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Neural Control of Cardiac Function, Rhythm, and Contraction

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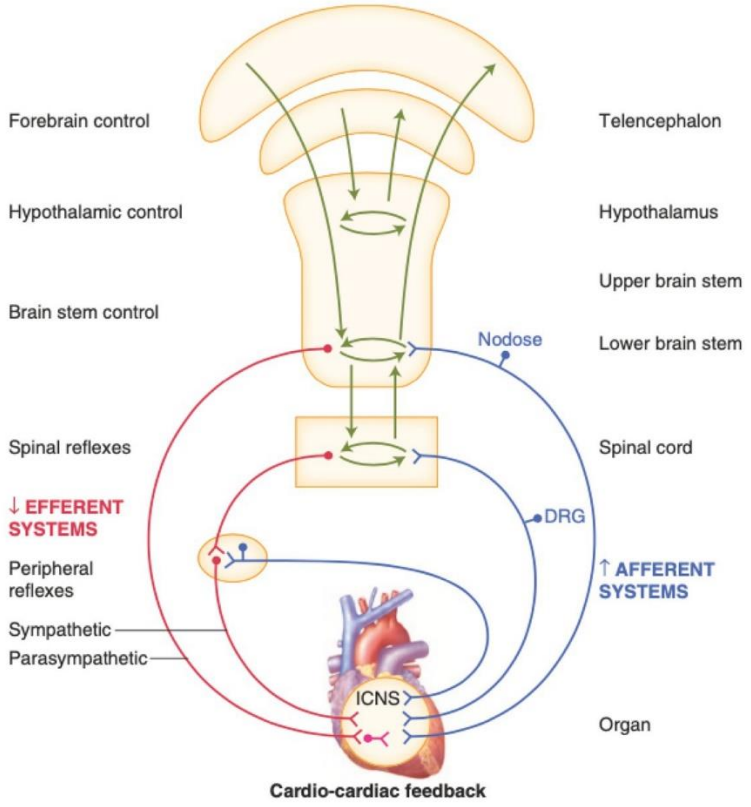

Figure 1. Autonomic Modulation of Cardiac Function [4]

I. ABSTRACT

This literature review discusses how researchers can control cardiac cells with neural networks. The cardiac system is controlled by the autonomic nervous system and coordinates with the respiratory system. Numerous approaches evaluate the efficiency, malfunction, and abnormalities of this connection between brain and heart, through computational analysis [3], with pharmacological influences [2], and with physiological analysis [1]. In Roger A. L. Dampney's paper [1], he discusses how the connection between the nervous system and cardiovascular system is achieved through feedforward and feedback regulation to maintain homeostasis, while Y. Zhong et al. [2] takes a more dynamic approach and manipulates the patients into supine and upright positions while administering the drug,

atropine, which involuntarily blocks the nervous system from working. Lastly, X. Chen et al. derived new PNS and SNS indexes by multisignal analysis of cardiorespiratory variability [3] using transfer functions and a combination of physiological and pharmacological experiments. He selected autonomic nervous system blockers to analyze the beta-sympathetic nervous system and its overlap with the parasympathetic nervous system. He sought to find where these systems overlap in low frequency bands and offer specific measurements of the cardiac autonomic nervous system due to inputs from heart rate. Overall, the purpose of the literature review is to study the techniques that are being used in research to evaluate the relationship between the nervous system and cardiovascular system. The literature review will range from computational analysis to physiological experiments and include the analysis of pharmacological influences on mediating the ANS. In the Introduction, I will explain some of the terminology that is necessary to understand the experiments that follow.

Keywords: cardiac, autonomic nervous system, feedforward, feedback, transfer functions, beta-sympathetic nervous system, computational analysis

II. INTRODUCTION

Let's revisit some of the ideas that I introduced in the above abstract. To begin, the ANS stands for 'Autonomic Nervous System' and can be seen below in Figure 2.

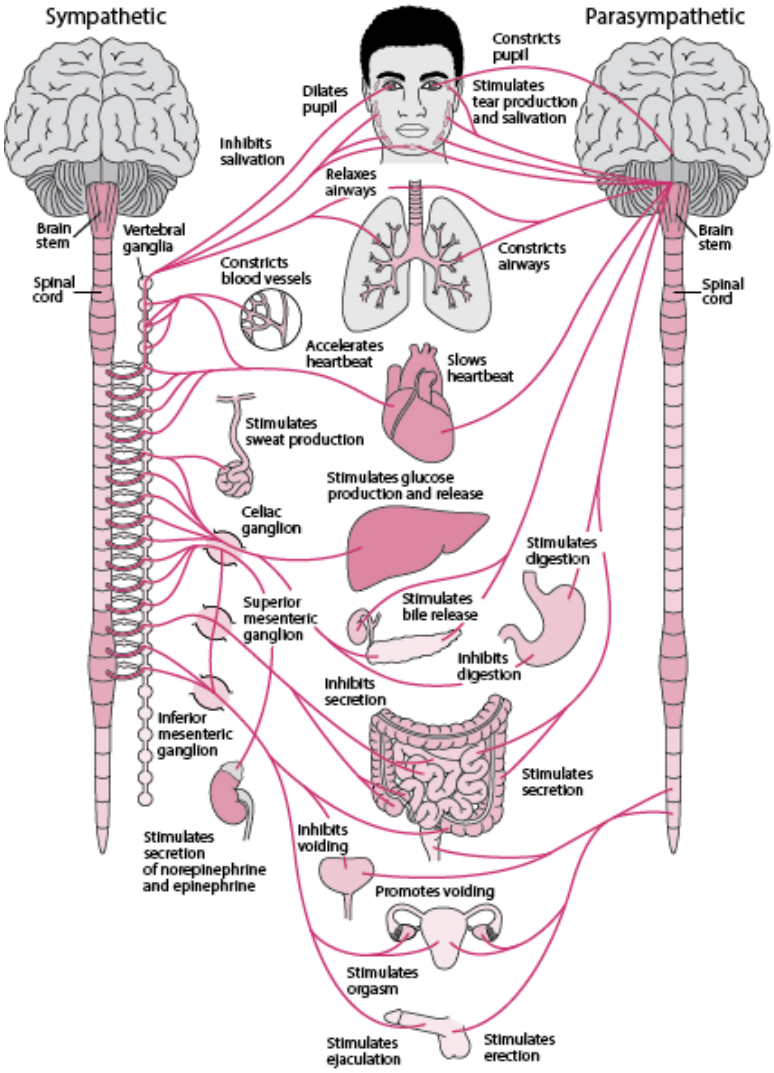

Figure 2. The Autonomic Nervous System [15]

The ANS has two branches named the Sympathetic Nervous System (SNS) and the parasympathetic nervous system (PNS) [2]. As you can see in Figure 2, together these two branches regulate the body [2, 12]. They both act unconsciously; without needing to be prompted, they beat your heart, stimulate digestion, make you sweat, and contract your pupils. Its important to know about the ANS because it's the source of the experiments that we'll be talking about in the next few sections. It is responsible for the results of each experiment and forms the basis for the neural and cardiac connection.

