

The Effect of Infralow Frequency Neurofeedback on Autonomic Nervous System Function in Adults with Anxiety and Related Diseases

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Abstract

Peripheral body monitoring of autonomic nervous system (ANS) response has been routinely applied during infralow fluctuation (ISF) neurofeedback training. This study hypothesized that ISF training has a distinct physiological effect on an individual that can be revealed by measuring autonomic function with peripheral biofeedback metrics that included heart rate variability (HRV), muscle tension, skin temperature, skin conductance, heart rate, respiration rate, and blood pressure. **Methods.** Thirty adults between the ages of 18 and 55, primarily with anxiety, were randomized into two groups: 20 in the experimental group and 9 in the control group. The experimental group completed 10 ISF neurofeedback training sessions while continuous monitoring of ANS changes was applied. The same process was completed for a control group that received one-channel sensorimotor rhythm (SMR) neurofeedback training. **Results.** Significant changes were seen in the skin conductance ($p < .0001$), electromyography ($p = .01$), very low frequency ($p = .004$), low frequency of HRV ($p = .05$) and blood pressure (systolic change $p = .049$) in the experimental group. No significant changes were seen in the control group. **Conclusion.** The study demonstrated that ISF neurofeedback training impacts the ANS as measured by peripheral biofeedback indicators.

Keywords: neurofeedback; infralow frequency; electroencephalogram; autonomic; blood pressure; electromyogram; skin conductance; breathing; heart rate variability; inter beat interval; autonomic function

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Introduction

The body has a natural and sophisticated mechanism which ensures that there is as much physiological stability as possible while we navigate through life. The control center for this homeostatic mechanism is the autonomic nervous system (ANS) which unconsciously controls and manages heart rate (HR), breathing, blood pressure, and various other functions. It consists of the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) which complement each other and so regulate physiological processes in response to external or

internal stimuli. When there is a stress reaction, the SNS will respond and shift the body from its normal state of equilibrium. Once the stimulus is over, the PNS will shift it back towards its point of equilibrium (Figure 1). If this process becomes less responsive and an individual remains in a state of increased or decreased arousal, it can lead to disease. Control of the ANS has largely been attributed to the midbrain structures and the hypothalamic pituitary adrenal axis. The contribution of behavioral networks in cortex to ANS regulation has only recently been understood (Beissner, Meissner, Bär, & Napadow, 2013; Thayer & Lane, 2000).

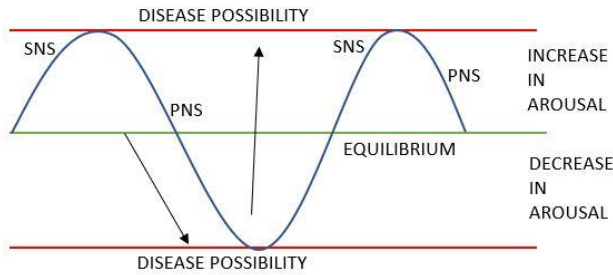


Figure 1. The autonomic nervous system and how it equilibrizes.

There is increasing evidence that mental and physical problems experienced by individuals are the result of flawed functional connectivity within resting state networks (Warren, Chou, & Steklis, 2020). Importantly, the underlying functional architecture of the brain is coordinated by infraslow frequencies. This superstructure of oscillations coordinate both the connections in and decoupling between active behavioral networks (Palva & Palva, 2012). These slow periodicities, described as less than 0.1 Hz, were first linked with behavior by Nina Aladjalova in the 1950s in the Soviet Union. With her crude chopper stabilized amplifiers, Aladjalova associated infraslow activity with parasympathetic, reparative response (Aladjalova, 1957). Recently, the development of commercially available direct current (DC) coupled amplifiers has led to an explosion of research of human behavior and the infraslow frequencies. In the last 20 years, studies of infraslow frequencies and attention-deficit/hyperactivity disorder (ADHD), hormone response, pain, memory, sleep, and seizure, to name just a few, have been published worldwide in journals and textbooks (Alshelh et al., 2016; Broyd, Helps, & Sonuga-Barke, 2011; Helfrich, Mander, Jagust, Knight, & Walker, 2018; Joshi et al., 2018; Lecci et al., 2017; Marshall, Mölle, Fehm, & Born, 2008). The centrality of the low regime in cortex is emphasized by recent evidence that suggests that these slow oscillations play a role in synchronizing faster activity and modulating cortical excitability (Hiltunen et al., 2014; Leong et al., 2018). The commercial availability of DC coupled amplifiers allowed clinicians to explore bandwidths outside of the traditionally defined analog limit of 0.5–50 Hz in clinical neurofeedback. Training these very low frequencies was dubbed infraslow fluctuation (ISF) training due to the interaction of frequency and DC potential shift (Smith, Collura, Ferrara, & de Vries, 2014).

