Cardiac-Brain Interactions in Macaques: Uncovering the Role of the Pulvinar and Other Thalamic Nuclei in Heart Evoked Potentials

Shamim Sasani Ghamsari[1,2,3], Kristin Kaduk[1], Liubov N. Vasileva[1], Lukas Schneider[1,2], Mathias Bähr[2,3], Igor Kagan*[1], Melanie Wilke*[1,2]

(1) German Primate Center — Leibniz Institute for Primate Research, Göttingen, Germany, (2) Dept. Cognitive Neurology, Heart & Brain Center, University Medical Center Göttingen, Germany, (3) Clinic of Neurology, University Medical Center Göttingen, Germany

DPZ

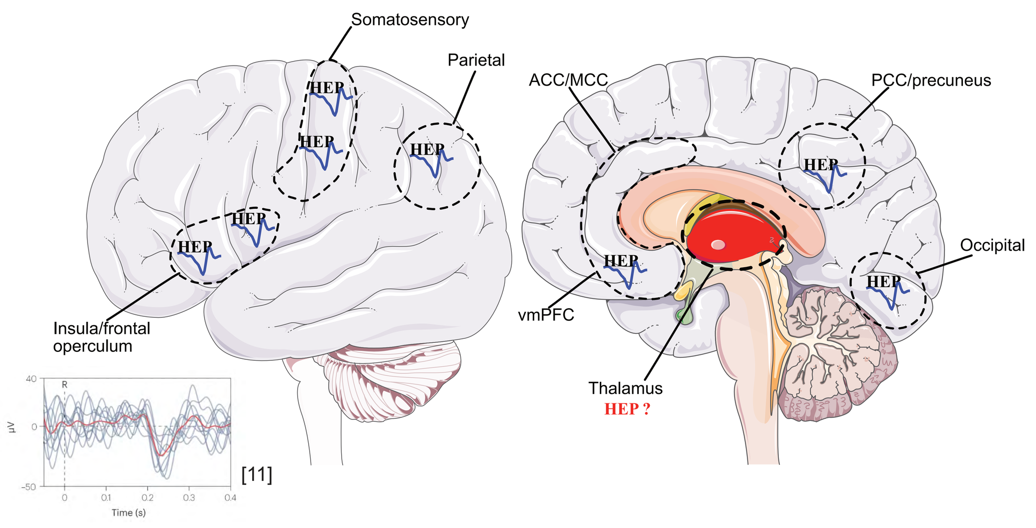
INTRODUCTION

Recent studies show that (i)EEG-based heart-evoked-potentials (HEPs) are useful for investigating heart-and-brain interactions, linking cardiac activity to cognitive, perceptual and emotional processes [1-4]. In humans, HEPs were observed in many cortical and subcortical regions, including somatosensory and frontoparietal cortex, and insula. Heart-related single neuron activity was also found in the motor thalamus [5]. Other thalamic nuclei, including higher-order medial **dorsal pulvinar (dPul)** and the medial dorsal thalamus (MD), likely also play a key role in heart-brain interactions due to their anatomical connections to relevant regions in the central autonomous network (CAN) such as amygdala, insula and prefrontal cortex [6-10]. However, due to clinical and methodological constraints in humans, the presence of HEPs in higher-order thalamic nuclei has not been studied.