Another important aspect of the neural and cardiac connection is feedforward and feedback control. These two controls are talked about extensively in R. A. L. Dampney's paper [1]. He asserts that the brain regulates the heart through feedforward and feedback control (also known as reflex regulation) [1, 6]. Feedforward and feedback control can be seen in Figure 3.

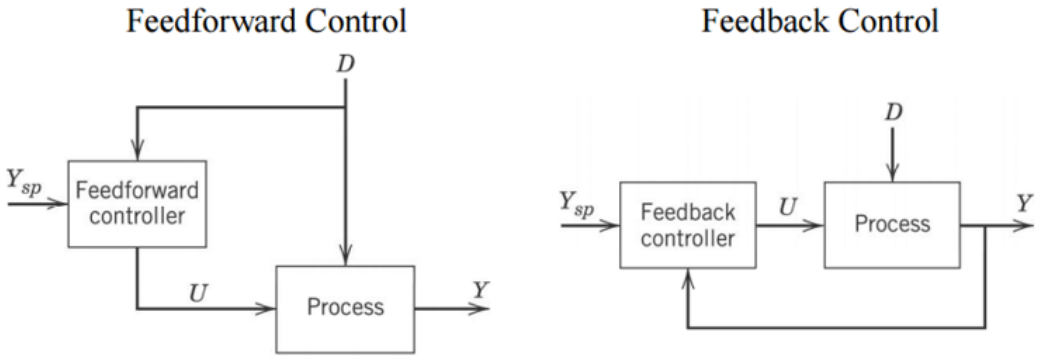

Figure 3. Feedforward Control versus Feedback Control [6]

Feedforward control is depicted as a diagram above on the left. There are a lot of moving parts to the diagram, but essentially it shows that the output, Y, is adjusted based on the knowledge that the system obtains over time [7]. It shows that descending inputs arise from higher centers of the brain [1] and indicates that it does not require inputs from peripheral receptors to function [10]. In essence, any potential disturbance to the system is measured and accounted for before it has time to affect the system. Here's an example of feedforward control:

> Nathalia is about to run a race. She goes to the start line and her heart begins to pound as she waits for the starting gun to sound. She sees the man with the starting gun raise it over his head. Nathalia leans over with her legs one behind the other and her muscles tense as the gun sounds with a cartoonish "POP!"

In the above example we see that Nathalia's posture changes as she waits for the gun to sound. Her muscles anticipate the activity and preadapt for the coming run. When her heart starts beating faster, the vascular system—which is comprised of her blood vessels—starts to increase the flow in anticipation of increased need for oxygenated blood.

The foil to feed*forward* control is feed*back* control. Feedback control can be seen in Figure 3 on the right. It shows that the output is adjusted based on *errors*, whereas, recall that feedforward regulation is adjusted based on *knowledge*. Some of the major feedback systems in the body are known as baroreceptors and chemoreceptors [8]. Their job is to keep the body at a normal level, depending on what's going on at the moment. Lets look at an example.

> Nathalia finishes the race in first place! Her blood pressure is high when she stops, but as she starts to cool down it returns to normal. She's tired and decides to go home and take a nap with Sawyer, her fluffy cat. As she's sleeping her blood pressure goes lower and she dreams about her victorious race.

Nathalia's blood pressure (aka BP) is regulated by her baroreceptors. As she runs, cools down, and sleeps her baroreceptors provide feedback to her body that tells it to raise her BP or lower it. Chemoreceptors act in a similar way to maintain the oxygen in arterial blood. They assess the amount of activity you're doing to keep you well-oxygenated [1].

There can be positive and negative feedback in the body, so this means that an error will result in an output that will increase (positive feedback) or decrease (negative feedback) the subsequent output [8]. An example of negative feedback is arterial baroreflexes which controls arterial blood pressure (or ABP) from moment to moment [9]. The baroreceptor reflex uses buffers to make small changes to your ABP depending on your posture, exercise, or emotions. Negative feedback also controls your dynamic heart rate so that it knows when to slow down or speed up in response to something. Positive feedback is a continuous relationship between spontaneous arterial pressure (AP) changes. And its heart period fluctuations are neurally-modulated through feedforward controls [9].

Although feedforward and feedback controls have different jobs, they both can be measured and monitored in the brain and heart using electroencephalogram (EEG) and electrocardiogram (EKG/ECG), respectively.

III. STUDYING THE CONNECTIONS BETWEEN BRAIN AND HEART

The following sections provide summaries of four studies. They use different techniques to evaluate the connection between the heart and brain, which will be dissected below.

i. Using the Principal Dynamic Mode (PDM)

In the experiment, 28 people (13 men and 15 women) all around 30-years old had electrodes attached to their chests for an ECG, which monitored the electrical activity in their hearts. The researchers instructed the people to breathe according to random interval breathing tones.

Zhong et al. split two groups of 28 people using the above procedure, but there's a catch. The two groups had different things happening to them. Lets divide the groups into A and B. Group A was lying down on their backs and were injected with a parasympathetic nervous system blocker (aka atropine). The PNS blocker means that the following things happened:

energy was *not* conserved, the heart rate did *not* slow down, intestinal and gland activity was *not* increased, and the sphincter muscles in the gastrointestinal tract were *not* relaxed.

Group A was subject to these conditions in the hope that their sympathetic-to-parasympathetic ratio (SPR) would be increased. This simply means that the body would start using the sympathetic nervous system to regulate itself when the parasympathetic nervous system was disabled. Which it did! The SPR increased.

In the other group, Group B, the people were instructed to stand in upright positions and were injected with a sympathetic nervous system blocker (aka propranolol). As you can imagine, the opposite thing happened in Group B that happened in Group A. The SPR decreased since the sympathetic nervous system was inhibited.

The researchers used the principal dynamic mode (PDM) to quantify ANS activities. PDM is defined as the ratio between low-frequency (LF) and high-frequency (HF) spectral power of heart rate. Spectral power simply means the concentration as a function of wavelength [16]. The PDM separated the sympathetic and parasympathetic nervous activities on the basis of ECG signals. And eventually the PDM was converted using a fast Fourier transform (FFT) from a time-based signal to a frequency-based signal. So it went from spectral power of the heart rate over time to the fast Fourier transform over frequency (in Hertz). Overall the study wanted to determine the balance in the ANS between the sympathetic and parasympathetic nervous systems.

