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Band Specific Changes in Thalamocortical Synchrony in Field Potentials after Cardiac Arrest Induced Global Hypoxia

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Abstract — **Cardiac Arrest (CA) leads to a global hypoxic-ischemic injury in the brain leading to a poor neurological outcome. Understanding the mechanisms of functional disruption in various regions of the brain may be essential for the development of improved diagnostic and therapeutic solutions. Using controlled laboratory experiment with animal models of CA, our primary focus here is on understanding the functional changes in the thalamus and the cortex, associated with the injury and acute recovery upon resuscitation. Specifically, to study the changes in thalamocortical synchrony through these periods, we acquired local field potentials (LFPs) from the ventroposterior lateral (VPL) nucleus of the thalamus and the forelimb somatosensory cortex (S1FL) in rats after asphyxial CA. Band-specific relative Hilbert phases were used to analyze synchrony between the LFPs. We observed that the CA induced global ischemia changes the local phase-relationships by introducing a phase-lag in both the thalamus and the cortex, while the synchrony between the two regions is nearly completely lost after CA.**

I. INTRODUCTION

The electroencephalogram and evoked potentials are used in neuro-critical care to assess brain dysfunction. This is particularly useful in monitoring the ischemia induced brain injuries as in general hypoxic ischemia from cardiac arrest (CA). However, very little is known of the underlying sub-cortical events that accompany changes in the EEG immediately after injury and particularly during the early recovery phase. Theoretical modeling studies suggest that components of the evoked potentials could have thalamic or sub-thalamic origins [1]. Our previous studies suggested thalamic origins of short-latency peaks in SSEPs [2-4]. Furthermore, region-specific vulnerabilities to ischemia have been previously suggested [5]. For example, the ventral posterior lateral (VPL) nuclei was shown to be more tolerant than cortical structures under focal ischemia [6, 7]. Studies with animal models showed evidence for selective vulnerability of subcortical regions [5]. However, the inter-region electrophysiological correlates of these effects are yet to be fully understood.

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Cardiac arrest (CA) leads to a disruptive changes from molecular to regional length-scales, which leads to overall neuronal dysfunction, and finally to a poor outcome [8]. These wide-spread "micro-injuries" can lead to changes in regional and inter-regional function, as characterized by the onset of synchrony or desynchrony in the collective neuro-electrophysiological signals in small vicinity around ischemia-affected zones. For example, previous investigations by Schiff et. al. suggested that the thalamic and cortical desynchrony may be responsible for the comatose state after CA and restoration of thalamic function may play a vital role in the coma arousal [9]. Therefore, the thalamic and cortical synchrony and its evolution after cardiac arrest was the focus of this exploratory study with a rat model of CA. Here we report band-specific, acute changes in phase relationships in the local thalamic and cortical LFPs as well as inter-regional desynchrony after CA-induced global hypoxic-ischemia in rats.

II. METHODS

A. Experimental Procedures

Adult male Wistar rats (n=3; 300-320gms; Charles River Laboratories, Germantown, MD) were used for these experiments. The animals were housed individually in cages and had free access to food and water. All the procedures were approved by the Institutional Animal Care and Use Committee at the Johns Hopkins University.

Briefly, after initial preparations with anesthesia, and stereotaxic fixing (Kopf, Model 957, Tujunga, CA), the rats were subjected to a controlled flow of the anesthetic (1.5% halothane) via a tight-fitting facemask and placed on a heat pad (TCAT-2 Temp Controller, Physitemp, Clifton, NJ). The controller's temperature probe was advanced into the rectum to monitor the temperature through the recording. A local anesthetic of 2% Lidocaine HCl (Abbott Laboratories, North Chicago, IL) was injected under the skin, and an incision was made along the midline. The cranium bone was cleaned by removing the tissue under the skin.

A standard dental drill (Fine Science Tools, North Vancouver, BC, Canada) was used to drill two small holes (located directly above the VPL and S1FL areas [10]) in the skull without puncturing the dura. Using the standard anatomical atlas coordinates two pairs of two-channel tungsten micro-electrodes (FHC, Bowdoinham, ME) were advanced to the layer IV-V of the somatosensory cortex and the VPL nucleus of the thalamus. Note that within VPL and S1FL, the pair electrodes were separated by 800µm each.