The clinician's primary goal in ISF training is to find a client's optimum frequency (OF). Clinical experience

has shown that this results in the best treatment response. Electrodes are placed at specific locations according to the internationally recognized 10/20 system (Silverman, 1963; Wei, Wu, & Tudor, 2017). To begin the optimization process, one of three potential bipolar montage sites are chosen depending on the results of the quantitative electroencephalogram (qEEG) and the client's chief complaint.

During ISF training the client experiences emergent state shifts that we refer to as symptoms of training. The symptoms that clients experience during and after the training session guide the clinician to the OF. Many clinicians use peripheral biofeedback measurements like skin temperature, skin conductance, or electromyography (EMG) as a guide to optimization as well. Once the optimum frequency is identified clients report improved sleep regulation, anxiety reduction, better appetite awareness and control, improved sexual function, and reduced reactivity to sound—all indications of improved sympathetic–parasympathetic response (Fink, Bronas, & Calik, 2018; McCorry, 2007).

The ANS has a central role in maintaining sympathetic–parasympathetic and cardiovascular homeostasis. It includes vagal cholinergic and sympathetic noradrenergic nerves supplying the heart and sympathetic noradrenergic nerves that enmesh arterioles. These nerves play a role in peripheral resistance to blood flow in the body, and therefore blood pressure. That is why clinicians and researchers have long sought valid, noninvasive, quantitative means to identify pathophysiologically relevant abnormalities of these systems (Goldstein, Benthó, Park, & Sharabi, 2011).

Heart rate variability (HRV) is one of the best-known means of physiological measurement and is defined as the beat to beat variability in the sinus rhythm over time. There is mounting evidence that points to the efficacy of HRV training in clinical practice due to its impact on sympathetic–parasympathetic function (Peper, Harvey, Lin, Tylova, & Moss, 2015). The monitoring of sympathetic–parasympathetic response during ISF neurofeedback training may aid in the identification of the client's optimum frequency (Camp, Remus, Kalburgi, Porterfield, & Johnson, 2012; Collura, 2013). Measurements of high frequency (HF) and low frequency (LF) power are good indicators of changes in HRV. It has been shown that HF mainly reflects respiratory sinus arrhythmia and HF HRV is understood to reflect the parasympathetic branch of the ANS (Akselrod et al., 1981; Stein, Bosner, Kleiger, & Conger, 1994). LF is

not as well understood, but it is believed that LF indicates baroreflex functionality and cardiac autonomic outflow (Goldstein et al., 2011). LF is often described in the literature as reflecting a combination of sympathetic and parasympathetic influences. HRV can be a valuable tool in the estimation of autonomic status especially when combined with other peripheral nervous system measures (Li, Rüdiger, & Ziemssen, 2019).

Studies propose that specific emotions may elicit distinct autonomic functions. Biofeedback measures may correlate with specific emotions; for example, temperature, HR, and skin conductance may correlate to fear, joy, sadness, and anger. This suggests that the correlation of emotional state with autonomic response may be possible through the implementation of biofeedback methods (Collet, Vernet-Maury, Delhomme, & Dittmar, 1997; Levenson, 1992).

Infraslow training is a recent addition to the relatively young field of neurofeedback. While the literature is growing rapidly (Leong et al., 2018; Mathew, Adhia, Smith, De Ridder, & Mani, 2020; Smith, 2013; Smith et al., 2014; Smith, Leiderman, & de Vries, 2017), the physiological systems involved and full impact on the body are not yet well understood. The aim of this research is threefold: (1) to contribute to the methods' scientific validity and eliminate speculation as to the physiological systems involved, (2) to identify the measurable responses that reveal the most sensitive and so the fastest path to optimization, and (3) to identify the best objective measure to help clients who lack subjective awareness of their physiological responses.

