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Case Report

Intracarotid amobarbital disrupts synchronous and nested oscillatory activity ipsilateral to injection☆

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ABSTRACT

The mechanism of amobarbital action during the intracarotid amobarbital procedure is poorly understood. We report a patient case who underwent IAP while implanted with bilateral stereo-EEG. We analyzed the spectral power, phase amplitude coupling, and cluster-phase group synchrony during the procedure. Delta and gamma power increased bilaterally. By contrast, phase amplitude coupling increased only ipsilateral to the injection. Similarly, 4–30 Hz cluster-phase group synchrony declines and gamma cluster-phase group synchrony increases only ipsilateral to the injection. These results suggest that a possible additional mechanism for amobarbital action in the IAP is by altering the precise timing of oscillatory activity.

1. Introduction

The intracarotid amobarbital procedure (IAP) is used to provide prognostic information prior to epilepsy surgery, but it may also provide interesting insights into brain function. Milner and Wada, the developers of the procedure, described the function of the amobarbital as to, "temporarily inactivate," the anterior circulation of one hemisphere of the brain [1,2], but this mechanism does not explain some observations during the procedure. For example, EEG changes are frequently bilateral, rather than merely ipsilateral to the injection side on scalp EEG [3,4] and intracranial EEG [5]. Although this could possibly be attributed to crossing of the drug to the contralateral hemisphere via the circle of Willis, nuclear medicine studies show that the drug passes to the other hemisphere a very small proportion of the time [6]. This suggests that the unilateral inactivation model for amobarbital action cannot adequately explain the unilateral deficits observed during the procedure. Other authors have speculated that amobarbital may function in this setting by, "deafferentation," from cortical and subcortical structures [6]; however, this description does not clarify the physiologic mechanism for this deafferentation.

To begin to clarify the mechanism of amobarbital in producing unilateral deficits, we report a case of a patient who underwent IAP while implanted with bilateral stereo-EEG. The activity during the procedure was evaluated using measures of nested and synchronous oscillations. Measures of nested oscillations such as phase-amplitude coupling (PAC) and synchrony such as cluster-phase group synchrony were selected because existing evidence indicates their importance in cognitive function [7,8], and dysfunction of these measures has been implicated in poor cognitive performance [9]. For example, pathological PAC has been recorded in Parkinson's disease [10].

2. Materials and methods

2.1. Consent

The study was conducted according to the principles of the Declaration of Helsinki, and the consent documentation and procedure were approved by the Mount Sinai Hospital Institutional Review Board.

2.2. Patient

The patient at the time of surgery was a 41-year-old right-handed male with drug resistant epilepsy since age 17. The semiology of his events was a feeling of coldness and nausea followed by bilateral automatisms of the hands, associated with amnesia for the event. These would proceed to a generalized convulsion very infrequently. He

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continued to have seizures on lamotrigine, levetiracetam, and oxcarbazepine, and had failed treatment with zonisamide, lacosamide, and carbamazepine. Interictal EEG showed bilateral frontotemporal sharp waves, and multiple left frontotemporal seizures were captured on video-EGG in the epilepsy monitoring unit. His MRI was normal. Because of the presence of bilateral interictal discharges and a nonlesional MRI, it was decided that the patient should undergo bilateral stereo-EEG. The IAP was performed while the patient was implanted with bilateral stereo-EEG due to unreliable follow-up after multiple attempts pre-implantation.

2.3. Data collection and pre-analysis

Electrophysiological data was collected for all subjects using a Natus Quantum amplifier (Natus Medical Incorporated; Pleasanton, CA). The sampling rate was 1024 Hz. All pre-analysis and analysis was performed with MATLAB (Mathworks, Natick, MA) using the FieldTrip software library [11]. Recordings were referenced to the average of all electrodes. Each trace was locally detrended. AC noise was removed using a 60 Hz notch filter.