After the rats were stabilized at 37±0.5°C, the 4-channel LFPs were recorded for 10mins. After baseline recordings, the animals were subjected to 7 minutes of asphyxial CA by interrupting the ventilation.
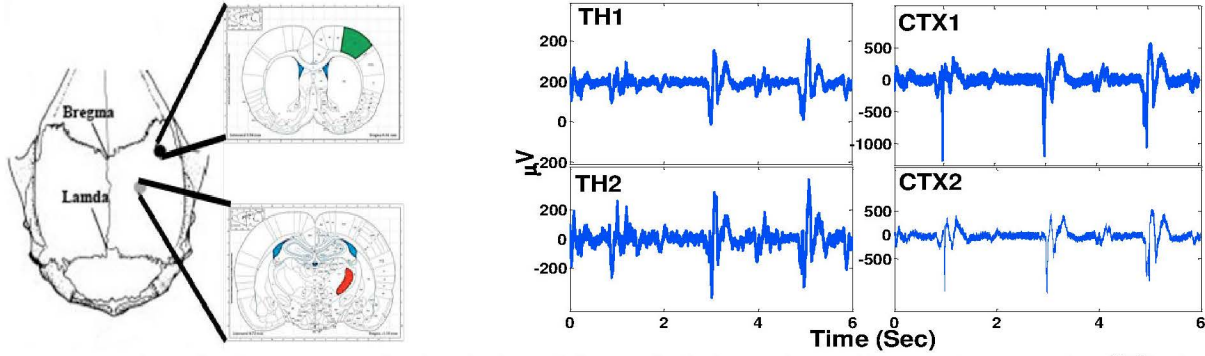
Figure1. Left: Electrode placements on the dorsal view of the rat skull shown along with coronal cross-section [10]; showing the somatosensory cortical region for forelimb (S1FL, Green) and the thalamic ventral postero-lateral nucleus (VPL, Red). Each of these anatomical locations was placed with two micro-electrodes each recording the LFPs. **Right:** An example trace of the recorded LFPs from the four channels.

Then cardiopulmonary resuscitation (CPR) was applied lasting ~1 minute until the return of spontaneous circulation (ROSC), after which we let rat recover until waking up. Details about the experimental procedures were previously described in [11, 12]. The heart rate and the blood pressure were monitored throughout. Spike and LFPs were digitally acquired at the sampling rate of 12.2 kHz using TDT System3 (Tucker-Davis Technologies, Alachua, FL); filtered (0.3-3kHz) and stored for further analysis. Finally, the rat was released from stereotaxic frame after the recording, and was euthanized using intracardiac injection of overdosed KCl.

B. Post-experimental Analysis-The Relative Hilbert Phase

The acquired raw signals were notch filtered to remove the 60Hz noise, band-pass filtered with 0.3-200Hz for LFP and further filtered into the five clinical bands (δ:0.5-4Hz; θ:4-8Hz; α:8-12Hz; β:12-30Hz; γ30-150Hz). The LFP signals in the five bands were subjected to analysis to compute the Relative Hilbert Phases. The distribution of the relative phases were then plotted on the Rose plots and the circular mean the circular SDs of the phases were reported as outcome measures. Given a recorded signal v(t), the so called complex analytic signal V(t) is then defined as,

$$V(t) = v(t) + i.u(t),$$

where u(t) is the Hilbert Transform of v(t) defined as,

$$u(t) = \frac{1}{\pi} PV(\int_{-\infty}^{+\infty} v(t') / (t - t') dt')$$

where PV denotes the so called Cauchy Principal Value of the integral. The Hilbert Phase of the signal v(t) is then defined as the angle φ given by,

$$\varphi = \tan^{-1}(u(t) / v(t)).$$

Given Hilbert phases of two signals φ_1 and φ_2, the relative Hilbert Phase can be simply defined simply as

$$\varphi_r = \varphi_1 - \varphi_2 \mod 2\pi.$$

$\varphi_r(t)$ is the relative phase angle between the two recorded signals. The time-domain distribution of $\varphi_r(t)$ can then be used to characterize the synchrony between the two recorded signals.

It should be noted that $\hat{\varphi}_r(t) = 0$, where the hat indicates a temporal average, will thus indicate a perfect synchrony between two signals; $\hat{\varphi}_r(t) = c$ where c is a non-zero constant will indicate a phase-lag with a constant phase difference. While both these cases will indicate synchrony, a wide distribution of the relative phase angle over the entire $[0,2\pi]$ interval will indicate a complete desynchrony between the two signals. It should be noted that since the dependent variable is an angle, the group results will be in the form of circular means.

III. RESULTS

Before and after the asphyxial CA induction in n=3 rats, we recorded a total of 4 channels: 2 from the VPL nucleus of the thalamus (labeled TH1, TH2) and 2 from the S1FL area (labeled CTX1, CTX2). The recorded signal was a wide-band signal sampled at 6.1kHz. This was separated as described in methods into the LFPs within the five clinical bands. **Figure 1** (right panel) shows an example trace of the recorded 4-ch signal, with the separated LFP (the low frequency component 0.3-200Hz). The analysis algorithm was implemented in MATLAB (Mathworks, Natick, MA) to calculate the instantaneous relative Hilbert phases between each pair of the 4 electrodes.

