

Graph Theoretical Analysis of Brain Functional Connectivity
Differences between Musicians and Nonmusicians

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Abstract

This thesis study evaluated the effect of musical training on brain functional connectivity using graph theoretical concepts from a holistic perspective. While most studies based on this topic include the effects of the types of music or noise on a population of musicians or nonmusicians, this study was designed to try and differentiate the two populations directly by comparing their functional connectivity while listening to classical musical versus listening to white noise to quantify any differences between the two populations using graph theory measures. It was found that musical training largely impacts the theta band during passive visual attention tasks such as facial recognition. Musicians and nonmusicians showed statistically significant difference in the average nodal degree, global efficiency, clustering coefficient, network densities, and modularity when considering the difference between the music and noise conditions in the theta band. Any differences between the populations in the alpha, mu, and beta bands were found to be statistically insignificant with a significance level of 0.05

Graph Theoretical Analysis of Brain Functional Connectivity

Differences between Musicians and Nonmusicians

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This thesis is dedicated to the loving memory of my mother, Melissa.

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Table of Contents

Introduction.....	1
Thesis Hypothesis and Significance.....	2
Background.....	4
Music, Memory, and Cognition	4
Musical Cognition.....	5
Electroencephalography	7
Brain Frequency Bands	8
Event-Related Potentials	8
ERP Waveforms	9
Time-Domain ERP analysis	10
Functional Connectivity: A Holistic Approach.....	11
Cross-Correlation and Coherence.....	12
Phase-Based Measures	13
Phase-Locking Value.....	13
Phase Lag Index.....	14
Weighted Phase Lag Index	16
Graph Theory Analysis	17
Segregation	17

Integration.....	18
Centrality	19
Assortativity.....	21
Methodology	23
Participants and Recruitment	23
Data Collection.....	24
Pre-processing	25
Time-Domain Analysis	26
Functional Connectivity Analysis	26
Graph Theoretical Analysis.....	27
Statistical Analysis	30
Results.....	32
Discussion	39
Conclusion	42
Recommendations.....	43
References.....	44
Appendix – IRB Approval Letter	47

Introduction

Music is an arrangement of auditory features in a regular and repeating manner, which often reflects the culture, time period, and class of its patrons. Music has been a subject of numerous scientific studies and therapies for decades. It has piqued the interest of cognitive neuroscientists due to the intricate and complex effects it has on the brain. Music has also found therapeutic applications in music therapy for individuals suffering from mental diseases and disorders such as various dementias, Alzheimer's Disease (AD), and autism. Even in some of the worst neurodegenerative diseases, music jogs memories and elicits emotions that patients have forgotten, albeit temporarily [1], [2]. This effect of memory preservation is especially pronounced in subjects who used to play instruments, as most can still play their instrument effectively [3]. Understanding how musical training changes the mind of the player could deepen our understanding of dementia and other cognitive impairments.

Musical training often begins early in life [4]. Some children start as early as two years old, while other children start much later in their teenage years. On occasion, adults may begin later in life as a hobby. Musicians, as well as other members of the performing arts, are trained in ways that engage the whole mind, which are believed to enhance the efficiency between many brain regions to allow precise and accurate coordination and hone decision-making skills that rely on a split-second response; however, the exact effects that musical training has on the human mind are widely debated and not well-understood. Despite work regarding music's effects on the brain being a highly researched topic by researchers of many disciplines such as cognitive neuroscience, biomedical engineering, and musical therapy, this research has not compared two mentally "normal" populations. Existing knowledge shows that engagement in cognitively stimulating

leisure activities is shown to be associated with a decreased incidence of dementia [5]. This includes musical training, and other activities such as dance; however, music has yet to be investigated independently [5].

Graph theoretic analysis (GTA) is an effective tool for the quantification of brain networks and can be used to describe the topological structure of the brain. GTA can provide an in-depth analysis of brain network regional segregations and integrations. Although research using functional connectivity and graph theory analysis has been increasing in recent years, the adoption of graph theoretic measures and functional connectivity is still uncommon in this area of study. Furthermore, research involving music and functional connectivity tends to dwell in the realm of musical cognition and perception, which focuses on how the brain reacts to musical or auditory stimuli. Understanding the underlying differences between the functional brain networks in musicians and nonmusicians may one day help decipher the mystery of how music alters the functionality of the mind. If GTA can show quantitative differences between musicians and nonmusicians, it could help future researchers understand the effects that musical training has on the brain.

Thesis Hypothesis and Significance

GTA-based measures provide solid representations of functional connectivity between distinct brain networks, and it has been used for many different imaging modalities such as fMRI, PET, and EEG [6]. The aims of this thesis are to determine 1) whether GTA can quantify the differences in graph theory measures between musicians and nonmusicians and 2) how the brain networks between these two populations differ. The hypothesis for this study is stated below:

Musicians will display increased functional connectivity compared to nonmusicians while listening to background music.

The degrees of integration, segregation, and level of network small world-ness is of interest in this study. It is expected that musicians will have notable network differences compared to nonmusicians.

While research does exist regarding music, functional connectivity and graph theoretic analysis, it is still an underutilized tool in this field of study [1], [2], [7], [8], [9], [10], [11]. A common theme in most of these studies is the analysis of one population or a comparison of populations discordant with mental health issues. This study sought to compare two healthy populations to determine whether there was a notable difference between the two populations. The utilization of functional connectivity and graph theory analysis in this manner helps to expand this knowledge base. To build on the knowledge in the area, this thesis sought to uncover whether musicians' neural networks differ from nonmusicians during non-music-related tasks while listening to music and noise.

To make this assessment, the ERP responses between musicians and nonmusicians during digitized oddball paradigm tests were quantified and analyzed. The population differences were assessed by applying GTA to wPLI functional connectivity results.

Background

Music, Memory, and Cognition

Music is one of the universal components of civilization [12] and has influenced human culture since time immemorial. Researchers across the world have studied the effects of music on the mind for decades, if not longer. Despite this abundance of research, a consensus on the effects of music on the mind vary wildly depending on context; although, a plethora of research would agree that musical training stimulates the entirety of the brain, acting as a type of whole-brain exercise, which engages the whole mind.

Over the years, studies into the differences between musicians and nonmusicians have deduced that there are structural and functional differences in musically relevant brain regions such as the sensorimotor areas, auditory areas, and multimodal integration areas [13]. It should be expected that musicians may utilize these areas of the brain more often than the average person. Musical training can be thought of as a strenuous mental exercise; however, a full understanding of the changes due to musical training has not been achieved. Existing literature has shown that engaging in these types of cognitively stimulating leisure activities is associated with a decreased incidence of dementia; however, the effect of musical training has yet to be investigated independently [5].

Musical training does appear to have impacts on mental development. A study performed at Harvard University showed that, even after controlling for variables such as IQ, academic performance, social, and economic factors, over the course of fifteen months children who underwent intensive musical training tended to outperform children with little-to-no training when evaluated in their ability to understand and comprehend complex, abstract geometries and

mathematics [12]. Another observational study involving children of approximately six years of age showed that there were noticeable, statistically significant cerebral changes in the children who underwent 15 months of piano lessons versus their control group who did not [13].

There are many factors and lifestyle differences confounding musical training as an independent variable, which can make isolating it very difficult; however, one study regarding 27 pairs of Swedish twins with discordance to playing an instrument and to dementia or mild cognitive impairment (MCI) estimated that there was a 64% decrease in the likelihood of dementia after adjusting for the effects of sex, education, and physical activity [5], [14]. Using the twin registry helped reduce many confounding variables which, including the ones aforementioned, also included age, upbringing, and lifestyle within groups.

Musical Cognition

Musical cognition often refers to how the human mind perceives and understands music. A plethora of research in this area has been documented including research involving EEG and fMRI [7], [8], [11]. The union of functional connectivity and graph theoretical analysis in this area of research has been relatively new within the last two decades and is currently lacking in data. The goal of functional connectivity of musical cognition is to understand what regions of the brain activate and communicate with one another during musical perception. Most prior research uses channel-by-channel, non-holistic approaches to analyze data rather than GTA, which can provide a holistic topological analysis of EEG data.