Methods

Participants and Setting

Sampling was randomized (Figure 1) and consisted of a population group that had already decided of their own volition to do neurofeedback training. These participants (Table 1) were randomly assigned to either the ISF or control group. All neurofeedback training was completed in a clinical setting.

Approval from the University of Pretoria Health Sciences Ethical Committee was obtained prior to the

start of the study, and all participants completed an informed consent document.

Inclusion/Exclusion Criteria

Inclusion criteria.

- Reports of high anxiety.
- Reports of daily problems with concentration and memory.
- Complaints of sleep problems.
- Reports of emotional or anger control problems.
- Subjects that were able to participate in at least two training sessions per week.
- Subjects that completed a minimum of 10 sessions of neurofeedback training.

Exclusion criteria.

- Subjects using recreational drugs.
- Subjects using benzodiazepines.
- Subjects using any new form of medication during the study period that may influence the outcome.
- Subjects unable to complete a minimum of 10 training sessions.
- Subjects unable to attend two training sessions per week.

Screening Questionnaires

The subjects completed a clinical interview and an evaluation questionnaire to determine current function. The questionnaire was used by all ISF practitioners participating in the study to develop a broad range of information on their subjects.

From clinical interviews and the questionnaire, it was determined that the five main complaints shared by participants were:

- Anxiety/panic attacks (19 participants)
- Difficulty with either falling asleep or maintaining sleep (16 participants)
- Irritation/anger problems (7 participants)
- Executive function problems: concentration/focus/memory complaints (20 participants)
- Constipation and or irritable bowels (6 participants)