The peoples' PDMs were recorded as they were in various states of standing and sitting. Then the scientists depicted the results with several graphs. These were the first set of graphs:

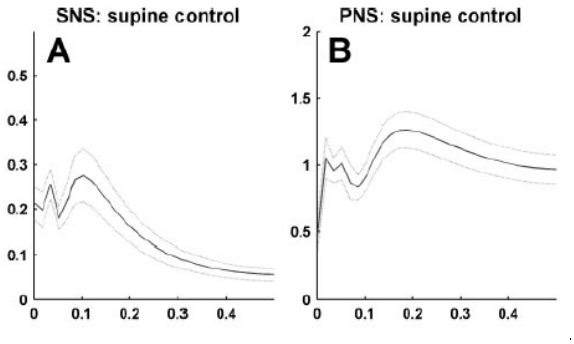

Figure 4. People laying down

The people in this set were lying down and didn't have any blockers injected in them. They served as a baseline for the other people *with* blockers. The sympathetic nervous system (SNS) in graph A dipped in FTT magnitude over time as it got higher in frequency and the parasympathetic nervous system (PNS) did the same on graph B but on a higher magnitude and with a slower decline.

The next set of people also didn't have any blockers injected, but they were standing rather than sitting:

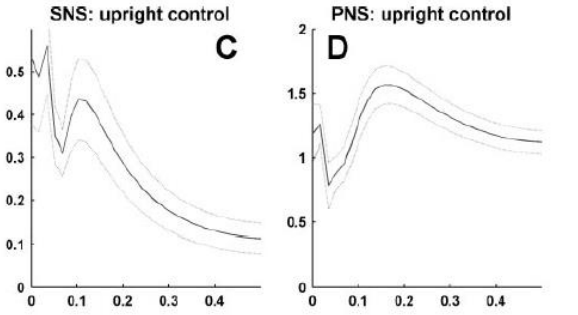

Figure 5. People standing up

In graph C, the SNS in the standing people had the same graphical shape, but functioned at a higher FFT magnitude. And the same happened in graph D for the PNS. It had the same shape, but functioned at a higher FFT magnitude.

The next set of people were lying down and injected with a parasympathetic nervous system blocker (aka atropine):

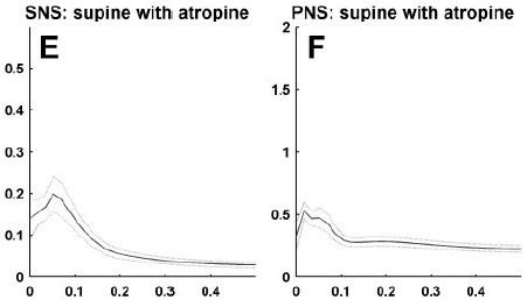

Figure 6. People laying down injected with PNS blocker

The activity in the SNS and PNS had both diminished. The peaks and troughs in the people without blockers weren't present in the people with PNS blockers. So it would seem that a PNS blocker blocks the SNS and PNS.

The next set of people were standing and injected with a parasympathetic nervous system blocker (aka atropine):

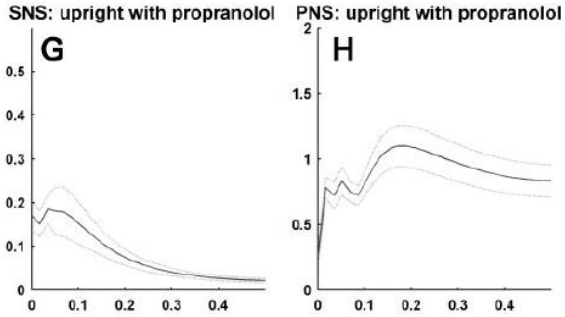

Figure 7. People standing up injected with PNS blocker

The graphs did not show similar drops in SNS and PNS activity. While the SNS dropped considerably in activity, the PNS had the same graphical shape as graph D in Figure 5 and was only slightly diminished in activity. This showed that the PNS blocker had less effects on the standing people as it did on the lying people.

The last set of laying people were given a sympathetic nervous system blocker (aka propranolol):

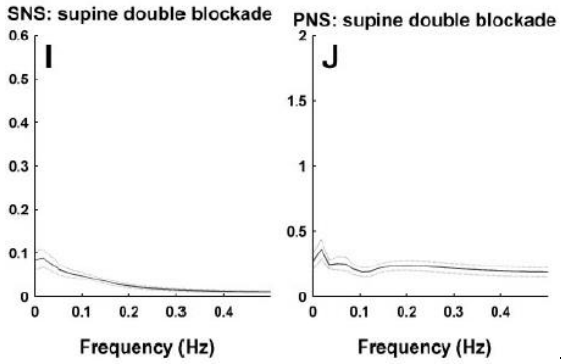

Figure 8. People laying down injected with SNS blocker

The people showed an almost entire diminishment of activity in the SNS and PNS activity. Suggesting that an SNS blocker has serious effects on the entire ANS when lying down.

The last group of standing people were given the SNS blocker:

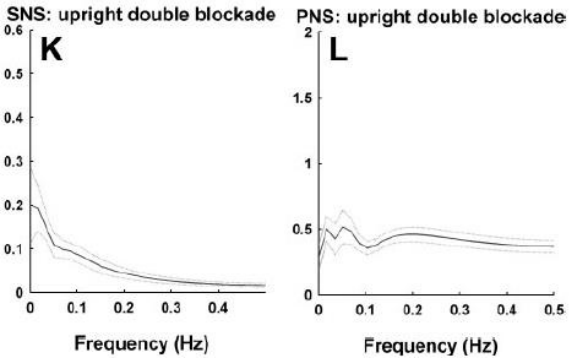

Figure 9. People standing up injected with SNS blocker

Although the SNS and PNS had slightly higher FFT magnitudes than the people laying down, the ANS was diminished considerably.

After several statistical and quantitative analyses, Zhong determined that there is a clear separation of the SNS and PNS. They both have similar frequency characteristics, but still act independently of one another. Zhong concluded that the PDM can determine ANS imbalances noninvasively and quantitatively using ECG and plotting the results graphically. He noted that PDM could be used to monitor ANS problems, which are commonly grouped into a single category known as dysautonomia [14].

ii. Using Multisignal Analysis of Cardiorespiratory Variability

The focus of this study by X. Chen et. al. was to create a new measure of the PNS and SNS that sufficiently separates the two signals into separate entities. Usually, the PNS and SNS are muddied by each other because they have overlapping signals. X. Chen was able to separate the systems by injecting 14 patients with an autonomic nervous system blocker.