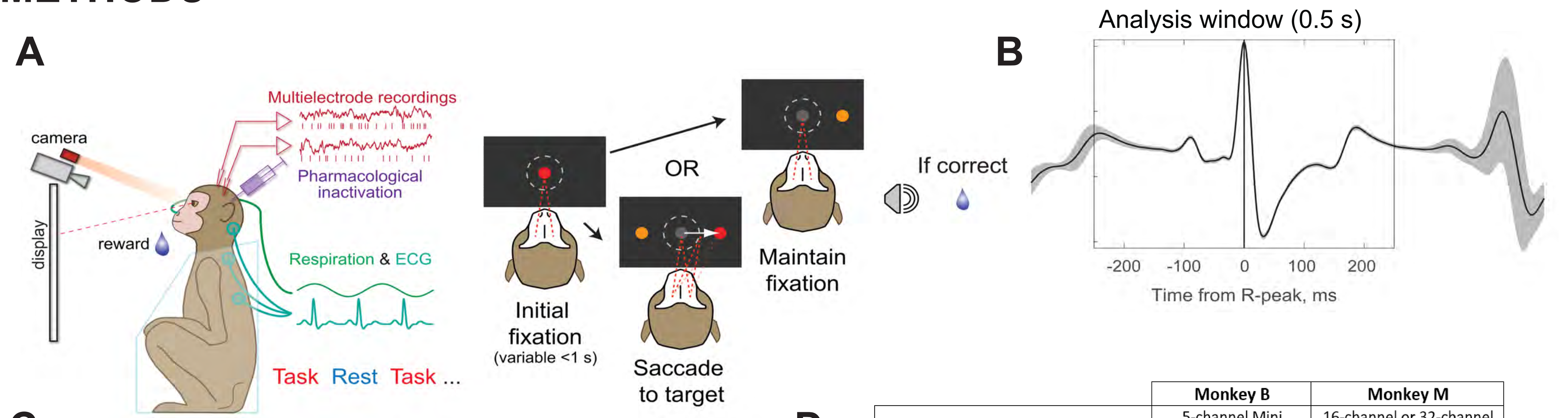
OBJECTIVES

We investigated the relationship between cardiac activity and intracranial local field potentials (LFP) using targeted multielectrode recordings in dPul, MD, and first-order somatosensory nucleus VPL in awake macaque monkeys, during task and rest conditions, to assess:

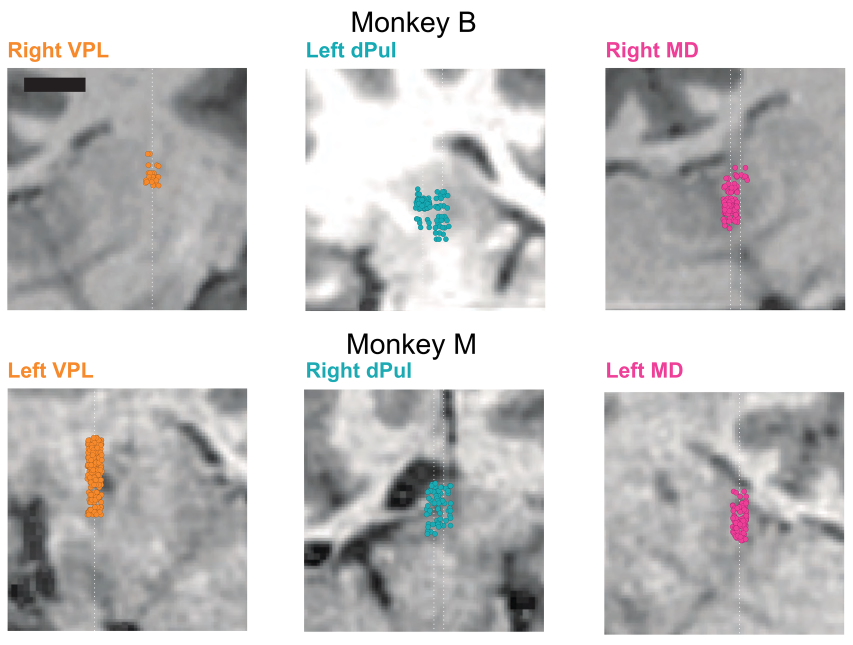
- Prevalence of HEPs
- Temporal dynamics
- Whether phase-resetting is the dominant mechanism
- Dominant frequency bands
- Potential differences between task and rest conditions



METHODS



C



D

	Monkey B	Monkey M
Neurophysiologic Recording Device	5-channel Mini Matrix Microdrive	16-channel or 32-channel V- or S-probes
Total Num. of Recording Sessions	41	29
Num. of Recording Sites in **VPL**	18	187
Num. of Recording Sites in **dPuL**	159	465
Num. of Recording Sites in **MD**	62	185