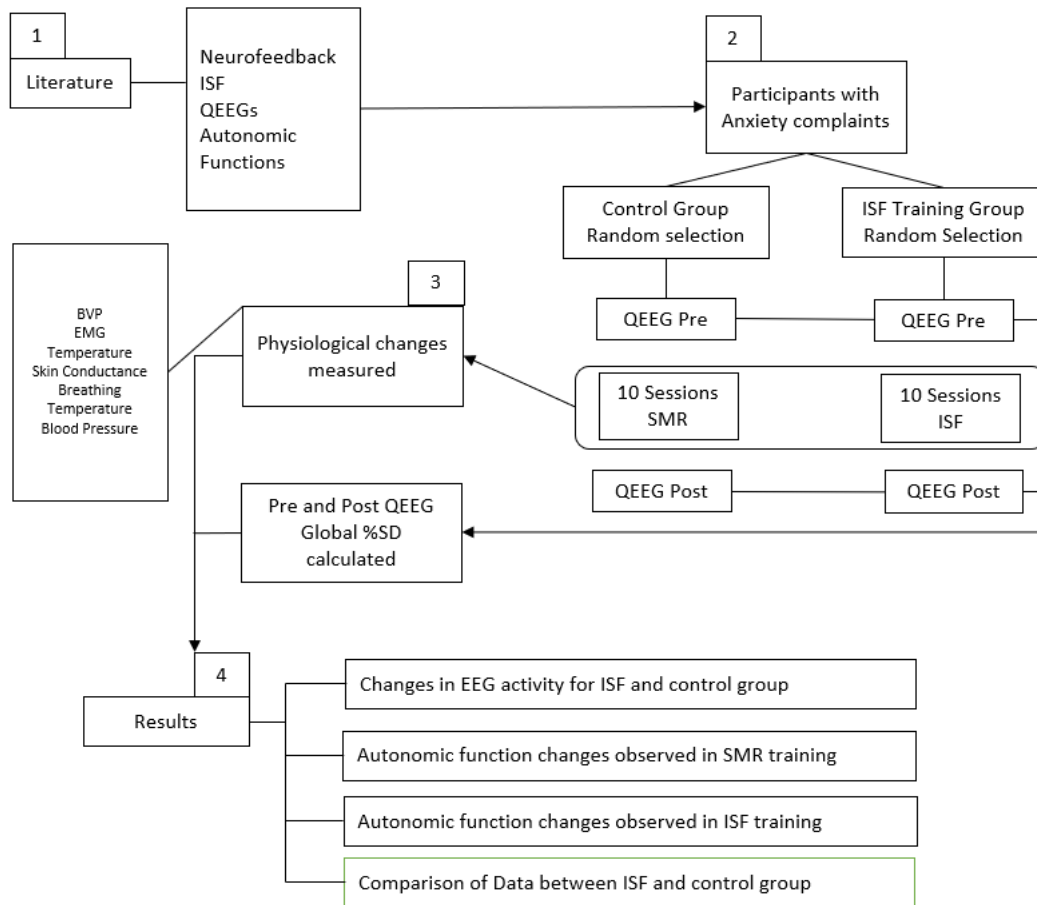


Figure 2. Consort flow chart.

Table 1
Participant demographics

Subject	Sex	Handedness	Age (Years)
C1	M	Left	36
C2	M	Right	39
C3	M	Right	26
C4	F	Right	36
C5	M	Left	19
C6	M	Right	55
C7	M	Right	18
C8	F	Right	55
C9	M	Left	26
S1	M	Right	35
S2	M	Right	22
S3	F	Right	23
S4	F	Right	24
S5	M	Right	49
S6	F	Left	36

Subject	Sex	Handedness	Age (Years)
S7	F	Right	23
S8	F	Right	23
S9	M	Right	37
S10	M	Right	24
S11	M	Right	48
S12	M	Right	49
S13	F	Right	38
S14	M	Right	22
S15	M	Right	55
S16	M	Right	38
S17	F	Right	49
S18	F	Right	34
S19	F	Right	27
S20	F	Right	18
Total Male	17	Mean Age	33.9
Total Female	12	- Control	34.4
		- Experimental	33.7

Physiological Data Monitoring

The ProComp Infiniti (Thought Technology Ltd., Montreal, Canada) was developed for the intended purpose of biofeedback, relaxation, and muscle re-education. It is an 8-channel multimodality device that provides real-time computerized biofeedback and data acquisition. The sampling rate is 2048 samples per second in two of the channels and 256 samples per second in the other six channels. The encoder can be used to render a wide range of physiological signs to be used in clinical observation as well as biofeedback.

The following measures were used in the study:

- Electromyography (EMG)
- Skin conductance
- Skin temperature
- Blood volume pulse (BVP), HR, and amplitude
- Breathing rate
- Blood pressure (Braun VitalScan 3 Wrist blood pressure monitor)

The BioGraph Infiniti software version 6.0 (Thought Technology Ltd., Montreal, Canada) allows simultaneous monitoring of the above mentioned physiological parameters (Huster, Mokom, Enriquez-Geppert, & Herrmann, 2014).

The EMG triode sensor was placed on the trapezius muscle on the right shoulder. The temperature sensor was fastened to the right thumb with a Velcro strap for all clients. The skin conductance sensor consists of two sensors that were placed on the second and third fingers. The BVP sensor was placed on the ring finger also with a Velcro strap. Breathing rate and amplitude was measured using a strap around the abdomen. The resting blood pressure was measured before and after each session while the participant remained in a seated position by making use of a wrist cuff and the values for systolic and diastolic blood pressure were recorded in millimeters of mercury (mmHg; Huster et al., 2014).

No biofeedback training was done, and the client never saw the physiological measurements so that they were never cognitively aware of any changes taking place. The measurements were recorded for 34 min, of which 30 min was the length of an ISF training session and 2 min pre- and postsession.

ISF Neurofeedback

The Discovery 24-channel EEG amplifier (BrainMaster Technologies, Inc., Bedford, OH) is a physiological monitoring and feedback system. It offers monitoring and feedback of brain signals that include the measurement of EEG, direct current, and slow cortical potentials (DC/SCP).

The BrainMaster Atlantis 4x4 (BrainMaster Technologies, Inc., Bedford, OH) 4-channel EEG amplifier is a physiological monitoring and feedback system. Just like the BrainMaster Discovery, it offers monitoring and feedback of EEG and DC/SCP. Each area on the scalp was cleaned using NuPrep skin preparation gel. Electrodes were then pressed onto the cleaned area using 10/20 conductive paste.