Figure 2 shows examples of band-specific changes in thalamic and cortical synchrony between local field potentials in a single rat after cardiac arrest. The top two rows correspond to the delta band (0.5-4Hz); and the bottom two rows correspond to the beta band (12-30Hz). The left two columns correspond to pre-injury and the right two columns correspond to post-injury LFPs. Each individual panel correspond to a Rose plot (circular histogram) for the relative Hilbert phases between a pair of channels indicated at the top (e.g. TH1-TH2), where each label correspond to a thalamic (TH) or cortical (CTX) channel 1 or 2

As expected, it is seen easily that before CA induced global injury, each local pair (e.g. TH1-TH2) showed a near-perfect synchrony in all bands (The electrode-separation ~800µm), which changed to a phase-lag after CA (see col 1 to col 3). This may be indicative of the local effects of ischemia.
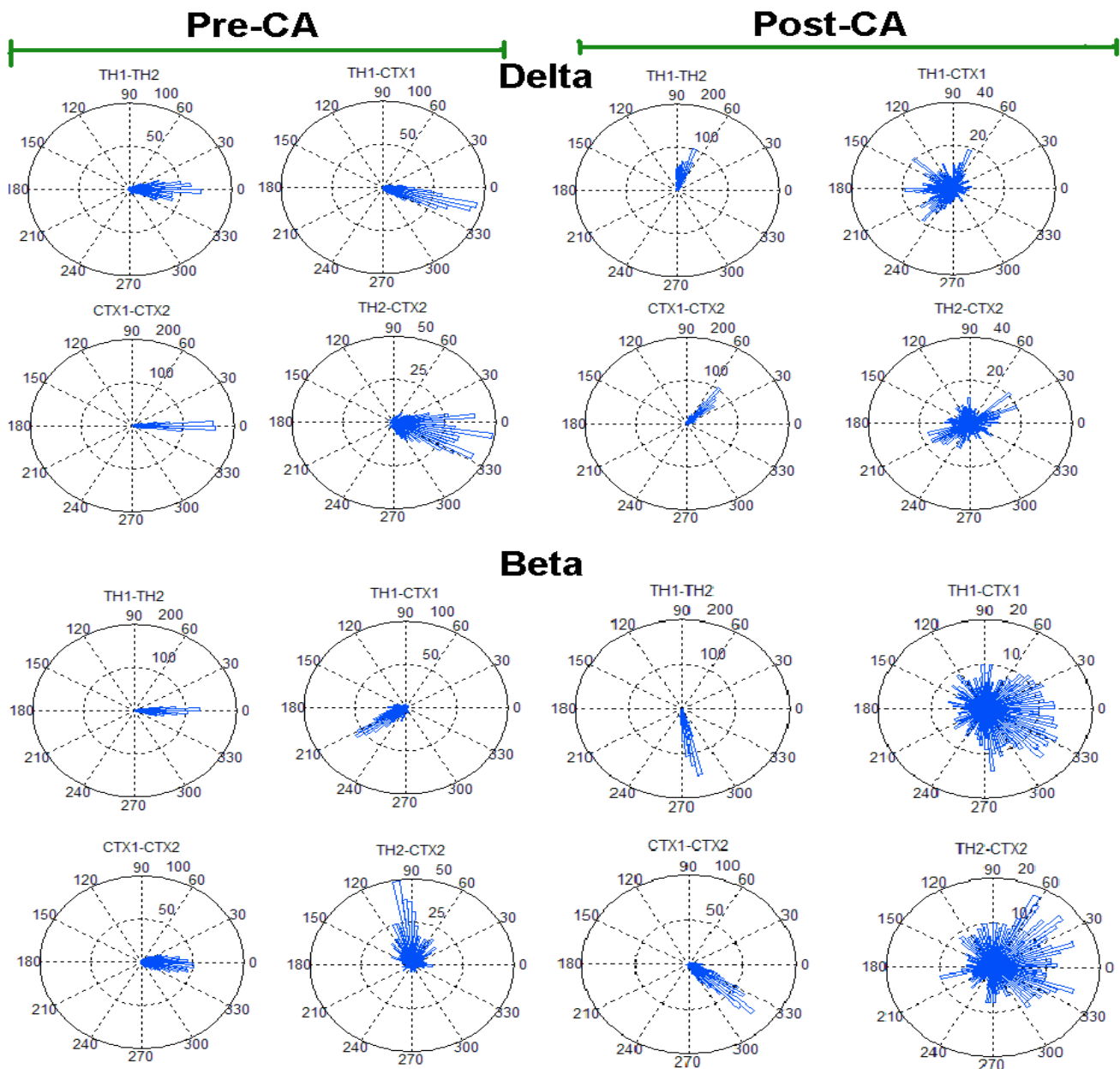
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The inter-regional relative phases showed a drastic post-CA desynchrony (see col 2 to col 4). Analysis in other bands yielded similar results (see Table 1). **Table 1** gives the band-specific relative Hilbert phases before and after cardiac arrest in n=3 rats. It can be easily seen that in each rat, for each clinical band, the local pair of channels was in near-perfect synchrony as expected due to the small distance between the electrodes (800μm) and no presence of injury.