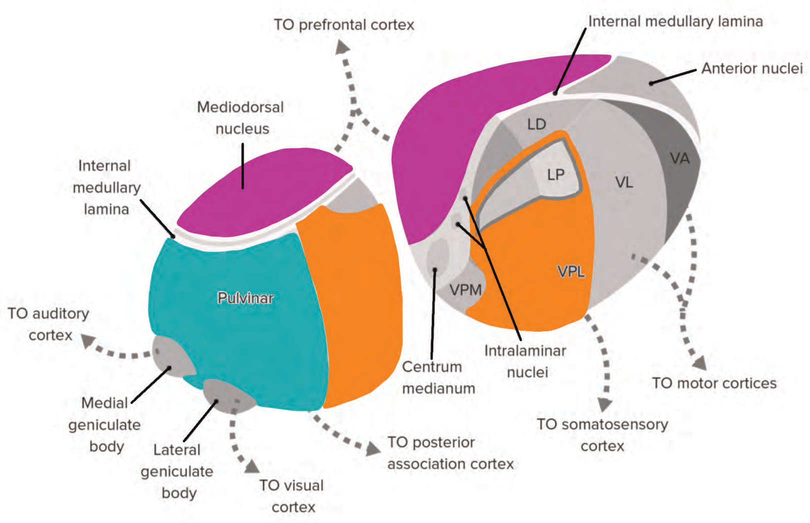
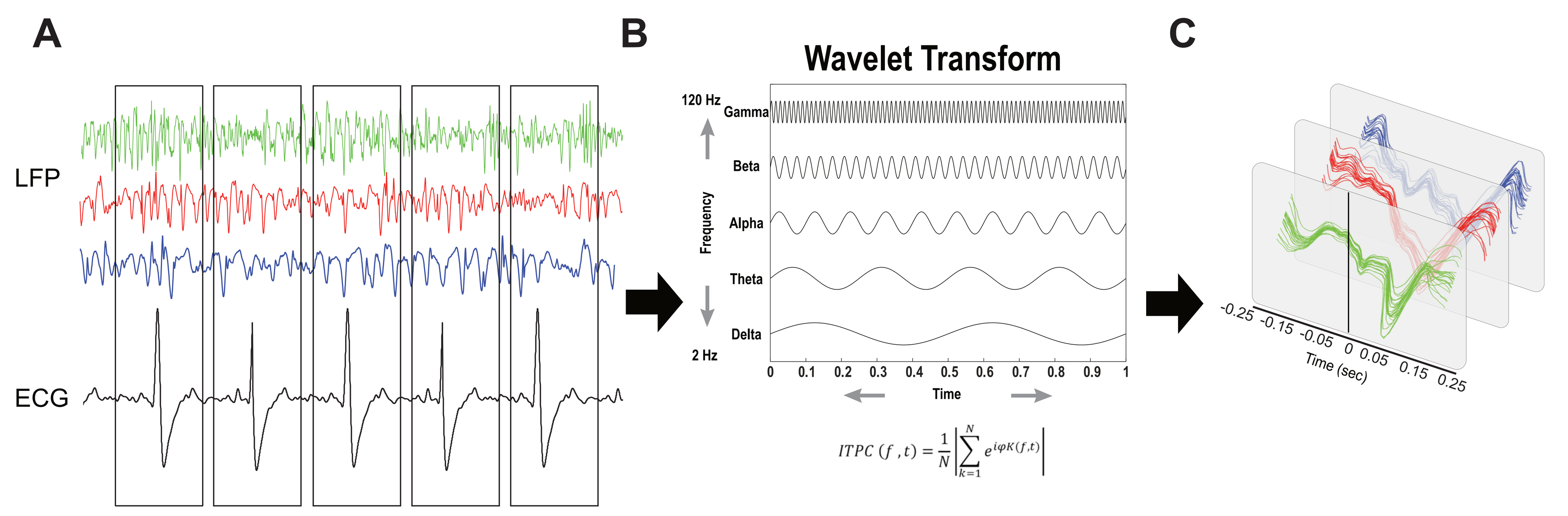


Figure 1. Experimental design and recording targets in the thalamus. **(A)** The monkey was seated in a primate chair in front of a screen. Session consisted of interleaved blocks of a visually guided task (**Task**) and idle period without stimulus (**Rest**). Neurophysiological data were recorded simultaneously with ECG and behavioral data. **(B)** R-peak triggered average ECG in one example session. **(C)** Chamber-normal MRI sections showing recording sites. Black scale bar: 5 mm. **(D)** Summary of recording sites, and schematic of thalamic nuclei and their connections ([modified from [12]).