During the literature review, only three articles mentioning both GTA and music were found; none of which compared musical and nonmusical populations directly. Wu et. al. showed that in nonmusician populations, actively listening to calm music amplified mean phase coherence

functional connectivity and enhanced small-world network organizations within the alpha-band [8].

Many previous studies, both musically related and otherwise, have shown that the alpha-band (8-13 Hz) phase synchronization is associated with attention, wakefulness, and many forms of working memory [8]. Research has shown that listening to music can result in an increase in the alpha-band synchronization; however, this is highly dependent on many factors such as the subject's musical tastes and expertise, musical tempo, and the genre of music [9], [10]. Music can function synergistically, but depending on the task or context, can sometimes be a hindrance to cognitive processing [9]. It is for precisely this reason that comparing two populations while listening to music is complex due to the addition of multiple confounding variables.

To better compare the two populations using music, control of the type of background music is imperative to generate consistent ERP responses. Calm music, i.e. music with low-arousal and moderate tempo, is associated with higher levels of attention and concentration [8]. Fast-paced music has been associated with impaired inhibitory control; furthermore, it was noted that the effects tempo had on ERP response was more significant than perceived pleasure or preference to the musical genre [10]. It is also important to note that musicians are especially prone to distractions while listening to music. A piece that is familiar to them or in their repertoire can incite distraction and loss of attention [9]. This is likely due to the limited capacity theory of Kahneman, positing that attention is limited and multitasking requires the mind to ration mental resources [9]. Despite this drop in attention, the theory also supports an increase in functional connectivity by suggesting that more of the brain is working together simultaneously.

A piece qualifying for its tonality, repetitious nature, and moderate pace is Mozart Piano Sonata No. 11 in A major K331, despite its familiarity in classical Western repertoire. As noted

by Burkhard et.al., there was no statistically significant difference in performance based on the type of background music playing; however, this was during reading comprehension and correction, which requires concentration [9], so during another activity, such as facial recognition, which is a passive task, the effect of background must be controlled for.

Electroencephalography

Electroencephalography (EEG) is a common method for recording electrical activity from the brain using differential amplification of signals detected with small, metal disks, referred to as electrodes, which contact with the scalp. It allows for safe and noninvasive approaches to study the psychophysiological tendencies of the brain and for measuring the different brain waves frequency bands: alpha, beta, gamma, theta, and delta [15].

EEG is based on neurophysiological principles. A variation of neurons known as pyramidal neurons are common in the cortical layer of the brain, and their apical dendrites extend throughout the cortical tissues. Signals known as excitatory and inhibitory post-synaptic potentials are dispersed through the apical dendrites where they reach the scalp in the form of dipolar currents. These currents produce alternating voltages and electromagnetic fields that, although small, are significant enough to be detected by specialized measurement instruments such as EEG and magnetoencephalography (MEG) [16].

EEG is not capable of detecting the activities of individual neurons, but rather reports the activities of macroscopic brain regions. A specific form of brain activity occurring over these macroscopic regions in response to external stimuli generates what is commonly referred to as an event-related potential (ERP). ERPs can be used to examine cognitive functions by comparing the elicited ERPs to a defined ERP stimulus [17].

Brain Frequency Bands

Brain waves are commonly broken into five frequencies that are believed to perform different tasks and functions. The bands are Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-30 Hz), and Gamma 30+ Hz). Each frequency band has a theoretical purpose, though the precise functions have not been identified. Delta and theta are most commonly related to sleep and drowsiness. Alpha is related to a calm and attentive state of mind, while beta represents a wakeful awareness. Gamma is highly debated amongst these bands as the frequencies in the band are very high and it is not known to which degree those oscillations are biological and which are noise. The bands of interest in this study were theta, alpha, and beta. Theta is an interesting band due to its ambiguous functionality. While often related to sleep pressure and drowsiness, it has also been noted to increase in band power during cognitive processes and intense cognition [18]. Theta has also been related to creativity, imagination, and problem-solving, likely due to its relationship with dream-like states of being. Theta was found to relate with working or episodic memory demands despite its precise function not being identified [19]. The theta and alpha bands are also theorized to be related to the formation and retrieval of memories, respectively [20].

Event-Related Potentials

An event-related potential (ERP) is the summation of minuscule voltages, which results from the response of neural networks to events or stimuli. ERP waveforms are associated with neural activity in sensory and cognitive processes [17] by reflecting the summation of postsynaptic potentials elicited in synchrony by a large number of pyramidal neurons within the cortical tissue while communicating and processing information.

ERP Waveforms

A classic ERP is comprised of a sequence of positive and negative deflections called peaks, waveforms, or components. The various components that comprise an ERP waveform are elicited in response to certain cognitive stimuli. Determining the source of the ERP through analysis of voltage distributions over the cortex remains a challenge. There are two primary categories of the ERP components: exogenous, which are stimulus-dependent and reflect the automatic processing of external stimulation, and endogenous, which are stimulus-independent and reflect controlled processing [21]. The ERP components are named by the direction of their deflection and their latency. This concept is illustrated in **Figure 1** [22].

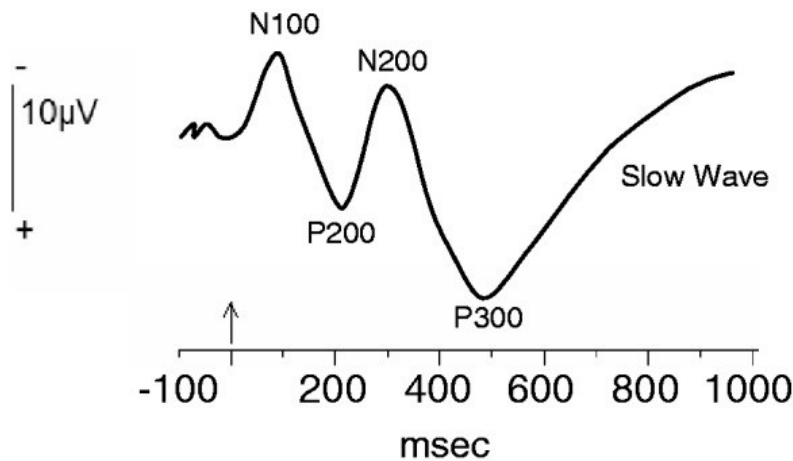


Figure 1: Generalized representation of an ERP waveform [22]. Standard convention for ERP waveform plots shows negative voltages above and positive voltages below.

The waveform and its components indicate the occurrence of distinct neural activities associated with cognitive function [23]. Simultaneous occurrences of components across channels gives indications as to how multiple neural network components contribute to specific events [24]. A summary of common ERP components is given in **Table 1**.

Table 1: ERP Components and Significance

ERP	Latency	Significance
P1	Initial Peak	Exogenous response that is elicited by visual stimuli, such as luminance [25].
N170	~170 ms	Response to facial stimuli, reflecting a mechanism for human face detection. This component's amplitude is reduced in schizophrenia patients [25].
N200/N2	~200 ms	Consists of three components [26]: N2a: Elicited by "oddball" paradigm, but it is mainly used in audition rather than vision. N2b: Appears during heightened conscious attention to changes in stimulus. N2c: Arises during classification tasks i.e., visual search tasks.
P200/P2	~100-250 ms	Signifies attentional recruitment and modulates perceptual processing [27].
N400/N4	~250-500 ms	Response to words and other meaningful (or potentially meaningful) stimuli [28].
P300/P3	~250-400 ms	Endogenous response. Like N2, it's a major component for auditory and visual stimulus. Elicited by the 'oddball' paradigm [26].
P600/P6	~500-600 ms	Also called Syntactic Positive Shift (SPS), elicited when hearing or reading (i.e., auditory, and visual stimuli) grammatical or other syntactic errors. Often used in neuro-linguistical studies [26].

Time-Domain ERP analysis

Time-domain ERP analysis considers the amplitude and latency of individual components and has been used as a fundamental tool for differentiating healthy individuals and those suffering from brain disorders. In general, shortened latencies are associated with faster responses and a better mental performance in contrast to longer latencies, which imply the opposite [23]. Similarly, larger amplitudes are associated with larger brain response compared to smaller amplitudes.

