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Principles of Neuroengineering Technical Report:

Motivation and System for the Recording of Peripherally Organized Electrographic Patterns

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Summary -- Here we present the motivation, hardware design, and signal acquisition and processing for the recording of peripherally organized electrographic patterns. Patterns from the periphery, specifically the enteric nervous system (ENS), can be afferent to the central nervous system and provide insight into our emotional experience and health. Despite being ignored by the vast majority of the literature, we can still look to the few published works to inspire the future of ENS recording. Barriers to ENS recording have been largely technical, with authors openly acknowledging the proper tools are lacking. Thus, we designed multipurpose biopotential recording hardware with a focus on ENS recording. Finally, we provide an overview of signal acquisition processes (skin preparation and electrode placement, recording procedure, and baseline establishment), and signal processing mechanisms (filtering, feature extraction, artifact reduction and rejection).

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1. Introduction

Background and Motivation

The enteric nervous system (ENS) is often called the "Second Brain" as it is the largest and most complex part of the peripheral nervous system. For centuries, people have spoken about gut feelings; however, recent research into how the ENS interacts with the brain is turning an age-old adage into a physiological phenomenon with scientific backing. Despite this, relative to other fields of research in neuroscience the ENS is criminally underrated (Figure 1). As we mentioned in our presentation, the gut-brain connection is largely ignored as are the tools used for studying the enteric nervous system.

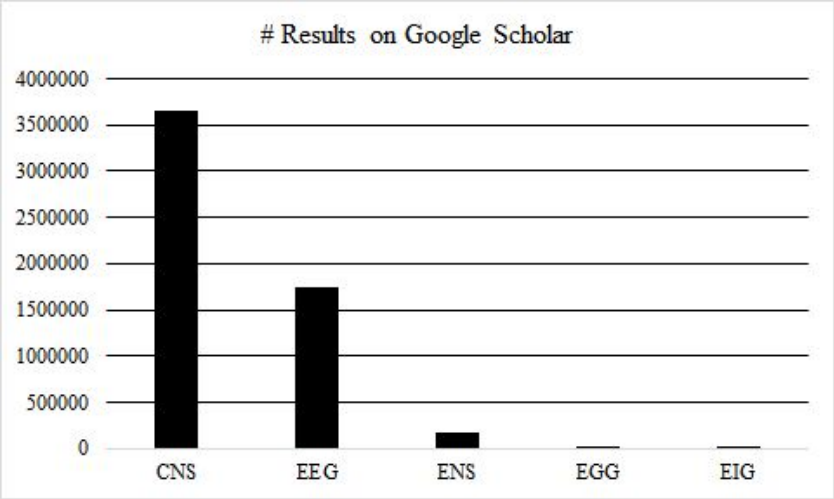

Figure 1. Dearth of Prior Literature in the Field

Anatomical Outline and Definitions

We learn in elementary school that when we get hungry, the brain tells our stomachs to rumble. However, what is less obvious is how the periphery communicates back to the central nervous system, and the effects that can have on feelings. The intestines can serve as an example of how neural information is relayed efferently and afferently in the gut-brain connection. At a local level, we have the enteric nervous system which modulates basic neural and myogenic reflexes through inhibition and activation (Koch, Morris, 2004). At a higher level, the prevertebral ganglia innervates the intestines and coordinates contractions and expansions of the tract. At an even higher rank, the vagus nerve descends from the medulla oblongata into the spinal cord where it connects distally to the prevertebral ganglia. However, the enteric nervous system has afferent communication back to the brain, essentially closing a homeostatic loop of neurophysiological information (Venkova, 2002).

In the case of afferent connectivity, is known that spinothalamic lamina I neurons form a crucial path for interoceptive communication to the central nervous system from the periphery (Craig, Andrew, 2011). These afferent fibers broadcast the state of all internal organs to the thalamus, through the brain stem. From there, these signals are often directed to the posterior insula, the a neural hub for sensorimotor information. The original papers that hypothesized the importance of this pathway focused on itch, heat sensation, and pain; however, more recent work has identified this circuit to be equally important in conveying neural signals from the enteric nervous system to the brain.