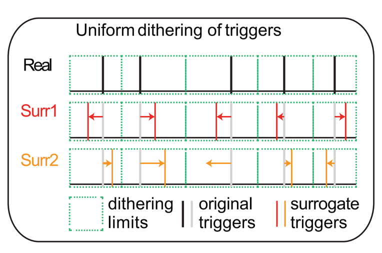
PREPOSSESSING AND ANALYSES



$$ITPC\,(f,t) = \frac{1}{N}\left|\sum_{k=1}^{N} e^{i\varphi K(f,t)}\right|$$

Figure 2. Data processing pipeline. **(A)** The electrophysiological signals were amplified and digitized at 24.4 kHz at 16-bit resolution, and broadband signal was processed offline. To obtain the LFP, we band-passed filtered the data between 1 to 250 Hz. The concurrent ECG recording was digitized at 2034.5 Hz and filtered online with a low-pass 2nd order Butterworth filter with the cutoff at 20 Hz. We used MATLAB for automated R-peak detection. **(B)** The continuous LFP data was convoluted with the complex Morlet wavelet, with frequency range of 2-120 Hz in 60 logarithmic steps. **(C)** The valid R-peaks timestamps were used for epoching the LFP, using complex values from -250 to 250 ms time-locked to the R-peaks. The degree of phase coherency across epochs was calculated using ITPC formula, where N represent the number of epochs, and is taken from Euler's Formula for polar representation of a phase angle K in each frequency f, and time sample t.