These analyses are complex and are performed channel by channel within the time domain. This method is riddled with inconsistency as single trials are known to have a poor signal-to-noise ratio and high trial-to-trial variability, possibly explaining the inconsistencies in results of multiple studies on the same response condition [29].

Because this method relies on the analysis of single trials, it cannot holistically provide information regarding the changes in the macroscopic brain network [29]; however, functional connectivity analysis is able to avoid these disadvantages and can provide information regarding the communication between distinct brain regions as a whole [30].

Functional Connectivity: A Holistic Approach

Functional connectivity is described as the temporal correlation of distant neurological events and can be described with certain statistical measures [30]. Two macroscopic regions of the brain can be considered functionally connected if they share a statistical relationship between the measures of activity between them so long as the assumptions hold that the two regions are not anatomically connected and that the detected connection is noncausal [31].

Functional connectivity offers another approach to analyze ERPs through the evaluation of phase synchronization between channels in each frequency band. This approach can show network changes in the brain over time. Choosing the proper FC measure is important for the type of analysis and data set as well as the desired level of sensitivity and specificity.

The quantification of neuronal interaction remains a challenge. The overwhelming diversity of quantification methods for oscillatory interactions, which is often demonstrated through copious amounts of technical detail, can make it a challenge to determine and justify a method of analysis. A limitation of functional connectivity analysis is its susceptibility to overinterpretation [32]. Depending on the measure used to identify connectivity, the strength of the connection can vary due to each approach having differing levels of sensitivity and specificity issues [33]. Functional connectivity measures can be either power-based or phase-based.

Phase-based connectivity measures are used to estimate the amount of phase stability between two distinct signals over time. This is known as inter-site synchronization. Other phase-based measures analyses include cross correlation, spectral coherence, phase lag index (PLI), and phase locking value (PLV). These measures have proved to be effective in assessing brain network connectivity in many study applications.

Cross-Correlation and Coherence

Cross-correlation is based on Pearson's correlation coefficient, and it measures linear connectivity through a linear analysis of signal similarity. This is determined by the convolution, or sliding dot product, of every point in a signal by every other point in the second signal [32]. A drawback of cross-correlation is that it is not time-dependent. This measure treats each point as a random variable. This measure is also used for linear connectivity which is useful for general applications of similarity detection; however neural signals are primarily bivariate and non-linear, so this measure is more difficult to apply to brain signal analysis [32].

Coherence, also known as cross-spectral density, is the spectral analysis of EEG signals. It is the frequency domain equivalent to the aforementioned cross-correlation function. This measure is calculated via frequency-wise multiplication of a signal by the complex conjugate of another signal. This conjugate takes the negative of the imaginary component or phase angle [32] as shown in **Figure 2**. This product results in a 2-D cartesian point where the vector represents the product of the two signal magnitudes, and the angle represents the phase difference between them.

The issue with using these measures is that they are directly proportional to ERP amplitude, a large ERP will imply a higher correlation or coherence.

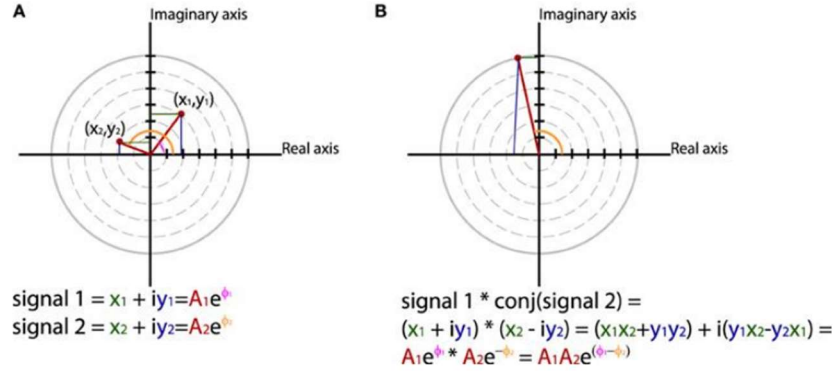


Figure 2: A) representation of two signals in the frequency domain. B) The cross-spectrum between the first signal and complex conjugate of the second signal. The vector length is the product of the two signal magnitudes and the angle from the real axis represents the phase difference between them [32].

Phase-Based Measures

The phase measures are calculated using the frequency domain representation of a pair of signals. This combination can be mathematically represented by Euler's form $Ae^{i\varphi}$. This value represents a vector in the 2D Cartesian coordinate system with an amplitude of A and an angle from the real axis φ .

Phase-Locking Value

The phase-locking value (PLV) or inter-site phase clustering (ISPC) is mathematically defined as the magnitude of the average phase difference between two signals and is shown in **Equation 1** below:

$$PLV = \left| n^{-1} \sum_{t=1}^n e^{i(\phi^j - \phi^k)_t} \right| \quad (1)$$

PLV is expressed as a unit length vector in the complex plane. Two signals will generate an array of multiple coherence vectors that represent the phase differences at each time point. The

clustering of the vectors can give an indication of level of synchrony between two signals [34]. This idea of phase synchrony is illustrated in **Figure 3** [35].

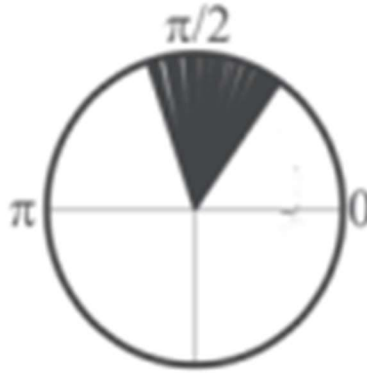


Figure 3: Graphical representation of phase-locking value (PLV) [35].

A disadvantage to using PLV is that it can fail to detect true synchrony if the phase angles differ across repeated trials. Another disadvantage of PLV is its failure to identify volume conduction and therefore may indicate spurious connectivity which is explained further in the next section.

Phase Lag Index

The phase lag index (PLI) measure is an estimate of how distributed or clustered the phase variations are across trials or observations [32]. A major difference between PLI and PLV is that PLI will disregard phase locking values that are centered around the real axis.

When signal phase differences approach zero or π , it is an indicator that two electrodes are detecting the same signal through the volume conduction effect resulting in the rejection of the signal in the PLI measure, see **Figure 4** [35]. While PLI eliminates spurious connectivity, it also may be ignoring true neural interactions occurring simultaneously [36].

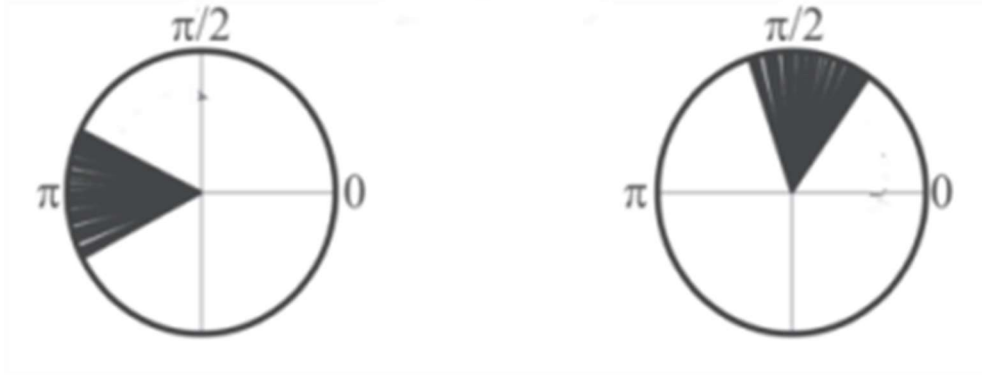


Figure 4: The two cases that may occur through PLI. The left demonstrates a consistent phase difference that can be disregarded for being centered around the real axis. The right demonstrates a strong phase locking which indicates true neural interaction [35].

The Phase-Lag Index is defined mathematically as:

$$PLI = \left| n^{-1} \sum_{t=1}^n \text{sgn} \left(\text{Im} \left[e^{i(\phi^j - \phi^k)_t} \right] \right) \right| \quad (2)$$

While equation 2 is similar to equation 1 with the phase differences over time being represented by Euler's complex form, the PLI equation also includes the *Im* and *sgn* operators. The *Im* operator projects the phase difference vectors onto the imaginary axis, and the *sgn*, representing the word sign, operator converts the imaginary components into unit vectors of magnitude 1 or -1 which are summed and averaged to calculate the index.