To separate the two systems, he evaluated two impulse responses that would be indicative of each system. The first impulse involves independent lung ventilation (ILV), which refers to the ability of your right and left lung to act independently of one another. There is an impulse response that connects the ILV to the heart rate (HR) which indicates the PNS, which was calculated as P_1 and S_1 in this study. The other impulse involves the arterial blood pressure (ABP), which indicates the pressure exerted by circulating blood on the walls of your blood vessels [17]. The impulse connects the ABP to your HR, which was calculated as P_2 and S_2 in this study.

For the experiment, 14 men were asked to sit for a series of tests. There were three tests: they had small nodes attached to their chests for a surface ECG. Additionally, a radial artery catheter was stuck into their arm to observe their ABP. And lastly wo straps were wrapped around their chest and stomach to observe ILV, as the chest and abdomen expanded with air.

All of the men were asked to breathe for 13 minutes while standing and laying down on their backs. Then seven of them were injected with atropine (which we've see before in the first study mentioned in this review) and asked to stand and lay for 13 more minutes. And then they were injected with propranolol (which we've also seen) and asked to stand and lay for another 13 minutes. The remaining seven men were asked to do the same tests, but the drugs were given in reverse order (propranolol and then atropine).

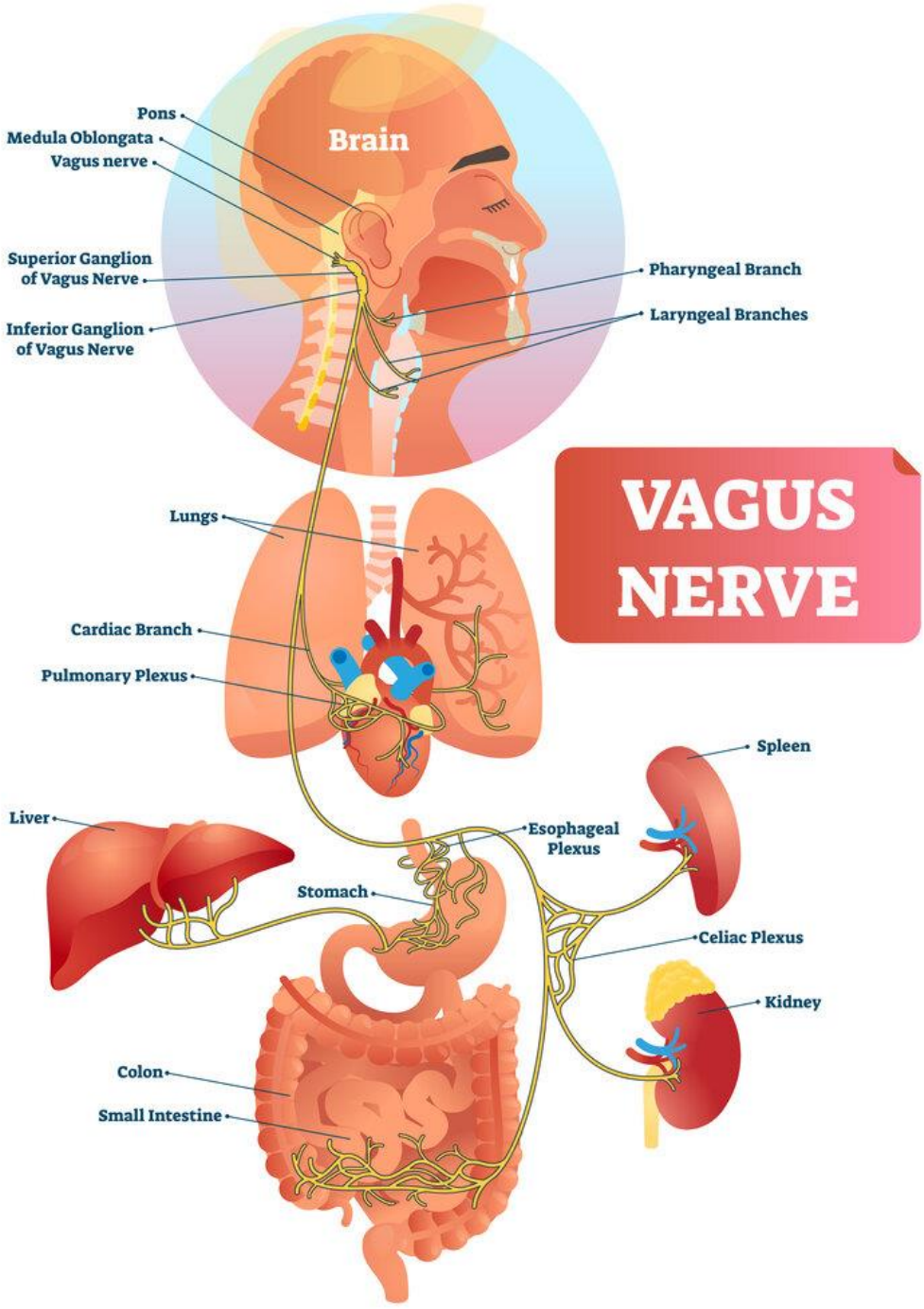

Figure 10. The Vagus Nerve [18]

Recall that atropine blocks the PNS' calming actions on the heart, so the heart rate becomes more excited. Atropine is known as a vagal blockade because it blocks the vagus nerve (seen in figure 10). The vagus nerve controls PNS function to the heart. Also recall that propranolol blocks the excitatory influence of the SNS, so the heart rate calms. Propranolol is also known as a β-sympathetic blockade because it uses beta (β) blockers, which are antagonists that block the influence of adrenaline to excite your body [19].