SURROGATE CORRECTION EXAMPLE



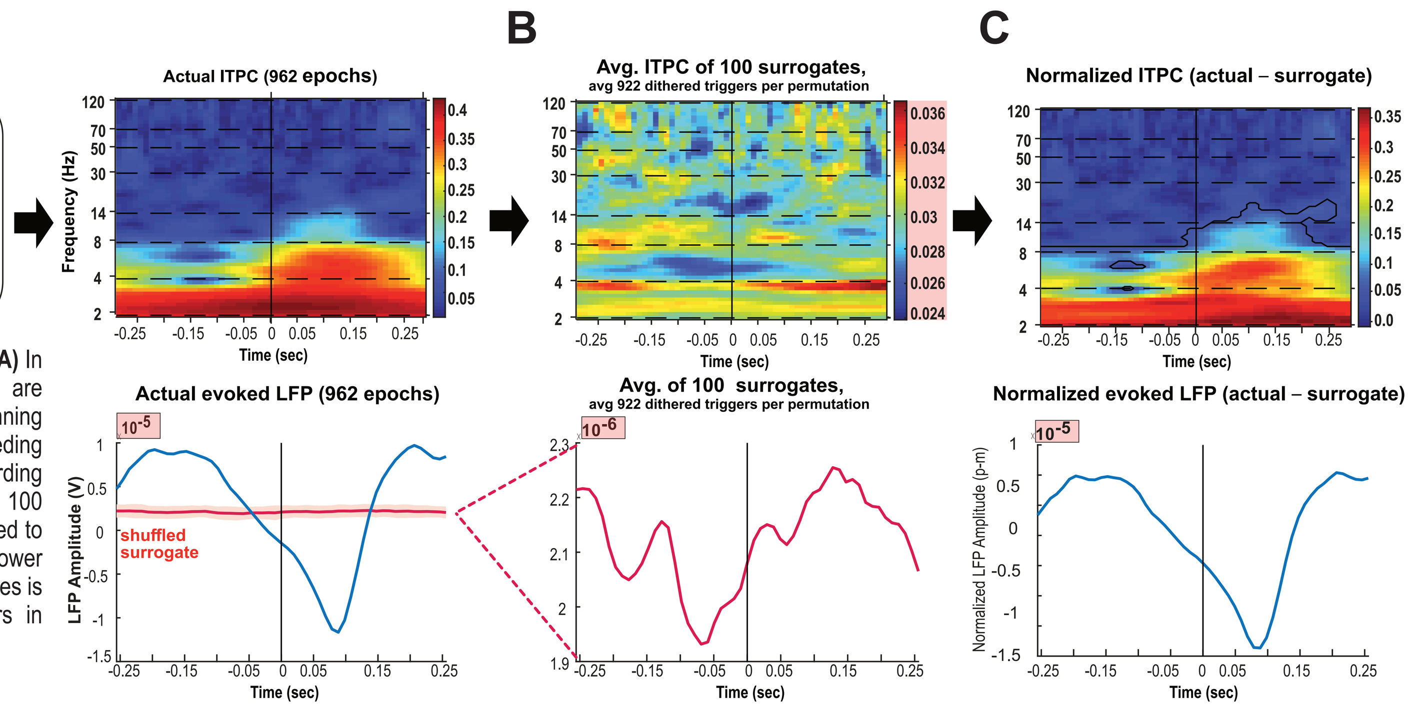
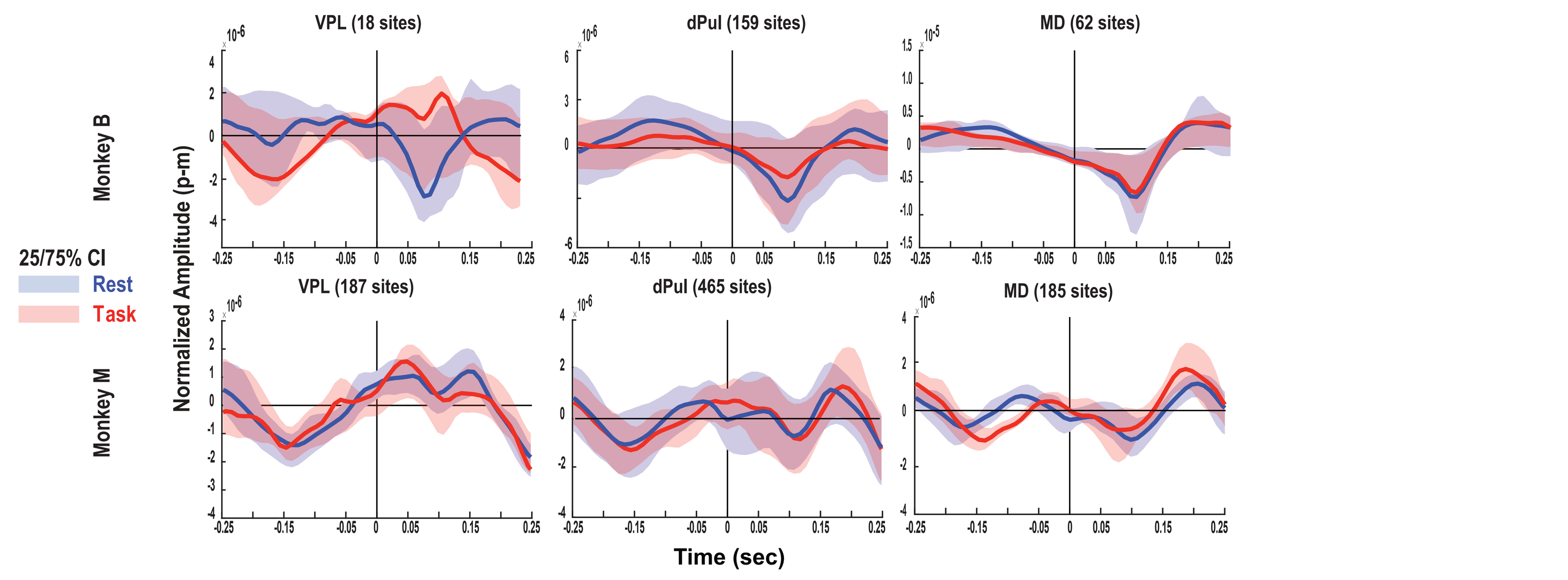