A PLI of 0 indicates the volume conduction effect and will be eliminated. A PLI of 1 is indicative of true interaction and functional correlation between two network nodes from which the signals originate [64]. The PLI measure provides information regarding interregional neural communication with little to no false positivity occurrences.

Weighted Phase Lag Index

While PLI protects against type II errors, one of its major disadvantages is its potential to reject true positives in signals with small phase differences near zero. This is due to the connectivity being identified as spurious and eliminated. To combat these shortcomings, the wPLI, like the PLI, also calculates the cross-spectra's imaginary components, but weighs the influences of phase by the magnitude of the imaginary component [37]. The wPLI is mathematically defined as:

$$\Phi = \frac{|E\{|\Im\{X\}| \cdot \text{sgn}(\Im\{X\})\}|}{E\{|\Im\{X\}|\}} \quad (3)$$

Where $\Im\{X\}$ is the imaginary component of the cross-spectrum. The normalization in the denominator by the imaginary component's magnitude reduces the impact of small perturbations and noises which may cause any phase leads and lags. This ensures that components projected closer to the real axis have smaller weights. In addition to its ability to reduce susceptibility to noise compared to PLI, the wPLI is important for the quantification of edge density, the magnitude of information transfer, or the strength of the nodal connection.

Graph Theory Analysis

Expanding upon previous measures, graph theory has become widely studied and utilized within the last decade for application to the analysis of connectivity measured in neural networks and has brought insights into the structure and function of distinct brain networks [38]. Graph theoretical analysis can represent the brain from a topological viewpoint through the illustration of nodes (vertices) and edges (pair-wise connections). The nodes represent distinct, macroscopic neural elements while edges represent their functional connections to one another. An adjacency matrix is the summarization of the nodes and edges where the nodes are represented by the number in an $n \times n$ matrix. The edges can be represented in a few modes. One such method is a binary representation based on a strength cutoff resulting in a 0 or 1, but in weighted adjacency matrices, the edges can be represented on a scale as a zero or non-zero element typically using color scales to represent the strengths of the connection between two nodes. The adjacency matrix can then be analyzed to compute multiple parameters to quantify the network's topology and efficiency [39].

Graph theory measures can quantify the functional networks of the brain in terms of segregation, integration, centrality, and assortativity. Some of these measures are useful to denote specific nodes in the network, while other measures can be used to quantify the entire network holistically. The following sections explain each of the GTA measures.

Segregation

Segregation is the measure which quantifies the degree to which network nodes have formed localized collections which perform a specialized task, for example, the parietal and occipital lobes. As illustrated in **Figure 5A**, there are two commonly used metrics for the quantification of segregation in neural networks: clustering coefficient and modularity. Clustering coefficient describes the local connectiveness to a common node [40]. These collectives are

referred to as modules [38]. The metric of modularity describes the strength with which the distinct modules in the network are separated [41].

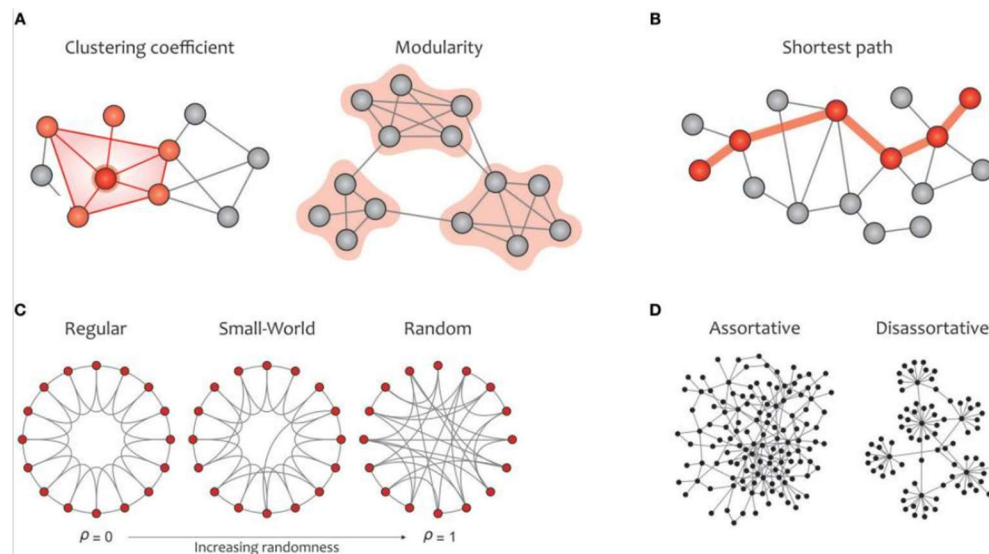


Figure 5: The four global graph measures: segregation, integration, centrality, and assortativity. A) Clustering coefficient which represents the strength of connections within a module, and modularity which represents the strength of connections to other modules. B) Integration which is represented through path length through the network. C) Three examples of network types: regular representing high segregation, random representing high integration, and small world-ness representing a natural balance of the two. D) The assortativity represents the resilience of the network. A highly assortative network is less susceptible to damage whereas highly disassortative network is very susceptible to damage and associated with reduced performance [38].

Integration

Integration is a measure of information communication efficiency between networks or the capability of distributed brain networks to rapidly combine specialized information to perform tasks of higher complexity. This is quantified by a measure termed as the characteristic path length as indicated in Figure 5B. Path length is the average distance between one node and all the other nodes. The shorter the path length between network modules, the higher the integration between them [40].

Centrality

Centrality, also referred to as small world-ness, represents an ideal balance between network segregation and integration. It is the parameter which describes how optimized a network is for specific tasks. High centrality involves the maximization of function segregation while maintaining high integration via short path length; note **Figure 5C**.

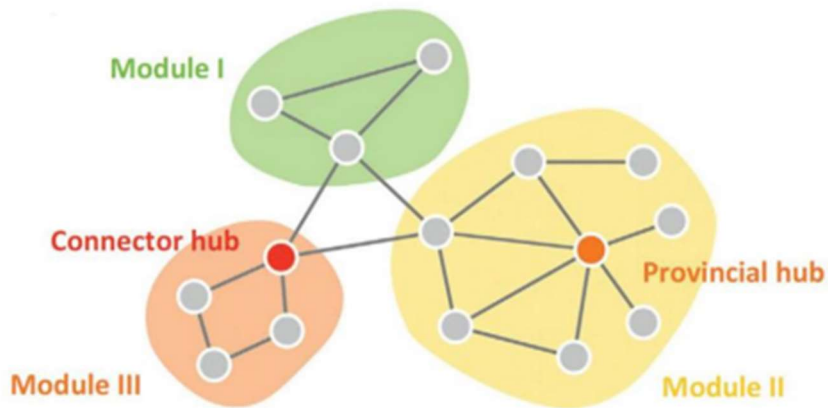


Figure 6: Illustration of Provincial and Connector Hubs within a network of modules.

Degree centrality refers to how many edges a node has as shown in **Figure 7**. It is mathematically described as a ratio between the number of edges a node has by the number it could have [42]. This measure lacks the capacity to identify an important node on a macroscopic level and can only capture importance for a local module.

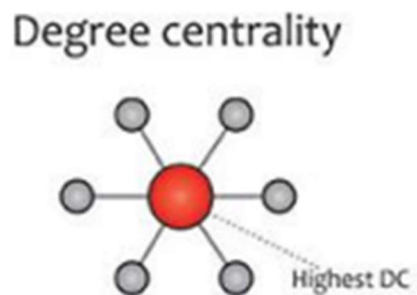


Figure 7: Degree centrality refers to the number of edges connected to a node [38].

Closeness Centrality quantifies how close one node is to all other nodes in the network and is visualized in **Figure 8**. Closeness is mathematically described as the reciprocal of the total distance between the node and all other nodes connected to it. A smaller total distance corresponds to a more centralized node [42].