The insular cortex integrates the body's physiological homeostasis with cognitive information from other parts of the brain. We can conceptualize the insula, which has connections to the amygdala, cingulate, and ventral striatum, as a signal converter at the fulcrum of the gut-brain-emotion connection. Therefore, it makes sense that we should be able to see evidence of the underlying physiological signals from the periphery in the insula and verify those signals by simultaneously recording from the enteric nervous system. And according to the following three papers, we can.

Simultaneous fMRI and Enteric Nervous System Studies

The extent to which visceral afferent signals influence emotional experience has been substantially elucidated in the past two decades. Most notably for our project, several fMRI studies have found correlations between the activation of the anterior insula and certain signals recorded from the enteric nervous system through electrogastrography (EGG) and electrointestinography (EIG).

In one study, thirty-seven adolescent females were tested with a 2D rollercoaster simulation to simulate nausea and queasiness while recording fMRI and EGG. The dorsal anterior insula was strongly correlated with changes in tachygastric signals of the EGG, one of the three major frequency bands measured from EGG (the others are bradygastic and normogastric signals which did not correlate). This paper is actually from a journal about developmental sciences, so their main focus is how older girls have a more developed relationship between interoception and context that heightens the effect of interoceptive information on their emotional experience. What is cool here with regards to EGG, is that changes in activity in the anterior insula of older girls relative to younger girls is accompanied by changes in the tachygastria frequency. Not only is the brain developing, but the whole gut-mind-emotion circuit develops. Additionally, given biofeedback in the form of visual realtime EGG the participants were able to use deep breathing techniques to shift their gut motility, causing a change in EGG signals and activation on fMRI. This explicitly shows a relationship between signals from the viscera and emotional regulation (Dawei, 2017).

Two other studies focused on simultaneous fMRI and EGG/EIG recordings within the context of disgust and anxiety. Again, these two studies found correlations between the dorsal anterior insula and the the tachygastria frequency of EGG. The anxiety focused study found a functional connection correlated with EIG between the anterior insula and the dorsal anterior cingulate cortex which has been identified as a potential region of interest for modulating anxiety (Hashimoto, 2015). The study on disgust found that different kinds of disgust reactions yielded both different insula activation and correlated EIG changes (Harrison, 2010).

Hypothesis for Significance of ENS in Paroxysmal EEG

In 1966 a Bulgarian scientist, Ana Varbanova, developed a feline model for testing the effects of mechanostimulation on the enteric nervous system. In classic Soviet fashion, they inserted a balloon into a cat's stomach and inflated it many times to simulate high levels of intestinal stress (all the figures in the paper are indexed in Cyrillic, which is delightful). They recorded EEG data from the vagus nerve, thalamus, reticular formation, and sigmoid gyrus as well as EGG data from the stomach perturbations. Two minutes, four, and eight minutes after mechanostimulation, there were clear bursts in activity throughout these deep brain regions (Varbanova, 1966). Additionally, EIG recordings from another experiment on mechanostimulation of the ENS showed eerily similar signals coming from the large intestine and the afferent fibers of the vagus nerve (patterns of 25-40 impulses per minute). Therefore, while no correlation between EEG and EGG has yet been found in humans, it is likely that certain stress-inducing factors may link the ENS and CNS within the context of paroxysmal attacks.

Fifty years later, a late-career cell biologist who studied under Varbanova published a hypothesis arguing that a cause of epileptic susceptibility may be stress-induced abnormally high force contraction of the stomach, basing their idea off of cat model data in mechanostimulation experiments. In fact, gut

symptoms (cramping, nausea, cyclical vomiting) are common in epileptic patients either chronically or right before an attack (Nikiforova, 2014). Researchers have previously shown that patients who are conscious of the precursors of an epileptic attack and undergo routines to reduce stress are less likely to have epileptic attacks (Nagai, 2011). The author also suggests that this may be verified in humans by monitoring ENS signals, EEG, and monitoring patients' mitochondria for signs of stress.

