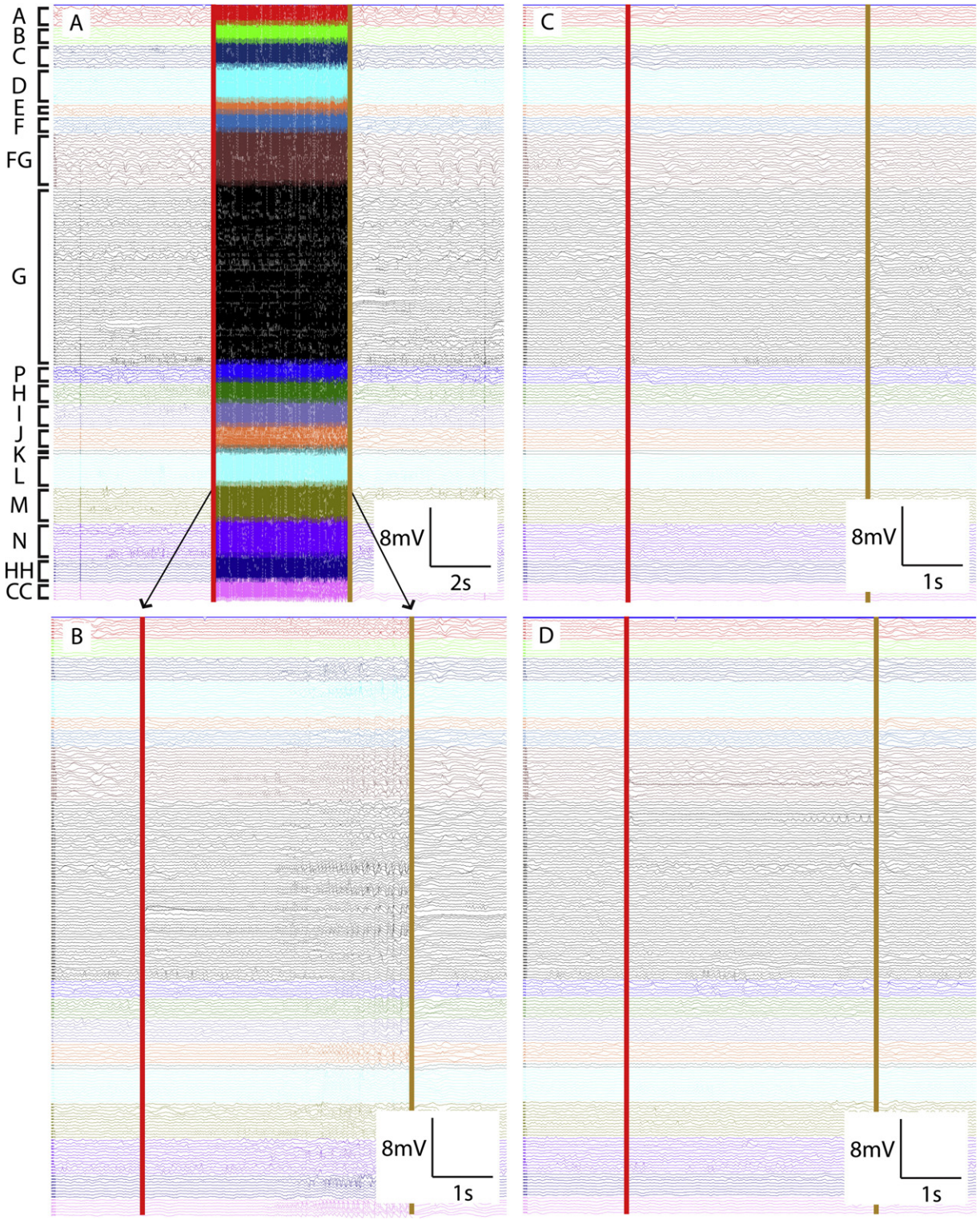

Fig. 3. Evoked responses were seen with stimulation of contacts 39-G40 that correlated with impairment of consciousness (A-B). As a control, we show EEG activity during stimulation of negative motor areas contacts K6-K7 (C) and language contacts G6-G14 (D). (B-C-D) are shown using low-frequency filter 1 HZ and high-frequency filter 30 Hz. Plate A shows 15-second icEEG activity before filtering. The red and orange lines mark the onset and the end of stimulation trains respectively. The responses seen in B are not seizures or after-discharges because i. They were time-locked to stimulation [i.e., they are not self-sustained] ii. There was a return to pre-stimulation background activity when the electrical stimulation was turned off. iii. The spatial extent of the intra-stimulation discharges is not commonly encountered during electrical stimulation mapping. iv. Refer to plate A for demonstration of how the activity was time-locked to the electrical stimulation and had no effect on background activity, similar in this way to photic driving or certain types of photoparoxysmal responses, and the thalamo-cortical evoked responses reported by Velasco et al. [18].

relatively higher amplitudes of interictal discharges. He did follow verbal pre-stimulus commands, and continued with motor tasks though with slowing. He was not able to carry out any tasks given during stimulation whether presented verbally or with visual cues.