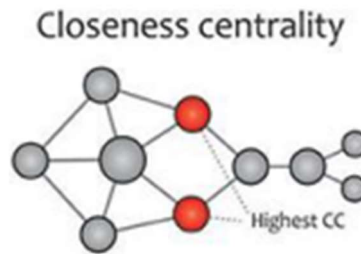


Figure 8: Closeness centrality is the measure of ease of access to other nodes [38].

Betweenness centrality, shown in **Figure 9**, describes whether the node functions as a connector or bridge between modules or groups of nodes. It is a quantification of the number of times a node acts as a connector on the shortest path between two nodes.

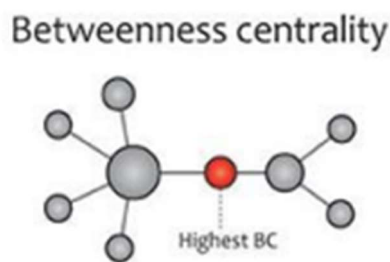


Figure 9: Betweenness describes the node's role as a connector or bridge to separate modules [38].

Eigenvector centrality, also referred to as prestige centrality, describes the significance of a node based on the significance of the nodes which connect with it. This measure assigns a relative score to all nodes in a network based on the idea that connections with highly central nodes contribute more than connections to nodes with lower centrality [43]. **Figure 10** below shows that

the red node would carry a higher prestige centrality due to its connection with a node with many connections; therefore, it would have a higher eigenvector centrality measure and carry higher prestige.

Eigenvector centrality

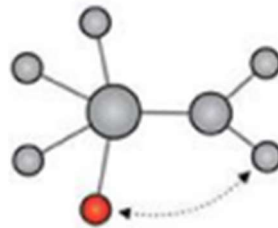


Figure 10: Eigenvector centrality, or prestige centrality, describes the significance a node based upon the significance of the node to which it is connected [38].

Assortativity

Highly connected nodes within a network, called hubs, result in the formation of local clusters known as modules. Network classification as assortative or disassortative is based on the level of similarity there are between nodes connections to other nodes. It describes the capability of one node being able to compensate for another node in the case of a network disruption or deficiency. Represented in **Figure 2D**, assortativity describes the network's overall resiliency to disruption. A highly assortative network will be very resilient against random or deliberate damage; however, it comes at the cost of a reduction in network efficiency. If a network is highly disassortative, it can be efficient but will lack resiliency to network disruption. An ideal balance is needed between network resiliency and efficiency [38].

The property of assortativity is particularly important for quantifying a network's ability to function due to the presence of a dysfunction such as physical damage, brain lesions, and strokes

as well as psychiatric disorders such as Alzheimer's, epilepsy, or multiple sclerosis. The application of graph theory is still expanding to other branches of psychiatric research and has yet to be heavily implemented in disorders such as major depressive disorder, obsessive-compulsive disorder, or insomnia. Research in these areas will help expand the current knowledge of brain function by identifying how brain networks change in relation to differing disorders [38].

Methodology

Human data collection was an integral requirement to test the research hypothesis. Data processing and analysis through the use of functional connectivity and graph theoretic analysis were required to validate any findings. The following sections will cover the process of data collection and analysis.

Participants and Recruitment

A total of twenty, healthy adults (6M:14F, mean: 21.78 years, std: 2.48 years), with ten subjects per population class, participated in the study. The two populations consisted of musicians (2M:8F, mean: 22.8 years, std: 2.56 years, avg years of training: 12.9, std: 2.62 years) and nonmusicians (4M:6F, mean: 20.6 years, std: 1.50 years, all with 0 years musical training). To be eligible to participate, subjects were required to meet the following criteria: (1) 18 years of age or older; (2) Right-handed; (3) No history of drug or substance abuse; (4) No recent history of medication; (5) No recent history of acute infection; (6) No history of diabetes or any endocrine disorders; (7) No history of psychiatric or neurological diseases; (8) No excessively thick or braided hair, as it would affect the quality of recorded EEG signals. Potential subject were refused recruitment if they (1) were under the age of 18; (2) were left-handed; (3) were in cognitive decline due to health or age; (4) had any hearing impairments; (5) had non-corrective vision impairment. Institutional review board (IRB) approval of this study was required and obtained. All participants provided informed consent and had an explanation of the experiment given to them prior to data collection.

Data Collection

To gather the required data, each subject participated in an EEG recording session. The g.Nautilus headset (shown in **Figure 11** below) was placed on their head and set up according to the 10-20 international system to cover the frontal, central, parietal, and occipital regions. Each subject was asked to sit comfortably in the lab. The investigator then went over the form and answered any questions the subject had about the procedure and study.



Figure 11: g.Tec Nautilus wireless EEG headset [44].

The 32-electrode cap was placed on the subjects' scalps with the ground and reference electrodes placed behind their lower ears. The room's doors and windows were covered, and white noise was played to promote sensory deprivation. Sensory deprivation helps to decrease signal noise and artifacts. Prior to the EEG recording process, each subject was asked to sit still and comfortably while watching the screen in front of them. Each subject was instructed to blink as little as possible during the paradigm to avoid artifacts in the signal and was told to close their eyes for 15 to 30 seconds to ensure signal quality prior to recording the ERP paradigm. There were two conditions for the study. The first condition was under white noise while the second condition was under a classical piece: Mozart Piano Sonata No. 11 in A major K331.

There were two categories of visual stimuli: familiar faces and face-like objects such as a flower or clock. Familiar faces included the faces of three, well-known individuals: Dwayne Johnson, Barack Obama, and Robert Downey Jr. The images swapped between the familiar faces and the random face-like objects at an approximate 1:8 ratio. The oddball paradigm was designed to trigger multiple ERP components such as P300, the ERP component of interest in this study.

The oddball paradigm followed the introduction with images being shown for 250 ms followed by a black screen for 750 ms over the course of approximately five minutes. This paradigm resulted in 30 target ERPs for each condition (60 total per subject). The subjects were asked to lift their right index finger when identifying a target image to keep them mentally engaged in the paradigm.

The data obtained was then processed using built-in MATLAB toolboxes to develop a graph theory projection of the subject's mind during the mental tasks to compare the structure of the brain network between the musician and nonmusician.

Pre-processing

The raw data collected in this experiment was preprocessed using MATLAB via a built-in EEGLAB toolbox. A 5th order, Butterworth bandpass filter with cutoff frequencies at 1 Hz and 30 Hz was applied to remove unwanted noise, artifacts, DC offsets, and isolate the main brain wave frequencies. The data was then segmented into epochs of 1000ms: 250ms of stimulus onset and 750ms of post stimulus. Each subject generated approximately 500 pieces of data. Each recording condition resulted in approximately 30 target ERPs and 220 non-target ERPs. The stimulus of interest in this study was familiar faces.

Time-Domain Analysis

The ERP for each subject was obtained by averaging 30 target trials per subject. This was a crucial step to get well-defined deflections, which cannot be obtained from individual epochs [40]. Due to EEG signals susceptibility to noise and external signal interference, a trial rejection process was performed to exclude epochs with interfering noise and unwanted artifacts such as ECG signals, blinking and movement artifacts (EMG signals with notably larger peaks). After ensuring the signal quality and cleanliness of the averaged ERPs, the waveforms were classified into two categories: Musician ERP waveforms and Nonmusicians ERP waveforms.

Functional Connectivity Analysis

To calculate functional connectivity, a weighted phase lag index (wPLI) adjacency matrix was necessary. The wPLI calculations were performed by a toolbox created by East Carolina University's Sensory-Motor Integration Lab (SMILe). Specifically, the Morlet wavelet transform in the toolbox that is used for time-frequency analysis. The convolution of a complex Morlet Wavelet with the pure, time series signal results in a complex signal where phase information can be extracted for every time point. The Morlet wavelet is used to calculate cross-spectral data: a 5-dimensional matrix of two channels, frequency, time, and trials.

Channel $\times$ Channel $\times$ Frequency $\times$ Time $\times$ Trial

This data was then split into the classic brainwave frequency bands of Delta (1-4 Hz), Theta (4-8 Hz), Alpha (8-13 Hz), and Beta (13-30 Hz). Data in each band was averaged and represented in a 4D matrix of two channels, time, and trials.