However, any sort of investigation into simultaneous recording of EGG/EIG and EEG is limited by the current available hardware which is 1) too expensive and 2) not designed for recording from the ENS.

2. Hardware Design

Design Rationale

To simultaneously record and monitor brain activity and abdominal activity, multi-channel biopotential measurement equipment capable of measuring up to one microvolt level is required. In the market, currently several electroencephalography (EEG) devices are capable of the measurement, but most of them with more than 64-channel simultaneous measurement capabilities are not accessible due to their expensive cost. Table 1 shows the estimated costs of commercial, research-grade EEG devices (IMotions, 2017).

Cost-Range(USD)	Products
1000 - 25000 USD	Wearable Sensing (ch7-24) / Neuroelectrics (ch8-32) / G.tec nautilus (ch8-64) / Cognionics (ch20-30) / BioSemi (ch16) / Brain Products LiveAmp (ch32) / mBrainTrain SMARTING(ch24)
20000+ USD	BioSemi (ch32-256) / ANT Neuro -eego mylab(ch32-256) / Brain Product GmBH (ch32-128)

Table 1. Estimated cost of commercial, research-grade EEG devices

We hypothesize that at least 128-channel simultaneous measurement is required for the experiment in order to get statistically meaningful data. The costs of commercial products for this product exceeded 25000 USD, and it is not affordable without proper funding. On top of that, the bandwidths of interests of brain activity and abdominal activity are not equal. Most of commercial EEG devices are engineered to record specific bandwidth only suitable for EEG. Thus, for preliminary study, it is decided to build custom biopotential measurement system with reasonable.

Design requirements

Several requirements has been decided to maximize the utility of this device. Table 2 shows the specific requirements of devices.

Requirement	
# Channels	> 64 Channels
Size	$< 200 \times 200\ mm^2$
Safety	Isolated by ground line
Sampling rate	> 250Hz
Noise Level	< 1uV
Portability	Fully portable, Wireless operation
Cost	< 2000 USD
Power Consumption	< 1W

Table 2. Device Requirements

Proposed hardware must meet all of the requirements and needs to be manufactured and tested.

New hardware specifications

Based on the requirement shown above, the new hardware equipment for multi-channel biopotential measurement is designed. Figure 1 shows the basic hardware architecture of the equipment.

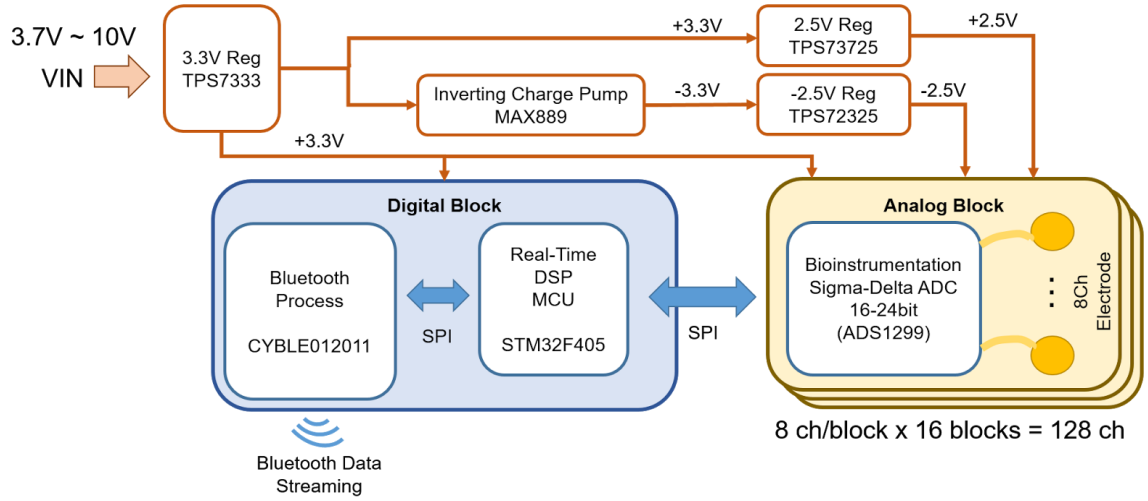

Figure 2. HW architecture of the equipment.

