Epilepsy & Behavior 37 (2014) 32–35

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

# Electrical stimulation of a small brain area reversibly disrupts consciousness

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ARTICLE INFO

*Article history:*
Received 12 February 2014
Revised 9 May 2014
Accepted 27 May 2014
Available online 24 June 2014

*Keywords:*
Consciousness
Electrical stimulation
Epilepsy
Insula
Claustrum

ABSTRACT

The neural mechanisms that underlie consciousness are not fully understood. We describe a region in the human brain where electrical stimulation reproducibly disrupted consciousness. A 54-year-old woman with intractable epilepsy underwent depth electrode implantation and electrical stimulation mapping. The electrode whose stimulation disrupted consciousness was between the left claustrum and anterior-dorsal insula. Stimulation of electrodes within 5 mm did not affect consciousness. We studied the interdependencies among depth recording signals as a function of time by nonlinear regression analysis ($h^2$ coefficient) during stimulations that altered consciousness and stimulations of the same electrode at lower current intensities that were asymptomatic. Stimulation of the claustral electrode reproducibly resulted in a complete arrest of volitional behavior, unresponsiveness, and amnesia without negative motor symptoms or mere aphasia. The disruption of consciousness did not outlast the stimulation and occurred without any epileptiform discharges. We found a significant increase in correlation for interactions affecting medial parietal and posterior frontal channels during stimulations that disrupted consciousness compared with those that did not. Our findings suggest that the left claustrum/anterior insula is an important part of a network that subserves consciousness and that disruption of consciousness is related to increased EEG signal synchrony within frontal–parietal networks.



## 1. Introduction

Although the neural mechanisms that underlie consciousness are unclear, clinicians tend to separate it into wakefulness and awareness. Wakefulness depends upon the functional integrity of subcortical arousal systems in the brainstem and thalamus [1]. Awareness refers to the content of experience as regards both the environment and the self and is thus defined as the capacity to respond to external stimuli while having an internal and qualitative experience of existence. The external awareness network seems to encompass bilateral dorsolateral prefrontal cortices and lateral posterior parietal cortices, whereas the internal awareness network seems to include the midline posterior cingulate cortex/precuneus and anterior cingulate/medial prefrontal cortices [2]. A complete disruption of consciousness during the waking state, involving the perception of both external and internal stimuli, is often experienced by patients with epilepsy, regardless of the area of seizure origin in the brain. Indeed, disruption of consciousness is one of the most disabling manifestations of epileptic seizures that affects quality of life [3]. However, the precise structures and pathophysiological mechanisms involved in impairment of consciousness in epileptic seizures remain a matter of debate [4–6].

Common brain regions are thought to be involved in all seizures that interfere with consciousness, regardless of their onset zones and variations in semiology. These regions include the frontoparietal association cortex and the subcortical arousal system in the brainstem and thalamus [6]. One hypothesis suggests that alteration of consciousness in partial seizures results from abnormal synchronization of cortical activity between distant brain regions [4] that overloads the structures involved in consciousness processing, affecting their ability to handle incoming information [5,7]. In this report, a finding from the electrical stimulation of the brain during presurgical evaluation of intractable epilepsy in a patient provided direct evidence that a small brain region that encompasses the anterior-dorsal insula and the neighboring claustrum (Fig. 1) is a key component of the network supporting both external awareness and internal awareness. No similar response to electrical stimulation of any other brain region has ever been reported, despite almost a century of experience in electrical cortical stimulation [8].

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http://dx.doi.org/10.1016/j.yebeh.2014.05.027
1525-5050/