Channel $\times$ Channel $\times$ Time $\times$ Trial

The wPLI was then calculated for each frequency band. At each iteration, a Monte Carlo simulation was performed in 60% of the trials.

Channel × Channel × Time × Trial

This resulted in a wPLI output that contained every pair of channels obtained over time for each trial. The wPLI can then be averaged over all the trials to result in a reduced 3D matrix output.

Channel × Channel × Time

This resultant matrix represents the average wPLI for each pair of channels in a 32×32 matrix at each time point. This process is summarized in Figure 12 below.

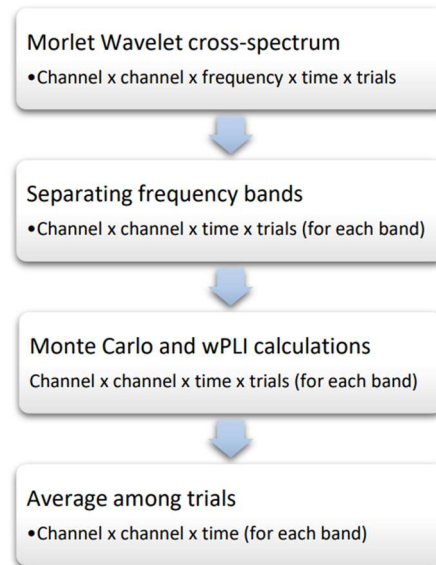


Figure 12: Flow chart for the data structure and matrix size during the functional connectivity analysis.

Graph Theoretical Analysis

The wPLI matrices act as weighted adjacency matrices. The wPLI values range from 0 to 1 and act as the weights of the edges in the network maps. Adjacency matrices in this study were undirected because causality cannot be assumed in the functional connectivity analysis. Multiple

measures were applied to these matrices to characterize the many different aspects of local and global brain connectivity between the control and musician populations in terms of information transfer efficiency. The characteristic path length is calculated using the following formula:

$$L = \frac{1}{n} \sum_i \left(\frac{\sum_{j \neq i} d_{ij}}{n-1} \right) \quad (4)$$

Where i and j denote the row and column, respectively. The total number of nodes in the networks is denoted by n , and d_{ij} is the shortest distance between the nodes i and j . The numerator is also known as the Wiener index and represents the summation of the shortest path lengths between every possible node pair in the network. The denominator represents the total number of nonzero distance values to all other nodes. This measure quantifies network integration. The shorter the average path length, the more integrated the modules in a network are. On the other hand, network segregation is quantified by the clustering coefficient formula:

$$C_i = \frac{\sum_j \sum_k w_{ij} w_{jk} w_{ik}}{(\sum_j w_{ij})^2 - \sum_j (w_{ij}^2)} \quad (5)$$

Where j and k are the immediate neighboring nodes of i in the graph, and w_{ij} , w_{jk} , and w_{ik} are the corresponding weights. A network with a low clustering coefficient is less segregated than one with a high clustering coefficient. If a network has a low clustering coefficient and short average path length, the network is labeled as random. If a network has a high clustering coefficient and a long average path length, the network is labeled as regular. A network with an ideal balance between segregation and integration is considering small world and is quantified by centrality. Multiple measures quantify centrality of a network. Degree centrality is the simplest measure. Degree, denoted by $d(i)$, is mathematically defined as number of nonzero values in the row or

column of the adjacency matrix related to the node which quantifies how many edges are connected to the node. Degree centrality is expressed by the following equation:

$$C_d(i) = \frac{d(i)}{n-1} \quad (6)$$

The denominator normalizes the degree $d(i)$ by dividing it by all possible nonzero edges a node can have. This brings the measure to a value between 0 and 1 inclusively. Because the adjacency matrix of an undirected simple graph is symmetric, the sum of a row is equal to the sum of the column that corresponds to the same node. Having the degree in the numerator shows this measure is directly proportionality to the number of nodes directly connected to it [45]. This is in contrast with the next measure which is dependent on path length between a given node to all other nodes in the network. The formula for closeness centrality is shown in the equation:

$$C_c(i) = \frac{n-1}{\sum_{j=0}^n d(i,j)} \quad (7)$$

Short path lengths grant centrality regardless of its degree. In an ideal scenario, the node would have a closeness centrality of 1 meaning that it is directly connected (i.e., the path length equals 1) to all nodes in the network [46]. The next measure is referred to as betweenness centrality. It quantifies a node based on how likely the node is to play a crucial role in communication or network connection between every two nodes in a network [46]. Betweenness centrality can be thought of as the significance to or impact that a node has on the information flow within a network. It is dependent on the node degree and path lengths to surrounding nodes. Betweenness centrality is mathematically described in the formula:

$$C_b(i) = \sum_{j \neq k} \frac{p_{jk}(i)}{p_{jk}} \quad (8)$$

Where p_{jk} represents the summation of the shortest path lengths between two nodes, j and k , where i is present in said route [46]. It is the ratio of all shortest paths between j and k that contain i to all shortest, equal-length paths from j to k [46].

Assortativity may give more insight into network robustness and efficiency. Assortativity describes the way nodes of similar degree associate with each other. Primarily, nodes of high degrees associate with each other while nodes of low degree associate with each other [47]. Disassortivity occurs when dissimilar nodes associate with each other. This association disrupts and negatively affects the robustness of the network. If a node of high degree is disrupted, system efficiency will not be compensated through adjacent nodes of lower degree. The assortativity index is measured using the Pearson correlation coefficient [47] given by:

$$r = \frac{\sum_{i=1}^n (X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^n (X_i - \bar{X})^2} \sqrt{\sum_{i=1}^n (Y_i - \bar{Y})^2}} \quad (9)$$

A positive correlation coefficient indicates that the network is exhibiting assortativity whereas a negative indicates disassortativity. If the value is near zero, the network is neutrally assortative [47].

Statistical Analysis

All statistical measures were performed with a significance set at 5%. Population differences were analyzed using a two-sample t-test for assessing means and variances in all global and local graph properties from the musician and nonmusician wPLI matrices. A t-test was appropriate for the two sets of data as they were collected from different subject groups; therefore, the groups are considered independent.

The graph theory measures of statistical interest in this study were average nodal degree, network density, global efficiency, modularity, clustering coefficient, and assortativity. Each measure had a graph theory value for each of the four brain frequency bands of theta, alpha, mu, and beta. A population t-test assessed each measure across the four bands of interest.

Results

Out of 20 subjects, 19 were able to be analyzed. Data file corruption resulted in the removal of nonmusician eight. This resulted in a musician population of 10 and nonmusician population of 9. To perform the analyses, the differences between the baseline noise condition and the stimulant musical condition, i.e. music – noise, were taken. Out of the four frequency bands evaluated, one primarily showed statistical difference between the two populations. The theta band displayed the most statistically significant difference between musicians and nonmusicians with five out of the six graph theory measures being statistically significant in only the theta band. Threshold levels of 50% and 70% were analyzed. The major changes found in the theta band were statistically significant with both threshold levels. This section will report on the p-values according to the 50% threshold level. Figure 13 below shows the average change in nodal degree in the two populations.

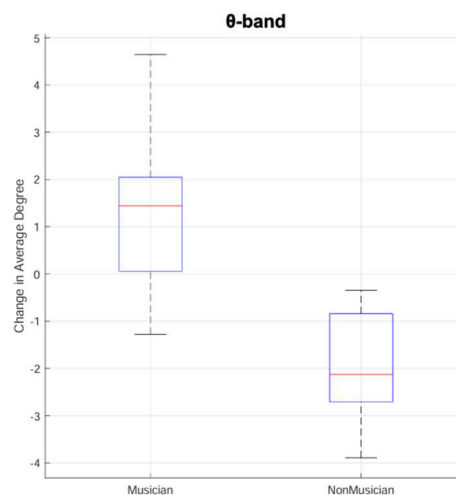


Figure 13: Change in the Average Nodal Degree *in* the Theta Band. Note the red line indicates a mean and not the average.