Sixteen of twenty-four bit sigma-delta analog-to-digital converters (ADC) are for biopotential measurement, TI ADS1299[1], are utilized to measure biopotential signals with theoretical resolution of 0.25uV. One of the ADC is able to measure 8-channel signals, and the device is capable of measuring 128-channel at the same time by utilizing sixteen of the ADCs. This ADCs are synchronized and controlled by real-time digital signal processing microcontroller, STM32F405[2]. The micro controller streams the data wirelessly to the computer through a Bluetooth processor, CYBLE012011[3]. The system

[1] http://www.ti.com/lit/ds/symlink/ads1299.pdf
[2] www.st.com/content/ccc/resource/technical/document/datasheet/98/9f/89/73/01/b1/48/98/DM00035129.pdf/files/DM00035129.pdf/jcr:content/translations/en.DM00035129.pdf
[3] http://www.cypress.com/file/212456/download

is designed based on the assumption to utilize 1-cell Lithium-Polymer battery with nominal voltage of 3.7V for wireless capability and safety, but the device can be powered by up to 10V power supply source. Figure 2 and Figure 3 show the rendering and inside structure of designed hardware. The size of the equipment is 150mm x 90mm which is capable of being utilized as a portable battery-powered device. Specifications and details are shown in the table 3.

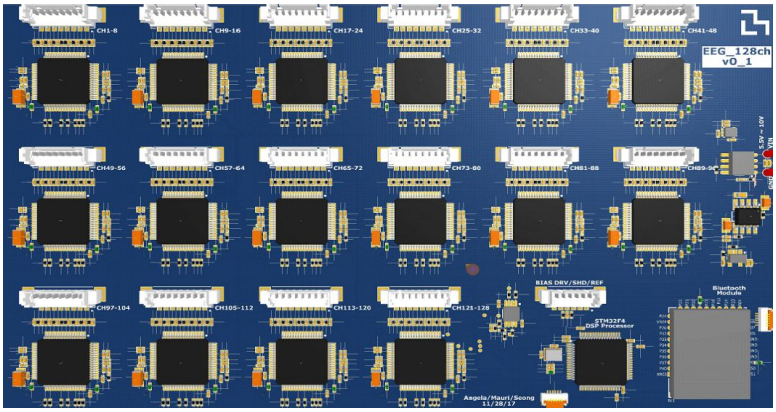

Figure 3. Rendering of designed hardware.

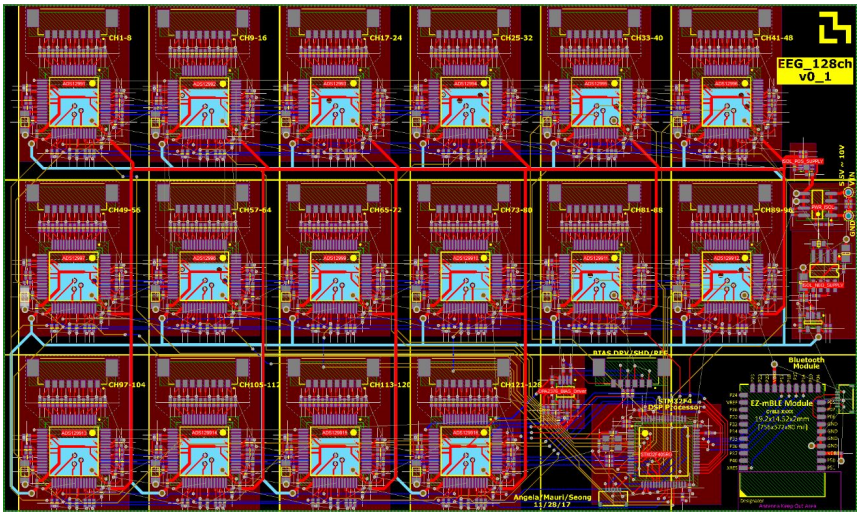

Figure 4. Rendering of designed hardware. To visualize, the ground plane and the power plane of the coppers are not shown.