After collecting data from the men, the researchers distilled their results in two sets of graphs. The first set of graphs shows what happened when the men were standing. The set focused on the ILV to HR impulse response and corresponding P_1 and S_1 values. In Figure 11, below, you can see what happened when the men were standing without any drugs:

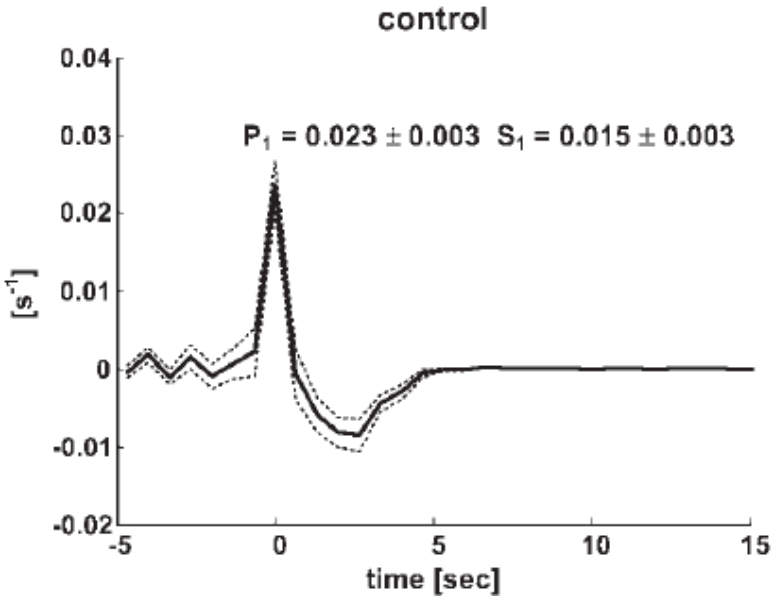

Figure 11. Standing Men without any Drugs

The ILV to HR impulse response over time showed a distinct peak and indicates normal function without any influence from drugs. The P_1 and S_1 are indicative of normal values. The next graph shows what happened when the men were injected with atropine only:

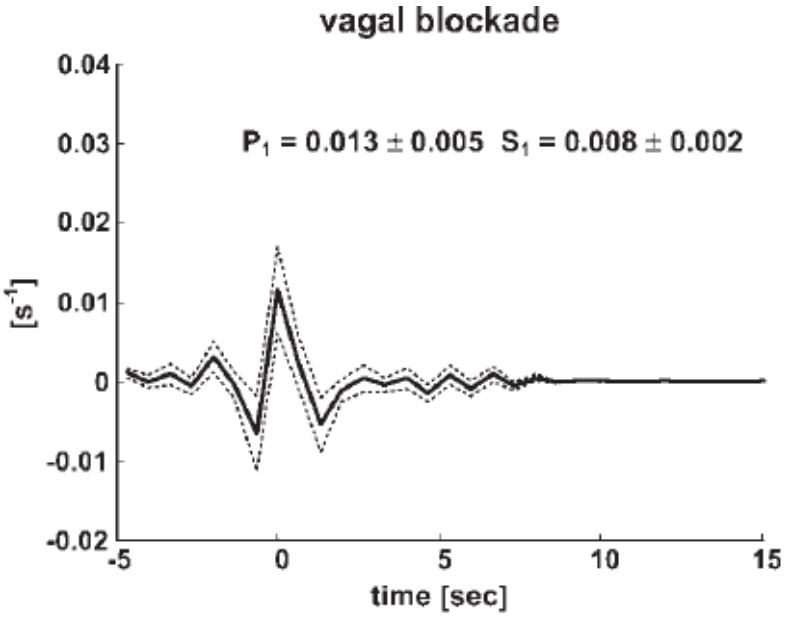

Figure 12. Standing Men injected with atropine

Figure 12 indicates that the P_1 and S_1 values dropped and the largest peak was less distinct. However, when the men were injected with just propranolol (Figure 13, below), the P_1 and S_1 dropped even lower, but the peak was more distinct:

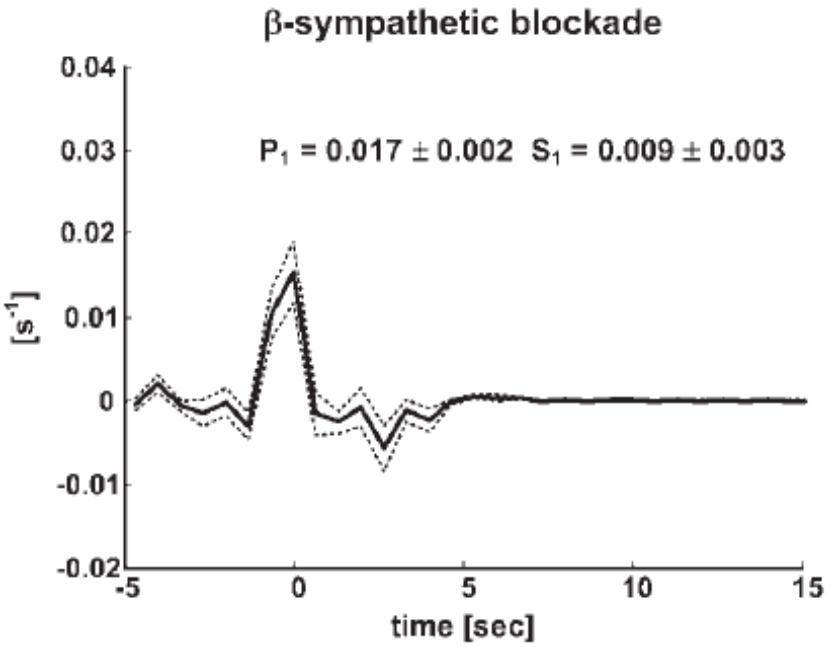

Figure 13. Standing Men injected with propranolol

The last graph shows the men under the influence of atropine and propranolol, forming a double blockade on the cardiac autonomic nervous system (CANS).

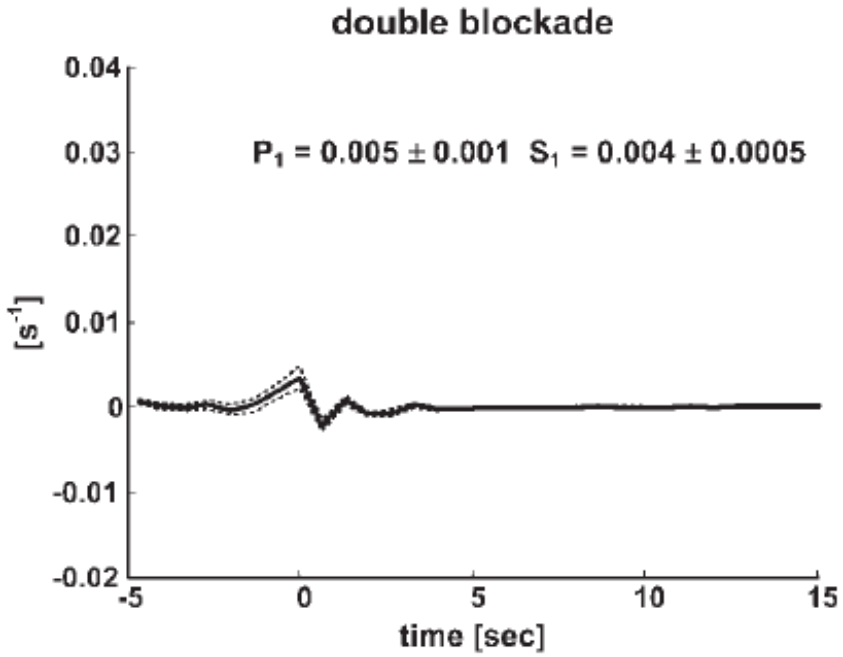

Figure 14. Standing Men injected with atropine and propranolol

The P_1 and S_1 values were the lowest when injected with both drugs and showed the least distinct peak.