Training was done using a bipolar montage. A two-channel linked ear electrode array was implemented. This allowed for Z-score and amplitude monitoring at each site in a linked ear montage while bipolar training was simultaneously accomplished in a third virtual channel. Two active electrodes were placed at either T3-T4 or T4-P4. Two references were placed on the mastoid bone behind the ears. The ground was placed centrally at the Cz position according to the International 10/20 System. The duration of a session was 30 min.

Training was done via visual and auditory feedback. The subjects heard two reward sounds—a low tone when the amplitude decreased and a high tone when it increased. It is an instant reward and continues for the duration of the condition. There was no refractory period between rewards which allows for the rapid transmission of information to the subject concerning changes in the amplitude and phase of the ISF signal (Smith et al., 2014).

The objective in infraslow neurofeedback training is to find a frequency that produces a state of focus and relaxation within a client. Changes in frequency are guided by the changes in state that the subject experiences. These changes in state or “symptoms of training” reflect shifts along the autonomic spectrum. For instance, a subject may experience her eyes watering, a parasympathetic response, or her pupils becoming dilated, a sympathetic response. The therapist makes changes in frequency that reduce the targeted symptom of training and so moves a client closer to autonomic quiescence.

Recorded data was stored to later be statistically analyzed to track changes that occurred in session and from session to session.

Sensorimotor Rhythm (SMR)/Control Group

Each area on the scalp was cleaned using NuPrep skin preparation gel. Electrodes were then pressed onto the cleaned area using 10/20 conductive paste. Three electrodes were used. One active placed at the C4 site, one reference placed on the left mastoid, and a ground placed on the right mastoid. The duration of the training session was 30 min. The client watched a movie as did clients in the experimental group. In the background they could hear a tone which sounded when all parameters were met. To aid as visual feedback, the screen was dimmed when the client was not meeting the required thresholds and brightened when conditions were met. Neurofeedback for the control group consisted of a sensorimotor rhythm (SMR) protocol that enhanced 12–15 Hz activity and inhibited 3.5–7.0 Hz and 20–30 Hz activity. For some clients, an adjustment was made to reward 12–16 Hz as they reported feeling more focused with this frequency band.

The same set of physiological measurements as described for the ISF training group were gathered for the SMR training sessions. Like the experimental group, the control group's physiological monitoring was also recorded for the 30-min duration of the session with an additional 2 min pre- and post-session.

Statistical Analysis

The following measurements were taken and statistically analyzed to determine which changes show the most statistically relevant results:

BVP amplitude, BVP inter-beat-interval (IBI), BVP HR from IBI, BVP HR (smoothed), BVP IBI peak frequency, BVP very low frequency (VLF) % power, BVP LF % power, BVP HF % power, respiratory amplitude (abdominal), respiration rate, HR max – HR min, BVP amplitude mean, BVP HR mean (beats/min), BVP peak frequency mean (Hz), BVP IBI standard deviation of the RR interval (SDRR), BVP VLF % power mean, BVP LF % power mean, BVP HF % power mean, BVP VLF total power mean, BVP LF total power mean, BVP HF total power mean, BVP LF/HF (means), EMG mean (μ V), skin conductance mean (μ S), temperature mean (deg), respiratory rate mean (breaths/min), BVP IBI peak amplitude, BVP IBI peak amplitude trigger, BVP IBI NN intervals, BVP IBI percentage of NN intervals (pNN), BVP IBI pNN intervals (%).

All electronic data was stored on a laptop of the investigator, and daily backups were made to a cloud storage account.

All physiological data gathered in the BioGraph Infiniti software was scanned for any artefact. Identified artefact was removed before raw data was analyzed statistically.

The mean, median, standard deviation, and inter-quartile range were used to describe the statistical findings. To determine if there were trends in the ISF parameters over the 10 sessions, a linear mixed model was used where random intercept and slope effects as well as the difference between pre–post sessions were evaluated. The test was evaluated at a level of 5% significance, and all analysis was done with STATA 14.

Results

HRV Very Low Frequency (VLF) and Low Frequency (LF) Power

By making use of a fast Fourier transform (FFT) allorhythmia, the heart rhythm can be decomposed into different frequencies. This can be graphically represented and distinguishes HF, LF, and VLF. The amplitude of these frequencies is usually very different for an individual in a high stress state than for one who is relaxed (Figure 3).