Specifications	
# Channels	128 channels
Size	150 $\times$ 90 mm^2
Sampling rate	500 Hz
Noise Level	~ 1 uV (in theory)
Portability	Fully portable with battery, Bluetooth data streaming
Power consumption	< 1W

Table 3. Device specifications meeting all requirements

The device is capable of measuring 128-channel biopotentials simultaneously with sampling rate of 500Hz. The device's noise level is lower than 1uV in theory, which is similar noise level to medical grade measurement device. Overall, the designed device meet all the technical requirements to execute the experiment and test the hypothesis.

The total cost of the device is 1100 USD. Cost breakdown of the device is shown in the table 4.

Components	Unit cost (USD)	Quantity	Cost (USD)
TI ADS1299 ADC	56.43	16	902.88
STM32F405 MCU	10.58	1	10.58
CYBLE-012011 BT Processor	11.97	1	11.97
Miscellaneous			159.86
Board Manufacturing	14.00	1	14.00
Total (USD)			**1099.29**

Table 4. Cost Analysis of the hardware

Table 4 shows that the device meets the cost requirements which is less than 2000 USD. In summary, we design 128-Channel precision biopotential measurement devices with significantly lower cost than commercial products while maintaining comparable functionality of the system. Still, the system is required to be manufactured and tested.

Experiment setup with newly designed hardware

The newly designed device streamlines the experimental procedures. Since the device is designed for general purpose biopotential measurement devices, it is capable of recording signals with wide bandwidths of interests. Therefore, the device is capable of measuring both brain activity and abdominal activity. By utilizing the two devices, each device for brain activity or abdominal activity monitoring, these devices are easily be synchronized and interfaced with computer through separate Bluetooth dongle. With this setup, biopotentials of brain and abdomen are simultaneously recorded and processed in real-time on the computer. Figure 5 shows the block diagram of the experimental setup.

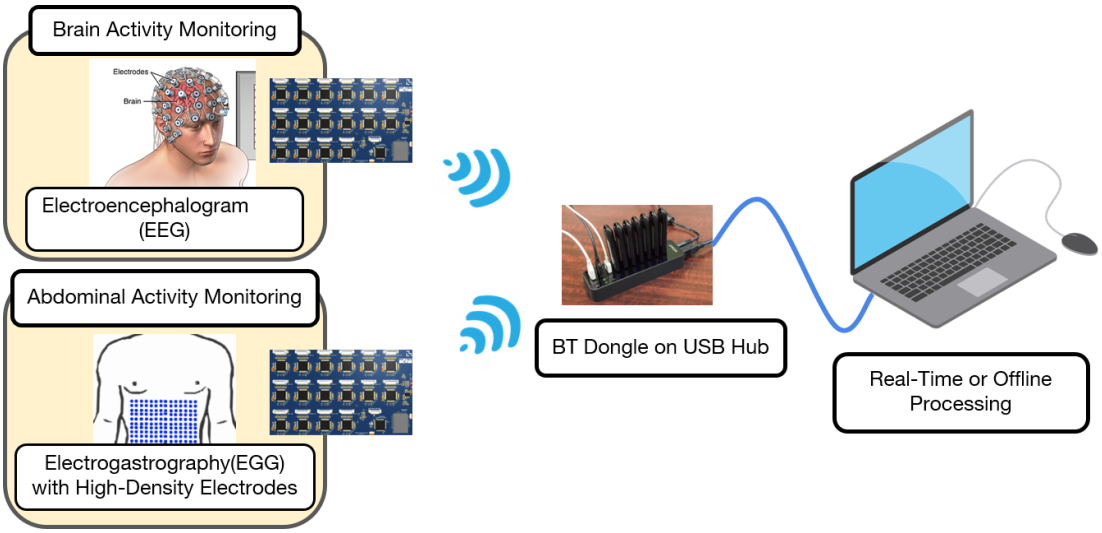

Figure 5. Experimental setup with newly designed hardware.