2.4. Electrode localization

Localization of electrodes was performed using pre-operative MRIs and post-operative CTs. Coregistration of MRI and CT was performed using iELVIS [12] and the location of each electrode was selected on the post-operative CT. A parcellated image of the patient's cortical surface was generated using FreeSurfer from the T1 series of the pre-operative MRI. Cortical parcellation used the DKT40 Atlas [13].

2.5. Analysis

The data from each electrode was divided into 10 s windows with 5 s step-size. Spectral power was calculated using a complex Morlet wavelet transformation (width = 7). Spectral power was calculated for all electrodes between 1 to 150 Hz, calculated at 1 Hz increments. Cluster-phase group synchrony – a global variable representing the phase locking of multiple signals at a given frequency — was calculated between all the electrodes in each frontal lobe between 1 to 150 Hz, calculated at 1 Hz increments [14]. Phase amplitude coupling – a measure of the tendency for high frequency oscillations to occur at particular phases of low frequency oscillations — was calculated for 1 to 20 Hz in 1 Hz increments (phase frequency) and 30 to 150 Hz in 10 Hz increments (amplitude frequency) [15].

3. Results

3.1. IAP results

Wada testing was performed during implantation with first left, then right intracarotid injection of 100 mg of amobarbital. After the left sided injection, the patient was aphasic and plegic on the right. The patient was plegic on the left after the right sided injection. Left sided memory function was 3 out of 10 exemplars. Right sided memory function was 4 out of 8 exemplars.

3.2. Electrode localization

Ninety-eight electrodes were placed bilaterally into this patient (Supplementary Fig. 1, Supplementary Table 1). Because the borders of the anterior circulation in the temporal lobe could not be clearly determined, the analysis divided electrodes that were in the frontal lobe from those in the temporal lobe. Of these, 23 electrodes were excluded because they were located more than 5 mm from a gray matter structure.

3.3. Spectral power

The Z-score of the average spectral power for the 1–150 Hz frequencies for electrodes from each frontal lobe are depicted in Fig. 1A. At the time of both the left and the right-sided injection there is a visible increase in delta (1–3 Hz) power and high gamma (80–150 Hz) power bilaterally. The Z-scored spectral power for these bands is depicted in Fig. 1B. A similar analysis for all of the electrodes in the right and left temporal lobe produced similar results (Supplementary Fig. 2A and B). Analysis of the spectral power in the beta range (15–29 Hz) and low gamma range (30–79 Hz) show bilateral increases, but less accurate at lateralizing the side of activity (Supplementary Fig. 3).

3.4. Phase amplitude coupling

Nested oscillations are speculated to support brain functions and are correlated with performance in tasks such as memory [7]. A measure of nested oscillations is the PAC, the tendency of the peaks of high frequency oscillations to cluster at a phase of a lower frequency oscillation. This measure was calculated for 1–20 Hz (phase frequency) and 30–150 (amplitude frequency) for all electrodes in the right and left frontal lobes. For the 2–3 Hz (phase frequency) and 30–70 Hz (amplitude frequency) there is an increase in PAC ipsilateral, but not contralateral to the injection (Fig. 1C). A similar analysis for all of the electrodes in the right and left temporal lobe produced similar results (Supplementary Fig. 2C).

3.5. Synchrony

Synchronous oscillations between brain regions are hypothesized to support brain function by organizing different units into functional networks [8]. A global measure of synchrony is cluster-phase group synchrony, the tendency of a group of oscillators to align to the same phase [15]. This measure was calculated between 1 to 150 Hz, calculated at 1 Hz increments for all the electrodes in the left and right frontal lobe. Fig. 1D shows a reduction in the Z-scored cluster-group synchrony in the 4–30 Hz ipsilateral to the injection and an increase in the Z-scored cluster group synchrony in the low and high gamma bands ipsilateral to the injection. These changes are present to a lesser degree contralateral to the injection. A similar analysis for all of the electrodes in the right and left temporal lobe produced similar results (Supplementary Fig. 2D). Thus, after intracarotid amobarbital, lower-frequency oscillators in the injected hemisphere tend to fall out of phase, whereas higher-frequency oscillators tend to increase phase synchrony. This pattern of synchrony closely resembles the pattern observed in poor memory performance in behavioral testing of patients implanted with intracranial EEG [9].