Similar effect on consciousness was observed on the right frontal convexity in electrodes L11-L12 at a higher current of 6 mA (intermittent response) to 9 mA (complete disruption). As a negative control, IOC was not observed in other brain regions tested as highlighted in

(Fig. 2). Findings from G32–G40 and L11–L12 were confirmed in another session the following day. All the stimulations, 3–5 per pair at minimum current that correlated with emergence of symptoms, led to complete IOC and amnesia. The IOC correlated with wide-spread evoked responses of admixed frequencies over the fronto-parietal convexities bilaterally, and in the mesial frontal and temporal structures that increased in amplitude, the longer the train and abated at the end of the trains (Fig. 3). The activity was not higher in amplitude over the contacts at seizure onset. This was not seen in other stimulations specifically, over the language and negative motor areas (Fig. 3).

4. Discussion

Upon ECS for motor, sensory and language mapping, there were two areas identified over the bilateral frontal convexity that correlated with reproducible IOC. Intra-stimulation widespread evoked responses of admixed frequencies were seen on simultaneous EEG recording. (Fig. 3 & legend).

We hypothesize that IOC in this case is due to facilitation of abnormal connectivity in widespread cortical-subcortical networks. Our findings bring up the following interesting points regarding cortical-subcortical vs cortical-cortical spread of abnormal activity: i) We are not aware of a *direct* connection between the prefrontal convexities to account for the evoked responses seen based on studies that investigated the connectivity of this region [10,11] ii) The evoked responses were seen within 2 seconds of stimulation, and not at the onset, which carries similarities with late abnormal evoked cortical responses [12–14]. On the other hand, physiologic and direct cortico-cortical evoked responses are seen typically within a short period following stimulation [15,16]. iii) Rarity of reports of IOC triggered by ECS suggests that it may only occur with stimulation of rare locations [17], or in patients with the diagnosis of genetic generalized epilepsy syndromes which are not commonly evaluated by icEEG. iv) The rhythms and spatial distribution of evoked responses, have some similarities with evoked responses reported by other investigators upon stimulation of the centromedian nucleus of the thalamus [18]. This area of the brain has been implicated in consciousness [19] and areas involved in slow waveforms [20] occurring with seizures that affect the level of consciousness.

It is practical to approach epilepsy as a continuum from focal to generalized where the generalized epilepsies may present one end of the spectrum whereas truly focal seizures may represent the other end of the spectrum. We believe the case we presented herein lies on the spectrum but closer to true genetic generalized epilepsy, as the MRI was negative for 'epileptogenic' lesions, and the patient had no known clear risk factors. Focal findings have been reported in a substantial percentage of patients diagnosed with jurvenile myoclonic epilepsy (JME) [21]. It is possible that the relatively low long-term chances of seizure freedom outcomes in frontal lobe epilepsies [22], may be accounted for at least in part by a subset of patients who lie in the gray area of the frontal lobe focal epilepsy-generalized epilepsy. The case presented here provides additional and direct evidence that highly focal frontal cortical electrical stimulation can affect widespread networks, leading to impairment of consciousness.

To our knowledge, reports of IOC during ECS are scarce. There is a single report of IOC induced by stimulation of claustrum and anterior insula as described by Koubeissi et al. [17]. However in the later case, IOC was seen at higher current intensities than the case presented herein, interestingly in a patient who failed prior surgery, and was associated with increased synchrony in the frontal and parietal regions similar to this case. Other reports of induced generalized discharges, were indeed generalized convulsions, with evolving electrographic seizures not time locked to stimulation unlike the case reported herein [23].

Future studies, may prospectively elucidate the correlation between IOC provoked by ECS and localization of seizures, burden of generalized seizures, and long term surgical outcomes. It is possible that this entity may be specific for generalized epilepsy, or focal epilepsies with frequent generalization. It is also possible that the entity has been overlooked or under-reported. This report highlights the importance of standardization of testing IOC during electrical stimulation for functional brain mapping as its occurrence may be misinterpreted as 'function'.

5. Conclusions

This report highlights the importance of testing for impairment of consciousness during sessions of electrical cortical stimulation. It also underlines the possibility that localized stimulation in some cases may produce widespread changes in brain physiology and in consciousness. Future prospective studies may elucidate the occurrence and prognostic value of impairment of consciousness during electrical cortical stimulation for mapping function.

Conflict of interest

Imran H Quraishi, Christopher F. Benjamin, Dennis D. Spencer, Hal Blumenfeld, Rafeed Alkawadri, all declare no conflict of interest.

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Authors contributions

Conceptualization R.A.; Methodology R.A., H.B.; Investigation I.Q., C.B., R.A., Data Curation I.Q.; R.A. Writing Original Draft I.Q. Writing – Review & Editing H.B., C.B., R.A. Supervision R.A., Project Administration R.A., Funding Acquisition R.A.

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