This measure was statistically significant in the theta band ($p = 0.0002$). It also shows that musician's neural networks tend to increase in connectivity while listening to music whereas a nonmusician's neural network tends to decrease in connectivity. The musicians' connectivity increased by approximately 1.25 nodes from 6.08 to 7.33 nodes showing a 20.54% increase. This is contrasted by nonmusicians' connectivity decreased by approximately 2 nodes or 27.63%.

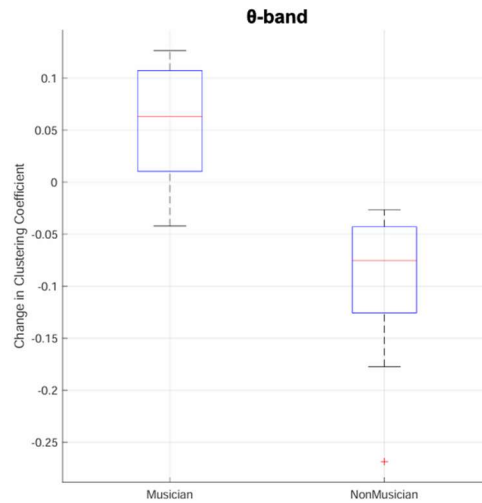


Figure 14: Change in the Clustering Coefficient in the Theta Band.

The next measure tested was segregation, also referred to as clustering coefficient, shown in **Figure 14**. This measure was also statistically significant in the theta band ($p = 0.0002$). On average, musician's neural networks tended to increase segregation by an approximate 0.0518 or 14.25% while nonmusician's decreased by 0.0974 or 24.42%.

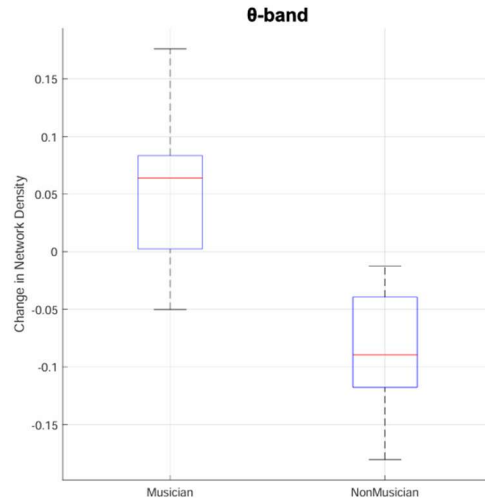


Figure 15: Change in the Network Density in the Theta Band

The change in the network density in the theta band was statistically significant ($p = 0.0001$). Musicians showed an approximate 19.35% increase in network density whereas nonmusicians displayed an approximate 26.04% decrease in network density (see **Figure 15**).

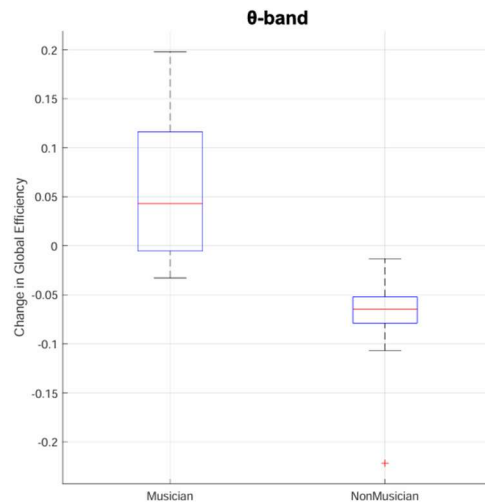


Figure 16: Change in the global efficiency in the Theta Band

Global efficiency was also found to have statistically significant difference in theta band ($p = 0.0003$). As shown in **Figure 16**, musicians showed a mean increase of 0.0582 or 10.21% whereas nonmusicians had a mean decrease of 0.0788 or 12.35%.

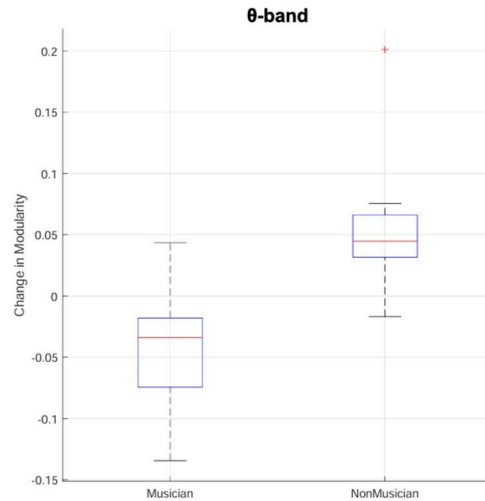


Figure 17: Change in modularity in the Theta Band

Modularity was the last statistically significant measure in the theta band ($p = 0.0011$). It was also the only measure in the theta band where the musicians showed a decrease while listening to music while nonmusicians showed an increase (**Figure 17**). The musician population showed an average decrease of 20.68% whereas the nonmusicians showed an increase of 30%.

Qualitative analyses illustrate the topological changes that occur within each population during the two conditions. As seen in **Figures 18** and **19** below, musicians initially had low functional connectivity during the noise condition but shifted during the music condition to the prefrontal cortex showing a drastic increase in cognition.

Musician-csTheta: Population Average-Noise

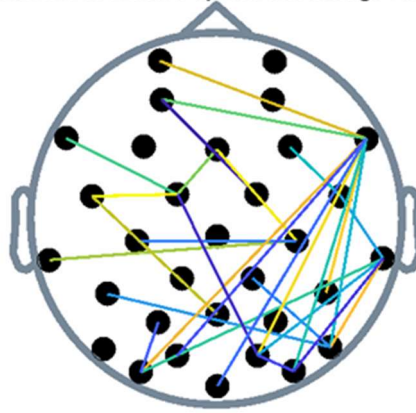


Figure 18: Average functional connectivity topology in the Musician population during white noise.

Musician-csTheta: Population Average-Music

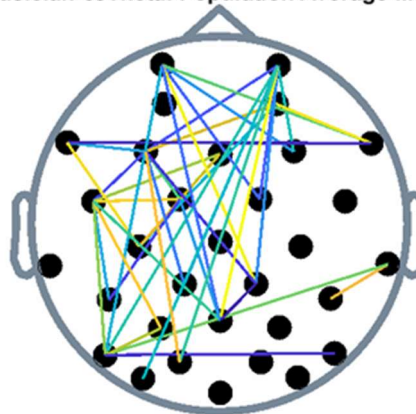


Figure 19: Average functional connectivity topology in the Musician population during classical music.

The opposite topological patterns can be seen in **Figures 20** and **21** showing the nonmusician population during the two conditions where nonmusicians started with a rather high functional connectivity which decreased during the musical condition.

NonMusician-csTheta: Population Average-Noise

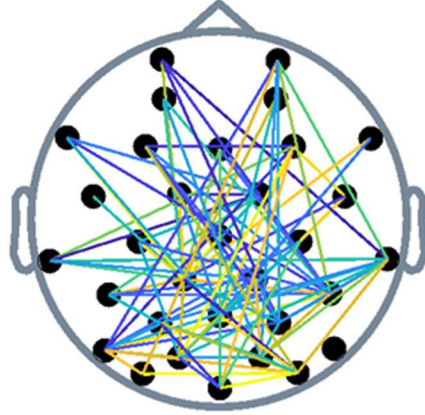


Figure 20: Average functional connectivity topology in the nonmusician population during white noise.

NonMusician-csTheta: Population Average-Music

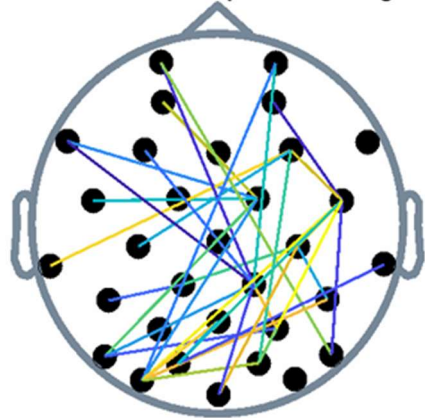


Figure 21: Average functional connectivity topology in the nonmusician population during classical music.

It was observed that the musician population had a strong tendency to activate in the prefrontal cortex. This implied the subjects' active listening to the music and, therefore, an increased functional connectivity. It was also shown that the musician and nonmusician functional networks have a nearly opposite reaction to the musical condition. A likely explanation for this is that the musicians find the white noise condition soothing while nonmusicians find the music condition more soothing.