4. Discussion

These results detail the electrophysiologic changes observed in a single patient who underwent IAP while implanted with bilateral stereo-EEG. As has been observed in prior scalp [3,4] and intracranial studies [5], there was a significant bilateral increase in delta power both ipsilateral and contralateral to the injection. Although the delta power increase was more prominent ipsilateral to the injection, the relative asymmetry in delta power may not fully explain the unilateral deficits in the patient after injection. By contrast, changes in phase amplitude coupling for 2–3 Hz (phase frequency) and 30–70 (amplitude frequency) and cluster-phase group synchrony in the 4–30 Hz and 30–150 Hz bands appear in this case to more accurately lateralize the deficits observed in this patient.

The additional observation that low and high gamma power increase bilaterally is incongruous with the purported action of amobarbital in decreasing neuronal firing. It is possible that cognitive load performing the task or patient movement account for these increases. Alternatively, early studies in a dog model of amobarbital showed increased bursting

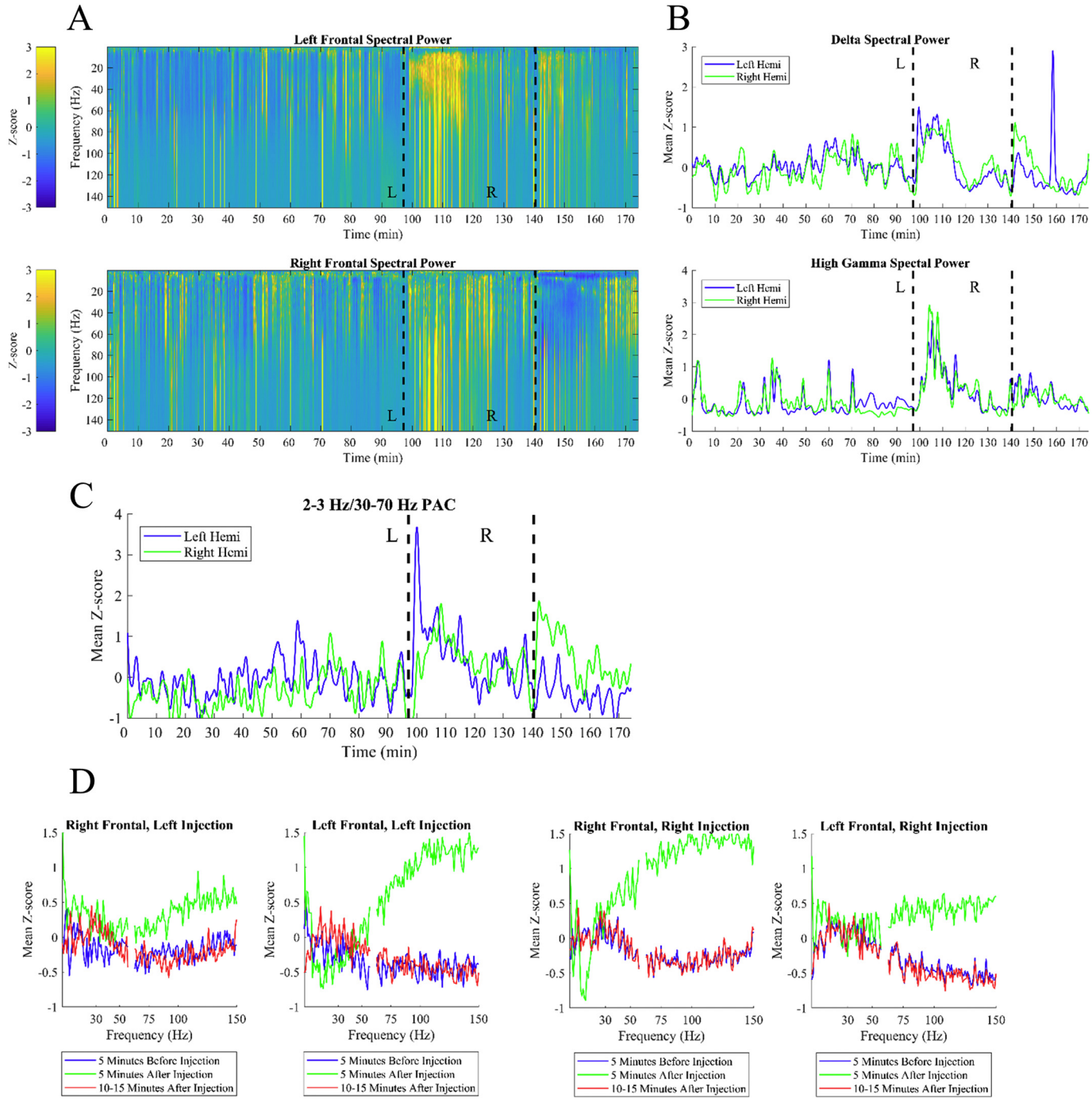

Fig. 1. (A) A heat plot demonstrates the Z-scored spectral power for 1–150 Hz averaged over electrodes from the left and right frontal lobes. The vertical lines indicate the times of the left and right injections, respectively. (B) The mean Z-scored spectral power for the delta (1 to 3 Hz) and high gamma bands (80 to 150 Hz) are shown averaged over electrodes in the left and right frontal lobes. The vertical lines indicate the times of the left and right injections, respectively. A 12 point Gaussian filter has been on the data for clarity. (C) The 2–3 Hz (phase frequency) and 30–70 Hz (amplitude frequency) are shown averaged over electrodes in the left and right frontal lobes. The vertical lines indicate the times of the left and right injections, respectively. A 12 point Gaussian filter has been on the data for clarity. (D) The Z-score cluster-phase group synchrony for windows 5 min before, 5 min after and 10–15 min after each injection, for each hemisphere, are shown.

activity after administration [16]. It is possible that this bursting activity is being recorded as an increase in spectral power in the gamma range.