In the next set of graphs, the men were standing. The set focused on the ABP to HR impulse response and corresponding P_2 and S_2 values. The first graph showed men standing without any drug injected into them:

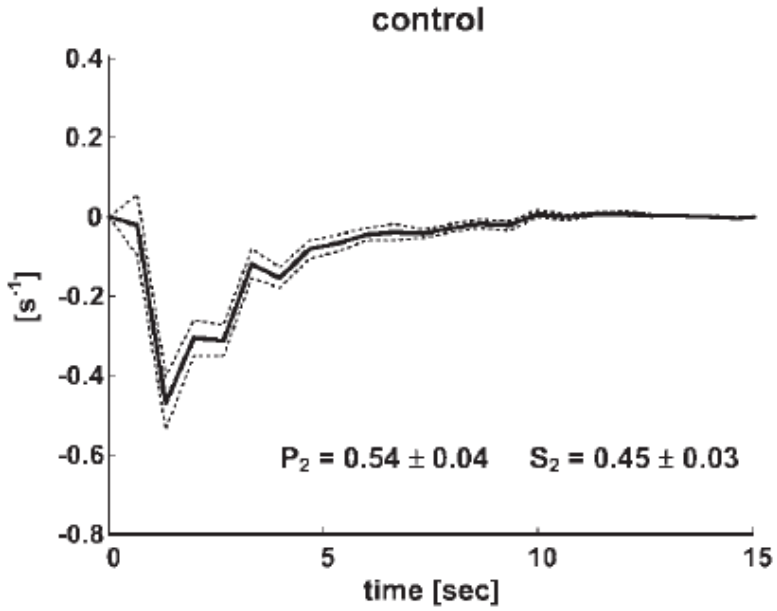

Figure 15. Standing Men without any Drugs

There weren't any peaks, however there was a distinct trough in the graph. The P_2 and S_2 in this graph indicated a normal value for the ABP to HR impulse. In the following graph, the men were administered with atropine:

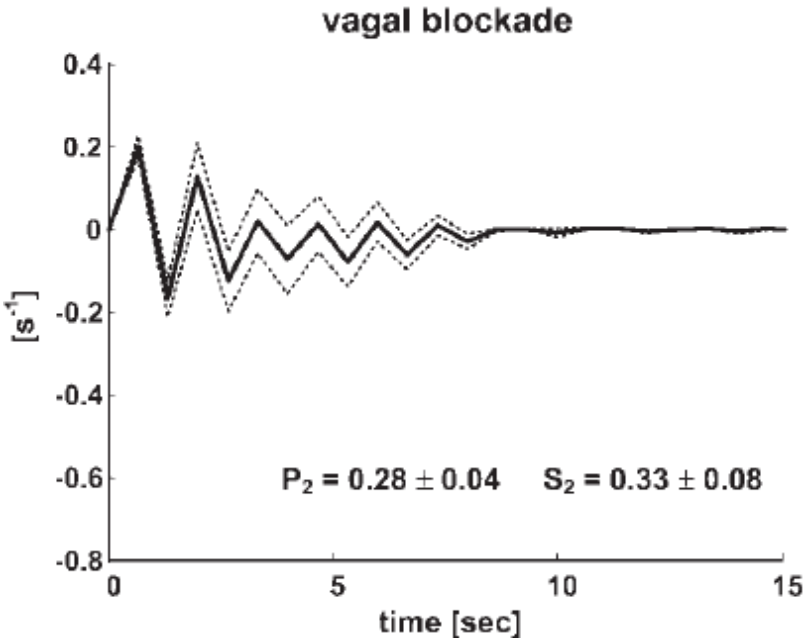

Figure 16. Standing Men injected with atropine

In Figure 15, the ABP to HR impulse seemed to approach some normal value over time; jumping jaggedly back and forth between positive and negative until it reached equilibrium. The P_2 and S_2 decreased as compared to the men without any drugs.

The men were then injected with propranolol:

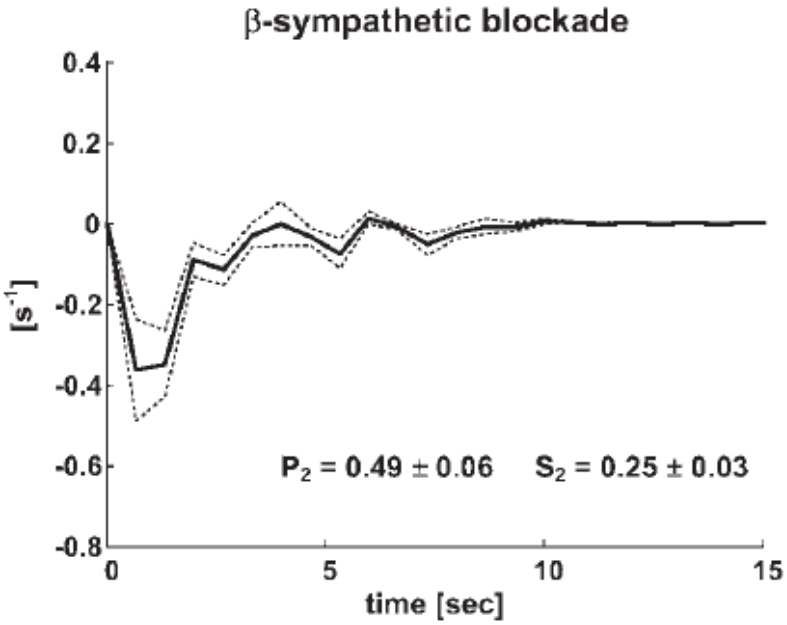

Figure 17. Standing Men injected with propranolol

While the P_2 increased, the S_2 decreased and the impulse seemed to approach some equilibrium over time after dipping significantly. Lastly, the men were observed under the influence of atropine and propranolol:

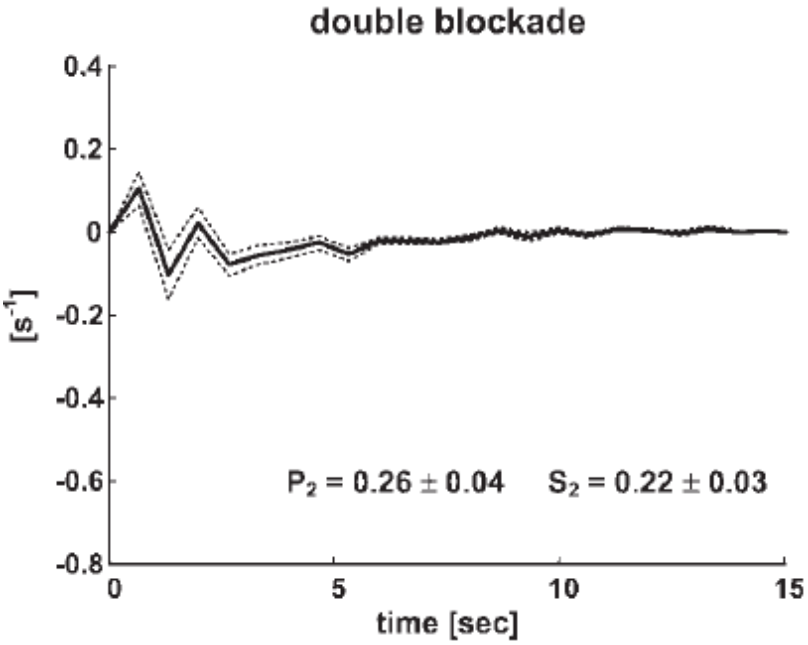

Figure 18. Standing Men injected with atropine and propranolol

The peaks and troughs were weak and approached equilibrium over time and the P_2 and S_2 decreased.

This study showed that the PNS and SNS can be separable with enough signal testing and computational separation. This is important because the P_1, S_1, P_2, and S_2 values could be a new vagal index that people have not seen before.

iii. Through Autonomic Modulation

The last study by J. Hadaya et. al. in the paper "*Autonomic Modulation for Cardiovascular Diseases*" looks at the effects of vagal nerve stimulation (VNS) on the autonomic nervous system. The review found that stimulating the vagus nerve reduced arrhythmogenesis, which is the onset of an irregular heartbeat. However, it should be noted that VNS is required chronically, so its not a one-time method and must be done over a lifetime.

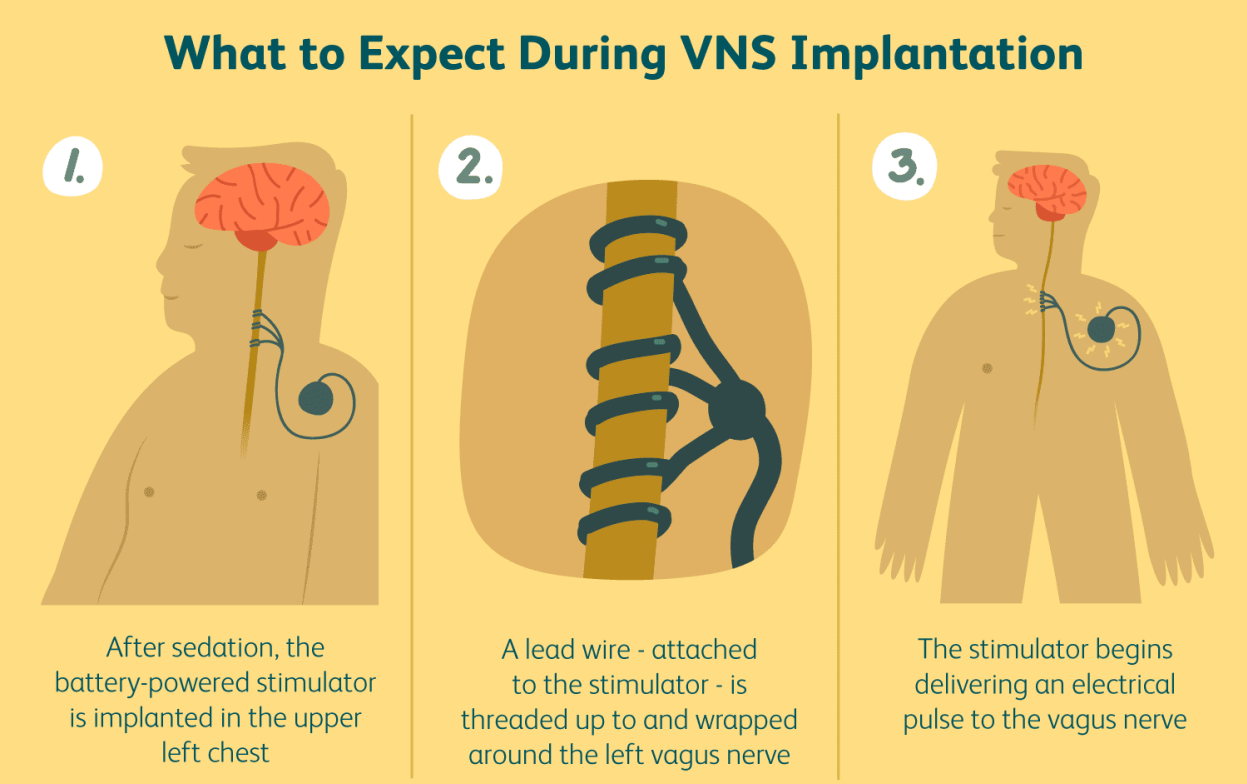

Figure 19. Vagus Nerve Stimulation [20]

The primary method for vagus nerve stimulation is through an implanted generator, as seen in Figure 18. In patients with arrythmia, a device is implanted near the heart and is attached to the vagus nerve via leads. Mild pulses are sent to the brain which mitigate these symptoms along with other diseases, such as seizures.

The use of VNS was shown to mitigate hypertrophy (i.e. the enlargement of the heart) and reduce the necessity of neural remodeling in rat and dog models. Overall, the study suggested that VNS can modulate pathologic responses that result in heart failure. In clinical models, the above-mentioned results are reflected suggesting that this could be a viable treatment for people with heart diseases.

IV. DISCUSSION and CONCLUSION

The three studies discussed in the previous section highlight the new research that tests and evaluates the connection between the brain and the heart. In Zhong's study he created a new mathematical quantity, PDM, for monitoring the PNS and SNS. In X. Chen's study he created P_1, S_1, P_2, and S_2 to quantify the PNS and SNS in the hopes that they were separable. And in J. Hadaya's review he elucidated on VNS and its impact on modulating the ANS to combat diseases such as arrhythmia and hypertrophy.