One rationale for these differences could be that white noise was likely more soothing for musicians as there was nothing to analyze: no melody, rhythm, or harmony. The study task was also trivial to complete for a musician. Watching and reacting to visual cues may have been a menial task for a musician as they are tasks which they engage in nearly every day while in a choir or ensemble.

This task should have been trivial to a nonmusician as well; however, it is to note that other factors such as inattentiveness and boredom may have been synergistic with the white noise causing the nonmusician group to have an increased functional network during the noise condition. The music condition appeared to have worked very well in soothing the nonmusician population as a very notable decrease in functional connectivity occurred with prefrontal cortex connections being greatly reduced.

Discussion

This study examined how musical training impacts the functional networks of the brain while listening to music. Results showed increased theta band activations and graph theory measures in the musician population while listening to music.

It was found that musicians demonstrated an increase in functional connectivity while listening to music compared to nonmusicians. Most notably, it was found that musicians demonstrated an increase in prefrontal activations while nonmusicians exhibited deactivations across the network. Musicians displayed an increase in network density, nodal degree, efficiency, and clustering coefficient with a decrease in modularity. Nonmusicians displayed a decrease in network density, nodal degree, efficiency, and clustering coefficient with an increase in modularity.

It is due to these findings that it is theorized that musicians engage actively with background music. The population is more likely to analyze the background music during task performance leading to an increase in prefrontal cortex activities and graph theory measures. Musicians were found to have the least functional connectivity during white noise as it is likely less stimulating for that population as there are no musical features to focus on and decompose. Nonmusicians, however, appear to be more stimulated during white noise while soothed with background music.

The theta band is related to deep relaxation and sleep pressures; however, it is also noted to counterintuitively play a role in intense cognition [18]. Theta band activity can be found during REM sleep, but it's also found during tasking relating to cognition, imagination, creative thinking,

and problem-solving such as arithmetic and spatial navigation [18]. The theta band is likely to have been the area of increase as these activities may have been occurring with deep attention.

The increase in theta band activity in musicians during the music condition is likely the result of cognitive processing of abstract information, in this case, music. Participating musicians who had never heard the piece may have also been in the process of forming new memories of the piece which may also explain the presence of a theta band increase since theta band activity is also prevalent in the memory formation [20].

Theta is also assumed to play a significant role in episodic (working) memory demands [19]. Only musicians showed significant increases in theta band activations between the music and noise conditions. Since both study conditions revolved around a working memory task, there may have been another reason for the theta activations to be higher within the musician population.

These patterns help explain the trends seen in the graph theory measures as well. Musicians saw an increase in average nodal degree and network density. Since more paths between nodes are being made, network density must also increase as more parts of the brain are being incorporated into the network. Clustering coefficient increases due to this as well as more connections implies that neighboring nodes are becoming more interconnected. Modularity decreases because as a network becomes more interconnected, the natural divisions within the network become more difficult to define. Finally, global efficiency increases because the average path length between any two nodes in the network tends to decrease as the density of the network increases.

Assortativity was not found to be statistically significant in any band at a significance level of 5%. It is the only measure quantified in the theta band found to not be statistically significant. The average change in assortativity within the theta band was also nearly zero in both populations,

but the standard deviation was far larger in the nonmusician population. This means that each network's assortativity did not significantly change due to musical training or condition; however, musical training may play a role in the stability of the networks assortativity coefficient and should be analyzed further.

Conclusion

The findings of this study suggest that musical training does have some impact on the functional networks of the brain. In particular, it was found that musicians have augmented theta band functional connectivity while listening to music when compared to white noise. A qualitative analysis of the functional connectivity shows a heightened response in the prefrontal cortex in musicians compared to nonmusicians while listening to music indicating an active vs. passive listening experience. As such, it can be understood that musicians may be actively analyzing the music they are listening to and anticipating the melodic phrases of the passages. This is contrasted by the nonmusician population which saw a decrease in functional connectivity and likely were soothed by the presence of musical stimulation. This shows that musicians are more likely to be distracted by rather than focused by background music.

A quantitative analysis of the results using graph theory analysis revealed five of six graph theory measures were statistically significant between the two populations in the theta band. Musicians experienced increases in their average nodal degree, network density, global efficiency, and clustering coefficient with a decrease in modularity. In contrast, the opposite trend was noted in the nonmusician population.

Recommendations

Future studies should seek to test multiple musical genres or, if possible, tailor the musical condition to fit the preferred genre of each subject. The genre of music can have major effects on the mental response of the listener. As each person is different, an individual's taste in music will likely influence their functional networks.

A larger population size should be evaluated to perform the best statistics. While current methods allow statistics to be performed on small sample sizes, a larger pool of subjects may provide access to more appropriate statistical analyses. A minimum of 30 subjects per class allows standard parametric statistics to be performed.

This study used a 32-electrode EEG cap. Future studies can expand on this by using a cap with a higher count of electrodes such as 64 or 128 in order to further increase spatial resolution by both increasing the coverage on the scalp and allowing source localization to be performed to increase the EEG depth resolution. While the goal of EEG is to allow cheaper access to perform neurological studies, being able to perform a follow-up study using fMRI would also allow for an increase in spatial resolution.

This study focused on the elicitation of visual ERPs to help compare musician and nonmusician functional connectivity over P300. Future studies could apply the evocation of auditory ERPs to compare the two populations. Musicians are trained to hear subtle auditory features and inaccuracies compared to nonmusicians. A study revolving around auditory ERPs could easily elicit them through the use of melodic perversion by slightly changing the pitches in well-known melodies and evaluating the auditory P600. Musicians would be anticipated to have a much stronger reaction to melodic perversions compared to nonmusicians.

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Appendix – IRB Approval Letter



EAST CAROLINA UNIVERSITY
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Notification of Initial Approval: Expedited

From: Biomedical IRB
To: [Sunghan Kim](#)
Date: 9/13/2023
Re: [UMCIRB 22-002548](#)
Graph Theoretical Analysis of Brain Functional Connectivity Differences between Musicians and Non-Musicians

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) occurred on 9/12/2023. The research study is eligible for review under expedited category # 4, and 7. The Chairperson (or designee) deemed this study no more than minimal risk.

As the Principal Investigator you are explicitly responsible for the conduct of all aspects of this study and must adhere to all reporting requirements for the study. Your responsibilities include but are not limited to:

1. Ensuring changes to the approved research (including the UMCIRB approved consent document) are initiated only after UMCIRB review and approval except when necessary to eliminate an apparent immediate hazard to the participant. All changes (e.g., a change in procedure, number of participants, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the UMCIRB before they are implemented;
2. Where informed consent has not been waived by the UMCIRB, ensuring that only valid versions of the UMCIRB approved, date-stamped informed consent document(s) are used for obtaining informed consent (consent documents with the IRB approval date stamp are found under the Documents tab in the ePIRATE study workspace);
3. Promptly reporting to the UMCIRB all unanticipated problems involving risks to participants and others;
4. Submission of a final report application to the UMCIRB prior to the expected end date provided in the IRB application in order to document human research activity has ended and to provide a timepoint in which to base document retention; and
5. Submission of an amendment to extend the expected end date if the study is not expected to be completed by that date. The amendment should be submitted 30 days prior to the UMCIRB approved expected end date or as soon as the Investigator is aware that the study will not be completed by that date.

The approval includes the following items:

Name	Description
AdamsInformedConsent	Consent Forms
AdamsNI_Thesis_Proposal	Study Protocol or Grant Application
Email Template	Recruitment Documents/Scripts
Musical Experience Questionnaire	Surveys and Questionnaires

For research studies where a waiver or alteration of HIPAA Authorization has been approved, the IRB states that each of the waiver criteria in 45 CFR 164.512(i)(1)(i)(A) and (2)(i) through (v) have been met. Additionally, the elements of PHI to be collected as described in items 1 and 2 of the Application for Waiver of Authorization have been determined to be the minimal necessary for the specified research.

The Chairperson (or designee) does not have a potential for conflict of interest on this study.