3. Signal Acquisition and Processing

Signal Acquisition for Gastric Myoelectric Activity

Cutaneous gastric recordings require special preparation, with similarities to that of EEG. We must prep skin adequately and place electrodes appropriately, paying special attention to ground and reference, for good electrogastrogram (EGG) and electrointestinogram (EIG) signal. Yin et al. (Yin et al., 2013) outlined procedures for recording medical EGG that we are able to adapt here for our purposes.

First we must abrade skin with exfoliating gel [Nu-Prep, Weaver & Co, Source: PatientSleepSupplies[4]] and apply electrode gel [Signagel, Parker, Souce: MFI Medical[5]] that sits for 1 minute to allow penetration. After 1 minute the excess gel is wiped clean with gamma sterilized 70% Isopropyl alcohol prep swabs [CareTouch, CareTouch, Source: Amazon[6]].

Next we place pre-gelled disposable silver/silver-chloride (Ag/Ag-Cl) electrodes [F-301 ECG Electrode, SkinTact, Source: Global Medical Solutions] in the required positions. We are adapting Hashimoto's work (Hashimoto et al., 2013) by using the umbilicus as a reference point with percentage distances and extending it using a high-density fixed electrode matrix. Similar to a EEG cap, the matrix of electrodes will have evenly spaced rows and columns 10% superior, 5% left, 5% right, 10% right-5% inferior, 10% right-5% superior, 10% left-5%inferior, and 10% left-5% superior to umbilicus.

The ground and reference electrodes will hang on wires separately from the fixed matrix to ensure proper placement. The ground electrode must be placed on a rib (a bone), not an intercostal muscle. The reference electrode must sit directly below the xiphoid process.

Gastroenterologists recommend at least four minutes (Koch and Stern, 2003) to establish a baseline for EGG and EIG signal.

Signal Preprocessing

We will obtain a baseline for EGG and EIG signal using the aforementioned 4-minute resting baseline. For the EGG signal, we will apply two 4th order Butterworth filters, first, low-pass, 0.25Hz and second, high-pass, 0.016Hz, and a fast Fourier transform (FFT) with a Hanning window and 75% overlap (Koch and Stern, 2003). We are going to analyze spectral estimates from 4 significant bands of EGG signal: normal (0.0416 - 0.0583 Hz), slower than normal (0.0083 - 0.0416 Hz), faster than normal (0.0625 - 0.183 Hz), and total power from the full range of signals (0.0083 - 0.183 Hz). We will extract features using the aforementioned fast Fourier transform (FFT). Figures 6 through 7 outline this process.

[4] http://www.patientsleepsupplies.com/NuPrep-TM-4-oz.-Tube-Box-of-3.html
[5] https://mfimedical.com/products/parker-signagel-electrode-gel
[6] https://www.amazon.com/Care-Touch-Sterile-Alcohol-Medium/dp/B01MDMA1ZB