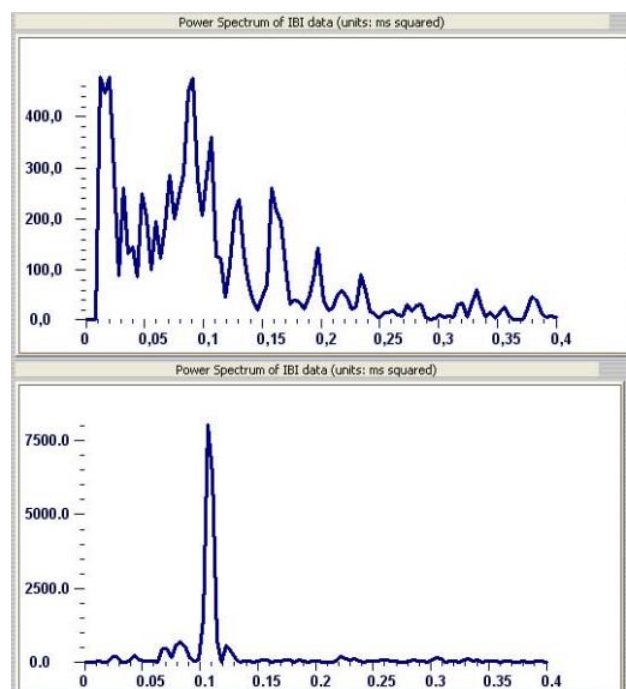


Figure 3. Comparison of HRV frequencies in a stress state (top) compared to a relaxed state (bottom; Thought Technology, 2014).

HRV depends on the activity of the ANS. The VLF has been found to be a major determinant of physical activity, and it has also been proposed as a marker of sympathetic activity. It is said to affect the vascular tone loop of the baroreflex system, thermal regulation, and activity of the renin-angiotensin system. A decrease in the VLF is hypothesized to be an indication of sympathetic blocking (Sztajzel, 2004).

The LF is an indication of both sympathetic and parasympathetic activity and is indicative of activity of the baroreflex function. The HF is indicative of parasympathetic activity (Sztajzel, 2004). A decrease in HF is theorized to reflect decreased vagal activity leading to decreased parasympathetic activation (Rodin, Bornfleth, & Johnson, 2017). There is controversy with respect to the ratio of LF to HF. Some consider it to be a measurement of balance between the sympathetic and parasympathetic nervous systems while others dispute that hypothesis (Eckberg, 1997; Malik, 1998).

When looking at the *t*-test results for the different components when comparing session 1 to session 10 the following values were obtained:

- VLF, $p = .05$. This indicates a significant decrease in the VLF % power. This may be an indication of decreased sympathetic activity as it is hypothesized that increased VLF represents sympathetic blocking (van der Kruijs et al., 2016).
- LF, $p = .004$. This indicates a significant increase in the LF % power. It reflects sympathetic and vagal influences on cardiac control via baroreceptor-mediated regulation of blood pressure according to some theories. Others suggest that it is a marker for sympathetic modulation (Prinsloo et al., 2011). The range for LF frequency is 0.04–0.15 Hz with PNS dominance believed to be from 0.04–0.70 Hz. When looking at the BVP peak mean frequency measured, the peak mean frequency measured at session 1 was 0.1 Hz and this decreased to 0.08 Hz at session 10. Due to it appearing insignificant the data was not further included in the larger results, but it does however indicate a possible shift towards being more parasympathetic dominant.

EMG Mean

Anxiety is often accompanied by muscle over-activity (Pluess, Conrad, & Wilhelm, 2009). The amplitude of action potentials recorded from the muscles of individuals with anxiety is higher than healthy controls. One would expect a decrease in muscle tension with relaxation and parasympathetic activation (Barrett, Barman, Boitano, & Brooks, 2012).

At rest there should be very low muscle activity as no muscle fibres are being recruited. Under chronic or repeated stress, certain muscles may not be able to return to a resting state. This is known as “residual” muscle tension and commonly causes back, shoulder, or neck pain. This can lead to increased fatigue (Sainsbury & Gibson, 1954). A high resting muscle tension also leads to an impedance of blood flow which slows down healing. Adaptive habits such as muscle guarding can also have a negative impact by reducing flexibility and decreasing muscular efficiency (Sainsbury & Gibson, 1954).