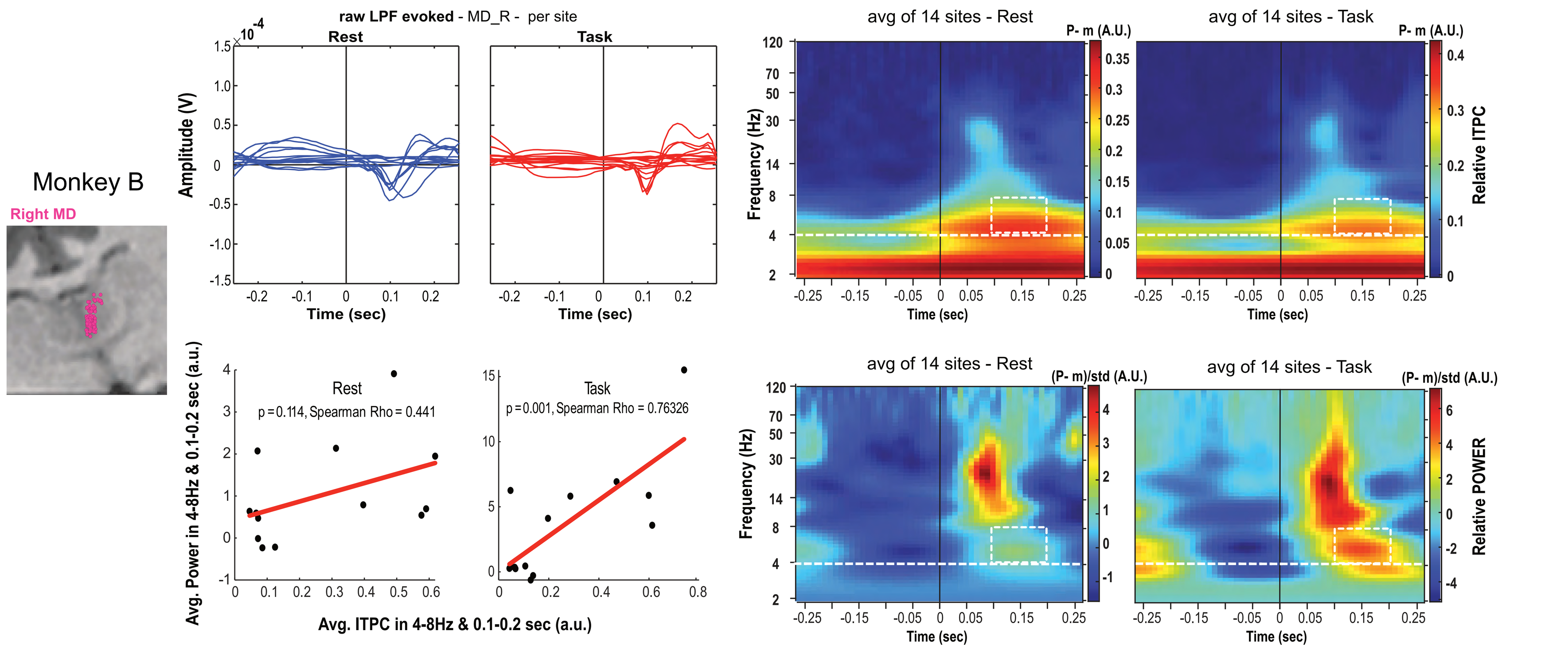
Figure 3. Surrogate correction steps. **(A)** In each iteration the surrogate triggers are dithered uniformly within limits spanning halfway into the interval between preceding and following original triggers per recording block, and this process is repeated 100 times. **(B)** Each surrogate trigger is used to generate evoked LFP, ITPC, and power estimates. **(C)** The mean of all surrogates is used to check for significant clusters in actual data, and for normalization.