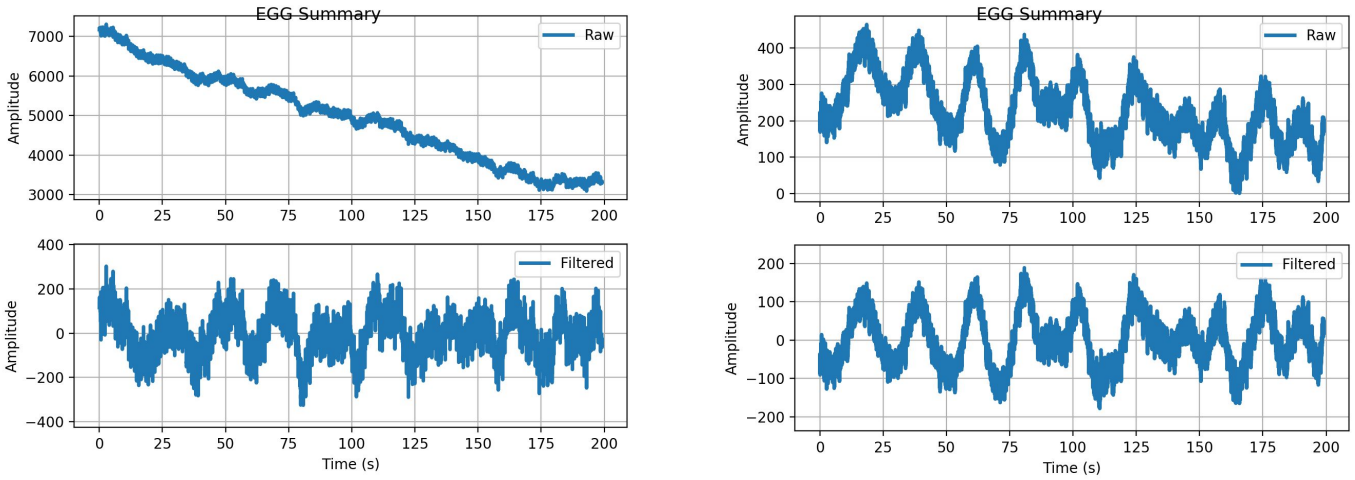

Figure 6. EGG recorded from one channel 5% superior to umbilicus, 251. Hz sampling rate. The left figure shows raw EMG (top), then EMG with 4th order Butterworth filter (bottom). The right figure shows signal minus heart and respiration artifacts.

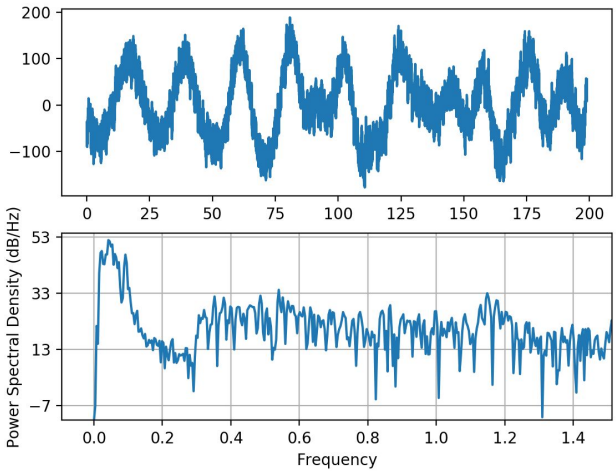

Figure 7. Fast Fourier transform applied to same sample as Figure 6., with Hanning window, 75% overlap.

We will use a similar process for the EIG signal as for the EGG signal. For the EIG signal, we will apply two 4th order Butterworth filters, first, low-pass, 0.29Hz and second, high-pass, 0.0083Hz, and a fast Fourier transform (FFT) with a Hanning window. We are going to analyze spectral estimates from 4 significant bands of interest: very low frequency (VLF) (0.0083 - 0.05 Hz), low frequency (LF) (0.06 - 0.13 Hz), middle frequency (MF) (0.14 - 0.21Hz) and high-frequency (HF) (0.22 - 0.29 Hz) (Hashimoto et al., 2013). We will extract features using the aforementioned fast Fourier transform (FFT).

Potential EGG and and EIG contamination includes respiratory, motion, cardiac, and possible myoelectric activity artifacts. To reduce artifacts in EGG and EIG, we will apply a method based on empirical mode decomposition (EMD) (Liang et al., 2000). The method decomposes given signal data into a finite number of intrinsic mode functions (IMF) that admit Hilbert transforms providing the

instantaneous frequency of each EGG and EIG signal component. We will automatically reject artifacts with amplitude greater than 500uV (the maximum for EGG signals).

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