In the control group a change was seen in the positive direction when comparing session 1 to session 10. However, it was not statistically significant.

The *p*-value for EMG in the experimental group is $p = .01$ when comparing session 1 to session 10, which shows a significant decrease in muscle tension and more specifically the resting muscle tension.

Skin Conductance Mean

Skin conductance is generally accepted as one of the most sensitive measures of emotional arousal (Lin, Lin, Lin, & Huang, 2011). Skin conductance biofeedback is used to help an individual become aware of unconscious physiological responses to stress. A certain level of arousal is important, but if this increases too much it can lead to fatigue and anxiety as shown in Figure 4.

The *p*-value for skin conductance was $p < .0001$, which indicates a significant decrease in the experimental group when comparing session 1 to session 10. This is indicative of lower arousal levels, which is a positive change in a high anxiety population group where very high arousal levels are typically noted. There is also a decrease noted in the standard deviation of the group as well as a decrease of the median. This can be an indication of decreased anxiety as an increase in electrodermal activity is commonly reported in high anxiety individuals.

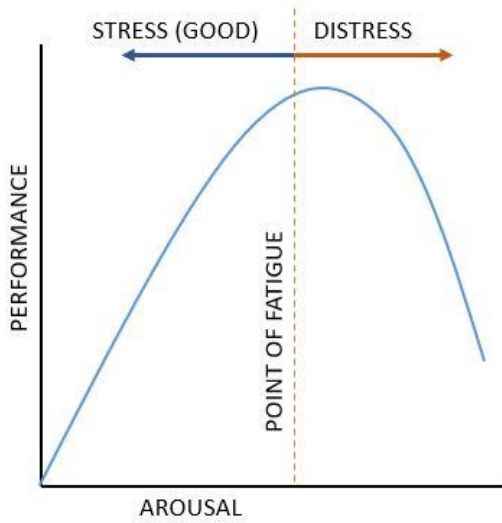


Figure 4. How stress and arousal influences performance.

Blood Pressure

The normal blood pressure in the brachial artery is approximately 120/70 mmHg in young adults (Figure 5). It is affected by cardiac output, peripheral resistance, and emotion. Individuals with hypertension were able to lower blood pressure by engaging in anxiety treatment (Grossman et al., 2005).

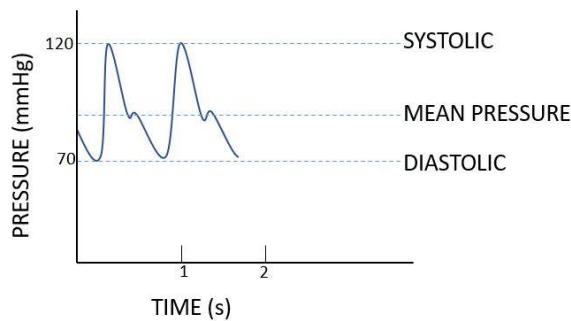


Figure 5. The Brachial artery pressure curve in a normal young adult indicating the relation of systolic and diastolic pressure to mean pressure.

There was a significant change noted in the post systolic comparison in the experimental group, *p*-value of .049. The diastolic value also approached a significant change, with a *p*-value of .083. Brachial artery pressure monitoring reveals a significant effect on the blood pressure of participants when doing ISF training when compared to the control group where no significant changes were noted.

As with the heart rate analysis there was also a very large change in the standard deviation of the group indicating that we are dealing with a nonlinear change. There appears to be a homeostatic change towards what is considered normal (Figure 6).

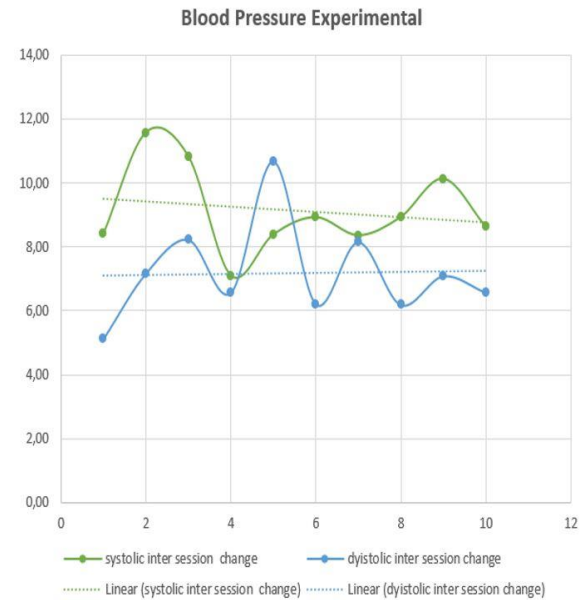


Figure 6a. In session change towards normal values for blood pressure experimental. *x* = session number, *y* = change towards normal.