After-CA, the local pairs showed a phase-lag synchrony with different phase-lags in nearly all bands. It is therefore interesting to note that in all bands the post-CA data showed a complete de-synchrony across the two regions examined. This may be characteristic of the break-down of thalamo-cortical oscillatory circuits during coma.

Table 1: Band-specific Relative Phases (Circular Mean ± Range in angle°) between LFPs in Thalamic, Cortical and Thalamo-cortical Pairs of Channels Before (green) and After (red) CA. All Angles are in degrees between [0,360]. Note that 0°≡360°.

Frequency Band	Rat 1			Rat 2			Rat 3		
	TH1-TH2	CTX1-CTX2	TH-CTX	TH1-TH2	CTX1-CTX2	TH-CTX	TH1-TH2	CTX1-CTX2	TH-CTX
δ:0.5-4Hz	0.0±12.1 70.3±24.4	0.0±8.2 53.4±18.2	345±30.1 xx	1.1±3.2 60.2±10.3	0.0±3.1 23±8.7	333.2±28.7 xx	0.0±15.2 29.4±20.4	0.0±4.8 45.9±13.2	3.4±24.2 115.2±96.2
θ:4-8Hz	0.0±7.6 30±4.2	358±34.6 330±8.3	341±26.0 xx	0.0±2.1 28.6±2.3	0.0±1.0 337±20.1	300.2±34.2 88.4±120.4	359.1±21.3 61.1±14.9	359.1±3.8 23.2±15.1	0.0±54.2 xx
α:8-12Hz	359.1±3.8 63.2±28.3	10.3±16.1 32.4±14.2	44.5±38.3 xx	355.1±54.1 100.6±28.8	14.1±26.2 110.2±21.3	n/a xx	0.0±15.8 19.2±12.7	0.0±8.7 30.0±2.3	353.1±31.9 xx
β:12-30Hz	358.3±10.7 119±9.6	1.1±0.02 91±11.4	150.2±35.1 xx	0.0±2.3 136.1±4.9	0.0±10.2 90±14.2	n/a xx	0.0±12.9 178.2±28.5	0.0±11.2 90.1±12.8	0.0±32.3 xx
γ:30-150Hz	5.2±9.1 48.2±12.1	0.0±3.1 270.0±10.8	n/a xx	0.0±15.3 140.7±13.6	359.2±18.3 243.4±13.3	n/a xx	0.0±11.1 243.1±8.4	13.2±10.6 220.2±60.1	n/a xx

NOTE: xx denotes complete desynchrony where the angle distribution was all over the [0,360] interval in all channels; **n/a** denotes that a meaningful mean could not be computed due to variability between pairs of channels.

IV. DISCUSSION

The thalamocortical relay circuits are important to study, because of their selective vulnerability to ischemic insults and their proposed important role in maintenance of consciousness and arousal after coma. Past studies point to a significant role for thalamocortical pathways in the generation of spike-wave electrical discharges during non-convulsive absence seizures. In a focal ischemic rat model, dissociation between VPL unit activity and cortical EPs has been reported [13]. Evidence is reported that cortical focal ischemic zones lead to deterioration in ipsilateral thalamus. The thalamo-cortical neurons famously exhibit spindle rhythms (7-14Hz) during anesthesia or deep sleep. All these results hint at a collapse of thalamocortical synchrony under ischemia.

Mathematically, it should be noted that while locally the thalamic and cortical rhythms in our studies resulted in a phase lag synchronization after cardiac arrest, there was a near-complete loss of synchrony between the two regions. This suggests a significant change in spectral profile in the thalamic and/or the cortical oscillations. Furthermore, it should be noted that the temporal information is lost when we analyzed the distribution of relative Hilbert phases. It might be interesting to look at the individual relative phases and investigate their dynamics in order to understand the time-dependency of the synchrony between the two regions.

V. CONCLUSION

Our preliminary results reported here suggest that the thalamocortical synchronization plays an important role in maintaining the healthy, conscious brain and a global injury to the system, such as hypoxic ischemia, can lead to breakdown of this synchrony. Further validation through more extensive and large number of simultaneous intra-cortical recordings of spike activity from neurons in thalamus and cortex will be needed to confirm this research and better understand the mechanisms.

Our ongoing pre-clinical studies with therapeutic approaches for hypoxic-ischemia in rat models, and associated thalamo-cortical changes could lead to improved understanding of mechanisms related with coma and arousal.

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