That synchronous and nested oscillations are better at lateralizing the side of injection draws into question the hypothesis that amobarbital functions solely by, "inactivating," the injected region. Rather, these suggest that an additional mechanism of amobarbital action may be by the disruption of the temporal structure of oscillations of the local field potential, which modifies the information encoded in nested oscillations and desynchronizes previously synchronous nodes in existing neural networks. Pathological increases in PAC have been noted in Parkinson's disease [10]. Similarly, a recent analysis of patients performing memory tasks while implanted with intracranial EEG showed that theta band synchronization and gamma desynchronization correlated with performance [9]. Our finding that the amobarbital injection causes a similar desynchronization in 4–30 Hz and synchronization in the gamma band demonstrates that the drug causes a brain state associated with poor memory performance suggests that these changes in synchrony may account for the drug's effect as an amnestic agent. Further, these

quantitative observations on the intracranial signal have implications to interpretation of the scalp EEG during the procedure. It may not be possible to determine the effectiveness of the drug on the basis of qualitative evaluation of scalp EEG.

These results should be interpreted with caution as this is a single case. Other agents sometimes used in the procedure such as propofol or methohexital may have other mechanisms of action. However, if validated and repeated in a larger series, these results have broad implications for our understanding of brain function. Synchronous and nested oscillations are hypothesized to organize neural networks, yet evidence to support this hypothesis is almost exclusively correlative [17]. The results of this case study add evidence to the hypothesis that temporal synchrony of oscillatory activity is necessary for brain function.

5. Conclusion

In this case, we show that measures of nested oscillations and synchrony may lateralize the deficits better than measures of spectral power. These results imply a possible alternative mechanism for amobarbital action and supports the hypothesis that nested and synchronous oscillations are necessary for brain function.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebcr.2018.04.003.

Conflict of interest

The authors have no conflicts of interest to declare.

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