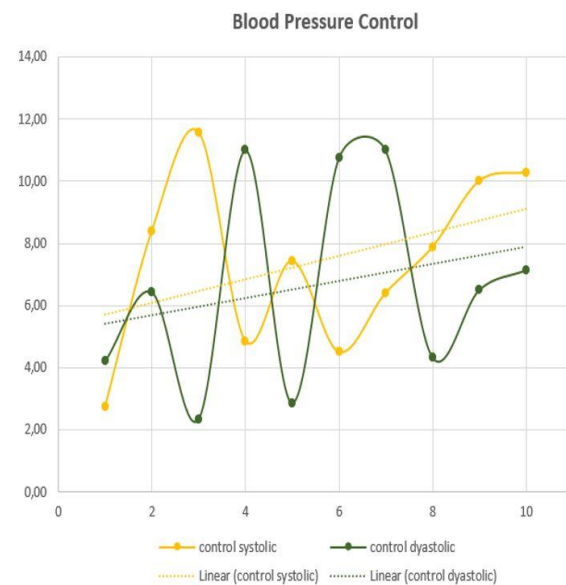


Figure 6b. In session change towards normal values for blood pressure control. *x* = session number, *y* = change towards normal.

Limitations of This Study and Recommendations for Future Research

The size of the experimental and control groups defines this research as a pilot study. A larger study is warranted with a larger group of both experimental and control participants. There was no blinding involved in this study. A future study may include blinding of the rater and the subject. That will give an even clearer indication of what variables are purely influenced by the ISF training.

Conclusion

In the evaluation of the changes in autonomic function, significant changes were noted in the experimental group for blood pressure (systolic), skin conductance, electromyogram, and, in the analysis of the frequency domain of HRV, for % power VLF and % power LF. Table 2 summarizes the most significant *p*-values that were measured during the study. Heart rate data showing significant decrease was not noted, but when looking at the change towards normal a definite trend was seen wherein the standard deviation of the experimental group decreased and their heart rates either increased or decreased towards what is known as an age- and sex-related norm. The same was noted in the blood pressure readings, where the standard deviation of the experimental group decreased, and more participants BP values increased or decreased towards more normal values. In other words, closer to the normal range of 120/70. No significant changes were observed in the control group.

Table 2
Summary of *p*-values obtained

Variable	<i>p</i> -value ISF	<i>p</i> -value Amplitude (SMR)
HRV VLF Power	.050	.30
HRV LF Power	.004	.98
EMG Mean	.010	.33
Skin Conductance Mean	< .0001	.39
Blood Pressure (Systolic)	.049	.74
Blood Pressure (Diastolic)	.083	.79

Physiological monitoring may be a useful tool in future studies to determine the ANS impact of neurofeedback training. In the present study, our data suggest that the mechanism of action of ISF neurofeedback training may involve the ANS. Our data also suggest that SMR training does not involve ANS function. While not unique in comparing one form of neurofeedback with another, the current study may be the first to provide data that differentiates the functional impact of one form of neurofeedback training from another. Finally, the results of this study suggest that peripheral biofeedback measures of electromyogram, skin conductance, the frequency bands of HRV, and blood pressure may help in the frequency optimization process of infraslow neurofeedback training. These peripheral measures help to clarify the physiological impact on clients who may lack the subjective awareness to report accurately.

Author Declaration

Mark Smith is the owner of Neurofeedback Therapy Services of New York. NTSNY produces neurofeedback workshops that include teaching infraslow fluctuation neurofeedback training. He provided neurofeedback protocols for this research and participated in editing of the final version of the manuscript. He did not participate in the research design, implementation, or evaluation of the data. All other authors declare no competing interests.

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