These are important scientific milestones in the niche of brain-heart interface. They show that the brain does control the cardiac system to a certain degree, not only the autonomic nervous system itself. There are still many parts of this hypothesis that need to be explored which haven't been found yet, such as a cleaner way to separate the

activities of the PNS and SNS. However, much progress has already been made. Researchers, clinicians, and scientists hope that this knowledge will enable medical professionals to mitigate some of the heart diseases through the influence of the brain. By stimulating certain parts of the brain and its connections, doctors hope that they can moderate the problems that affect the heart. The purpose of this review was simply to highlight *some* of these scientific advancements, but there are many more out there to be explored; new tangents that haven't been imagined.

V. REFERENCES

[1] R. A. L. Dampney, "Central neural control of the cardiovascular system: current perspectives," Advances in Physiology Education, vol. 40, no. 3, pp. 283–296, Jul. 2016, doi: 10.1152/advan.00027.2016.

[2] Y. Zhong, K.-M. Jan, K. H. Ju, and K. H. Chon, "Quantifying cardiac sympathetic and parasympathetic nervous activities using principal dynamic modes analysis of heart rate variability," *Am J Physiol Heart Circ Physiol*, vol. 291, no. 3, pp. H1475-1483, Sep. 2006, doi: 10.1152/ajpheart.00005.2006.

[3] X. Chen and R. Mukkamala, "Selective quantification of the cardiac sympathetic and parasympathetic nervous systems by multisignal analysis of cardiorespiratory variability," Am J Physiol Heart Circ Physiol, vol. 294, no. 1, pp. H362-371, Jan. 2008, doi: 10.1152/ajpheart.01061.2007.

[4] J. Hadaya and J. L. Ardell, "Autonomic Modulation for Cardiovascular Disease," Front. Physiol., vol. 11, 2020, doi: 10.3389/fphys.2020.617459.

[5] M. J. Ferreira, A. Zanesco, M. J. Ferreira, and A. Zanesco, "Heart rate variability as important approach for assessment autonomic modulation," *Motriz: Revista de Educação Física*, vol. 22, no. 2, pp. 3–8, Jun. 2016, doi: 10.1590/S1980-65742016000200001.

[6] "Feedforward Vs Feedback Control," *Instrumentation Tools*, Mar. 27, 2016. https://instrumentationtools.com/feedforward-vs-feedback-control/ (accessed Mar. 11, 2021).

[7] "Difference between Feedback and Feed Forward control systems," *GeeksforGeeks*, Jun. 08, 2020. https://www.geeksforgeeks.org/difference-between-feedback-and-feed-forward-control-systems/ (accessed Mar. 11, 2021).

[8] Legramante J. M., Raimondi G., Massaro M., and Iellamo F., "Positive and Negative Feedback Mechanisms in the Neural Regulation of Cardiovascular Function in Healthy and Spinal Cord–Injured Humans," *Circulation*, vol. 103, no. 9, pp. 1250–1255, Mar. 2001, doi: 10.1161/01.CIR.103.9.1250.

[9] E. E. Benarroch, "The arterial baroreflex: Functional organization and involvement in neurologic disease," *Neurology*, vol. 71, no. 21, pp. 1733–1738, Nov. 2008, doi: 10.1212/01.wnl.0000335246.93495.92.

[10] R. K. Pradhan, E. O. Feigl, M. W. Gorman, G. L. Brengelmann, and D. A. Beard, "Open-loop (feed-forward) and feedback control of coronary blood flow during exercise, cardiac pacing, and pressure changes," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 310, no. 11, pp. H1683–H1694, Apr. 2016, doi: 10.1152/ajpheart.00663.2015.

[11] K. Miki, M. Yoshimoto, and M. Tanimizu, "Acute shifts of baroreflex control of renal sympathetic nerve activity induced by treadmill exercise in rats," J Physiol, vol. 548, no. Pt 1, pp. 313–322, Apr. 2003, doi: 10.1113/jphysiol.2002.033050.

[12] S. C. Gandevia et al., "Respiratory sensations, cardiovascular control, kinaesthesia and transcranial stimulation during paralysis in humans.," J Physiol, vol. 470, pp. 85–107, Oct. 1993.

[12] "Autonomic nervous system," Wikipedia. Mar. 01, 2021, Accessed: Mar. 11, 2021. [Online]. Available: https://en.wikipedia.org/w/index.php?title=Autonomic_nervous_system&oldid=1009649174.

[13] M. O. Franz, "Volterra and Wiener series," Scholarpedia, vol. 6, no. 10, p. 11307, Oct. 2011, doi: 10.4249/scholarpedia.11307.

[14] "Dysautonomia: Symptoms, Causes, Types, & How to Live With," Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/6004-dysautonomia (accessed Mar. 11, 2021).

[15] "Overview of the Autonomic Nervous System - Brain, Spinal Cord, and Nerve Disorders," Merck Manuals Consumer Version. https://www.merckmanuals.com/home/brain,-spinal-cord,-and-nerve-disorders/autonomic-nervous-system-disorders/overview-of-the-autonomic-nervous-system (accessed Apr. 03, 2021).

[16] "Spectral power distribution," Wikipedia. Oct. 05, 2019, Accessed: Apr. 04, 2021. [Online]. Available: https://en.wikipedia.org/w/index.php?title=Spectral_power_distribution&oldid=919694673.

[17] "18.5B: Arterial Blood Pressure - Medicine LibreTexts." https://med.libretexts.org/Bookshelves/Anatomy_and_Physiology/Book%3A_Anatomy_and_Physiology_(Boundless)/18%3A_Cardiovascular_System%3A_Blood_Vessels/18.5%3A_Systemic_Blood_Pressure/18.5B%3A_Arterial_Blood_Pressure (accessed Apr. 09, 2021).

[18] "Acupuncture and The Vagus Nerve," Morningside Acupuncture. https://www.morningsideacupuncturenyc.com/blog/acupuncture-and-the-vagus-nerve (accessed Apr. 09, 2021).

[19] "Beta blocker," Wikipedia. Mar. 12, 2021, Accessed: Apr. 09, 2021. [Online]. Available: https://en.wikipedia.org/w/index.php?title=Beta_blocker&oldid=1011736869.

[20] "how is vagus nerve stimulated - Google Search." https://www.google.com/search?q=how+is+vagus+nerve+stimulated&sxsrf=ALeKk03VgCa1vFfU64fQS89ndtpj3THWCw:1618055354938&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjenKH1zfPvAhWWU80KHVRpBLEQ_AUoAXoECAEQAw&biw=1745&bih=815#imgrc=DIrbceqP9OPIlM (accessed Apr. 10, 2021).