RESULTS

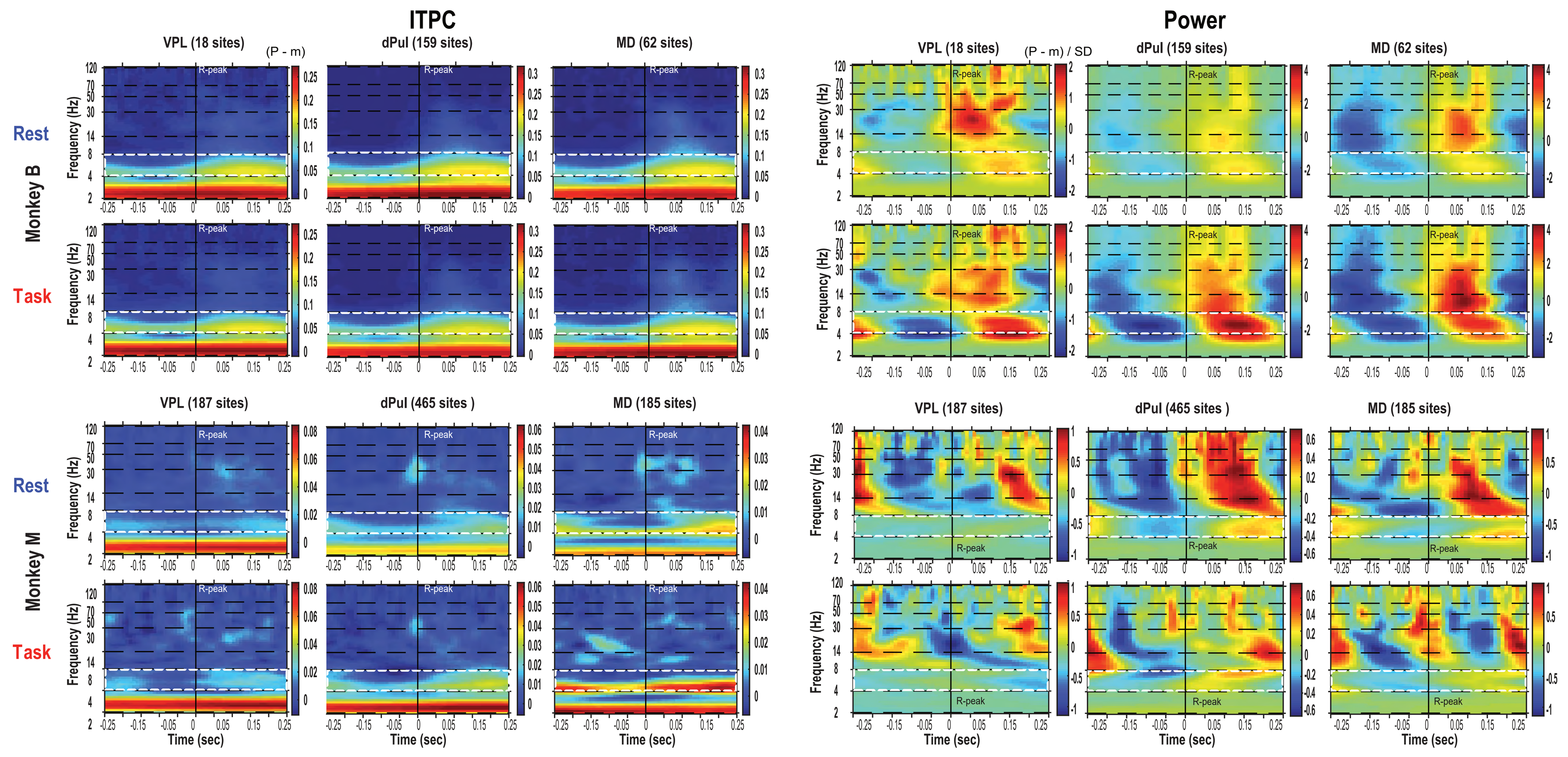
1 VPL, dPul and MD exhibit heartbeat-evoked potentials