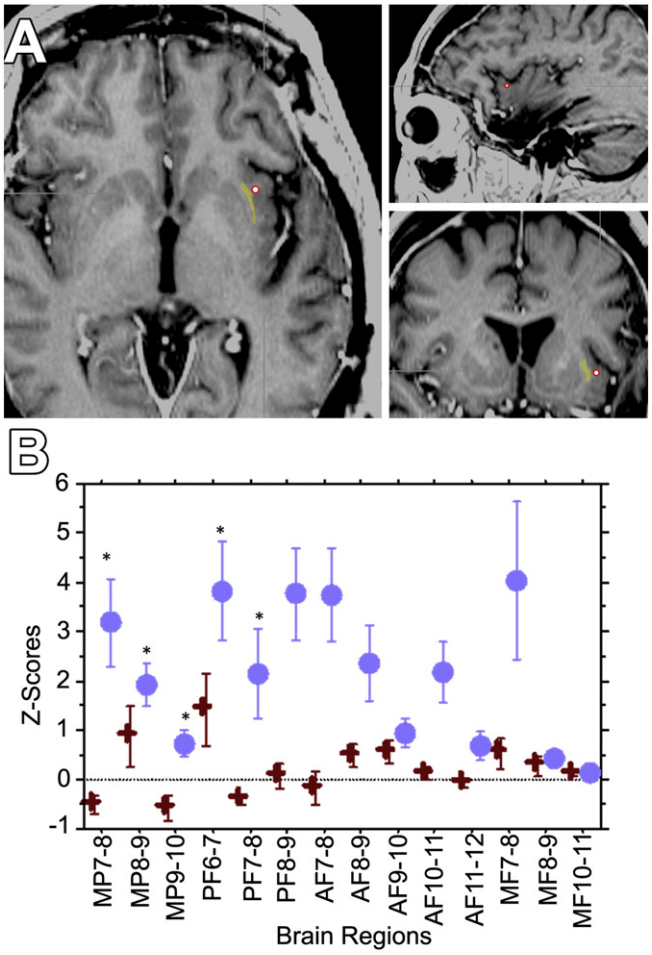


**Fig. 1.** A. Location of the AI4 contact (red circle) whose stimulation elicited impairment of consciousness. The location, shown in three different planes, was determined by superimposition of preoperative brain MRI with postoperative volumetric head CT scan according to anatomic fiducials. The claustrum is highlighted in yellow to show its proximity to the stimulating contact. B. Variations of $h^2$ coefficients estimated by Z-scores relative to the prestimulation period in 15 selected bipolar channels. Blue circle: Two stimulations of AI4, chosen at random from among ones that cause disruption of consciousness and red cross: 2 stimulations chosen at random stimulations of AI4 that did not interfere with consciousness at lower current intensities. The significant variations are mainly observed in medial parietal (MP) channels and posterior frontal (PF) channels. AF, anterior frontal; MF, medial frontal.

## 2. Methods

### 2.1. Subject and clinical setting

A 54-year-old woman with a history of intractable epilepsy, characterized by olfactory auras followed by disruption of consciousness and occasional secondarily generalized seizures, underwent left hippocampectomy sparing the amygdala. The patient remained seizure-free for four years before habitual seizures recurred, necessitating depth electrode evaluation. Since the seizures were consistent with a mesial temporal origin, intraparenchymal electrodes were implanted in the anterior hippocampal remnant and in structures that have known connectivity with the mesial temporal structures: the left amygdala, posterior cingulate gyrus, medial and lateral frontal regions, and anterior and posterior insula, in addition to two electrodes in the posterior quadrant sampling the temporoparietal and temporooccipital regions. Bilateral scalp electrodes were also placed. No subdural electrodes were placed. One depth electrode that sampled the left anterior insula included a contact, AI4, in the extreme capsule and in close proximity to the anterior insular cortex and the claustrum (Fig. 1).

### 2.2. Cortical synchrony assessment

We studied interdependencies between signals from different brain regions by using nonlinear regression analysis during stimulations that interfered with consciousness and those that did not. For this, our aim was to assess changes in synchronization between remote brain regions, particularly frontoparietal networks, during AI4 stimulations that induced disruption of consciousness (14 mA) and compare them with control stimulations of the same electrode at lower current intensities (2–12 mA) that did not interfere with consciousness. Interdependencies between bipolar signals recorded from 15 contacts that sampled evenly most implanted regions, including frontoparietal areas, were estimated as a function of time by using nonlinear regression analysis. Details of the method are described elsewhere [4]. Nonlinear regression analysis provides a parameter, referred to as the nonlinear correlation coefficient $h^2$, whose values lie in the range [0, 1]. Low values of $h^2$ denote independence of signals, whereas high values of $h^2$ denote signal dependence by signifying that one signal is related via a (likely nonlinear) transformation to another. The analysis was performed over a sliding window of two-second duration by steps of 0.25 s. The $h^2$ values were averaged over each period of interest defined for each of the 105 considered pairs of signals and for two AI4 stimulations that interfered with consciousness and two control stimulations (at 6 mA) of the same electrode that did not interfere with consciousness.

To assess the functional connectivity between parietofrontal cortices, we chose 3 bipolar channels from the medial parietal cortex, including the precuneus; 4 from lateral frontal region; 5 from anterior frontal region; and 3 from medial frontal region. The $h^2$ values were computed on broadband signals (0.5–90 Hz), providing a global estimation of nonlinear interdependencies. Two periods were considered for analysis: a 10-second background (BG) period chosen just before the start of the stimulation and an 8-second period covering the stimulation period (SP). The $h^2$ values were averaged over BG and SP periods. Changes in $h^2$ values obtained during the SP period relative to the BG period were evaluated by calculating the variation of $h^2$ values in terms of Z-scores [$Zh^2 = ((\text{mean } h^2\ (SP) - \text{mean } h^2\ (BG)) / SD\ (BG))$]. These values were then averaged over time in order to get an estimate (mean +/− SD) of the degree of coupling between selected channels. For each selected channel, we calculated the $h^2$ values between all possible pairs. The differences in values obtained from positive (disrupting consciousness) versus negative (asymptomatic) stimulations of AI4 were compared using a Mann–Whitney test and corrected for multiple comparison using Bonferroni correction.

## 3. Results

The patient's seizures originated from the left amygdala. Electrical stimulation of medial frontal electrodes was done initially, and no symptoms were elicited at currents reaching 18 mA. Then, one of these "clinically silent" electrodes was used as a reference for electrical stimulation of all remaining contacts. Stimulating AI4 using biphasic waves at 14 mA (50 Hz, 0.2-ms pulse width, 3- to 10-second train duration), but not at lower intensities, resulted in immediate impairment of consciousness, in 10 out of 10 times, with arrest of reading, onset of blank staring, unresponsiveness to auditory or visual commands, and slowing of spontaneous respiratory movements. The patient returned to baseline as soon as the stimulation stopped with no recollection of the events during the stimulation period. Occasionally, the induced impairment of consciousness was associated with scanty, perseverative, and incomprehensible verbal output consisting of one or two syllables, with a confused look on the face. No abnormal discharges outlasting the stimulation were seen on depth electrode recordings or scalp electroencephalogram (EEG). Specifically, the raw EEG in frontoparietal regions did not show any deviation from baseline during the stimulation step that elicited disruption of consciousness as well as during those that did not. Stimulation of the adjacent electrode contacts did not elicit the same phenomena.