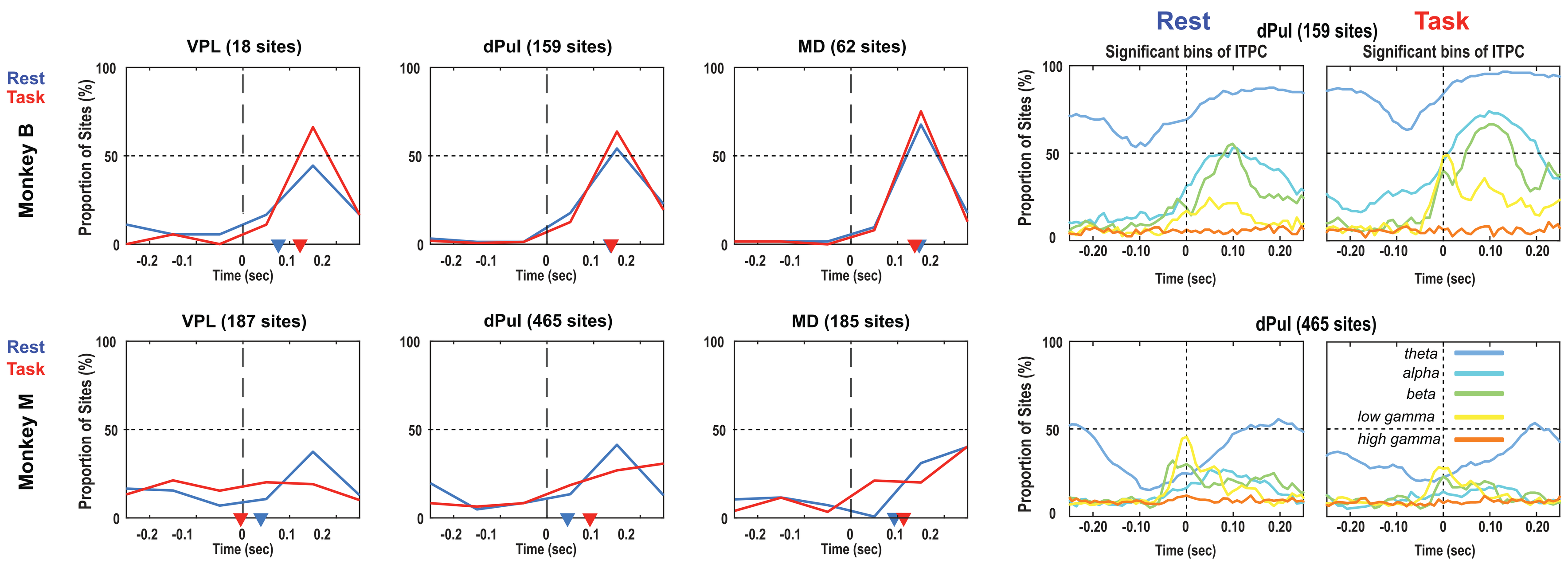
2 Example recording session in MD: HEPs exhibit phase-resetting mechanism



3 The increase of ITPC after R-peak in theta band (4-8 Hz) is consistent across nuclei



4 The time of maximum ITPC in theta band is similar across sites and nuclei



SUMMARY

We show that:

1. HEPs are indeed present in dPul and MD, similarly to the expected presence in VPL.
2. ITPC significantly increased after the R-peak in all three nuclei, similarly to human iEEG data in insula and other CAN regions [13] - but with a faster timecourse corresponding to the faster heart rate in macaques.
3. The strongest ITPC enhancement occurred in a time window of 100–250 ms after the R-peak.
4. The dominant frequency band was theta (4 to 8 Hz), but effects in other frequencies were also present.
5. The data shows some evidence of phase-resetting mechanism behind HEP generation in thalamic nuclei, indicating that heartbeats synchronize ongoing brain oscillations rather then generating "additional" activity.

FUTURE DIRECTIONS

1. HEP differences in Task vs. Rest
2. Investigating the effect of common average re-referencing in HEPs
3. Investigating the effect of cardiac phase in task-related events such as cue and saccade responses

[1] B. Couto et al. 2015 AUTONOMIC NEUROSCIENCE. [2] Salamone et al. 2021 JOURNAL OF NEUROSCIENCE. [3] Schulz et al. 2015 FRONTIERS IN PSYCHOLOGY. [4] Al et al. 2021 NEUROIMAGE. [5] de Falco et al. 2024 PNAS. [6] Critchley et al. 2005 JOURNAL OF COMPARATIVE NEUROLOGY. [7] Phelps & LeDoux 2005 NEURON. [8] Rafal et al. 2015 JOURNAL OF NEUROPHYSIOLOGY. [9] Horie & Yokota 1990 BRAIN RESEARCH. [10] Arend et al. 2015 NEUROPSYCHOLOGY. [5] Engelen et al. 2023 NATURE NEUROSCIENCE .[12] https://www.lecturio.com/ [13] Park et al. 2018 CEREBRAL CORTEX .

shamim.sasani@med.uni-goettingen.de

http://dpz.eu/dag

RTG 2824
Heart & Brain diseases:
integrative research across organs

DFG Deutsche Forschungsgemeinschaft

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN

Member of Leibniz Association